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EFFECTIVENESS OF STATIN AND EZETIMIBE COMBINATION ON ATHEROSCLEROTIC PLAQUE IN PATIENTS WITH CORONARY HEART DISEASE

Efektivitas Kombinasi Statin dan Ezetimibe terhadap Plak Aterosklerotik pada Pasien dengan Penyakit Jantung Koroner

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ABSTRAK

Penyakit jantung koroner mengacu pada kondisi penyumbatan pembuluh darah arteri yang dikenal dengan istilah aterosklerosis. Statin bekerja dengan mengurangi produksi kolesterol di hati serta menjaga stabilisasi plak pada pasien dengan penyakit jantung koroner. Namun demikian pemberian statin tidak dapat ditoleransi dengan baik pada pasien tertentu, sehingga dipertimbangkan penggunaan kombinasi statin dengan ezetimibe. Tinjauan artikel ini bertujuan untuk mengetahui efektivitas kombinasi statin dan ezetimibe terhadap plak aterosklerosis pada pasien dengan penyakit jantung koroner. Penelusuran pustaka dilakukan menggunakan basis data PubMed dan EBSCO (MEDLINE Ultimate) pada bulan Februari 2025 dengan menggunakan kata kunci "Ezetimibe", "Hydroxymethylglutaryl-CoA Reductase Inhibitors","Atherosclerotic Plaque" dan "Coronary Artery Disease". Artikel dipilih berdasarkan kriteria inklusi yaitu artikel berbahasa Inggris, diterbitkan dalam sepuluh tahun terakhir, penelitian pada manusia, dan merupakan *randomized controlled trial* pada pasien jantung koroner dengan atau tanpa penyakit penyerta. Kriteria eksklusi meliputi: tinjauan/review, studi protokol, editorial, tinjauan sistematis dan meta analisis, dan topik/hasil yang tidak relevan. Penelusuran awal menghasilkan 34 artikel dengan 10 duplikasi dan 14 kriteria eksklusi, sehingga diperoleh 10 artikel penelitian yang berfokus di Jepang, Korea, dan Cina. Hasil tinjauan artikel menunjukkan bahwa kombinasi statin dengan ezetimibe lebih efektif dalam menurunkan *low density lipoprotein-cholesterol* (LDL-C), mengurangi respon inflamasi, serta menghasilkan regresi plak aterosklerosis yang lebih besar dibandingkan monoterapi statin. Dengan demikian, penggunaan kombinasi statin dosis rendah hingga sedang dan ezetimibe dapat menjadi terapi pilihan bagi pasien dengan penyakit jantung koroner yang berisiko tinggi.

Kata kunci: ezetimibe, penghambat HMG-CoA reduktase, penyakit jantung koroner, plak aterosklerosis, statin

ABSTRACT

Coronary heart disease is a condition of blockage of the arteries known as atherosclerosis. Statins reduce cholesterol production in the liver and maintain plaque stability in patients with coronary heart disease. However, statin administration is not well tolerated in certain patients; therefore, the use of a combination of statins with ezetimibe is considered. This article review aims to determine the effectiveness of combining statins and ezetimibe in reducing atherosclerotic plaque in patients with coronary heart disease. Literature searches were conducted using the PubMed and EBSCO (MEDLINE Ultimate) databases in February 2025 using the keywords "Ezetimibe",

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"Hydroxymethylglutaryl-CoA Reductase Inhibitors", "Atherosclerotic Plaque ", and "Coronary Artery Disease". Articles were selected based on inclusion criteria, e.g., language in English, published in the last ten years, human studies, and randomized controlled trial research methods in coronary heart disease patients with or without comorbidities. Exclusion criteria included: reviews, protocol studies, editorials, systematic reviews and meta-analyses, and irrelevant topics/results. The initial search yielded 34 articles with 10 duplicates and 14 exclusion criteria, resulting in 10 research articles conducted in Japan, Korea, and China. The article review results showed that the combination of statins and ezetimibe was more effective in lowering low-density lipoprotein-cholesterol (LDL-C), reducing the inflammatory response, and producing greater atherosclerotic plaque regression than statin monotherapy. Thus, the use of a combination of low to moderate dose statins and ezetimibe may be a therapy of choice for patients with high-risk coronary heart disease.

Keywords: *atherosclerotic plaque, coronary artery disease, ezetimibe, hydroxymethylglutaryl-CoA reductase inhibitors, statins*

INTRODUCTION

Coronary heart disease (CHD) or coronary artery disease generally refers to conditions involving impaired or blocked blood flow in the coronary arteries, which can result in ischemia, angina pectoris, acute coronary syndrome (ACS), or sudden cardiac death[1]. Based on data from the World Health Organization (WHO) in 2021, deaths due to cardiovascular disease are estimated to reach 17.9 million people.[2] In Indonesia, data from the 2018 Basic Health Research (Riskesdas) shows that the incidence of heart and blood vessel disease has been increasing year by year. At least 15 out of 1,000 Indonesians suffer from heart disease[3].

Various preventive measures are implemented to reduce the risk of complications and mortality in CHD patients, one of which is managing risk factors for dyslipidemia. Statins have become first-line therapy for treating elevated cholesterol due to their ease of dosing, limited drug interactions, and good safety profile[4]. However, in some patients, statin use can cause muscle-related side effects (myopathy) and elevated serum transaminases when used in high doses[5]. Several studies have shown that the use of simvastatin doses of 40-80 mg significantly increases the risk of myopathy[6], [7]. In addition, high-dose statin therapy, especially in intensive therapy, such as atorvastatin 80 mg and rosuvastatin 20 mg, has also been shown to carry a slightly increased risk of developing type 2 diabetes mellitus (T2DM) compared to moderate or low doses[8], [9], [10]. Because the side effects of statins are dose-related, combination therapy is a consideration in optimizing statin doses, especially for patients who cannot tolerate high doses of statins or patients who are susceptible to statin-induced myopathy, including geriatrics, Asians, or patients with renal insufficiency[7].

Based on the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines, the use of a combination of statins with ezetimibe is recommended to lower LDL-C if the therapeutic goal with the maximum tolerated statin dose is not achieved Unlike statins, ezetimibe does not appear to increase the incidence of new-onset T2DM, and may even provide benefits for glycemic control [11]. Major clinical trials, such as IMPROVE-IT and RACING, have shown that the combination of a statin with ezetimibe significantly lowers low-density lipoprotein-cholesterol (LDL-C), especially in high-risk atherosclerotic cardiovascular disease (ASCVD) patients. However, further investigation is needed to determine whether the combination of statins with ezetimibe can also affect the development and/or regression of atherosclerotic plaque. Therefore, this article will briefly describe the effectiveness of the combination of statins with ezetimibe compared to statin monotherapy on atherosclerotic plaque and changes in lipid profiles in patients with coronary heart disease.

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METHODS

A literature search was conducted using the PubMed and EBSCO (MEDLINE Ultimate) databases in February 2025 using the keywords “Ezetimibe”, “Hydroxymethylglutaryl-CoA Reductase Inhibitors”, “Atherosclerotic Plaque”, and “Coronary Artery Disease”. The search strategy in the database search can be seen in Table 1.

Table 1. Search Strategies in Database Search

Database	Search Terms
PUBMED	"Ezetimibe"[Mesh] AND "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors" [Pharmacological Action] AND "Plaque, Atherosclerotic"[Mesh] AND "Coronary Artery Disease"[Mesh]
EBSCO	Ezetimibe AND Hydroxymethylglutaryl-CoA Reductase Inhibitors AND Atherosclerotic Plaque AND Coronary Artery Disease

After searching, articles were selected and screened based on inclusion criteria: articles in English, published within the last ten years (2015–2025), human studies, and randomized controlled trials (RCTs) research methods in CHD patients with or without comorbidities. Exclusion criteria included: reviews, protocol studies, editorials, systematic reviews and meta-analyses, animal studies, and irrelevant topics/results. The PRISMA flowchart was used to illustrate the article selection process. Data extracted from articles that met the inclusion and exclusion criteria covered various parameters, including author details, year of publication, country, number of patients, patient characteristics, intervention and control doses, monitoring time, and results obtained.

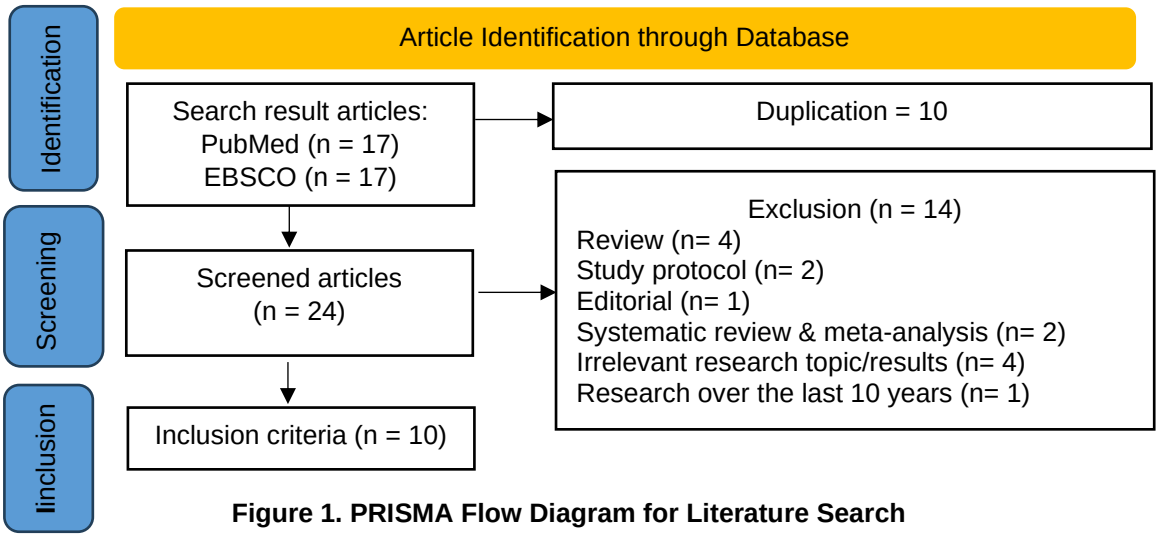

Figure 1. PRISMA Flow Diagram for Literature Search

Figure 1 illustrates the PRISMA flowchart for the literature search. The initial search yielded 34 articles, consisting of 17 articles from the PUBMED database and 17 articles from the EBSCO database. From this initial search, there were 10 duplicates, resulting in 24 articles. The subsequent selection process resulted in 14 articles that met the exclusion criteria, resulting in 10 articles that met the inclusion criteria for review.

RESULT

Table 2 lists the articles included in the review. The publications spanned from 2015 to 2023 and primarily focused on Asian countries, including Japan, Korea, and China. The study designs were randomized control trials (RCTs) with follow-up periods of 3–12 months and a participant population of 41–246 patients. The sampling techniques used in most studies were probability sampling, including simple random sampling, block randomization, and stratified random sampling. In the subanalysis, purposive sampling

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was used because participants were drawn from the primary study and had specific clinical characteristics relevant to the subanalysis's objectives. Of the ten articles reviewed, three were subanalyses of the PRECISE-IVUS study, and one was a subanalysis of the CuVIC study.

Table 2. List of Articles Related to the Effectiveness of the Combination of Statins and Ezetimibe against Atherosclerotic Plaque

No.	Author and Year	Country	Study Name	Research Design and Sampling Techniques	Number of Patients	Monitoring Time
1	Wang X, et al (2015)	China	-	Prospective, parallel-group RCT, *Simple Random Sampling*	106	12 months
2	Tsujita, et al (2015)	Japan	PRECISE -IVUS	Multicenter, open-label RCT The main PRECISE-IVUS study, *Simple Random Sampling*	202	9-12 months
3	Tsujita, et al (2016)	Japan	PRECISE -IVUS	PRECISE-IVUS subanalysis in ACS patients, *Purposive Sampling*	100	9-12 months
4	Tsujita, et al (2016)	Japan	PRECISE -IVUS	PRECISE-IVUS subanalysis in patients with a history of prior statin use, *Purposive Sampling*	202	9-12 months
5	Lee, et al. (2016)	Korea	-	Prospective, single-center, open-label RCT, *Simple Random Sampling*	70	3 months
6	Ueda, et al. (2017)	Japan	ZIPANGU	Multicenter, double-blinded RCT, *Block Randomization*	131	9 months
7	Wang J, et al (2017)	China	-	Single-center RCT, open, *Simple Random Sampling*	100	12 months
8	Fujisue, et al. (2018)	Japan	PRECISE -IVUS	PRECISE-IVUS subanalysis based on PGK status, *Purposive Sampling*	Total: 202 (52 GGK)	9-12 months
9	Oh, et al. (2021)	Korea	-	Single-center RCT, open, *Simple Random Sampling*	41	12 months
10	Nakano, et al. (2023)	Japan	CuVIC	Subanalysis of the CuVIC study based on oxysterols, *Purposive Sampling*	79	6-8 months

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Table 3. Article Summary: The Role of Statin and Ezetimibe Combination on Atherosclerotic Plaque

No.	Writer	Year	Research Population	Intervention Dose	Control Dose	Evaluation Method	Parameters assessed	Results
1	Wang X, et al.	2015	Coronary artery disease patients with hyperlipidemia	Rosuvastatin 10 mg/ Ezetimibe 10 mg	Rosuvastatin 10 mg	VH-IVUS	1. Lipid profile: TC, TG, HDL-C, and LDL-C 2. Inflammatory profile: hsCRP, IL-6, MMP-9, 3. Changes in plaque composition and size	Rosuvastatin/ezetimibe combination was more effective in reducing LDL-C, hs-CRP, IL-6, and MMP-9 ($p<0.05$), and in reducing plaque burden and plaque area compared to rosuvastatin monotherapy ($p<0.05$).
2	Tsujita, et al	2015	Coronary artery disease patients with PCI procedures	Routine dose of Atorvastatin/ Ezetimibe 10 mg	Atorvastatin routine dose	IVUS	1. Lipid profile: TC, TG, HDL-C, LDL-C 2. Inflammatory profile: hsCRP 3. Changes in plaque composition and size: PAV	Atorvastatin/ezetimibe combination showed a more significant reduction in LDL-C levels and plaque regression than atorvastatin alone ($p<0.001$).
3	Tsujita, et al	2016	ACS patients with PCI procedures	Routine dose of Atorvastatin/ Ezetimibe 10 mg	Atorvastatin routine dose	IVUS	1. Lipid profile: TC, TG, HDL-C, LDL-C 2. Inflammatory profile: hsCRP 3. Changes in plaque composition and size: PAV	Reductions in LDL-C and residual cholesterol levels were associated with stronger plaque regression in the combination group compared with monotherapy ($p=0.047$).
4	Tsujita, et al	2016	CHD patients with a history of previous statin use	Routine dose of Atorvastatin/ Ezetimibe 10 mg	Atorvastatin routine dose	IVUS	1. Lipid profile: TC, TG, HDL-C, LDL-C 2. Inflammatory profile: hsCRP 3. Changes in plaque composition and size: PAV	Patients who had previously undergone statin therapy experienced significantly more plaque regression with the atorvastatin/ezetimibe combination compared to those receiving atorvastatin alone ($p=0.002$).
5	Lee, et al.	2016	ACS patients undergoing plaque evaluation with IVUS.	Simvastatin 40 mg/ Ezetimibe 10 mg	Pravastatin 20 mg	VH-IVUS	1. Lipid profile: TC, TG, HDL-C, LDL-C 2. Inflammatory profile: hsCRP 3. Plaque composition (fibrous, fibro-fatty, dense calcium, necrotic core)	Significant reduction in fibro-fatty plaque volume in the simvastatin/ezetimibe combination therapy group compared to pravastatin monotherapy ($p=0.024$).

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6	Ueda, et al.	2017	Stable CHD patients who have undergone PCI procedures and have had yellow plaques.	Atorvastatin 10-20 mg/ Ezetimibe 10 mg	Atorvastatin 10-20 mg	Angioscopy + IVUS	1. Lipid profile: TC, TG, HDL-C, LDL-C 2. Inflammatory profile: hsCRP 3. Plaque color 4. Plaque volume changes: PAV	Atorvastatin/ezetimibe combination was more effective in lowering LDL-C (P<0.001) and reducing plaque volume (p=0.03), but there was no significant difference between the two groups in plaque stabilization based on plaque color change (p=0.373).
7	Wang J, et al.	2017	Carotid atherosclerosis patients with T2DM and CHD	Atorvastatin 20 mg/ Ezetimibe 10 mg	Atorvastatin 20 mg	Carotid US	1. Lipid profile: TC, TG, HDL-C, LDL-C 2. Inflammatory profile: hsCRP 3. Glycemic profile: fasting blood sugar, HbA1c 4. *Intima media thickness*(IMT) and plaque area	Atorvastatin/ezetimibe combination was more effective in reducing LDL-C and hs-CRP levels, and reducing intima-media thickness (IMT) and plaque area compared to atorvastatin alone (p<0.05).
8	Fujisue, et al.	2018	Coronary artery disease patients with or without CKD who have undergone PCI	Routine dose of Atorvastatin/ Ezetimibe 10 mg	Atorvastatin routine dose	IVUS	1. Lipid profile: TC, TG, HDL-C, LDL-C 2. Inflammatory profile: hsCRP 3. Changes in plaque composition and size: PAV	Atorvastatin/ezetimibe combination showed a greater plaque regression effect than atorvastatin alone, both in patients with and without CKD (p=0.04).
9	Oh, et al.	2021	Stable angina patients who have undergone PCI procedures and have intermediate lesions	Atorvastatin 10 mg and Ezetimibe 10 mg	Atorvastatin 40 mg	NIRS-IVUS	1. Lipid profile: TC, TG, HDL-C, LDL-C 2. Inflammatory profile: hsCRP 3. Glycemic profile: fasting blood sugar, HbA1c 4. Percentage of atheroma volume (PAV) 5. *Lipid core burden index*	Atorvastatin/ezetimibe combination has equivalent effectiveness to high-dose atorvastatin in atherosclerosis regression, but does not show a statistically significant difference (p>0.05).
10	Nakano, et al.	2023	Coronary artery disease patients with PCI (stent) procedures	Atorvastatin and Ezetimibe	Atorvastatin alone	IVUS	1. Lipid profile: TC,TG, HDL-C, LDL-C 2. Inflammatory profile: hsCRP 3. Non-cholesterol sterols 4. Plaque regression: PAV	Atorvastatin/ezetimibe combination reduced LDL-C more significantly (P=0.0143) and provided a greater plaque regression effect than statin monotherapy (P=0.042).

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Table 3 presents a summary of articles related to the effectiveness of the combination of statins and ezetimibe on atherosclerotic plaque, including the study population, intervention and control doses, parameters assessed, evaluation methods, and study results. Of the ten articles obtained, four were PRECISE-IVUS studies conducted on CHD patients in Japan.[17], [18], [19], [20].The difference lies in the populations studied. The main study (2015) was conducted on patients with ACS and stable angina after PCI. Subsequently, a sub-analysis by Tsujita et al. (2016) was conducted on patients with ACS, and a sub-analysis on CHD patients with a history of prior statin therapy. A sub-analysis by Fujisue et al. (2017) was conducted on CHD patients with and without CKD. The subjects of the other six articles were CHD patients with hyperlipidemia[16]; ACS patients undergoing plaque evaluation[22]; Stable CHD patients after PCI procedure with yellow plaque (ZIPANGU study)[18]; Carotid atherosclerotic patients with T2DM and CHD[19]; Stable CHD patients post PCI procedure with intermediate lesions[20], as well as CHD patients with stent placement (CuVIC study)[21].

This review compared statin–ezetimibe combinations with statin monotherapy. Eight of ten studies used atorvastatin plus ezetimibe at varying intensities: five compared titrated-dose atorvastatin/ezetimibe 10 mg with titrated-dose atorvastatin, one compared moderate-intensity atorvastatin/ezetimibe (10/10 mg) with high-intensity atorvastatin (40 mg), one compared moderate-intensity atorvastatin/ezetimibe (20/10 mg) with atorvastatin 20 mg, and one compared flexible-dose atorvastatin/ezetimibe (10–20/10 mg) with flexible-dose atorvastatin (10–20 mg). The remaining two studies evaluated rosuvastatin and simvastatin combined with ezetimibe.

Seven out of ten studies used intravascular ultrasound (IVUS) as the primary evaluation method. IVUS is an invasive intravascular imaging technique that uses ultrasonic waves to characterize lesion morphology, measure plaque burden, and identify blood vessel abnormalities[22]. Two studies used the virtual histology (VH)-IVUS method, which can provide a virtual histology image of plaque.[16],[17] And one study used near-infrared spectroscopy (NIRS)-IVUS, which is highly sensitive to lipids and was used to assess the lipid core burden index (LCBI) [20]. In addition, there is one study using angioscopy[18], which is an invasive imaging procedure using X-rays and contrast material to visualize blood vessels, as well as one study using carotid ultrasound[19], which is a non-invasive procedure to determine the morphology of blood vessel walls in patients with cerebrovascular ischemia[23].

The assessed parameters included lipid profiles (LDL-C), LCBI, inflammatory biomarkers (hs-CRP, IL-6, MMP-9), plaque morphology (PAV, IMT), metabolic markers (campesterol, sitosterol, lathosterol, oxysterol), and plaque color for stabilization and atherosclerosis risk. Results showed that statin–ezetimibe combinations were more effective than statin monotherapy in reducing LDL-C and hs-CRP. One study also reported greater reductions in IL-6, MMP-9, campesterol, and 27-hydroxycholesterol. Nine studies demonstrated significant plaque regression with the combination ($p<0.05$), while one found comparable effects to high-dose atorvastatin ($p>0.05$). For plaque stabilization, no significant difference was observed between groups ($p=0.373$).

DISCUSSION

Ten research articles examining the effectiveness of the combination of statins with ezetimibe in three Asian countries: Japan, Korea, and China, showed that the combination of statins with ezetimibe was more effective in reducing LDL-C and hs-CRP compared to statin monotherapy in CHD patients, both ACS and stable angina, after PCI or stent placement, CHD patients with comorbidities such as hyperlipidemia, carotid atherosclerosis, CKD and T2DM. In addition, the combination of statins and ezetimibe can reduce other inflammatory biomarkers such as IL-6 and MMP-9, metabolic markers of campesterol and oxysterol (27-hydroxycholesterol), and reduce atherosclerotic plaque

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regression. The most widely used statin type in combination with ezetimibe is atorvastatin.

Niemann-Pick C1-Like1 Mechanism and Its Impact on Lipid Profile, Sterol Biomarkers, and Plaque Regression

The combination of statins with ezetimibe is more effective in lowering LDL-C because they work by different mechanisms, thus suppressing the compensatory increase in cholesterol absorption.[17].Statins work by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme that catalyzes the conversion of HMG-CoA to mevalonic acid, which plays a key role in cholesterol biosynthesis. Unlike statins, ezetimibe does not increase bile acid excretion or inhibit cholesterol synthesis in the liver. Ezetimibe works by inhibiting cholesterol absorption in the intestinal microvilli by binding to the Niemann-Pick C1-Like1 (NPC1L1) protein, thereby reducing cholesterol supply to the liver, upregulating hepatic LDL-C receptors, and increasing LDL-C metabolism. This results in decreased total cholesterol (TC), triglycerides (TG), and increased high-density lipoprotein cholesterol (HDL-C).[29].A study conducted by Oh et al. (2021) showed that although there was no significant difference in the reduction of LCBI between the use of the atorvastatin/ezetimibe combination and atorvastatin 40 mg (P>0.05), the combination of statins with ezetimibe reduced LDL-C by up to 40%, almost equivalent to high-dose atorvastatin monotherapy[20].

In addition to affecting lipid profiles, ezetimibe can also reduce non-cholesterol sterols such as campesterol and oxysterols, which are biomarkers of intestinal cholesterol absorption. Oxysterols are oxidized cholesterol products produced enzymatically during cholesterol catabolism and are detected in serum at very low concentrations compared to cholesterol [25]. A subanalysis study conducted by Nakano et al. (2023) showed that a decrease in campesterol and oxysterol levels (especially 27-hydroxycholesterol) was significantly correlated with coronary plaque regression (p=0.042)[21]. This demonstrates that NPC1L1 inhibition directly reduces atherosclerotic burden.

Inflammatory Response and Its Relation to Plaque Regression and Stabilization

The results of the literature search in this article indicate that the combination of statins with ezetimibe, in addition to lowering lipid profiles, has also been shown to reduce the inflammatory response, which is associated with plaque regression and stability. In a study conducted by Wang et al. (2015), the combination of rosuvastatin/ezetimibe was significantly more effective in reducing hs-CRP, interleukin-6 (IL-6), and matrix metalloproteinase-9 (MMP-9) than rosuvastatin monotherapy (P<0.05). hs-CRP is involved in the formation and progression of unstable plaques. IL-6, a pro-inflammatory cytokine, plays a direct role in activating endothelial monocytes and macrophages, thereby accelerating plaque accumulation and atherosclerosis. Increased IL-6 concentrations indicate that the plaque is susceptible to rupture [16]. Similarly, MMP-9, a zinc-containing enzyme produced by cells in the walls of blood vessels, has been significantly associated with an increased risk of CHD [26]. Excessive secretion of MMP-9 can promote rupture of atherosclerotic plaque by degrading collagen within the fibrous layer.[34].The reduction in hs-CRP, IL-6, and MMP-9 demonstrates the potent anti-inflammatory effect of the combination of statins and ezetimibe and reinforces the finding that ezetimibe provides a protective effect against plaque.

The PRECISE-IVUS study conducted by Tsujita et al. (2015) showed a greater reduction in plaque regression effect compared to atorvastatin monotherapy, with inferior percent atheroma volume (PAV) values, especially in patients with ACS (P<0.001)[12]. The results of the subanalysis showed that coronary plaque regression in ACS patients mostly occurred in patients with lower LDL-C levels, both in the use of dual lipid-lowering agents and statin monotherapy[18].Ezetimibe enhanced plaque regression in patients previously treated with statins and unresponsive to statin dose increases[19].The use of a combination of statins with ezetimibe provides benefits in better coronary plaque

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regression in both CKD and non-CKD patients [20].The overall results of the PRECISE-IVUS study reaffirm the role of ezetimibe in inhibiting cholesterol absorption and statin-induced coronary plaque regression. Plaque regression correlated with lower LDL-C levels, suggesting a potential correlation between greater plaque regression in vulnerable and unstable patients.

In this literature review, the patients included in the study were CHD patients with comorbidities such as hyperlipidemia, carotid atherosclerosis, CKD, and type 2 diabetes mellitus (T2DM). Epidemiological studies have shown that the rate of cardiovascular and cerebrovascular events in T2DM patients is significantly higher than in non-T2DM patients[28]. In a study conducted by Wang et al. (2017) on patients with carotid atherosclerosis with T2DM and CHD, it was found that the combination of atorvastatin with ezetimibe significantly reduced plasma LDL-C levels, hs-CRP levels, and intima-media thickness (IMT) and plaque area compared to atorvastatin monotherapy ($P<0.05$)[19]. This suggests that combination therapy has a systemic effect on atherosclerosis, which is associated with ezetimibe's role in inhibiting the oxidative stress response, increasing endothelial nitric oxide synthase expression, improving arterial elasticity, and inhibiting vascular inflammation. This study also suggests that the combination of statins and ezetimibe is beneficial for high-risk cardiovascular patients, including CHD patients with carotid atherosclerosis and type 2 diabetes mellitus (T2DM).

The ZIPANGU study conducted by Ueda et al. (2017) compared the plaque stabilization and plaque regression effects between the combination of statin and ezetimibe with statin monotherapy based on the color index and coronary artery plaque volume[18]. Plaque stabilization effect was evaluated by reduction of the yellow color level using angioscopy, and plaque regression effect was examined by reduction of plaque volume percentage using IVUS.[29] From the results of the article review, it was found that the plaque stabilization effect between the statin and ezetimibe combination group was not different from the statin monotherapy group, as indicated by a similar decrease in the level of yellow color between the two regimens. However, the statin and ezetimibe combination group provided a greater plaque regression effect through a significant reduction in the percentage of plaque volume compared to statin monotherapy ($p= 0.03$). From the study, it was concluded that statins were able to increase fibrous cap thickening while reducing plaque volume, while ezetimibe worked primarily by reducing plaque volume through its anti-inflammatory effect, which is different from statins. This suggests that ezetimibe may have a greater impact on plaque regression than plaque stabilization.

Statin Intensity Comparison

The interventions used in all studies in the reviewed articles compared the combination of a statin and ezetimibe to statin monotherapy (control). The statin dose intensities used varied, with atorvastatin at 10–20 mg, rosuvastatin at 10 mg, and simvastatin at 40 mg being moderate-intensity statins, while pravastatin at 20 mg was a low-intensity statin[30]. The purpose of using statins at various intensities is to assess the effectiveness of the dose on lowering LDL-C, measure the effect of plaque regression, and individualize the therapeutic dose according to the patient's condition.

Research by Lee et al (2016) demonstrated that a combination of simvastatin 40 mg/ezetimibe 10 mg compared to pravastatin 20 mg, resulted in significant alterations in coronary plaque components over a short term of three months ($P=0.024$). Specifically, there was a reduction in the absolute volume of fibro-fatty plaque and a decrease in LDL-C levels in ACS patients, relative to pravastatin monotherapy[17]. In previous studies, it was reported that maximal intensive statin treatment with rosuvastatin (40 mg) for 24 months in 36 patients and with atorvastatin (80 mg) in 35 patients resulted in regression of coronary atheromatous plaques and reduction of the fibro-fatty component[31].

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Therefore, the combination of statin and ezetimibe is important for early intervention in ACS patients to control LDL-C and initiate rapid and effective plaque modification.

The results of a study conducted by Oh et al. (2021) using a combination of moderate-intensity statin and ezetimibe compared with high-intensity statin (atorvastatin 10 mg/ezetimibe 10 mg vs atorvastatin 40 mg) showed a comparable decrease in LDL-C and regression of coronary atherosclerosis in intermediate lesions.[25].This supports the concept that ezetimibe combined with a low-intensity statin may be effective in patients who are intolerant or at risk of side effects with high-intensity statins [20]. Another study conducted by Fujisue et al. (2018) using atorvastatin with dose titration highlighted the benefits of statin and ezetimibe combination therapy in patients with CKD who are more susceptible to high-dose statins. The results showed that the combination of atorvastatin and ezetimibe has been shown to provide a stronger coronary plaque regression effect compared to atorvastatin monotherapy[15].

The most commonly used statin is atorvastatin, while other statins include rosuvastatin, simvastatin, and pravastatin. Atorvastatin is the most commonly used statin in research because it significantly lowers lipid levels compared to simvastatin and pravastatin[32]. It has been proven to reduce the incidence of heart attacks and strokes, and has a lower risk of side effects such as T2DM and cataract surgery compared to rosuvastatin, and shows a consistent safety profile across populations, especially in Asia[33].

Study Limitations

This review has several limitations. Some studies were subanalyses of the main study, making them susceptible to selection bias. The follow-up durations ranged from 3 to 12 months, which may not have been sufficient to capture long-term changes, including slower plaque stabilization. The evaluation methods used varied (IVUS, VH-IVUS, and NIRS-IVUS), so the parameters measured also varied and did not have equivalent sensitivity for assessing plaque volume, composition, and stability. Finally, no studies directly compared the types of statins used within a single trial framework, so the choice of the best statin can only be inferred indirectly.

Clinical Implications

Based on the presented results, this review article continues to make an important contribution to strengthening the scientific evidence regarding the effectiveness of the combination of statins and ezetimibe in reducing atherosclerotic plaque burden, stabilizing plaque composition, and reducing inflammatory biomarkers. Furthermore, this review article can serve as a supporting reference for healthcare professionals in using the combination of statins and ezetimibe as the preferred therapy for high-risk CHD patients who are unresponsive to statin monotherapy.

CONCLUSION

Statin combination therapy with ezetimibe is more effective in reducing LDL-C, inflammatory biomarkers, and providing a greater plaque regression effect compared to statin monotherapy in CHD patients (ACS or stable angina), post-PCI or stent placement, and CHD patients with comorbidities such as hyperlipidemia, carotid atherosclerosis, CKD, and T2DM. Thus, the use of a combination of statins and ezetimibe can be a therapy of choice for high-risk CHD patients, such as patients with comorbid hyperlipidemia, carotid atherosclerosis, T2DM, and CKD, as well as patients who are unresponsive or intolerant to the use of high-dose statins.

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