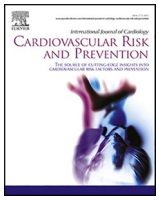
International Journal of Cardiology Cardiovascular Risk and Prevention 22 (2024) 200298

Contents lists available at ScienceDirect

International Journal of Cardiology
Cardiovascular Risk and Prevention

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-cardiovascular-risk-and-prevention



Efficacy and safety of drugs in residual cardiovascular risk: A systematic review of the literature

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ARTICLE INFO

Handling Editor: Dr D Levy

Keywords:
Atherosclerotic cardiovascular disease
Residual cardiovascular risk

ABSTRACT

Background: The objective of this research is to evaluate the efficacy and safety of drugs in the residual risk in any of its three components: lipid, inflammatory and thrombotic risk.
Methods: A systematic review was conducted of randomized clinical trials that included as a primary outcome, at least one of the conditions related to atherosclerotic cardiovascular disease. The databases used were PUBMED/MEDLINE, Scopus and ClinicalTrials.gov. The risk of bias of the studies was assessed using the Risk of Bias 2 tool.
Results: and discussion: 18 studies were included in the analysis. Half of the studies had low risk of bias or some concerns. Several drugs were effective in reducing the primary outcome: ethyl eicosapentaenoeic acid (17.2 % E-EPA versus 22 % placebo HR: 0.75; 95 % CI 0.68–0.83; $p < 0.001$), colchicine in stable coronary artery disease (6.8 % vs placebo 9.6 %, HR 0.59, 95 % CI 0.57–0.83; $p < 0.001$), Canakinumab (150 mg vs placebo ARR 15 %, HR 0.85, 95 % CI 0.74–0.98; $p = 0.021$) and Rivaroxaban with Aspirin in stable atherosclerotic disease (4.1 % versus aspirin 5.4 %, HR 0.76, 95 % CI 0.66–0.86, $P < 0.001$). Serious adverse events did not differ between study groups, except for a higher rate of bleeding with the use of combination antithrombotic therapy.
Conclusion: The residual risk can be reduced through the use of different drugs that act by modifying atherogenic lipid levels, modulating inflammatory pathways and the risk of thrombosis, with an acceptable safety profile in most studies.

1. Introduction

In recent decades, the treatment of Atherosclerotic Cardiovascular Disease (ASCVD) has been focused on the control of LDL cholesterol (LDL–C) with statins [1]; however, studies have shown that despite achieving optimal LDL–C levels, patients continue to experience major adverse cardiovascular events (MACE), which has been defined as residual cardiovascular risk [2,3]. This concept includes non–modifiable factors such as family history, age, sex, and ethnicity, among others, that influence the onset and progression of atherosclerotic plaque, such as chronic inflammation, prothrombotic states, concentrations of certain lipoproteins and triglycerides [4].

In the pathogenesis of atherosclerotic plaque, clinical and experimental studies suggest that inflammation plays a key role, independent of LDL–C [5], especially through the increase of proinflammatory cytokines such as interleukin–1 (IL–1), interleukin–6 (IL–6), interleukin–8, and tumor necrosis factor–alpha [6]. Other conditions, such as hypertriglyceridemia and high levels of lipoprotein (a), can amplify the process by penetrating the endothelial barrier and depositing directly into the arterial wall [7,8]. Finally, rupture of the atherosclerotic plaque exposes thrombogenic material, such as the tissue factor produced by macrophages and smooth muscle cells, capable of generating an occlusive thrombus rich in fibrin and platelets [5,9,10].

The purpose of this research is to evaluate the quality of studies on the efficacy and safety of pharmacological therapies for the reduction of MACE in adults with residual cardiovascular risk. To this end, a systematic review of the literature was performed that included phase III clinical trials addressing the lipid, inflammatory, and thrombotic components of atherosclerotic plaque.

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https://doi.org/10.1016/j.ijcrp.2024.200298
Received 5 March 2024; Received in revised form 4 June 2024; Accepted 13 June 2024
Available online 15 June 2024

2. Materials and methods

For the preparation of this study, the verification criteria of the Preferred Reporting Items for Systematic Reviews and Meta–Analyses (PRISMA) statement in its 2020 version were followed. In addition, using the PICO tool, the research question was developed considering 1) the population: individuals with established ASCVD or at high risk of developing it, with residual cardiovascular risk; 2) the intervention: drugs that reduce residual cardiovascular risk; 3) the comparator: drug products compared with each other or against placebo; and 4) the outcomes: efficacy and safety in the reduction of MACE.

2.1. Inclusion and exclusion criteria

We included phase III Randomized Clinical Trials (RCTs), or pre–specified subgroup analyses of RCTs that evaluated within their

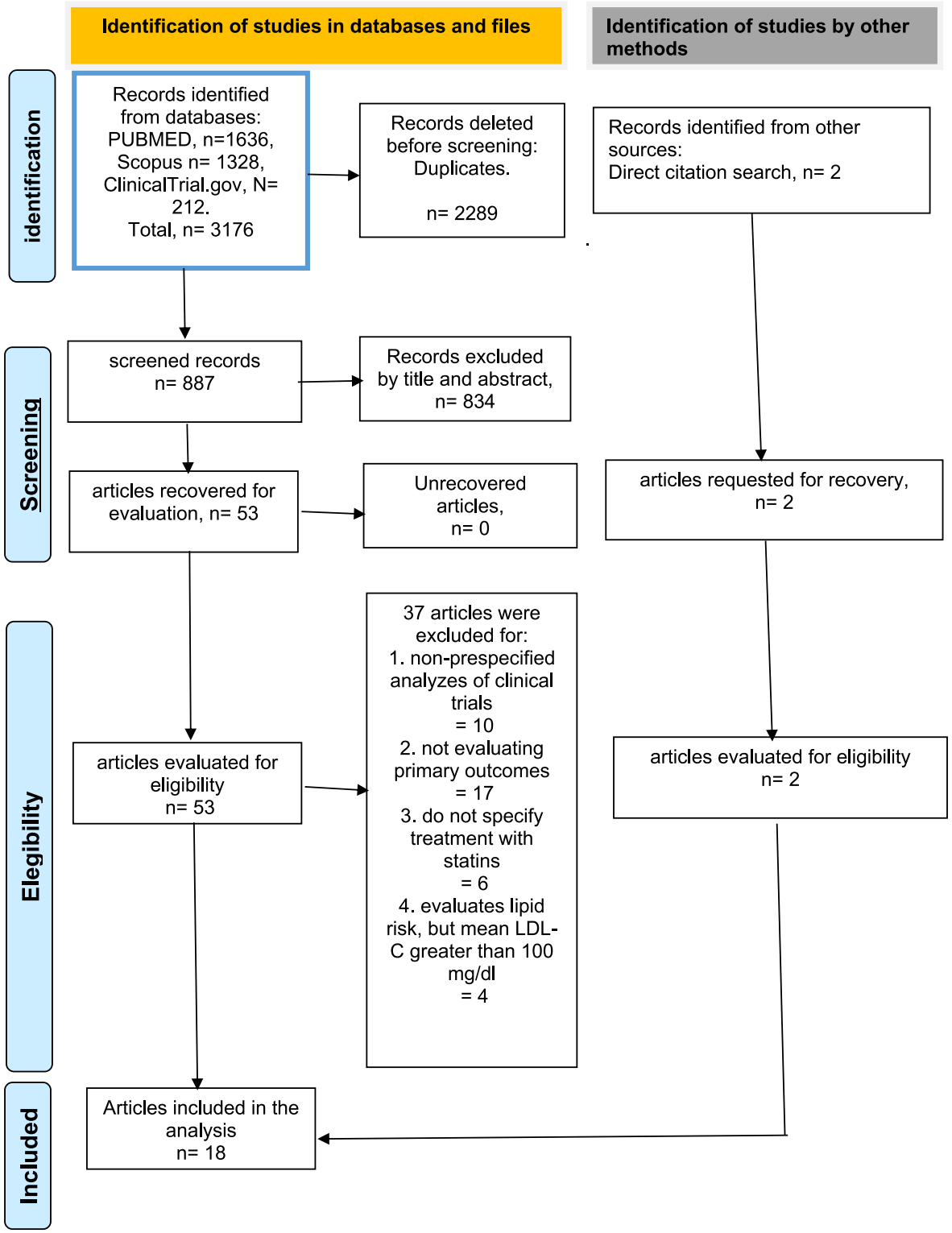


Fig. 1. PRISMA flow diagram.

primary outcomes at least one of the ASCVD–related conditions: acute coronary syndrome (ACS), stroke, peripheral artery disease, cardiovascular or all–cause mortality, in subjects older than 18 years old. Studies that included patients not treated with statins, that evaluated only lipid, inflammatory, or thrombotic biomarkers, and with follow–up of less than 6 months were excluded.

2.2. Data extraction

The search and selection of studies were performed independently by the three investigators, without time limits or language restrictions. Three electronic databases were used: PUBMED/MEDLINE, Scopus and ClinicalTrials.gov. Disputes were resolved by consensus. The first query was held between November 28, 2022, and December 5, 2023. A subsequent query with the same search criteria was performed on February 1, 2024. The search strategy is detailed in Annex A.

To meet the research objectives, the studies were classified according to the three components of residual cardiovascular risk: lipid, inflammatory, and thrombotic, considering the pathophysiological mechanisms involved in the atherosclerosis process.

2.3. Risk of bias

The open–access Risk of Bias 2 (ROB–2) tool was used to assess the quality of the studies included in the analysis. A table with the findings, including an evaluation of the methodological quality of each study, was prepared.

3. Results

3.1. Identification and selection of studies

The search strategy yielded 1636 articles in PUBMED/MEDLINE, 1328 in Scopus, and 212 articles in ClinicalTrials.gov. Two articles identified through the direct citation method during the document review were included. A total of 3178 documents were identified and 2289 were withdrawn due to duplication. A total of 887 articles were screened, of which 834 were excluded by title and abstract due to incompatibility with the inclusion criteria, review articles, letters to the editor, editorials and meta-analysis.

A total of 53 studies were evaluated for eligibility by full–text reading. At this point, 37 articles were excluded. Finally, 18 original articles were included in the analysis, most of which were obtained from the PUBMED/MEDLINE database. The selection process is detailed in the PRISMA flow chart (Fig. 1).

3.2. Residual lipid risk

Four studies were included in the analysis. Two were RCTs [11,12], and two were subgroup analyses of the FOURIER study [13,14]. All studies selected patients with established ASCVD and increased cardiovascular risk. The primary efficacy outcome was MACE, and patient follow–up ranged from 2.2 to 4.9 years. The population consisted predominantly of men, with a mean age of 65 years on statin treatment and LDL–C levels between 70 mg/dL (1.81 mmol/L) and 100 mg/dL (2.59 mmol/L).

The studies by Bhatt [11] and Nicholls (2020) [12] selected subjects with hypertriglyceridemia and evaluated the efficacy of omega–3 fatty acids, with a sample of 8179 and 1384 patients, respectively. As a result, the use of ethyl eicosapentaenoic acid (EPA) decreased the primary outcome by 25 % compared to the placebo, while the use of omega–3 carboxylic acids, a combination of EPA and docosahexaenoic acid (DHA) did not significantly reduce outcomes.

Moreover, subgroup analyses from the FOURIER study suggest a 20 % relative risk reduction in people with recent cardiac infarctions and a history of multiple cardiac infarctions with evolocumab (Sabatine, 2018) [13]. Likewise, this drug product achieved a reduction in the relative risk of MACE by 23 % in patients with lipoprotein (a) levels greater than 50 mg/dL in the study by O'Donoghue et al. [14].

Regarding safety, the study by Bhatt et al. [11] found no significant differences in adverse events leading to the discontinuation of EPA. However, the increase in atrial fibrillation (5.3 % vs. 3.9 %) and peripheral edema (6.5 % vs. 5.0 %) in patients treated with EPA compared to placebo is striking. On the other hand, in the study by Nicholls et al. [12], the combination of EPA and DHA showed greater adverse drug reactions and the need for discontinuation or dose reduction, especially due to digestive intolerance (Table 1).

3.3. Residual inflammatory risk

Six RCTs met the inclusion criteria (27,813 patients). Of these, four studies used colchicine in a sample of 11,594 patients [15–18], one study with methotrexate [19] that enrolled 6158 participants, and one with canakinumab [20] that included 10,061 subjects.

All included studies had a double–blind design, except for the Nidorf 2013 study [15], which only blinded the investigators and did not use a placebo. The study population consisted of patients in secondary prevention, mainly for acute myocardial infarction and proven coronary artery disease. The sample was predominantly male, with ages ranging from 35 to 85 years old, and the follow–up ranged from 1.8 to 3.7 years [15–20].

Studies with colchicine used low doses (0.5 mg daily). A significant reduction of MACE in stable coronary artery disease was demonstrated in three of them (Nidorf, 2013: HR 0.3; 95 % CI: 0.18–0.59; $p = 0.02$) [15]. In a study of patients with recent ACS, colchicine showed no decrease in the risk of MACE and, on the contrary, increased total mortality over placebo (Tong, 2020) [18].

In terms of colchicine safety, all four studies reported early discontinuation of the drug product for digestive symptoms in 5–11 % of patients. However, there were no significant differences between groups in terms of long–term tolerability, serious adverse events, or requiring hospitalizations for digestive symptoms, infection, or sepsis [15,16,18].

For the case of Il–1 inhibitors, Ridker et al. [20] evaluated the efficacy of canakinumab in individuals with acute myocardial infarction and high–sensitivity C–reactive protein (hs–CRP) levels greater than 2 mg/dL, and found that dosing 150 mg subcutaneously every three months achieved a significant reduction in the primary outcome (HR 0.85; 95 % CI: 0.74–0.98; $p = 0.021$) and a decrease in hs–CRP.

In that same study, canakinumab was significantly associated with higher mortality from infection and sepsis compared to placebo (incidence rate of 0.31 vs. 0.18 events per person–years, $p = 0.02$); similarly, a higher frequency of thrombocytopenia was observed, although without differences in the rate of bleeding. The overall rates of serious adverse events were similar in both groups, as were injection site reactions [20].

However, only one study with methotrexate was included in the analysis. In this clinical trial, Ridker et al. [19] used low–dose methotrexate compared to placebo, finding no significant difference in primary outcomes at 2.3 years of follow–up (incidence rate of 3.46 vs. 3.43 events per 100 person–years (HR 1.01; 95 % CI: 0.82–1.25), which led to discontinuation due to futility.

Safety outcomes report a higher incidence rate of painful oral ulcers in the methotrexate group compared to placebo (1.95 vs. 1.13 person–years, $p = 0.001$), as well as higher unintentional weight loss (2.1 vs. 1.47 person–years, $p = 0.02$), elevated alanine aminotransferases (0.97 vs. 0.37, $p < 0.001$), and leukopenia (5.14 vs. 3.6, $p < 0.001$) in the methotrexate group. There were no significant differences in serious adverse events [19]. Table 2 summarizes the main characteristics of the studies on inflammatory residual risk.

Table 1
Characteristics of studies included in lipid risk.

Source	Design	Population/sample	Intervention/ follow–up	Primary outcome	Efficacy result	Safety result	Conclusion
Bhatt Dl et al. 2019 (11)	RCT, double-blind	ASCVD or diabetes with another risk factor, TG 135–499 mg/dL and LDL of 41–100 mg/dL. Mean age: 64 years old. n = 8.179	EPA 4 g/day or placebo/4.9 years	MACE	17.2 % EPA vs. 22 % placebo HR: 0.75 (95 % CI: 0.68–0.83), p < 0.001	No difference in serious adverse effects. Higher rates of atrial fibrillation in the intervention group.	EPA significantly reduces MACE.
Nicholls SJ et al. 2020 (12)	RCT, double-blind	High–risk ASCVD, TG 180–500 mg/dL, c–LDL less than 100 mg/dL. Mean age: 62.5 years old. n = 1384	Omega–3 carboxylic acids vs. corn oil/3.5 years	MACE	Omega–3 carboxylic acids 12 % vs. placebo 12.2 %, HR: 0.99 (95 % CI: 0.9–1.09), p = 0.84	Greater adverse drug reactions in the intervention group, mainly digestive.	There is NO significant difference between omega–3 carboxylic acids and placebo in reduction of MACE.
Sabatine et al. 2018 (13)	Pre–specified analysis of a RCT, (FOURIER study)	Previous cardiac infarction, residual coronary artery disease with stenosis >40 % in 2 or more vessels. c–LDL lower than 100 mg/dL. Age: 40–85 years old. n = 22,351	Evolocumab 280 mg or 420 mg monthly vs. placebo/2.2 years	MACE	RRR 20 % with evolocumab in subjects with recent infarction (HR: 0.80; 95 % CI: 0.71–0.91), 18 % in subjects with multiple prior infarctions (HR: 0.82; 95 % CI: 0.72–0.93)	Not reported.	Evolocumab reduces residual cardiovascular risk in people with high–risk ASCVD.
O'Donoghue ML et al. 2019 (14)	Pre–specified analysis of a RCT (FOURIER study)	Established ASCVD and high–risk predictors with Lp(a) levels. c–LDL lower than 100 mg/dL. Age: 40–85 years old. n = 25,096	Evolocumab 280 mg or 420 mg monthly vs. placebo/2.2 years	MACE	RRR 23 % with evolocumab in subjects with Lp(a) greater than 50 mg/dL. HR: 0.77; 95 % CI: 0.67–0.88)	Not reported.	Evolocumab reduces MACE in people with Lp(a) greater than 50 mg/dL.

Table 2
Characteristics of studies included in inflammatory risk.

Source	Design	Population/sample	Intervention/ follow–up	Primary outcome	Efficacy result	Safety result	Conclusion
Nidorf SM et al. 2013 (15)	PROBE–type trial, blinded for the investigator	Secondary prevention of ASCVD, with angiographically proven coronary artery disease, in stable phase. Age: 35–85 years. n = 532	Colchicine 0.5 mg/ day vs. no colchicine/3 years	ACS, out–of–hospital cardiac arrest, non–cardioembolic ischemic stroke	Colchicine 5.3 % vs. no colchicine 16 %, HR 0.3 (95 % CI: 0.18–0.59), p < 0.001.	Not clearly reported. Greater digestive symptoms in the colchicine group.	Colchicine reduces MACE in subjects with stable coronary artery disease.
Nidorf SM et al. 2020 (16)	RCT, double-blind	Proven coronary artery disease, stable in the last 6 months. Age: 35–82 years. n = 5522	Colchicine 0.5 mg/ day vs. placebo/2.3 years	MACE	Colchicine 6.8 % vs. placebo 9.6 %, HR 0.69; (95 % CI: 0.57–0.83); p < 0.001)	No differences in digestive and other adverse effects.	Colchicine reduces the risk of MACE in subjects with stable coronary artery disease.
Tardif JC et al. 2019 (17)	RCT, double-blind	Subjects with myocardial infarction 30 days before randomization. Mean age: 60.5 years. n = 4745	Colchicine 0.5 mg/ day vs. placebo/1.8 years	MACE	Colchicine 5.5 % vs. placebo 7.1 %, HR 0.77 (95 % CI: 0.61–0.96); p = 0.02	No differences in adverse drug reactions or serious events.	Colchicine reduces MACE in subjects with recent myocardial infarction.
Tong DC et al. 2020 (18)	RCT, double-blind	People with ACS and proven coronary artery disease. Mean age: 59.8 years. n = 795	Colchicine 0.5 mg twice daily for one month and then 0.5 mg daily for 11 months vs. placebo	MACE/total death	Colchicine: 24 events, placebo 38 events, p = 0.09/ Colchicine 8 vs. placebo 1, p = 0.017	No significant differences in adverse events in the groups.	Colchicine does not reduce MACE and increases total mortality compared to placebo.
Ridker PM et al. 2019 (19)	RCT, double-blind	People with previous myocardial infarction or multivessel coronary artery disease with diabetes or metabolic syndrome. Mean age: 65.6 years. n = 6158	Methotrexate 15 mg weekly and at fourth month 20 mg weekly vs. placebo/ 2.3 years	Composite: cardiovascular death, myocardial infarction or non–fatal stroke	Methotrexate incidence rate 3.46 vs. 3.43 per 100 person–years, HR 1.01 (95 % CI: 0.82–1.25);	Methotrexate was associated with increased elevation of liver enzymes, leukopenia, anemia and non basal-cell cancer.	Methotrexate does not reduce MACE compared to placebo.
Ridker *Pm* et al. 2017 (20)	RCT, double-blind	People with previous myocardial infarction and hs–CRP greater than or equal to 2 mg/dL. Mean age: 61.1 years. n = 10,061	Canakinumab, three doses (50 mg, 150 mg and 300 mg) every 3 months vs. placebo/3.7 years	Composite: cardiovascular death, myocardial infarction or non–fatal stroke	Canakinumab 150 mg vs. placebo RRA 15 %, HR 0.85, (95 % CI: 0.74–0.98); p = 0.021	Canakinumab increases the risk of serious infections, with no difference in mortality.	Canakinumab 150 mg every three months decreases the risk of MACE.

3.4. Residual thrombotic risk

Eight RCTs were selected for analysis. One study evaluated the efficacy of rivaroxaban after a recent ACS with a sample of 1526 participants (Mega, 2010) [21], and three more studies did so with the combination of rivaroxaban and low–dose aspirin (Eikelboom 2017, Anand 2018, and Bonaca 2020) [22–24] in a total of 41,429 patients. The remaining four clinical trials evaluated dual antiplatelet therapy (DAPT) versus Aspirin alone (Bhatt 2006, Park 2010, Lee 2014, and Bonaca 2015) [25–27] in a sample of 44,511 subjects. In total, a population of 84,466 subjects was collected in the eight studies.

All studies were randomized, controlled, double–blind clinical trials and included subjects with a mean age between 61 and 67 years, predominantly male, and with established ASCVD. Three studies selected patients with peripheral arterial disease (Anand 2018, Bhatt 2006, and Bonaca 2020) [23–25]; the remaining were conducted mainly in patients with ischemic heart disease (Mega 2012, Eikelboom 2017, Park 2010, Lee 2014, and Bonaca 2015) [21,22,26–28].

In the study by Mega et al. [21], the efficacy of low–dose rivaroxaban was evaluated against a placebo in people with recent ACS, and a significant decrease in the primary outcome was demonstrated (8.9 % vs. 10.7 %; HR 0.84; 95 % CI: 0.74–0.96; p = 0.008). Three other studies with the combination of rivaroxaban 2.5 mg twice daily plus aspirin compared to rivaroxaban alone at a dose of 5 mg twice daily or aspirin monotherapy showed similar results, even in major lower limb adverse events (Eikelboom, 2017: rivaroxaban plus aspirin 4.1 % vs. aspirin alone 5.4 %, HR 0.76; 95 % CI: 0.66–0.86; p < 0.001; Anand, 2018: rivaroxaban plus aspirin 1 % vs. aspirin alone 2 %, HR 0.54; 95 % CI:

Table 3
Characteristics of studies included in thrombotic risk.

Source	Design	Population/sample	Intervention/follow-up	Primary outcome	Efficacy result	Conclusion
Mega JL et al. 2012 (21)	RCT, double-blind	Subjects with ACS. Mean age: 61.5 years. n = 1526	Rivaroxaban 2.5 mg or 5 mg twice daily vs. placebo/2 years	Composite: cardiovascular death, myocardial infarction or non–fatal stroke	Rivaroxaban 8.9 % vs. placebo 10.7 %, HR: 0.84 (95 % CI: 0.74–0.96); p = 0.008	Rivaroxaban reduces the risk of MACE in subjects with recent ACS.
Eikelboom JW et al. 2017 (22)	RCT, double-blind, double-dummy	Stable ASCVD. Mean age: 68.2 years. n = 27,395	Rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily, rivaroxaban 5 mg twice daily or aspirin 100 mg daily./1.91 years	Composite: cardiovascular death, myocardial infarction or non–fatal stroke	Rivaroxaban plus aspirin 4.1 % vs aspirin alone 5.4 %, HR: 0.76 (95 % CI: 0.66–0.86), p < 0.001	Rivaroxaban plus aspirin reduces more MACE than aspirin alone, in subjects with stable ASCVD.
Anand SS et al. 2018 (23)	RCT, double-blind, double-dummy	Peripheral arterial disease of lower limbs, carotid disease, coronary artery disease with ankle–brachial index less than 0.9. Mean age: 67.8 years. n = 7470	Rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily, rivaroxaban 5 mg twice daily or aspirin 100 mg daily/3 years	Composite: cardiovascular death, myocardial infarction or stroke and major adverse events in lower limbs, including amputation	Major adverse events in lower limbs: rivaroxaban plus aspirin 1 % vs. aspirin alone 2 %, HR: 0.54 95 % CI: 0.35–0.82); p = 0.0037	Rivaroxaban plus aspirin reduces MACE and lower limb adverse events compared to aspirin alone.
Bonaca MP et al. 2020 (24)	RCT, double-blind	Subjects older than 50 years old, taken for revascularization of peripheral arterial disease in the previous 10 days. Mean age: 67 years. n = 6564	Rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily or aspirin 100 mg daily/3 years	Composite: acute lower limb ischemia, major vascular amputation, myocardial infarction, stroke, or cardiovascular death	Rivaroxaban plus aspirin 15.5 % vs. aspirin plus placebo 17.8 %, HR: 0.85 (95 % CI: 0.76–0.96); p = 0.009	Rivaroxaban plus aspirin reduces the incidence of the primary outcome compared to aspirin alone.
Bhatt Dl et al. 2006 (25)	RCT, double-blind	Subjects older than 45 years old with coronary artery disease, cerebrovascular disease, peripheral arterial disease, or multiple cardiovascular risk factors. Median age: 64 years. n = 15,603	Clopidogrel 75 mg plus aspirin between 75 and 162 mg or aspirin 75–162 mg plus placebo/2 years	Composite: cardiovascular death, myocardial infarction or non–fatal stroke	Clopidogrel plus aspirin 6.8 % vs. aspirin plus placebo 7.3 %, HR: 0.93 (95 % CI: 0.83–1.05); p = 0.22	Clopidogrel plus aspirin does not reduce the primary outcome compared to aspirin plus placebo.
Park SJ et al. 2010 (26)	RCT, open–label, includes data from two studies: REAL–LATE y ZEST–LATE	Subjects with drug–eluting stent implantation in the last 12 months, without MACE or major bleeding. Mean age: 62 years. n = 2701	Clopidogrel 75 mg plus aspirin 100–200 mg daily or aspirin 100–200 mg alone for more than 12 months/ 1.6 years	Composite: cardiovascular death or myocardial infarction	Clopidogrel plus aspirin 1.8 % vs. aspirin alone 1.2 %, HR: 1.65 (95 % CI: 0.8–3.36); p = 0.17	DAPT beyond 12 months does not significantly reduce the primary outcome compared to aspirin monotherapy.
Bonaca MP et al. 2015 (27)	RCT, double-blind	Subjects older than 50 years old with myocardial infarction between 1 and 3 years prior. Mean age: 65.4 years. n = 21,162	Ticagrelor 90 mg or 60 mg twice a day or placebo/2.8 years	Composite: cardiovascular death, myocardial infarction, or stroke	Ticagrelor 90 mg 7.85 %, ticagrelor 60 mg 7.77 %, placebo 9.04 %. Ticagrelor 90 mg vs. placebo, HR: 0.85 (95 % CI: 0.75–0.96; p = 0.008, ticagrelor 60 mg vs. placebo, 0.84 (95 % CI: 0.74–0.95); p = 0.004.	Ticagrelor significantly reduces the primary outcome compared to placebo. The 60 mg twice–daily dose had the best efficacy–to–risk ratio.
Lee CW et al. 2014 (28)	RCT, open–label	Subjects with drug–eluting stent implantation in the last 12 months, without MACE or major bleeding. Mean age: 62.4 years. n = 5045	Clopidogrel 75 mg plus aspirin 100–200 mg daily or aspirin 100–200 mg alone for more than 12 months/ 3.5 years	Composite: cardiovascular death, myocardial infarction, or stroke 24 months after randomization	Clopidogrel plus aspirin 2.6 % vs. aspirin alone 2.4 %, HR: 0.94 (95 % CI: 0.66–1.35); p = 0.75	The extension of DAPT beyond 12 months does not reduce the primary outcome compared to aspirin monotherapy.

0.35–0.82; p = 0.0037; and Bonaca 2020: rivaroxaban plus aspirin 15.5 % vs. aspirin plus placebo 17.8 %, HR 0.85; 95 % CI: 0.76–0.96; p = 0.009) [22–24].

On the other hand, DAPT with clopidogrel 75 mg daily and low–dose aspirin did not lower the primary outcome compared to aspirin monotherapy (Bhatt, 2006: HR 0.93; 95 % CI: 0.83–1.05; p = 0.22 [25]. Similar findings were seen in people with coronary stent implantation and DAPT with clopidogrel for at least 12 months, where extension for more than 1 year was not associated with decreased MACE (Park, 2010: HR 1.65; 95 % CI: 0.8–3.3; p = 0.17, and Lee, 2014: HR 0.94; 95 % CI: 0.66–1.35; p = 0.75 [26,28]. In this same scenario, Bonaca et al. (2015) [27], with a much larger sample than previous studies (21,162 patients), reported a significant reduction in MACE when continuing DAPT with ticagrelor for more than 12 months (ticagrelor 60 mg vs. placebo, 0.84; CI 95 %: 0.74–0.95; p = 0.004) (Table 3).

Regarding the safety profile, both rivaroxaban monotherapy and combination therapy with aspirin evidenced a significantly increased risk of major bleeding when compared against placebo or aspirin alone (Mega, 2012: rivaroxaban 2.1 % vs. placebo 0.6 %, HR 3.96; 95 % CI: 2.46–6.48; p < 0.001; Eikelboom, 2017: rivaroxaban plus aspirin 3.1 % vs. aspirin alone 1.9 %, HR 1.7; 95 % CI: 1.4–2.05; p < 0.001) [21,22]. Other adverse events showed no differences between groups.

On the other hand, the use of DAPT in the different scenarios evaluated did not significantly increase the risk of bleeding concerning aspirin monotherapy (Bhatt, 2006: clopidogrel plus aspirin 1.7 % vs. aspirin vs. placebo 1.3 %, RR 1.25; 95 % CI: 0.97–1.61; p = 0.09, and Lee, 2014: clopidogrel plus aspirin 1.4 % vs. aspirin alone 1.1 %, HR 0.71; 95 % CI: 0.42–1.2; p = 0.20) [25,26]. On the contrary, the use of ticagrelor, even at doses of 60 mg twice daily, increased the rate of major bleeding compared to placebo (ticagrelor 60 mg 2.3 % and placebo 1.06 %; p < 0.001) [27].

3.5. Risk of bias

When applying the ROB–2 tool, of the 18 studies evaluated, seven showed a low risk of bias, five had some concerns, and six showed a high risk of bias. The high methodological quality of most of the studies of colchicine and canakinumab on residual inflammatory risk and the studies with rivaroxaban plus aspirin on thrombotic risk is highlighted. Table 4 shows the evaluation of the included articles.

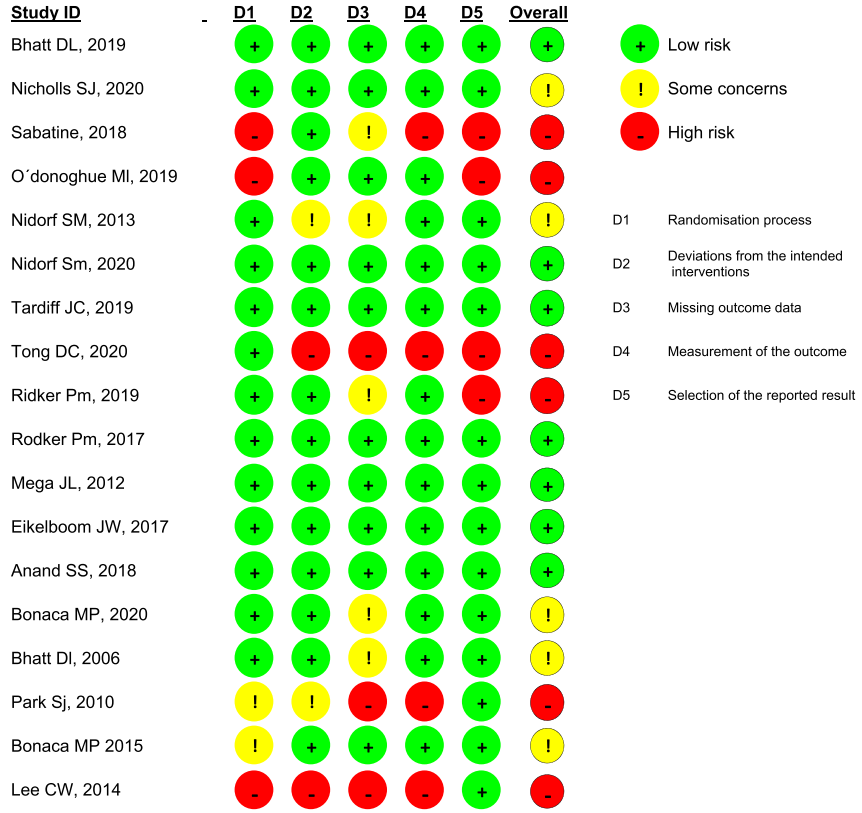
4. Discussion

In this systematic literature review, we analyzed the results of RCTs that evaluated the efficacy and safety of drug products in reducing residual cardiovascular risk. The research found several drug products that, added to statin therapy, can significantly reduce MACE in people achieving LDL–C targets, with an acceptable safety profile for use in clinical practice.

In the lipid component of residual risk, according to the study by Bhatt et al. [11], EPA was shown to be effective in the secondary prevention of MACE in patients with hypertriglyceridemia. It is noteworthy that these outcomes occurred even in people with triglyceride levels below 150 mg/dL (1.71 mmol/L), which raises the hypothesis of a positive effect beyond the known lipid–lowering effect of the molecule.

These results contrast with those obtained previously in other studies with omega–3 fatty acids. In the meta–analysis by Aung et al. [29] with a sample of 77,977 patients, EPA at doses up to 1.8 g daily did not

Table 4
Evaluation of the risk of bias with the ROB-2 tool.



demonstrate efficacy in reducing coronary heart disease deaths or non–fatal myocardial infarction. These findings could be explained by the difference in dosage, since in the Bhatt 2019 study [11], both the doses (4 g daily) and the purity of EPA were superior.

Along the same lines, the study by Nicholls et al. [12] used a combination of EPA and DHA at a dose of 4 g daily in patients at high cardiovascular risk. This dosage made it possible to achieve serum EPA levels similar to the molecule used in the Bhatt 2019 study [11]. However, the trial was discontinued due to futility. In both studies, triglyceride levels were reduced by 18 % after 12 months, and there was no substantial increase in LDL–C to explain the results. This could be explained by the proportion of purified EPA in each formulation and, of course, by the possibility of deleterious effects related to DHA.

It is clear then that the findings of the Bhatt 2019 study [11] cannot be generalized to other omega–3 fatty acid presentations, and that a mode of action other than the lipid–lowering effect should be explored. In this sense, the decrease in hs–CRP levels with highly purified EPA raises the hypothesis of an anti–inflammatory action that deserves to be tested with clinical studies designed for this purpose.

In this field of residual lipid risk, two sub-analyses of the FOURIER study were included to explore hypotheses, in particular the usefulness of lowering lipoprotein (a) levels on cardiovascular outcomes. In the study by O'Donoghue M [14], evolocumab reduced the relative risk of MACE in patients with lipoprotein (a) levels greater than 50 mg/dL by 23 %, from a lipoprotein (a) decrease of about 27 %.

On the other hand, in the modulation of the inflammatory component of residual risk, the study by Ridker with canakinumab [20], which proves the inflammatory hypothesis of atherothrombosis and demonstrates that lowering hs–CRP and Il–6 improves cardiovascular outcomes independently of the level of LDL–C, is noteworthy. This is explained by the effect of II–1 beta on atherosclerotic plaque, which includes mobilization of white cells by increased adhesion to endothelial cells, proliferation of smooth muscle cells, and activation of coagulation [30].

The results of this study are consistent with those obtained in the JUPITER study [31], where rosuvastatin reduced cardiovascular events in people with hsCRP levels greater than 2 mg/dL. This benefit was maintained even in patients at low cardiovascular risk and with LDL–C levels below 100 mg/dL (2.59 mmol/L). It should be noted that JUPITER was excluded from this systematic review, as its inclusion criterion was an LDL-C level of up to 130 mg/dL (3.37 mmol/L).

In contrast, the use of low–dose methotrexate [19] did not decrease MACE in patients with stable ischemic heart disease, nor did it affect Il–1 beta, Il–6, or hs–CRP levels. This suggests that drugs capable of impacting hs–CRP levels could be more effective in terms of clinical outcomes. Taken together, these results highlight the need to consider a diversity of inflammatory mechanisms involved in atherosclerosis and to explore different interventions for their inhibition.

Several studies performed with colchicine in the setting of residual inflammatory risk were also included [15–17]. The Nidorf, 2013; Tardiff, 2019; and Nidorf, 2020 studies with colchicine, the latter two with high methodological quality, were consistent with the results of the Ridker study with canakinumab [20]; an effect on hs–CRP decline with both drugs could support these similar outcomes.

Consistently with these results, the 13 clinical trials by Kofler (2021) [32] and 14 clinical trials by Grajek (2021) [33] meta–analyses evaluating the efficacy of colchicine in patients with coronary artery disease found a reduction in MACE of 35 % and 30 %, respectively, relative to placebo, positioning this drug product as one of the therapies of choice in this setting alongside usual medical therapy.

Regarding residual thrombotic risk, the included studies analyzed two types of intervention in secondary prevention: firstly, the use of combined antithrombotic therapy and secondly, the extension of DAPT for more than 12 months.

Polytherapy of low–dose rivaroxaban and aspirin was effective in reducing MACE in all clinical trials where it was tested [22–24], confirming the importance of activated factor X in the procoagulant mechanisms of ASCVD. The best risk–benefit ratio was obtained with rivaroxaban 2.5 mg twice daily, compared with 5 mg twice daily or aspirin alone.

These studies were included in the Chen (2021) [34] and Debasu (2022) [35] meta–analyses, and a significant reduction in MACE was found in both patients with stable coronary artery disease and peripheral arterial disease. Similarly, these results were maintained when patients with a history of percutaneous coronary intervention were analyzed in the study by Bainey et al. [36]. In all scenarios, there was a significant increase in the risk of bleeding with the use of polytherapy [34,35].

Concerning DAPT for more than 12 months followed by an ACS, the studies evaluating clopidogrel with aspirin versus aspirin alone [25,26,28] did not demonstrate a decrease in MACE. These findings were consistent even in patients with recent stent implantation [26,28]. However, it should be clarified that the high risk of bias in the estimation of the effect in the methodological evaluation makes it necessary to conduct randomized clinical trials with a better design.

In contrast, the Bonaca 2015 study [27] with ticagrelor and aspirin achieved statistical significance for the reduction of MACE in subjects with infarction between 1 and 4 years before. As in studies with clopidogrel, increased bleeding rates should be considered before use in clinical practice.

In this context, the Yin et al. [37] meta–analysis, which included 17 studies and 46,864 patients, found that extended DAPT was associated with an increased risk of death and major bleeding, even after the implantation of a coronary stent. A DAPT duration of fewer than 12 months may decrease the risk of bleeding without increasing cardiovascular adverse events, as demonstrated by the of Knijnik et al. [38] meta–analysis.

Regarding the safety of the drug products evaluated, the serious adverse effects reported for EPA did not differ significantly from placebo [11], except for a higher rate of hospitalization for atrial fibrillation and flutter, for which there is no clear explanation. Increased discontinuation of omega–3 fatty acids treatment for digestive symptoms was reported in both studies. These same symptoms were found in studies with colchicine [15–17], especially during the first month of treatment; after this time, the incidence of digestive disorders was similar to placebo.

In terms of thrombotic risk, bleeding rates were more frequent in the rivaroxaban groups, which was to be expected considering that placebo was used as a comparator and not another anticoagulant drug product. Therefore, a strict choice of patients who are candidates for this type of therapy, based on the inclusion criteria of the studies, is necessary to provide them with maximum efficacy, weighing the associated risk of bleeding.

This systematic review has several limitations. First, the inclusion of articles that analyze subgroups of phase III RCTs should be carefully interpreted since they may generate treatment recommendations from studies with questionable external validity. Likewise, half of the included studies showed a high risk of bias, and therefore, adequate clinical judgment should be used for their interpretation.

Secondly, by dividing the residual risk into its three components, the number of studies included in each component may have been limited. This is particularly true for the lipid component, where only two clinical trials met eligibility criteria, albeit with a low risk of bias and high methodological quality. Further studies are needed to corroborate the efficacy of omega–3 fatty acids in this setting.

The results of this systematic review allow us to raise some issues for the future. On the one hand, studies are needed to directly evaluate the clinical usefulness of PCSK–9 inhibitors and other lipid–lowering molecules, such as inclisiran, an RNA silencer, in reducing the levels of atherogenic molecules and their impact on residual lipid risk. The reduction achieved in LDL-C levels to less than 30 mg/dL with these molecules has been shown to be safe and continues to reduce the risk of residual events, therefore, it is necessary to redefine the concept of residual risk in light of these findings.

On the other hand, it is plausible to evaluate whether a combined

pharmacological intervention that includes lowering atherogenic lipids, modulating the inflammatory process, and the prothrombotic condition that accompanies ASCVD could have an additional impact on the reduction of cardiovascular events in this type of patients.

5. Conclusion

The persistence of cardiovascular events in patients who achieve LDL-C targets with the use of statins raises the need to use other drugs that impact this residual risk, based on the modification of atherogenic lipid levels, the modulation of inflammatory pathways, and the prothrombotic state that accompanies ASCVD.

In this systematic review, several drugs demonstrated efficacy in reducing MACE in patients with LDL-C levels below 100 mg/dL (2.59 mmol/L). Such is the case of EPA, which reduced them by 25 % compared to placebo in people with hypertriglyceridemia. Likewise, colchicine in studies of high methodological quality reduced events in patients with stable coronary artery disease and after ACS, and canakinumab did so in those with hs–CRP elevation greater than 2 mg/dL. Among patients with stable cardiovascular disease, including peripheral arterial disease, the use of low–dose rivaroxaban and aspirin consistently achieved better cardiovascular outcomes than rivaroxaban alone or aspirin alone.

On the other hand, an acceptable safety profile was found for most of the aforementioned drug products. The combination of rivaroxaban and aspirin requires special attention since a significant increase in the risk of bleeding, particularly of the digestive tract, has been reported, which requires an individualized risk–benefit analysis in patients who are candidates for its use.

The authors declare

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

CRediT authorship contribution statement

Mario Andres Hernandez-Sómerson: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Fernando Montoya-Agudelo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Gustavo Huertas-Rodriguez:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Acknowledgments

None.

References

[1] M.E. Makover, M.D. Shapiro, P.P. Toth, There is urgent need to treat atherosclerotic cardiovascular disease risk earlier, more intensively, and with greater precision: a review of current practice and recommendations for improved effectiveness, Am. J. Prev. Cardiol. 12 (2022) 100371, https://doi.org/10.1016/j.ajpc.2022.100371.
[2] D.S. Dhindsa, P.B. Sandesara, M.D. Shapiro, N.D. Wong, The evolving understanding and approach to residual cardiovascular risk management, Front. Cardiovasc. Med. 7 (2020), https://doi.org/10.3389/fcvm.2020.00088.
[3] R. Ferrari, et al., Current practice in identifying and treating cardiovascular risk, with a focus on residual risk associated with atherogenic dyslipidaemia, Eur. Heart J. Suppl. 18 (suppl_C) (2016) C2–C12, https://doi.org/10.1093/eurheartj/suw009.
[4] A.W. Aday, P.M. Ridker, Targeting residual inflammatory risk: a shifting paradigm for atherosclerotic disease, Front. Cardiovasc. Med. 6 (2019), https://doi.org/10.3389/fcvm.2019.00016.
[5] K. Huynh, Inflammation in plaque erosion and rupture, Nat. Rev. Cardiol. 19 (2) (2022), https://doi.org/10.1038/s41569–021–00654–w, 80–80.
[6] S.J. Kottoor, R.R. Arora, The utility of anti–inflammatory agents in cardiovascular disease, J. Cardiovasc. Pharmacol. Therapeut. 23 (6) (2018) 483–493, https://doi.org/10.1177/1074248418778548.
[7] M. Farnier, M. Zeller, D. Masson, Y. Cottin, Triglycerides and risk of atherosclerotic cardiovascular disease: an update, Arch. Cardiovasc. Dis. 114 (2) (2021) 132–139, https://doi.org/10.1016/j.acvd.2020.11.006.
[8] M.F. Wu, K.Z. Xu, Y.G. Guo, J. Yu, Y. Wu, L.M. Lin, Lipoprotein(a) and atherosclerotic cardiovascular disease: current understanding and future perspectives, Cardiovasc. Drugs Ther. 33 (6) (2019) 739–748, https://doi.org/10.1007/s10557–019–06906–9.
[9] A. Hafiane, Vulnerable plaque, characteristics, detection, and potential therapies, J. Cardiovasc. Dev. Dis. 6 (3) (2019) 26, https://doi.org/10.3390/jcdd6030026.
[10] P. Libby, et al., Atherosclerosis, Nat. Rev. Dis. Prim. 5 (1) (2019) 56, https://doi.org/10.1038/s41572–019–0106–z.
[11] D.L. Bhatt, et al., Cardiovascular risk reduction with Icosapent ethyl for hypertriglyceridemia, N. Engl. J. Med. 380 (1) (2019) 11–22, https://doi.org/10.1056/NEJMoa1812792.
[12] S.J. Nicholls, et al., Effect of high–dose omega–3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk, JAMA 324 (22) (2020) 2268, https://doi.org/10.1001/jama.2020.22258.
[13] M.S. Sabatine, et al., Clinical benefit of evolocumab by severity and extent of coronary artery disease, Circulation 138 (8) (2018) 756–766, https://doi.org/10.1161/CIRCULATIONAHA.118.034309.
[14] M.L. O'Donoghue, et al., Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk, Circulation 139 (12) (2019) 1483–1492, https://doi.org/10.1161/CIRCULATIONAHA.118.037184.
[15] S.M. Nidorf, J.W. Eikelboom, C.A. Budgeon, P.L. Thompson, Low–dose colchicine for secondary prevention of cardiovascular disease, J. Am. Coll. Cardiol. 61 (4) (2013) 404–410, https://doi.org/10.1016/j.jacc.2012.10.027.
[16] S.M. Nidorf, et al., Colchicine in patients with chronic coronary disease, N. Engl. J. Med. 383 (19) (2020) 1838–1847, https://doi.org/10.1056/NEJMoa2021372.
[17] J.-C. Tardif, et al., Efficacy and safety of low–dose colchicine after myocardial infarction, N. Engl. J. Med. 381 (26) (2019) 2497–2505, https://doi.org/10.1056/NEJMoa1912388.
[18] D.C. Tong, et al., Colchicine in patients with acute coronary syndrome, Circulation 142 (20) (2020) 1890–1900, https://doi.org/10.1161/CIRCULATIONAHA.120.050771.
[19] P.M. Ridker, et al., Low–dose methotrexate for the prevention of atherosclerotic events, N. Engl. J. Med. 380 (8) (2019) 752–762, https://doi.org/10.1056/NEJMoa1809798.
[20] P.M. Ridker, et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease, N. Engl. J. Med. 377 (12) (2017) 1119–1131, https://doi.org/10.1056/NEJMoa1707914.
[21] J.L. Mega, et al., Rivaroxaban in patients with a recent acute coronary syndrome, N. Engl. J. Med. 366 (1) (2012) 9–19, https://doi.org/10.1056/NEJMoa1112277.
[22] J.W. Eikelboom, et al., Rivaroxaban with or without aspirin in stable cardiovascular disease, N. Engl. J. Med. 377 (14) (2017) 1319–1330, https://doi.org/10.1056/NEJMoa1709118.
[23] S.S. Anand, et al., Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double–blind, placebo–controlled trial, Lancet 391 (10117) (2018) 219–229, https://doi.org/10.1016/S0140–6736(17)32409–1.
[24] M.P. Bonaca, et al., Rivaroxaban in peripheral artery disease after revascularization, N. Engl. J. Med. 382 (21) (2020) 1994–2004, https://doi.org/10.1056/NEJMoa2000052.
[25] D.L. Bhatt, et al., Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events, N. Engl. J. Med. 354 (16) (2006) 1706–1717, https://doi.org/10.1056/NEJMoa060989.
[26] C.W. Lee, et al., Optimal duration of dual antiplatelet therapy after drug–eluting stent implantation, Circulation 129 (3) (2014) 304–312, https://doi.org/10.1161/CIRCULATIONAHA.113.003303.
[27] M.P. Bonaca, et al., Long–term use of ticagrelor in patients with prior myocardial infarction, N. Engl. J. Med. 372 (19) (2015) 1791–1800, https://doi.org/10.1056/NEJMoa1500857.
[28] S.-J. Park, et al., Duration of dual antiplatelet therapy after implantation of drug–eluting stents, N. Engl. J. Med. 362 (15) (2010) 1374–1382, https://doi.org/10.1056/NEJMoa1001266.
[29] T. Aung, et al., Associations of omega–3 fatty acid supplement use with cardiovascular disease risks, JAMA Cardiol. 3 (3) (2018) 225, https://doi.org/10.1001/jamacardio.2017.5205.
[30] C.A. Dinarello, Interleukin–1 in the pathogenesis and treatment of inflammatory diseases, Blood 117 (14) (2011) 3720–3732, https://doi.org/10.1182/blood–2010–07–273417.
[31] P.M. Ridker, et al., Rosuvastatin to prevent vascular events in men and women with elevated C–reactive protein, N. Engl. J. Med. 359 (21) (2008) 2195–2207, https://doi.org/10.1056/NEJMoa0807646.
[32] T. Kofler, et al., Colchicine in patients with coronary artery disease: a systematic review and meta-analysis of randomized trials, J. Am. Heart Assoc. 10 (16) (2021), https://doi.org/10.1161/JAHA.121.021198.
[33] S. Grajek, M. Michalak, T. Urbanowicz, A. Olasińska–Wiśniewska, A meta–analysis evaluating the colchicine therapy in patients with coronary artery disease, Front. Cardiovasc. Med. 8 (2021), https://doi.org/10.3389/fcvm.2021.740896.

[34] C. Chen, et al., Low dose rivaroxaban for atherosclerotic cardiovascular diseases: a systematic review and meta–analysis, Front. Pharmacol. 11 (2021), https://doi.org/10.3389/fphar.2020.608247.
[35] Z. Debasu, H.M. Kedir, T.A. Tadesse, Comparison of aspirin and rivaroxaban plus aspirin in the management of stable coronary artery disease or peripheral artery disease: a systematic review of randomized controlled trials, Int. J. Gen. Med. 15 (2022) 7201–7208, https://doi.org/10.2147/IJGM.S383485.
[36] K.R. Bainey, et al., Rivaroxaban plus aspirin versus aspirin alone in patients with prior percutaneous coronary intervention (COMPASS–PCI), Circulation 141 (14) (2020) 1141–1151, https://doi.org/10.1161/CIRCULATIONAHA.119.044598.
[37] S.-H.-L. Yin, et al., Duration of dual antiplatelet therapy after percutaneous coronary intervention with drug–eluting stent: systematic review and network meta–analysis, BMJ (2019) l2222, https://doi.org/10.1136/bmj.l2222.
[38] L. Knijnik, et al., Meta–analysis of duration of dual antiplatelet therapy in acute coronary syndrome treated with coronary stenting, Am. J. Cardiol. 151 (2021) 25–29, https://doi.org/10.1016/j.amjcard.2021.04.014.