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REVIEW ARTICLE

Efficacy and Safety of Extended Antithrombotic Therapy in Stable Coronary Artery Disease: Systematic Review of the Literature

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ABSTRACT

Extended dual antithrombotic therapy, which entails the concurrent administration of acetylsalicylic acid and a P2Y12 inhibitor or anticoagulant beyond the initial 12 months of presenting with acute coronary syndrome, has been the subject of considerable research in recent years. The objective of this study was to evaluate the impact of dual antithrombotic therapy in stable coronary artery disease. We conducted a registered (PROSPERO CRD42023394771) assessing the safety and efficacy of antithrombotic therapy published over the past 20 years up to May 2021 in four databases (PubMed, EMBASE, BVSalud /LILACS, Cochrane Reviews). Using the RoB2 tool, we evaluated the risk of bias. We performed a literature search using keywords and identified 95 eligible articles, of which 23 were excluded as duplicates. After applying the inclusion and exclusion criteria, we found 29 articles for a detailed review and assessment of bias by applying the ROB2 toll, and we found that five articles had a low risk of bias. Our analysis found that extended dual antithrombotic therapy reduces ischemic cardiovascular outcomes, but it comes at the cost of an increased risk of bleeding when compared with acetylsalicylic acid monotherapy.

Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide and is associated with high comorbidity and significant costs to health systems. In patients who have previously experienced a cardiovascular event, several strategies have been proposed to prevent subsequent events, including extended dual antithrombotic therapy.

Extended dual antithrombotic therapy involves the simultaneous administration of acetylsalicylic acid (ASA) and a P2Y12 inhibitor or an anticoagulant beyond the initial 12 months of presenting with acute coronary syndrome. The European Society of Cardiology (ESC) guidelines propose three management alternatives for patients with established coronary artery disease within chronic coronary syndrome. These alternatives include the use of the combination of ASA and Ticagrelor (PEGASUS strategy), ASA and Clopidogrel/Prasugrel (DAPT strategy), or the combination of ASA and Rivaroxaban (COMPASS strategy).

When initiating therapy, clinicians must evaluate and analyze multiple management alternatives to select the one that offers the best benefit and lowest risk for each patient. Given the challenges faced by clinicians in decision-making, a systematic review of the literature has been proposed to explore the evidence of antithrombotic therapy in the context of stable coronary artery disease.

Background

Cardiovascular disease is the leading cause of mortality worldwide and represents a major burden of disease and high cost to any health care system[1]. Patients with established coronary artery disease (CAD) are at a high risk for cardiovascular death and disabling vascular events, including stroke, acute myocardial infarction, and amputations[2,3]. These patients are considered to have a high cardiovascular risk, and to prevent new events, secondary prevention strategies should include a combination of optimal control of modifiable risk factors to halt the progression of atherosclerosis and use of antithrombotic therapies to reduce the occurrence of new acute thrombotic events[4].

Currently, a well-established body of knowledge exists regarding the risk factors for atherosclerosis. Some of these factors, such as genetic predisposition, sex, and age, are non-modifiable. Conversely, there are several cardiovascular risk factors that are modifiable [5]. There is ample evidence supporting the control of blood pressure, smoking cessation, prevention and treatment of diabetes, reduction in blood cholesterol levels, reduction in obesity, and increased physical activity in patients with previous cardiovascular events. Nevertheless, despite strong recommendations to systematically evaluate and control these risk factors, many patients fail to attain optimal control goals [6,7].

This situation has led to the development of new research strategies aimed at reducing risk, such as the use of new antithrombotic therapies, novel lipid-lowering drugs, anti-inflammatory molecules, and hypoglycemic agents with cardioprotective effects[6]. Recent clinical studies have shown that antithrombotic therapy can be used beyond 12 months following a cardiovascular event as a strategy for controlling risk factors for secondary prevention[8].

Pharmacological treatment with ASA has been demonstrated to decrease the risk of major cardiovascular events and cardiovascular death by 19% and 9%, respectively[9], rendering it an effective strategy for the management of stable ischemic cardiovascular disease[4]. Due to the multiple pathways leading to thrombus formation and the multicausal process of endothelial dysfunction, more aggressive antithrombotic strategies, such as dual antithrombotic therapy, which involves the use of two drugs, have been enthusiastically pursued[7]. Dual antithrombotic therapy has shown clear benefits in the setting of acute coronary syndrome[10] and established cardiovascular risk by preventing new major cardiovascular events (MACE). However, it comes at the cost of increased bleeding events[7,11-13]. Clinical guidelines for the management of chronic coronary syndrome[4], which includes patients with established cardiovascular disease, recommend the long-term use of dual antithrombotic therapy for patients considered at high (recommendation class IIa, level of evidence A) or moderate (IIb A) risk of ischemic events and without high bleeding risk criteria. These management guidelines include the combination of ASA + Ticagrelor (PEGASUS strategy)[13], ASA + Clopidogrel/Prasugrel (DAPT strategy)[11], or ASA + Rivaroxaban (COMPASS strategy)[12].

The aim of the present study was to perform a systematic review of the safety and efficacy of antithrombotic therapy and of different applicability scenarios according to the comorbidities present in this group of patients. Given the absence of studies comparing head-to-head management alternatives, we believe that this information may be useful to readers for decision-making in clinical settings.

Methodology

This systematic review followed Cochrane methodology. Protocol was registered un the International Prospective Register of Systematic Reviews (PROSPERO), # CRD42023394771).

Information was searched using keywords and independently by two authors in the following databases: MEDLINE (PUBMED), EMBASE (ELSEVIER), and LILACS. Additionally, a manual search was performed using the references of the selected studies following the "snowball" strategy[14].

A comprehensive literature search was conducted (full search strategy and term described in Supplemental Appendix).

Inclusion criteria:

- Randomized controlled trials from the last 20 years until May 2021 (in English or Spanish).
- Adult patients over 18 years of age under management with single or dual antiplatelet therapies or a combination of anticoagulant therapy with aspirin compared to each other or with placebo for the prevention of recurrent ischemic heart disease or to reduce the risk of cardiovascular events.
- Patients with a history of coronary artery disease [ST-segment Elevation Myocardial Infarction (STEMI), Non ST-segment Elevation Myocardial Infarction (NSTEMI), or unstable angina] or a history of surgical or percutaneous revascularization at more than 1 year of age.
- Reporting data on major cardiovascular outcomes (MACE): death, death due to cardiovascular disease, acute myocardial infarction, or stroke.
- Reporting clinically relevant major bleeding and non-major bleeding data.

Exclusion criteria:

- Reviews that did not comply with patient follow-up for > 12 months after the cardiovascular event.
- Articles that included pregnant women.
- Other indications for antiplatelet therapy and anticoagulation as primary indications (atrial fibrillation, prosthetic valves, intracavitary thrombi, pulmonary thromboembolism, cancer, antiphospholipid syndrome, orthopedic surgery, peripheral arterial disease, and COVID-19).
- Use of low-molecular-weight heparin as an anticoagulant.

Statistical analysis

The two authors, Gustavo Lemus (G.L), and Jesús Beltran (J.B), conducted independent searches in databases and selected relevant articles of interest. A review of the title and abstract of the articles was performed, selecting those articles that, according to the reviewers, could be adapted for the review. Duplicate articles were discarded, and compliance with the inclusion and exclusion criteria was defined in a subsequent detailed reading. Articles that met the selection criteria were analyzed using the Cochrane RoB2 application (risk-of-bias tool for randomized trials)[15] to assess biases and validity through an individual review by two of the authors. In case of discrepancies between the article selection and evaluation by the two authors, a discussion was held until an agreement was reached. Finally, a critical summary of the findings in the literature was synthesized and provided.

Results

We performed a literature search using keywords (see attached table), identifying 996 articles in MEDLINE, 1940 in EMBASE, 47 articles in the Cochrane database, and 6 articles in LILACS. After reading the titles and abstracts, we identified 95 eligible articles; 23 articles were excluded because they were duplicates (see figure 1). After applying the inclusion and exclusion criteria, we found 29 articles (see table 1) for a detailed review and assessment of bias by applying the ROB2 toll and found that 5 articles met a low risk of bias (see Table 2).

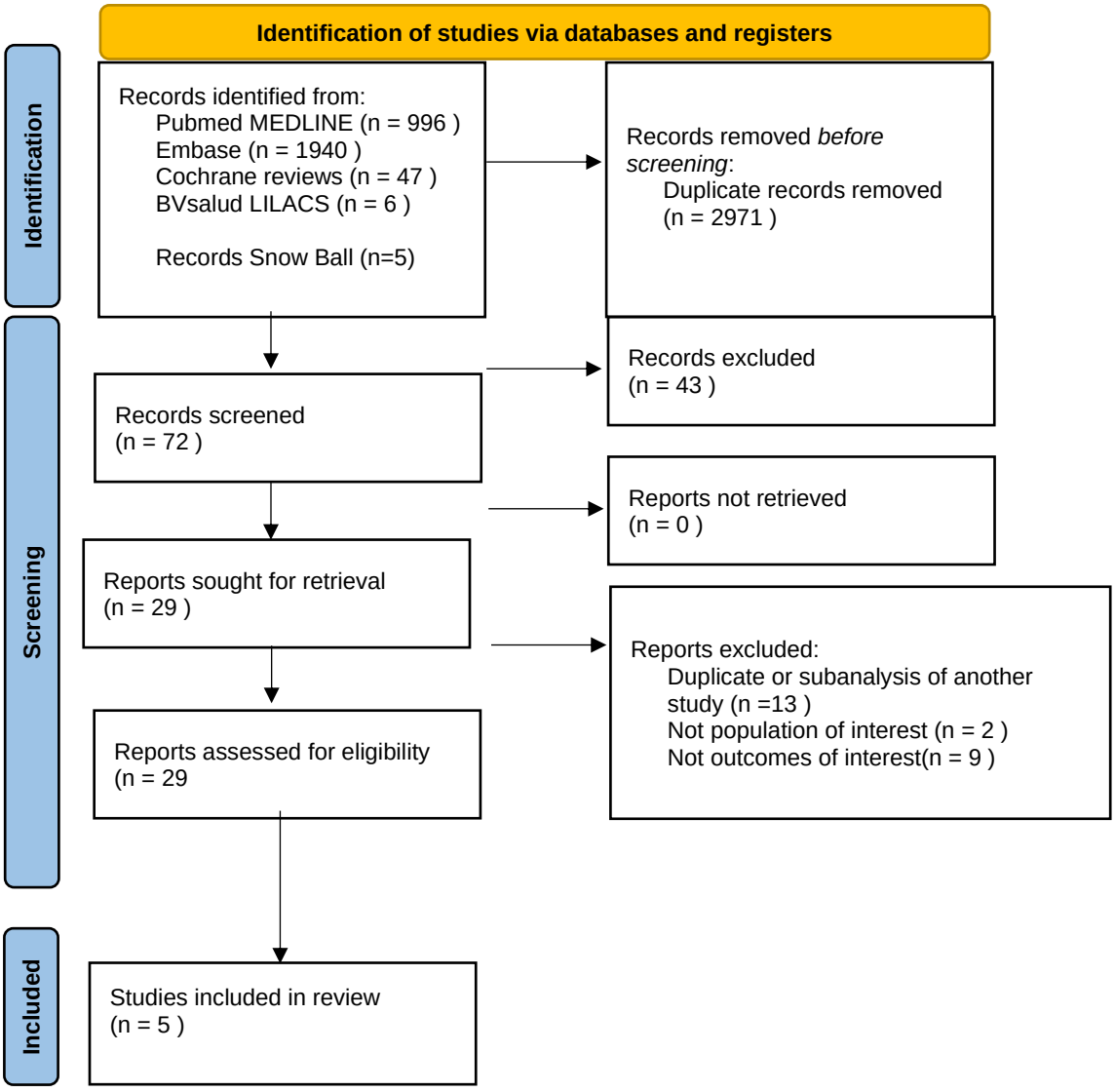

Figure 1.

Table 1. Articles selected for detailed review and assessment of bias applying the *ROB2 toll* .

Article	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
COMPASS- Eikelboom (2017)[12]	(+)	(+)	(+)	(+)	(+)	(+)
Eikelboom (2021)[16]	(+)	(+)	(+)	?	?	-
COMANDER HF (2018)[17]	(+)	(+)	?	(+)	(+)	?
Branch (2019)[18]	?	?	?	(+)	(+)	-
Bhatt (2020)[19]	?	(+)	?	(+)	?	-
Guzik (2021)[20]	?	(+)	?	(+)	?	-
Fox (2019)[21]	(+)	(+)	?	?	¿	-
Vanassche (2020)[22]	?	?	(+)	?	?	-
Greenberg (2019)[23]	(+)	?	(+)	?	?	-
Eikelboom(2019)[24]	(+)	(+)	(+)	?	?	-
Mehra (2019)[25]	(+)	?	(+)	?	?	-
Liang (2021)[26]	?	?	(+)	(+)	(+)	-

Article	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Steffel (2020)[27]	?	?	(+)	(+)	(+)	-
Sharma (2019)[28]	?	?	?	(+)	(+)	-
PEGASUS-TIMI-54 - Bonaca (2015)[13]	(+)	(+)	(+)	(+)	(+)	(+)
DAPT - Mauri (2014)[11]	(+)	(+)	(+)	(+)	(+)	(+)
Magnani (2021)[29]	?	(+)	(+)	?	?	-
Bonaca (2016)[30]	-	?	(+)	?	?	-
Bansilal (2018)[31]	?	(+)	(+)	(+)	?	-
THEMIS (Steg 2019)[32]	(+)	?	(+)	(+)	(+)	?
Eikelboom (2022)[33]	-	-	?	(+)	(+)	-
Vanassche (2021)[34]	?	?	(+)	?	(+)	-
Perera (2019)[35]	?	(+)	?	?	(+)	-
Bainey (2020)[36]	?	(+)	?	(+)	?	-
OPTIDUAL – Helft (2016)[37]	(+)	?	?	(+)	(+)	-
DESLATE - Lee (2013)[38]	-	-	?	(+)	(+)	-
ARCTIC-Interruption Collet- (2014)[39]	?	-	?	(+)	(+)	-
ITALIC trial -Gilard (2018)[40]	-	?	-	(+)	(+)	-
PRODIGY trial Valgimigli (2012)[41]	?	-	(+)	(+)	(+)	-

Table 2. Articles selected for systematic review

Article	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
COMPASS-Eikelboom et al. (2017).	(+)	(+)	(+)	(+)	(+)	(+)
COMANDER HF - Zannad et al. (2018).	(+)	(+)	?	(+)	(+)	?
PEGASUS-TIMI-54 - Bonaca et al. (2015).	(+)	(+)	(+)	(+)	(+)	(+)
DAPT - Mauri et al.(2014).	(+)	(+)	(+)	(+)	(+)	(+)
THEMIS - Steg et al. (2019).	(+)	?	(+)	(+)	(+)	?

The fundamental characteristics of the studies included in this review are presented in Table 3. All studies were multicenter, randomized, double-blind, with a duration ranging from 23 to 39,9 months, and with a study population ranging from 5.022 to 25.682 subjects. All studies were sponsored by the pharmaceutical industry. These studies were published between 2014 and 2019. Four of the studies showed significant results regarding the evaluated primary outcome [11-13,32], while one did not show a statistically significant difference[17].

Table 3. Characteristics of the studies included in the review.

Feature	THEMIS	COMPASS	PEGASUS-TIMI 54	DAPT	COMMANDER HF
Home	February 10, 2014	March 12, 2013	October, 2010	August, 2009	September, 2013
Completion	May 24, 2019	May 10, 2016	May, 2013	July 1, 2011	April, 2018
Publication	September 1, 2019	November 11, 2017	March 14, 2015	November 16, 2014	October, 2018
Design	Prospective, randomized, double-blind, placebo controlled	Prospective, randomized, double-blind, placebo controlled	Prospective, randomized, double-blind, placebo controlled	Prospective, randomized, double-blind, placebo controlled	Prospective, randomized, double-blind, placebo controlled
Assignment	Ticagrelor at a dose of 90 mg twice daily and then switched to 60 mg twice daily or placebo alone. And all patients also received aspirin (75 to 150 mg once daily).	Low-dose rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily) or rivaroxaban alone (5 mg twice daily) or aspirin alone (100 mg once daily).	Ticagrelor orally at a dose of 90 mg twice daily, ticagrelor orally at a dose of 60 mg twice daily, or placebo. And all patients also received aspirin (75 to 150 mg once daily).	Clopidogrel at a maintenance dose of 75 mg daily or prasugrel at a maintenance dose of 10 mg daily (with doses of 5 mg daily). And all patients also received aspirin (75 to 162 mg once daily).	Rivaroxaban 2.5 mg twice daily with standard of care for heart failure and coronary artery disease (as prescribed by the participant's treating physician) or placebo 2 times daily plus standard of care
Main inclusion criteria	Known history of at least one vessel stenosis ≥ 50% after PCI or CABG or angiography, and history of type 2 diabetes mellitus.	MI within the last 20 years, multivessel coronary artery disease with symptoms or a history of stable or unstable angina, multivessel PCI, multivessel CABG, or coronary artery disease with peripheral arterial disease.	Patients had a spontaneous MI of 1 to 3 years.	Patients had undergone PCI with stent implantation for 12 months and there was no MACE or major bleeding during this period.	3-month history of CHF, an LVEF 40% or less, and coronary artery disease and who had been treated for an episode of worsening heart failure (i.e., the index event) within the previous 21 days. BNP* of at least 200 pg per milliliter, or NT-proBNP of at least 800 pg.
Main exclusion criteria	Known history of myocardial infarction or stroke, or were receiving dual antiplatelet therapy or anticoagulant therapy	Whether patients were receiving dual antiplatelet therapy or anticoagulant therapy.	Whether patients were receiving dual antiplatelet therapy or anticoagulant therapy.	Whether patients were receiving dual antiplatelet therapy or anticoagulant therapy.	High risk of bleeding, atrial fibrillation or other condition requiring long-term anticoagulation, either acute myocardial infarction or surgical or percutaneous coronary artery

Feature	THEMIS	COMPASS	PEGASUS-TIMI 54	DAPT	COMMANDER HF
					intervention during the index event, a GFR of less than 20 ml per minute per 1.73 m^2 , recent stroke or previous intracranial hemorrhage, or HF of cause other than coronary artery disease.
Effectiveness unraveling	The primary efficacy outcome was a composite of cardiovascular death, myocardial infarction, or stroke. Secondary efficacy outcomes were tested hierarchically according to the following sequence: cardiovascular death, myocardial infarction, ischemic stroke, and death from any cause.	The primary efficacy outcome was a composite consisting of first occurrence of stroke, myocardial infarction, or cardiovascular death. These secondary outcomes were a composite of death from coronary heart disease, myocardial infarction, ischemic stroke, or acute limb ischemia; occurrence of myocardial infarction, ischemic stroke, cardiovascular death, or acute limb ischemia; and overall mortality.	The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. Secondary end points were cardiovascular death and death from any cause.	The coprimary efficacy end points were the cumulative incidence of definite or probable stent thrombosis (assessed according to Academic Research Consortium definitions) and major adverse cardiovascular and cerebrovascular events (defined as the composite of death, myocardial infarction, or stroke).	Composite of death from any cause, myocardial infarction or stroke.
Security Unlocking	The primary safety outcome was major bleeding, which was defined according to the TIMI classification.	The primary safety outcome was major bleeding defined as fatal bleeding, symptomatic bleeding in a	The primary safety endpoint was TIMI major bleeding. Other safety endpoints included intracranial hemorrhage and fatal hemorrhage.	The primary safety endpoint was the incidence of moderate or severe bleeding during this same period (assessed	Compound of fatal hemorrhage or hemorrhage into a critical space with potential to cause permanent disability.

Feature	THEMIS	COMPASS	PEGASUS-TIMI 54	DAPT	COMMANDER HF
		critical organ or area, bleeding at the surgical site leading to reoperation, or bleeding leading to hospital visit or admission.		according to [TASTE]).	

BNP = brain natriuretic peptide, NT-proBNP = N-terminal brain natriuretic peptide, PCI= percutaneous coronary intervention, MI: myocardial infarction, CHF= congestive heart failure, LVEF= left ventricular ejection fraction. MACE= Major adverse cardiovascular events. GFR= Glomerular filtration rate. TIMI= Thrombolysis in Myocardial Infarction TIMI bleeding Score. GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries.

EFFECTIVENESS

Table 4 displays the primary results of the studies included in the systematic review regarding effectiveness.

In the COMPASS trial, the majority of participants had a history of myocardial infarction within the previous 20 years, multivessel coronary artery disease (CAD), multivessel percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG), with 20% of the population also having peripheral arterial disease. The study lasted 23 months, but was terminated early by the Data Safety Monitoring Board due to clear evidence of the superiority of combination therapy with aspirin plus rivaroxaban 2.5 mg BID. This may have underestimated the potential benefit of the therapy beyond the study period. COMPASS also included patients with coronary artery disease but without previous myocardial infarction, indicating potential usefulness beyond this background. However, the study included a very low number of patients with extreme body weight (weight >120 kg or BMI > 40 kg/m2 and in BMI < 18.5 kg/m2),only 166 subjects had BMI< 18.5 kg/m2 and 528 obese subjects with BMI > 40 kg/m2, so given important changes in pharmacokinetics and pharmacodynamics in obese patients and uncertain data in low BMI[42] no conclusions can be drawn from the use of Rivaroxaban in this group of patients. Another important consideration is that patients with GFR of less than 15 mL/min were excluded.

Table 4. Main results of the studies included in the systematic review.

Study/ # participants/ Duration	PEGASUS TIMI-54 (N=21.162) 33 months		COMPASS (N= 27.395) 23 months		DAPT (N= 25.682) 30 months		THEMIS (N= 19220) 39.9 months		COMMANDER HF (N= 5.022) 21.1 months	
Outcome	**RAR**	**NNT**	**RAR**	**NNT**	**RAR**	**NNT**	**RAR**	**NNT**	**RAR**	**NNT**
CV/MI/stroke death	**1.27**		**1.3**	**163**	**1.6**	**63**	**0.8**		**n.s**	**n.s**
CV death	**0.53**	**189**	**0.5**		**n.s**	**n.s**	**n.s**	**n.s**	**n.s**	**n.s**
CAD death	**0.40**		**0.4**		**n.s**	**n.s**	**n.s**	**n.s**	**n.s**	**n.s**
MI	**0.72**		**0.3**	**333**			**n.s**	**n.s**	**n.s**	**n.s**
Stroke	**0.47**	**213**	**0.7**		**n.s**	**n.s**	**n.s**	**n.s**	**n.s**	**n.s**

CV: cardiovascular; MI: myocardial infarction; CAD: coronary artery disease; ARR: absolute risk reduction; NNT: number needed to treat. n.s = no significant.

Table 5. Bleeding outcomes of the COMPASS study.

Type of bleeding	Group A: Rivaroxaban (2.5 mg) BID + ASA N= 9152	Group B: ASA + Placebo N= 9126	Group A VS Group B HR (95% CI)	*Value of p*
ISTH major (modified)	3. 1 %. (288)	1. 9 %. (170)	1. 70 (1. 40 - 2. 05)	< 0. 001
ISTH major	2. 3%. (206)	1.3 (116)	1. 78 (1. 41 - 2. 23)	< 0. 001
ISTH minor	9. 2%. (838)	5. 5%. (503)	1. 70 (1. 52 - 1. 90)	< 0. 001
Need for transfusion	1. 0% (87)	0. 5% (44)	1. 97 (1, 37-2, 38)	< 0. 001

ISTH: bleeding definition released by the International Society of Thrombosis and Haemostasis

In the DAPT study, which included only patients with a history of stent implantation, two thienopyridines were evaluated in the intervention group, Clopidogrel (65.2%) and, to a lesser extent, prasugrel (34.8%), showing less protection against cardiovascular events with clopidogrel than with prasugrel. Differences were also found according to the type of stent implanted; approximately one-third of the patients included in the DAPT had been managed with first-generation stents, with better protection documented with latest-generation drug-eluting stents. Another interesting finding was that patients in the DAPT treatment group had a significantly lower rate of non-stent-related myocardial infarction, with a number needed to treat (NNT) of 91.

The PEGASUS TIMI-54 study showed a significant 14% relative reduction in the net composite endpoint of cardiovascular death, myocardial infarction, stroke, intracranial hemorrhage, and fatal hemorrhage in the ticagrelor group versus the placebo group. A greater reduction in MACE was observed in patients with myocardial infarction and concomitant PAD, which represented approximately 5% of the total population.

The THEMIS study evaluated dual therapy with ASA and ticagrelor VS ASA monotherapy in diabetic patients with stable ischemic heart disease defined as a history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), or stenosis ≥50% in a major coronary artery, excluding patients with a history of AMI and cerebrovascular disease. In the treatment group, there was a reduction in the primary efficacy outcome of cardiovascular death, myocardial infarction, or stroke (7.7% in the ticagrelor/aspirin group vs. 8.5% in the placebo/aspirin group (p = 0.04); however, the secondary outcome, which was a hierarchical prespecified no difference in cardiovascular death, was found: 3.8% with ticagrelor/aspirin vs. 3.7% with placebo/aspirin (p = 0.79); therefore, formal analysis was stopped. The intervention group had an increase in major bleeding events compared with the placebo/aspirin group; therefore, the net clinical benefit was not greater in the ticagrelor group. Additionally, more patients in the ticagrelor/aspirin group discontinued the study medication due to bleeding or dyspnea than those in the placebo/ASA group; therefore, there was no significantly lower incidence of exploratory composite efficacy and safety outcomes with ticagrelor than with placebo.

In patients with heart failure with reduced ejection fraction (HFrEF <40%), COMMANDER HF did not achieve statistical significance in the primary outcome. The scenarios are discussed below.

SAFETY

Assessment of safety points is essential in studies involving antithrombotic therapy. Given the mechanism of action of these drugs, the primary adverse effects were related to bleeding. Several methods can be used to evaluate these outcomes, including: 1. the International Society on Thrombosis and Hemostasis (ISTH) 2. TIMI (Thrombolysis In Myocardial Infarction TIMI bleeding Score) 3. GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activators for Occluded Coronary Arteries), and 4. Bleeding Academic Research Consortium (BARC).

Concerning the bleeding registry, the COMPASS study utilized the International Society on Thrombosis and Hemostasis Bleeding Scale, incorporating definitions for nonsurgical and surgical patients[43]. The ISTH definition of major bleeding in surgical patients encompasses the components included in the nonsurgical patient definition, with the addition of surgical site bleeding.

COMPASS also employed the ISTH definition modified by the FDA (U.S.). Food and Drug Administration (FDA) recommendations comprise fatal bleeding, symptomatic bleeding in a critical area or organ, surgical site necessitating

reoperation, and bleeding resulting in hospitalization or presentation to an intensive care facility without an overnight stay; the modified definition excluded hemoglobin drop or need for transfusion. Any bleeding event not fulfilling the modified ISTH definition of major bleeding was deemed minor bleeding. All bleeding events were centrally adjudicated without knowledge of treatment assignment. Moreover, investigators independently classified bleeding according to intensity as mild, moderate, or severe based on their evaluation of the bleeding's impact on the patient's daily activities (mild: generally transient and typically not interfering with normal activities; moderate: bothersome enough to disrupt normal activities; severe: hinders normal activities). Investigator-reported bleeding intensity was not adjudicated.

When comparing the dual therapy groups (ASA + rivaroxaban VS ASA monotherapy), statistically significant differences were observed (Table 5).

Major bleeding rates were approximately one-third more frequent with the modified ISTH definition than with the original ISTH definition. Additionally, a proportion of "major" bleeds occurring in COMPASS may not be considered "major" bleeds in other clinical trials, particularly due to the definition of intensive care unit stay accounting for 70% of all major bleeding definitions in COMPASS.

The gastrointestinal (GI) tract was the most common site of increased major bleeding (140 of 9152 [1.5 %] VS 65 of 9126 [0.7 %]) (HR:2.15; 95 % CI:1.60 to 2.89; $p < 0.001$), followed by intracranial, skin or injection site, eye, nasal, urinary, respiratory, and genital bleeding. Increased bleeding was predominantly reported in the first year after randomization.

Combination therapy of rivaroxaban and aspirin compared with aspirin alone did not significantly elevate fatal bleeding (HR: 1.49; 95% CI: 0.67 to 3.33; $p = 0.32$), symptomatic critical organ bleeding (HR: 1.37; 95% CI: 0.96 to 1.95; $p = 0.08$), or bleeding at a surgical site requiring reoperation (HR: 1.24; 95% CI: 0.58 to 2.65; $p = 0.58$).

The TIMI bleeding scale was used in PEGASUS-TIMI 54, as shown in Table 6. As observed, ticagrelor increased the risk of TIMI major and minor bleeding, although it did not increase intracranial hemorrhage (ICH) or fatal bleeding.

Table 6. Bleeding outcomes in the PEGASUS-TIMI 54 study.

Bleeding	Ticagrelor 90 mg (N= 6968)	Ticagrelor 60 mg (N= 6958)	Placebo (N= 6996)	Ticagrelor 90 mg Vs Placebo HR (95% CI) *p-value*	Ticagrelor 60 mg Vs Placebo HR (95% CI) *p-value*
TIMI major	2.6% (127)	2.3% (115)	1.06% (54)	2. 69 (1.96 -3.70) < 0.001	2.32 (1.68-3.21) < 0.001
TIMI minor	1.31%. (66)	1.18% (55)	0.36%. (18)	4.15 (2.47-7.00) < 0.001	3.31 (1.94-5.63) < 0.001
Transfusion requirement	2.43% (122)	2.09% (105)	0.72% (37)	3.75 (2.59 -5.42) < 0.001	3.08 (2.12-4.48) < 0.001
Leading to discontinuation of management	7.81%. (453)	6.15% (354)	1.50% (86)	5.79 (4.60-7.29) < 0.001	4.40 (3.48 -5.57) < 0.001
Fatal or intracranial hemorrhage	0.63% (32)	0.77 1% (30)	0.. 60% (30)	1.22 (0.74-2.01) 0.43	1.20 (0.73-1.97) 0.43
Intracranial hemorrhage	0.56% (29)	0.61% (28)	0.47% (23)	1.44 (0.83-2.49) 0.19	1.33 (0.77-2.31) 0.31
Hemorrhagic stroke	0.07% (4)	0.19% (8)	0.19% (9)	0.51 (0.16- 1.64) 0.26	0.97 (0.37-2.51) 0.94
Fatal	0.11% (6)	0.25% (11)	0.26% (12)	0.58 (0.22-1.54) 0.27	1.0 (0.44-2.27) 1.00

TIMI= Thrombolysis in Myocardial Infarction TIMI bleeding Score, HR: Hazard ratio

One of the main differences between the PEGASUS and DAPT strategies is that DAPT (table 7) included only patients without clinically significant bleeding who could continue taking a P2Y12 receptor antagonist. In contrast, in PEGASUS, most patients started treatment with ticagrelor after an interruption in dual antiplatelet therapy (most patients were enrolled approximately 2 years after myocardial infarction), and patients were not necessarily excluded from the trial if they had a bleeding episode.

Bleeding data from the DAPT study are presented in Table 7.

Table 7. Bleeding outcomes in the DAPT study

Bleeding	Continued thienopyridine N= 4710	Placebo N= 4649	Percentage difference (95% CI)	*p* - value
Severe or moderate GUSTO	2.5% (119)	1.6% (73)	1.0 (0.4-1.5)	0.001
Severe	0.8% (38)	0.6% (26)	0.2 (-0.1 - 0.6)	0.150
Moderate	1.7% (81)	1.0% (48)	0.7 (0.2-1.2)	0.004
BARC type 2, 3 or 5	5.6% (263)	2.9% (137)	2.6 (1.8-3.5)	< 0.001
Type 2	3.1% (145)	1.5% (72)	1.5 (0.9-2.1)	<0.001
Type 3	2.6% (122)	1.5% (68)	1.1% (0.6-1.7)	<0.001
Type 5	0.1% (7)	0.1% (4)	0.1 (-0.1-0.2)	0.38

Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries, BARC: Bleeding Academic Research Consortium

Table 8. Bleeding outcomes in the THEMIS study.

Result	Ticagrelor	Placebo	HR (95% CI)	*p*-value
TIMI major bleeding	2.2% (206)	1.0% (100)	2.32 (1.82 - 2.94)	< 0.001
TIMI major or minor bleeding	3.0% (285)	1.4% (129)	2.49 (2.02 -3.07))	< 0.001
TIMI major or minor bleeding with medical care	11.2% (1072)	5.1% (485)	2.51 (2.26-2.80)	< 0.001
PLATO major bleeding	3.2% (310)	1.5% (145)	2.41 (1.98-2.93)	< 0.001
BARC bleeding				
3,4 o 5	3.6% (341)	1.7% (163)	2.36 (1.96-2.84)	< 0.001
4 o 5	0.2% (17)	0.1% (11)	1.73 (0.81-2.69)	0.16
5	0.2% (17)	0.1% (10)	1.90 (0.87 - 4.15)	0.11
Intracranial bleeding	0.7% (70)	0.5% (46)	1.71 (1.18-2.48)	0.005

TIMI= Thrombolysis in Myocardial Infarction TIMI bleeding Score, BARC: Bleeding Academic Research Consortium, HR: Hazard ratio

In the THEMIS study (table 8), the bleeding scale was the TIMI, where the incidence of major bleeding was 2.2% in the ticagrelor plus aspirin group vs. 1.0% in the aspirin alone group (HR, 2.32; p <0.001), and the incidence of intracranial hemorrhage in the ticagrelor group was higher than that in the aspirin group (0.7% and 0.5%, respectively; hazard ratio [1.71; p = 0.005). There was no significant difference in the incidence of fatal bleeding between the groups (0.2% vs. 0.1%; p = 0.11). The presence of these adverse events limits the efficacy and safety of the exploratory composites.

OTHER SAFETY OUTCOMES

The presence of dyspnea in the PEGASUS-TIMI 54 group occurred early in the ticagrelor group at both 60 and 90 mg doses and was relevant given that it contributed to significantly higher rates of study drug discontinuation. In the THEMIS study, dyspnea leading to discontinuation of the study medication was 6.9% in the ticagrelor/aspirin group and 0.8% in the placebo/aspirin group (p < 0.001).

RENAL DISEASE

Patients with established cardiovascular disease frequently have impaired renal function, which influences not only thrombotic events[44,45] but also hemorrhagic events[46]. In this group of patients,

antithrombotic therapy may be useful; however, a careful balance should be struck between the benefits and risks of this management strategy, particularly in advanced stages. The COMPASS study included patients with stable cardiovascular disease; if the participant was younger than 65 years of age, they had to have an additional risk factor, such as documentation of arteriosclerosis, revascularization of at least two vascular beds, or at least two additional risk factors. Among the additional risk factors was GFR < 60 ml/min. A total of 22.9% of all patients (n=6,276) had this characteristic; however, patients with a GFR < 15 mL/min were excluded from the study. Therefore, the combined use of ASA with Rivaroxaban is not recommended for this population. In COMPASS, baseline renal function and diabetes were predictors of subsequent MACE, and in the intervention group, there was a consistent relative benefit for ischemic events across the spectrum of baseline renal function, irrespective of diabetes status.

The PEGASUS TIMI 54 trial included patients with a history of MI in the past 1-3 years who were older than 50 years and another risk factor with GFR < 60 ml/min. Those receiving ticagrelor had a better outcome than those receiving placebo; however, regardless of renal dysfunction, those receiving ticagrelor had higher rates of bleeding.

DIABETES MELLITUS

Diabetes Mellitus frequently accompanies stable coronary artery disease and amplifies cardiovascular risk, particularly in patients with evidence of polyvascular disease[19]. Strategies focused on lipid control, management of arterial hypertension, and optimization of metabolic control with glycemic modifying drugs contribute to risk reduction. Data reporting a prothrombotic state in diabetic patients has made the use of antithrombotic therapy attractive as part of the diabetic patient's residual risk reduction, particularly for the case of ASA where primary prevention may have a benefit at the cost of increased bleeding. Dual antithrombotic therapies continue to be of interest in the diabetic patient setting. In the DAPT study, less protection from dual therapy was observed in patients with diabetes. COMPASS included 37.7% (n=10,341) of subjects with diabetes mellitus, predominantly young female subjects. Although a pre-specified sub-analysis of patients with diabetes was performed, there was no statistical power to assess the effectiveness or safety of this therapy, partly associated with a limited follow-up time due to early termination of the study[19]. An additional limitation of the subanalysis is the case definition of diabetes mellitus, with medical record data without a definition of the time of evolution of the disease, which may modify the risk. Dual antithrombotic therapy in the COMPASS strategy reduces thrombotic events independent of the presence of diabetes mellitus in patients with stable coronary artery disease. The THEMIS study focused on the diabetic population and defined stable coronary artery disease as documentation of at least 50% coronary artery stenosis in a vessel, a history of PCI, surgical Mitral valve repair (MVR), or both. The primary efficacy and safety outcomes were previously mentioned and did not meet the criteria for good net clinical benefit.

HEART FAILURE

A significant number of patients with heart failure have concomitant coronary artery disease, and the presence of a new cardiac ischemic event can lead to worsening heart failure and a predisposition to adverse outcomes[47]. Patients with heart failure have been observed to have greater thrombin activation[48], particularly in the context of decompensated heart failure[49]; thus, antithrombotic therapy could, from a pathophysiological point of view, provide an opportunity for antithrombotic treatment. The COMMANDER HF study evaluated the usefulness of rivaroxaban at a dose of 2.5 mg twice daily (BID) in patients in sinus rhythm, with HFrEF less than 40% and with a recent episode of decompensated heart failure (defined as less than 21 days), the composite outcome of stroke, acute myocardial infarction, or all causes of mortality had no statistically significant differences versus placebo. COMPASS with the combined use of ASA and Rivaroxaban (2.5 mg BID) included 5902 participants with a history of heart failure; however, it had exclusions in subjects with HFrEF less than 30% and patients in NYHA functional class III or IV were excluded. In subjects with heart failure, ventricular function was recorded in 84% (n = 4971), of which only 12% of participants had HFrEF < 40%, and ventricular function was unknown in 15.8% (n=931); therefore, subgroup analyses should be interpreted with caution. Patients in the COMMANDER HF study had higher rates of all-cause disease than those in other studies, probably because they included patients with recently decompensated heart failure, an event clearly related to increased mortality.

Based on current evidence, the use of rivaroxaban is not indicated in the most recent clinical guidelines on heart failure as a targeted therapy for heart failure, and its use would only be indicated in conditions where there is an additional condition that justifies its use: atrial fibrillation and intraventricular thrombus (at anticoagulation doses)

or stable coronary and/or vascular disease with EF greater than 30% and NYHA functional class I and II.

Discussion

The development of antithrombotic therapy has allowed the expansion of management strategies for stable cardiovascular disease, particularly in patients at a moderate or high risk of ischemic events. Patients at high ischemic risk According to the chronic coronary syndrome guideline[50] are defined as those with multivessel coronary artery disease (CAD) and at least one additional risk factor, such as diabetes mellitus, recurrent myocardial infarction, peripheral arterial disease (PAD), or renal failure, whereas moderate-risk patients are those with at least one multivessel/diffuse CAD or diabetes mellitus, recurrent myocardial infarction, PAD, chronic renal failure, and heart failure. An alternative to assessing thrombotic risk is the DAPT score (51), which allows simultaneous assessment of bleeding risk; a high score (> 2) would allow selection of the patient profile with potential benefit from prolonged antithrombotic therapy. The DAPT, PEGASUS-TIMI 54, and COMPASS studies provide options to define the strategy that best suits the profile of each patient. A practical approach to selecting an antithrombotic strategy can be based on recognizing a moderate or high ischemic risk profile, taking into account the indications and contraindications that characterize each study. When a patient does not present with some of the exclusion criteria shared by the studies, such as high bleeding risk, history of hemorrhagic stroke, intracranial bleeding, severe liver disease, or dialysis. Based on the inclusion criteria, rivaroxaban at a dose of 2.5 mg BID plus aspirin may represent the only strategy for patients with stable cardiovascular disease without previous AMI; however, patients with GFR less than 15 mL/min or those with extreme weights would not be the ones of choice for the use of rivaroxaban. Regarding the use of iP2Y12, it should be considered that the best evidence regarding MACE reduction results is provided by ticagrelor in high-risk groups and prasugrel, particularly in the post-infarction setting. Clopidogrel shows less protection from ischemic events than prasugrel and was only evaluated in the post-infarction setting. It is crucial to know the degree of bleeding associated with each therapy because studies differ in the way they present safety data, and it is important to know whether these bleeding events confer a higher risk of mortality than a new ischemic event. It is reasonable to question whether a patient who has been receiving therapy with iP2Y12 during the first year of the acute event without experiencing any adverse effects should be switched to a different therapy that may expose him to an adverse reaction. For the use of ticagrelor, the possibility of discontinuation of therapy due to side effects, in addition to bleeding such as dyspnea or bradycardia, should be considered. Current evidence supports the use of antithrombotic therapy up to 3.5 years after the occurrence of an acute coronary syndrome; further studies are required to evaluate its efficacy and safety beyond this time, although preliminary studies have shown that discontinuation of antithrombotic therapy may increase the risk of new cardiovascular events[52].

Conclusion

There are significant differences among studies evaluating dual antithrombotic therapy in patients with established cardiovascular disease. We identified five pivotal studies with a low risk of bias, which allowed us to conclude that combining acetylsalicylic acid (ASA) with a P2Y12 inhibitor or even an anticoagulant reduces ischemic cardiovascular outcomes. However, this benefit comes at the cost of an increased risk of bleeding compared to ASA monotherapy. The inclusion and exclusion criteria varied between studies, as did the safety outcomes.

Adopting a comprehensive secondary prevention approach that individualizes each individual's ischemic and bleeding risk based on their comorbidities may better profile subjects with the greatest potential benefit from extended antithrombotic therapy

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Supplemental Appendix

MEDLINE SEARCH		
		TERMS
	coronary artery disease [MeSH Terms].	**Coronary artery disease**
SCA, SCC, ICP, CABG	"artery disease coronary"[Title/Abstract].	Artery Disease, Coronary
	"artery diseases coronary"[Title/Abstract].	Artery Diseases, Coronary
	"coronary artery diseases"[Title/Abstract].	Coronary Artery Diseases
	"coronary arteriosclerosis"[Title/Abstract].	Coronary Arteriosclerosis
	Arteriosclerosis, Coronary[Title/Abstract].	Arteriosclerosis, Coronary
	Coronary Arteriosclerosis[Title/Abstract].	Coronary Arteriosclerosis
	"atherosclerosis coronary"[Title/Abstract].	Atherosclerosis, Coronary
	Atherosclerosis, Coronary[Title/Abstract].	Atherosclerosis, Coronary
	Coronary Atherosclerosis[Title/Abstract].	Coronary Atherosclerosis
	"coronary atherosclerosis"[Title/Abstract].	Coronary Atherosclerosis
	"coronary arteriosclerosis"[Title/Abstract].	Arteriosclerosis, Coronary
	"chronic coronary syndromes"[Title/Abstract].	Chronic Coronary Syndromes
	"Chronic Coronary Syndrom[Title/Abstract]".	Chronic Coronary Syndrom
	"myocardial infarction"[MeSH Terms].	**Myocardial Infarction**
	((((((((((((Coronary artery disease [MeSH Terms]) OR (Artery Disease, Coronary [Title/Abstract])) OR (Artery Diseases, Coronary[Title/Abstract])) OR (Coronary Artery Diseases, Coronary [Title/Abstract])) OR (Coronary Arteriosclerosis [Title/Abstract])) OR (Arteriosclerosis, Coronary [Title/Abstract])) OR (Coronary Arteriosclerosis [Title/Abstract])) OR (Atherosclerosis, Coronary [Title/Abstract])) OR (Atherosclerosis, Coronary [Title/Abstract])) OR (Coronary Atherosclerosis, Coronary [Title/Abstract])) OR (Coronary Atherosclerosis [Title/Abstract])) OR (Arteriosclerosis, Coronary [Title/Abstract])) OR (Chronic Coronary Syndromes [Title/Abstract])) OR (Chronic Coronary Syndromes [Title/Abstract])	**MeSH + Entry terms**
	"percutaneous coronary intervention"[MeSH Terms].	**Percutaneous coronary intervention**
	"coronary intervention percutaneous"[Title/Abstract].	Coronary Intervention, Percutaneous
	"coronary percutaneous interventions"[Title/Abstract].	Coronary Interventions, Percutaneous, Coronary Interventions, Percutaneous
	"percutaneous coronary intervention"[Title/Abstract].	Intervention, Percutaneous Coronary
	"percutaneous coronary interventions"[Title/Abstract].	Interventions, Percutaneous Coronary
	"percutaneous coronary interventions"[Title/Abstract].	Percutaneous Coronary Interventions
	"percutaneous coronary revascularization"[Title/Abstract].	Coronary Revascularization, Percutaneous, Percutaneous
	"percutaneous coronary revascularizations"[Title/Abstract].	Percutaneous Coronary Revascularizations
	"percutaneous coronary revascularization"[Title/Abstract].	Revascularization, Percutaneous Coronary
	"percutaneous coronary revascularizations"[Title/Abstract].	Revascularizations, Percutaneous Coronary
	(((((((("percutaneous coronary intervention" [MeSH Terms]) OR (Coronary Intervention, Percutaneous [Title/Abstract])) OR (Coronary Interventions, Percutaneous [Title/Abstract])) OR (Intervention, Percutaneous Coronary [Title/Abstract])) OR (Interventions, Percutaneous Coronary [Title/Abstract])) OR (Interventions, Percutaneous Coronary Interventions [Title/Abstract])) OR (Coronary	**MeSH + Entry terms**

	Revascularization, Percutaneous [Title/Abstract])) OR (Percutaneous Coronary Revascularizations [Title/Abstract])) OR (Revascularization, Percutaneous Coronary [Title/Abstract])) OR (Revascularizations, Percutaneous Coronary [Title/Abstract])	
	"coronary artery bypass [MeSH Terms].	**Coronary artery bypass grafting**
	"artery bypass coronary"[Title/Abstract].	Artery Bypass, Coronary
	Artery Bypasses, Coronary[Title/Abstract].	Artery Bypasses, Coronary
	Bypasses, Coronary Artery[Title/Abstract].	Bypasses, Coronary Artery
	"coronary artery bypasses"[Title/Abstract].	Coronary Artery Bypasses
	"coronary artery bypass surgery"[Title/Abstract].	Coronary Artery Bypass Surgery
	"coronary artery bypass"[Title/Abstract].	Bypass, Coronary Artery
	"aortocoronary bypass"[Title/Abstract].	Aortocoronary Bypass
	"aortocoronary bypasses"[Title/Abstract].	Aortocoronary Bypasses
	"aortocoronary bypass"[Title/Abstract].	Bypass, Aortocoronary
	Bypasses, Aortocoronary[Title/Abstract].	Bypasses, Aortocoronary
	"bypass surgery coronary artery"[Title/Abstract].	Bypass Surgery, Coronary Artery
	((((((((((coronary artery bypass [MeSH Terms]) OR (artery bypass coronary [Title/Abstract])) OR (Artery Bypasses, Coronary [Title/Abstract])) OR (Bypasses, Coronary Artery [Title/Abstract])) OR (Coronary Artery Bypasses, Coronary [Title/Abstract])) OR (coronary artery bypass surgery [Title/Abstract])) OR (coronary artery bypass surgery [Title/Abstract])) OR (coronary artery bypass [Title/Abstract]) OR (aortocoronary bypass surgery [Title/Abstract])) OR (aortocoronary bypasses [Title/Abstract])) OR (aortocoronary bypass [Title/Abstract])) OR (Bypasses, Aortocoronary [Title/Abstract])) OR (bypass surgery coronary artery [Title/Abstract])	**MeSH + Entry terms**
Antiplatelet therapy	"aspirin"[MeSH Terms]	Aspirin
	"acetylsalicylic acid"[Title/Abstract].	Acetylsalicylic Acid
	"acetylsalicylic acid"[Title/Abstract].	Acid, Acetylsalicylic
	"clopidogrel"[MeSH Terms].	Clopidogrel
	"prasugrel hydrochloride"[MeSH Terms].	Prasugrel
	"hydrochloride prasugrel"[Title/Abstract].	Hydrochloride, Prasugrel
	"prasugrel hcl"[Title/Abstract].	Prasugrel HCl
	"HCl"[All Fields] AND "Prasugrel"[Title/Abstract].	HCl, Prasugrel
	"ticagrelor"[MeSH Terms].	Ticagrelor
	"p2y12 inhibitors"[Title/Abstract].	P2Y12 inhibitors
	"Thienopyridine"[Title/Abstract].	Thienopyridine
	("dual"[All Fields] AND ("antiplatelet"[All Fields] OR "antiplatelets"[All Fields])) AND "therapeutics"[MeSH Terms])	**Dual Antiplatelet Therapy Study**
	((((((((((Aspirin [MeSH Terms]) OR (Acetylsalicylic Acid [Title/Abstract])) OR (Acid, Acetylsalicylic Acid [Title/Abstract])) OR (Clopidogrel [MeSH Terms])) OR (Prasugrel [MeSH Terms])) OR (Hydrochloride, Prasugrel [Title/Abstract])) OR (Prasugrel HCl [Title/Abstract])) OR (HCl, Prasugrel [Title/Abstract])) OR (Ticagrelor [MeSH Terms])) OR (P2Y12 inhibitors [Title/Abstract])) OR (Thienopyridine [Title/Abstract]))	**MeSH + Entry terms**
	"warfarin"[MeSH Terms].	Warfarin

	"vitamin k antagonists"[Title/Abstract].	vitamin K antagonists
Anticoagulant therapy	"dabigatran"[MeSH Terms].	Dabigatran
	"rivaroxaban"[MeSH Terms].	Rivaroxaban
	"Apixaban"[Title/Abstract].	Apixaban
	"Edoxaban"[Title/Abstract].	Edoxaban
	"factor xa inhibitors"[MeSH Terms].	Factor Xa inhibitor
	"new oral anticoagulants"[Title/Abstract].	new oral anticoagulants
	(("direct"[All Fields] OR "directed"[All Fields] OR "directing"[All Fields] OR "direction"[All Fields] OR "directional"[All Fields] OR "directions"[All Fields] OR "directivities"[All Fields] OR "directivity"[All Fields] OR "direcs"[All Fields] OR "directs"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields])) AND "anticoagulants"[MeSH Terms] AND "anticoagulants"[MeSH Terms])	Direct oral anticoagulants
	(((((((((Warfarin [MeSH Terms]) OR (vitamin K antagonists [Title/Abstract])) OR (Dabigatran [MeSH Terms])) OR (Rivaroxaban [MeSH Terms])) OR (Apixaban [Title/Abstract])) OR (Edoxaban [Title/Abstract])) OR (Factor Xa inhibitor [MeSH Terms])) OR (new oral anticoagulants [Title/Abstract])) OR (Direct oral anticoagulants [MeSH Terms]))	**MeSH + Entry terms**

	SEARCH PACKAGE
	TERMS
SCA, SCC, ICP, CABG	
# 1 Coronary heart disease	coronary artery disease`':'ti,ab OR 'coronary heart disease' OR 'chronic coronary syndrome'/mj OR ('heart infarction'/exp OR 'cardiac infarct' OR 'cardiac infarction' OR 'cardial infarct' OR 'heart attack' OR 'heart infarct' OR 'heart infarction' OR 'heart micro infarction' OR 'heart muscle infarction' OR 'infarction, heart' OR 'myocardial infarct' OR 'myocardial infarction' OR 'myocardium infarct' OR 'myocardium infarction' OR 'premonitory infarction sign' OR 'second heart attack' OR 'subendocardial infarction' OR 'transmural cardiac infarction' OR 'transmural heart infarction' OR 'transmural infarction, heart') OR 'myocardial infarction':ti,ab OR ('acute coronary syndrome'/mj OR 'acute coronary syndrome' OR 'acute coronary syndromes') OR 'percutaneous coronary intervention':ti,ab OR ('coronary artery bypass graft'/mj OR 'aorta coronary artery bypass graft' OR 'aorta coronary artery bypass graft' OR 'aorta coronary vein bypass graft' OR 'aorta coronary vein bypass graft' OR 'aorta coronary vein shunt' OR 'aortic coronary artery shunt' OR 'aortic coronary artery bypass bypass' OR 'aortic coronary bypass' OR 'aorticocoronary anastomosis' OR 'aorto coronary artery bypass' OR 'aorto coronary bypass graft' OR 'aorto coronary vein bypass' OR 'aortocoronary anastomosis' OR 'aortocoronary artery bypass' OR 'aortocoronary artery bypass graft' OR 'aortocoronary bypass' OR 'aortocoronary bypass graft' OR 'aortocoronary shunt' OR 'aortocoronary vein bypass' OR 'aortocoronary vein bypass graft' OR 'aortocoronary venous bypass' OR 'aortocoronary venous bypass graft' OR 'coronary artery bypass' OR 'coronary artery bypass graft' OR 'coronary artery bypass graft' OR 'coronary artery bypass grafting' OR 'coronary artery graft' OR 'coronary bypass' OR 'coronary bypass graft' OR 'coronary bypass grafting' OR 'coronary vein bypass graft' OR 'coronary venous bypass graft' OR 'coronary venous bypass graft') OR 'coronary stenting'/mj
# 2Antiplatelet therapy	acetylsalicylic acid'/mj OR clopidogrel/mj OR prasugrel/mj OR ticagrelor/mj
# 3Anticoagulant therapy	warfarin/or apixaban/or edoxaban/or rivaroxaban/or rivaroxaban/or dabigatran/or 'factor xa inhibitor':ti,ab OR 'new oral anticoagulants':ti,ab OR 'direct oral anticoagulants':ti,ab
Common search	#1 AND #2 AND #3

COCRHANE SEARCH	
	TERMS
# 1 Coronary heart disease	MeSH descriptor: [Coronary Artery Disease] explode all trees
# 2Antiplatelet therapy	MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees

# 3Anticoagulant therapy	MeSH descriptor: [Anticoagulants] explode all trees
Common search	MeSH descriptor: [Coronary Artery Disease] explode all trees AND MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees AND MeSH descriptor: [Anticoagulants] explode all trees

LILACS SEARCH	
	TERMS
mh: "Coronary Disease" AND (db:("LILACS"))	**Coronary artery disease**
coronary diseases AND (db:("LILACS"))	Arterioscleroses, Coronary
coronary heart disease AND (db:("LILACS"))	Coronary Heart Disease
coronary heart diseases AND (db:("LILACS"))	Coronary Heart Diseases
disease, coronary AND (db:("LILACS"))	Disease, Coronary
disease, coronary heart AND (db:("LILACS"))	Disease, Coronary Heart
diseases, coronary AND (db:("LILACS"))	Diseases, Coronary
diseases, coronary heart AND (db:("LILACS"))	Diseases, Coronary Heart
heart disease, coronary AND (db:("LILACS"))	Heart Disease, Coronary
heart diseases, coronary AND (db:("LILACS"))	Heart Diseases, Coronary
chronic coronary syndromes AND (db:("LILACS"))	Chronic Coronary Syndromes
Chronic Coronary Syndrom AND (db:("LILACS"))	Chronic Coronary Syndromes
((((((((((mh: "Coronary Disease" AND ((db:("LILACS")))) OR (coronary diseases AND ((db:("LILACS")))) OR (coronary heart disease AND (db:("LILACS")))) OR (coronary heart diseases AND (db:("LILACS")))) OR (disease, coronary AND (db:("LILACS")))) OR (disease, coronary heart AND (db:("LILACS")))) OR (diseases, coronary AND (db:("LILACS")))) OR (diseases, coronary heart AND (db:("LILACS")))) OR (heart disease, coronary AND (db:("LILACS")))) OR (chronic coronary syndromes AND (db:("LILACS")))) OR (chronic coronary syndrom AND (db:("LILACS"))))	**DeCS/MeSH + Entry terms**
(mh:("Myocardial Infarction")) AND (db:("LILACS"))	**Myocardial Infarction**
(mh:("Percutaneous Coronary Intervention")) AND (db:("LILACS"))	**Percutaneous Coronary Intervention**
coronary intervention, percutaneous AND (db:("LILACS"))	Coronary Intervention, Percutaneous
coronary interventions, percutaneous AND (db:("LILACS"))	Coronary Interventions, Percutaneous, Coronary Interventions, Percutaneous
coronary revascularization, percutaneous AND (db:("LILACS"))	Coronary Revascularization, Percutaneous, Percutaneous
coronary revascularizations, percutaneous AND (db:("LILACS"))	Coronary Revascularizations, Percutaneous, Percutaneous
intervention, percutaneous coronary AND (db:("LILACS"))	Intervention, Percutaneous Coronary
interventions, percutaneous coronary AND (db:("LILACS"))	Interventions, Percutaneous Coronary
percutaneous coronary interventions AND (db:("LILACS"))	Percutaneous Coronary Interventions
percutaneous coronary revascularization AND (db:("LILACS"))	Percutaneous Coronary Revascularization
percutaneous coronary revascularizations AND (db:("LILACS"))	Percutaneous Coronary Revascularizations
revascularization, percutaneous coronary AND (db:("LILACS"))	Revascularization, Percutaneous Coronary
revascularizations, percutaneous coronary AND (db:("LILACS"))	Revascularizations, Percutaneous Coronary
(((((((((((mh:("Percutaneous Coronary Intervention"))) AND (db:("LILACS")))) OR (coronary intervention, percutaneous AND (db:("LILACS"))))) OR (coronary interventions, percutaneous AND (db:("LILACS")))))) OR (coronary revascularization, percutaneous AND (db:("LILACS")))) OR (coronary revascularizations, percutaneous AND (db:("LILACS")))) OR (intervention, percutaneous coronary AND (db:("LILACS")))) OR (interventions, percutaneous coronary AND (db:("LILACS")))) OR (percutaneous coronary interventions AND (db:("LILACS")))) OR (percutaneous coronary revascularization AND (db:("LILACS")))) OR (percutaneous coronary revascularizations AND (db:("LILACS")))) OR (revascularization, percutaneous coronary AND (db:("LILACS")))) OR (revascularizations, percutaneous coronary AND (db:("LILACS"))))	**DeCS/MeSH + Entry terms**
(mh:("Coronary Artery Bypass")) AND (db:("LILACS"))	**coronary artery bypass grafting**
aortocoronary bypass AND (db:("LILACS"))	Aortocoronary Bypass

aortocoronary bypasses AND (db:("LILACS"))	Aortocoronary Bypasses
artery bypass, coronary AND (db:("LILACS"))	Artery Bypass, Coronary
artery bypasses, coronary AND (db:("LILACS"))	Artery Bypasses, Coronary
bypass surgery, coronary artery AND (db:("LILACS"))	Bypass Surgery, Coronary Artery
bypass, aortocoronary AND (db:("LILACS"))	Bypass, Aortocoronary
bypass, coronary artery AND (db:("LILACS"))	Bypass, Coronary Artery
bypasses, aortocoronary AND (db:("LILACS"))	Bypasses, Aortocoronary
bypasses, coronary artery AND (db:("LILACS"))	Bypasses, Coronary Artery
coronary artery bypass grafting AND (db:("LILACS"))	Coronary Artery Bypass Grafting
coronary artery bypass surgery AND (db:("LILACS"))	Coronary Artery Bypass Surgery
coronary artery bypasses AND (db:("LILACS"))	Coronary Artery Bypasses
(((((((((((mh:("Coronary Artery Bypass"))) AND (db:("LILACS")))) OR (aortocoronary bypass AND ((db:("LILACS"))))) OR (aortocoronary bypasses AND ((db:("LILACS")))) OR (artery bypass, coronary AND (db:("LILACS")))) OR (artery bypasses, coronary AND (db:("LILACS")))) OR (bypass surgery, coronary artery AND (db:("LILACS")))) OR (bypass, aortocoronary AND (db:("LILACS")))) OR (bypasses, coronary artery AND (db:("LILACS")))) OR (bypasses, coronary artery AND (db:("LILACS")))) OR (coronary artery bypass grafting AND (db:("LILACS")))) OR (coronary artery bypass surgery AND (db:("LILACS")))) OR (coronary artery bypasses AND (db:("LILACS"))))	**DeCS/MeSH + Entry terms**
((((((((((((mh: "Coronary Disease" AND ((db:("LILACS")))) OR (coronary diseases AND ((db:("LILACS")))) OR (coronary heart disease AND (db:("LILACS")))) OR (coronary heart diseases AND (db:("LILACS")))) OR (disease, coronary AND (db:("LILACS")))) OR (disease, coronary heart AND (db:("LILACS")))) OR (diseases, coronary AND (db:("LILACS")))) OR (diseases, coronary heart AND (db:("LILACS")))) OR (heart disease, coronary AND (db:("LILACS")))) OR (chronic coronary syndromes AND (db:("LILACS")))) OR (chronic coronary syndrom AND (db:("LILACS")))) OR (((((((((((((mh:("Percutaneous Coronary Intervention")) AND (db:("LILACS")))) OR (coronary intervention, percutaneous AND ((db:("LILACS")))) OR (coronary interventions, percutaneous AND (db:("LILACS")))))))) OR (coronary revascularization, percutaneous AND (db:("LILACS")))) OR (coronary revascularizations, percutaneous AND (db:("LILACS")))) OR (intervention, percutaneous coronary AND (db:("LILACS")))) OR (interventions, percutaneous coronary AND (db:("LILACS")))) OR (percutaneous coronary interventions AND (db:("LILACS")))) OR (percutaneous coronary revascularization AND (db:("LILACS")))) OR (percutaneous coronary revascularizations AND (db:("LILACS")))) OR (revascularization, percutaneous coronary AND (db:("LILACS")))) OR (revascularizations, percutaneous coronary AND (db:("LILACS")))) OR (((((((((((((mh:("Coronary Artery Bypass")) AND (db:("LILACS")))) OR (aortocoronary bypass AND ((db:("LILACS"))))) OR (aortocoronary bypasses AND ((db:("LILACS")))) OR (artery bypass, coronary AND (db:("LILACS")))) OR (artery bypasses, coronary AND (db:("LILACS")))) OR (bypass surgery, coronary artery AND (db:("LILACS")))) OR (bypass, aortocoronary AND (db:("LILACS")))) OR (bypasses, coronary artery AND (db:("LILACS")))) OR (bypasses, coronary artery AND (db:("LILACS")))) OR (coronary artery bypass grafting AND (db:("LILACS")))) OR (coronary artery bypass surgery AND (db:("LILACS")))) OR (coronary artery bypasses AND (db:("LILACS"))))	
((((((((((((mh: "Coronary Disease" AND ((db:("LILACS")))) OR (coronary diseases AND ((db:("LILACS")))) OR (coronary heart disease AND (db:("LILACS")))) OR (coronary heart diseases AND (db:("LILACS")))) OR (disease, coronary AND (db:("LILACS")))) OR (disease, coronary heart AND (db:("LILACS")))) OR (diseases, coronary AND (db:("LILACS")))) OR (diseases, coronary heart AND (db:("LILACS")))) OR (heart disease, coronary AND (db:("LILACS")))) OR (chronic coronary syndromes AND (db:("LILACS")))) OR (chronic coronary syndrom AND (db:("LILACS")))) OR (((((((((((((mh:("Percutaneous Coronary Intervention")) AND (db:("LILACS")))) OR (coronary intervention, percutaneous AND ((db:("LILACS")))) OR (coronary interventions, percutaneous AND (db:("LILACS")))))))) OR (coronary revascularization, percutaneous AND (db:("LILACS")))) OR (coronary revascularizations, percutaneous AND (db:("LILACS")))) OR (intervention, percutaneous coronary AND (db:("LILACS")))) OR (interventions, percutaneous coronary AND (db:("LILACS")))) OR (percutaneous coronary interventions AND (db:("LILACS")))) OR (percutaneous coronary revascularization AND (db:("LILACS")))) OR (percutaneous coronary revascularizations AND (db:("LILACS")))) OR (revascularization, percutaneous coronary AND (db:("LILACS")))) OR (revascularizations, percutaneous coronary AND (db:("LILACS")))) OR (((((((((((((mh:("Coronary Artery Bypass")) AND (db:("LILACS")))) OR (aortocoronary bypass AND ((db:("LILACS"))))) OR (aortocoronary bypasses AND ((db:("LILACS")))) OR (artery bypass, coronary AND (db:("LILACS")))) OR (artery bypasses, coronary AND (db:("LILACS")))) OR (bypass surgery, coronary artery AND (db:("LILACS")))) OR (bypass, aortocoronary AND (db:("LILACS")))) OR (bypasses, coronary artery AND (db:("LILACS")))) OR (bypasses, coronary artery AND (db:("LILACS")))) OR (coronary artery bypass grafting AND (db:("LILACS")))) OR (coronary artery bypass surgery AND (db:("LILACS")))) OR (coronary artery bypasses AND ((db:("LILACS")))) OR ((mh:("Myocardial Infarction")) AND (db:("LILACS"))))	
(mh:("Aspirin")) AND (db:("LILACS"))	Aspirin
acetylsalicylic acid AND (db:("LILACS"))	Acetylsalicylic Acid
acid, acetylsalicylic AND (db:("LILACS"))	Acid, Acetylsalicylic
(mh:("Clopidogrel")) AND (db:("LILACS"))	Clopidogrel
plavix AND (db:("LILACS"))	Plavix
(mh:("Prasugrel Hydrochloride"))	Prasugrel Hydrochloride
hcl, prasugrel AND (db:("LILACS"))	HCl, Prasugrel
hydrochloride, prasugrel AND (db:("LILACS"))	Hydrochloride, Prasugrel
prasugrel hcl AND (db:("LILACS"))	Prasugrel Hydrochloride

prasugrel hcl AND (db:("LILACS"))	Prasugrel HCl
effient AND (db:("LILACS"))	Effient
efient AND (db:("LILACS"))	Efient
(mh:("Ticagrelor")) AND (db:("LILACS"))	**Ticagrelor**
brilinta AND (db:("LILACS"))	Brilinta
brilique AND (db:("LILACS"))	Brilique
(mh:("Purinergic P2Y Receptor Antagonists"))	Purinergic P2Y Receptor Antagonists
(mh:("Thienopyridines")) AND (db:("LILACS"))	Thienopyridines
(mh:("Dual Anti-Platelet Therapy")) AND (db:("LILACS"))	Dual Anti-Platelet Therapy
anti-platelet therapies, dual AND (db:("LILACS"))	Anti-Platelet Therapies, Dual
anti-platelet therapy, dual AND (db:("LILACS"))	Anti-Platelet Therapy, Dual
dual anti platelet therapy AND (db:("LILACS"))	Dual Anti Platelet Therapy
dual anti-platelet therapies AND (db:("LILACS"))	Dual Anti-Platelet Therapies
(((((((((((((((((((mh:("Aspirin"))) AND (db:("LILACS")))) OR (acetylsalicylic acid AND (db:("LILACS"))))) OR (acid, acetylsalicylic acid AND ((db:("LILACS")))) OR ((mh:("Clopidogrel"))) AND (db:("LILACS")))) OR ((plavix AND ((db:("LILACS")))) OR ((mh:("Prasugrel Hydrochloride")))) OR (hcl, prasugrel AND ((db:("LILACS")))) OR (hydrochloride, prasugrel AND (db:("LILACS")))) OR (prasugrel hcl AND (db:("LILACS")))) OR (effient AND (db:("LILACS")))) OR (efient AND (db:("LILACS")))) OR ((mh:("Ticagrelor")) AND (db:("LILACS")))) OR ((brilique AND ((db:("LILACS")))) OR ((mh:("Purinergic P2Y Receptor Antagonists")))) OR ((mh:("Thienopyridines"))) AND ((db:("LILACS")))) OR ((mh:("Thienopyridines"))) AND (db:("LILACS")))) OR ((mh:("Dual Anti-Platelet Therapy"))) AND (db:("LILACS")))) OR (anti-platelet therapies, dual AND ((db:("LILACS")))) OR (anti-platelet therapy, dual AND ((db:("LILACS")))) OR (dual anti-platelet therapy AND (db:("LILACS")))) OR (dual anti-platelet therapies AND (db:("LILACS"))))	**DeCS/MeSH + Entry terms**
(mh:("Warfarin")) AND (db:("LILACS"))	Warfarin
vitamin k antagonists AND (db:("LILACS"))	vitamin K antagonists
(mh:("Dabigatran")) AND (db:("LILACS"))	Dabigatran
(mh:("Rivaroxaban")) AND (db:("LILACS"))	Rivaroxaban
apixaban AND (db:("LILACS"))	Apixaban
edoxaban AND (db:("LILACS"))	Edoxaban
(mh:("Factor Xa Inhibitors")) AND (db:("LILACS"))	Factor Xa inhibitors
new oral anticoagulants AND (db:("LILACS"))	new oral anticoagulants
direct-acting oral anticoagulant AND (db:("LILACS"))	Direct-Acting Oral Anticoagulant
((((((((((mh:("Warfarin"))) AND (db:("LILACS")))) OR (vitamin k antagonists AND ((db:("LILACS"))))) OR ((mh:("Dabigatran"))) AND ((db:("LILACS")))) OR ((mh:("Rivaroxaban"))) AND (db:("LILACS")))) OR (apixaban AND ((db:("LILACS")))) OR (edoxaban AND (db:(("LILACS")))) OR ((mh:("Factor Xa Inhibitors"))) AND (db:("LILACS")))) OR (new oral anticoagulants AND ((db:("LILACS")))) OR (direct-acting oral anticoagulants AND (db:("LILACS"))))	**DeCS/MeSH + Entry terms**