Systematic Review

Dual antiplatelet therapy in secondary prevention for coronary and cerebrovascular disease and thrombocytopenia: A Systematic Review

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ABSTRACT

Introduction: Coronary heart disease and cerebrovascular disease are the main causes of mortality and disability. Association with thrombocytopenia increases the risk of complications. Single and dual antiplatelet therapy are part of secondary prevention. However, antiplatelet therapy in patients with thrombocytopenia raises the risk of bleeding.

Objective: The objective of this systematic review is to synthesize information on the potential risks and benefits of dual antiplatelet therapy compared to single or no antiplatelet therapy, in adults with thrombocytopenia in secondary prevention of coronary heart disease and cerebrovascular disease.

Methods: A systematic literature review of randomized and non-randomized studies reporting efficacy and safety outcomes was performed in the main databases. Evidence quality was evaluated with the ROBINS I tool, and outcomes were reported through evidence profile tables.

Results: Given the heterogeneity between studies, a meta-analysis of the data was not possible. Two studies indicated a lower rate of mortality and ischemic events with clopidogrel-based dual antiplatelet therapy, while one study found higher mortality with ticagrelor-based therapy. Major bleeding events were more frequent with ticagrelor-based therapy, while they were lower with clopidogrel-ASA.

Conclusions: Evidence suggests a possible benefit of dual antiplatelet therapy in patients with thrombocytopenia in secondary prevention of coronary heart disease and cerebrovascular disease, especially with clopidogrel-ASA. The absence of randomized clinical trials and the limited information from non-randomized studies limits the possibility of making solid recommendations. The decision to use dual antiplatelet therapy should be guided by clinical judgment, considering individualized risks and benefits.

LIST OF ABBREVIATIONS

ACS: acute coronary syndrome
CAD: coronary artery disease
CVD: cerebrovascular disease
CKD: chronic kidney disease
DAPT: dual antiplatelet therapy
HTN: hypertension
SAPT: single antiplatelet therapy

INTRODUCTION

Coronary artery and cerebrovascular diseases are the two main causes of mortality and disability at world level, with an estimate of 7 million deaths per year and 129 million disability-adjusted life years (DALY) and 6 million deaths and 143 millions of DALY, respectively [1,2]. However, advancements in their treatment have increased survival in these patients, which favors the coexistence with other comorbidities, including thrombocytopenia.

Up to 5% of patients with acute coronary syndrome (ACS) have base thrombocytopenia, and up to 13% of them develop it later[3]. Likewise, a low platelet count has been reported in 2.3% of patients with ischemic cerebrovascular disease (CVD), being a prognostic factor that increases up to six times the risk of in-hospital mortality[4]. In fact, the conditions that lead to thrombocytopenia increase the risk of developing CAD and CVD by multiple mechanisms, including different infectious diseases, autoimmune diseases, cancer, nutrition deficiencies, hypersplenism and related to medications, which entails a cardiovascular risk of up to 38% more[3].

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It has been shown that dual antiplatelet therapy (DAPT) decreases up to 50% the risk of mortality and thrombotic events after an acute ischemic event, a benefit that could be particularly important during the first month of management[5,6]. However, in the population with thrombocytopenia, its use generates the dilemma of administering an antiplatelet treatment to a population with an inherent risk of bleeding. To this date, few studies have sought to assess the benefit and risks of DAPT in this population, and the evidence they show has not been summarized systematically[7,8,9]. This has conditioned a lack of consensuses from scientific societies about which is the ideal management of these patients, representing a challenge in clinical practice[10,11,12,13].

The aim of this systematic review is to summarize the information on the potential risks and benefits of DAPT in comparison with SAPT or with no antiplatelet therapy, in adult patients with thrombocytopenia who are in secondary prevention for acute coronary syndrome and cerebrovascular event.

MATERIALS AND METHODS

Design and approval

A systematic review was made on the literature, including randomized and non-randomized studies, taking into account specific recommendations for the combined summaries of both types of studies[14,15]. The study was approved by the committee on ethics of the Pontificia Universidad Javeriana (Article N° FM-CIE-0595-24). The protocol was published in PROSPERO (CRD42024544138).

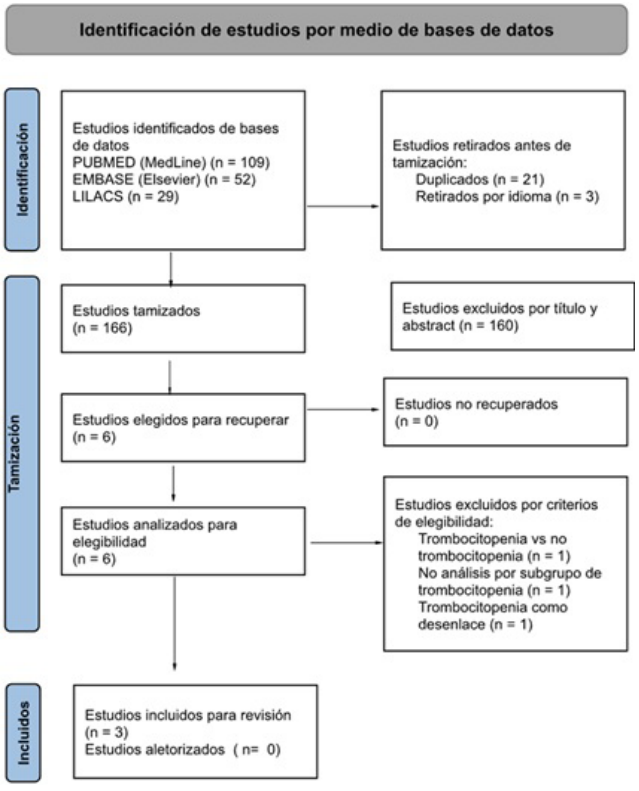


FIGURE 1.
PRISM flowchart[18].

Inclusion and exclusion criteria

To be included, the studies had to evaluate patients older than 18 years, with thrombocytopenia (defined as a platelet count <150,00 cell/μL), in secondary prevention for acute coronary syndrome, acute ischemic stroke or transient ischemic attack. Furthermore, they had to compare two treatment arms: DAPT (defined as aspirin plus a P2Y12 receptor inhibitor), with SAPT (defined as aspirin or clopidogrel or ticagrelor or prasugrel individually) or no therapy. Finally, they had to report at least one of the follow outcomes of interest: death, reinfarction, new cerebrovascular event, major bleeding, minor bleeding or hypersensitivity to medication. One-arm studies or those reporting the combination of anticoagulation with DAPT or 3 or more antiplatelet drugs were excluded.

Search and selection

The following databases were consulted: PubMed (MedLine), EMBASE (Elsevier) and LILACs until May 2024. Randomized clinical studies and observational studies were included, that had been published in Spanish and English since 1997, a time when FDA approved clopidogrel to be used. The search terms used were: "Thrombocytopenia", "Blood Platelet Disorders", "Coronary Disease", "Acute Coronary Syndrome", "Myocardial Infarction", "Stroke", "Ischemic Attack, Transient", "Aspirin", "Acetylsalicylic acid", "Clopidogrel", "Prasugrel Hydrochloride", and "Ticagrelor". The search strategies for each database can be checked in Appendix 1. Duplicate references were removed with the Mendeley tool.

Two investigators (MMS and MIG) independently selected the articles by title and abstract. From the potentially eligible articles, the full text was evaluated. All discrepancies that emerged were identified and solved by consensus or by a third investigator (OMM). The selection process is shown according to the PRISMA recommendation in *Figure 1.*

Data extraction

Once the initial selection was made, data extraction was made in a paired, independent and standardized manner by two reviewers (MMS and MIG). Once again, the discrepancies that emerged were identified and solved by consensus or by a third investigator (OMM). The relevant data collected from the articles were: author, year of publication, type of study, intervention used (DAPT), control (SAPT), number of participants, indication of therapy, age, gender, etiology and degree of thrombocytopenia, comorbidities (hypertension, diabetes mellitus, CAD, diabetes, previous CVD, cancer, cirrhosis, chronic kidney disease and anemia), previous bleeding and time of follow-up.

Evaluation of quality

For the randomized studies, the plan was to use version 2 of the Cochrane tool (RoB2)[16]. For nonrandomized stu-

TABLE 1.
Characteristics of the studies included

Author	Type of study	Intervention	Control	Number of patients	Indication of therapy	Age	Male gender	Etiology of thrombocytopenia	Degree of thrombocytopenia*	Previous bleeding	Comorbidities	Time of follow-up
Yu-Ying, 2022	Observational retrospective	ASA + clopidogrel 64%	ASA 21% or Clopidogrel 15%	468	ACS	SAPT 72.52 (+13.6) DAPT 70.77 (+12.5)	73%	Decrease in production: 62 (13.2%) Hypersplenism: 87 (18.5%%) Unknown: 319 (68.3%)	Mild 83.7% Moderate 13.7% Severe 2.6%	NR	DM 35%, previous CVD 15.5%, CAD 23.5%.	30 days
Chen, 2021	Observational retrospective	ASA + ticagrelor 4%	ASA or Clopidogrel 96%	936	ACS	67:1 ± 10:2	81%	NR	Average 85 x 103/μL (IQR 74-94 x 103/μL)	NR	HTN 55%, CKD 6%, chronic liver disease 2%, previous CVD 2.2%	In-hospital. Median 5 days (IQR 3-7 days)
Iliescu, 2018	Observational retrospective	ASA + clopidogrel 28%	SAPT 42% No therapy 31%	98	ACS	66.9 (+8.52)	83%	Cancer 100%	Mild-Moderate 42.9% Severe 20.4% Deep 36.7%	NR	HTN 86%, cancer 100%	22 months

ASA: acetylsalicylic acid; **DAPT:** dual antiplatelet therapy; **DAPTica:** dual antiplatelet therapy with ticagrelor; **DM:** diabetes mellitus; **CAD:** coronary artery disease; **CVD:** cerebrovascular disease; **CKD:** chronic kidney disease; **SAPT:** single antiplatelet therapy; **HTN:** hypertension; **NR:** not reported; **IQR:** interquartile range; **ACS:** acute coronary syndrome. *Mild thrombocytopenia 100,000-150,000 cell/μL, moderate 50,000-100,000 cell/μL, severe 30,000-50,000 cell/μL, deep <30,000 cell/μL

dies, the plan was to conduct a quality evaluation by the ROBINS I tool[17]. This tool allows to classify the global bias risk for each study and each outcome, defining it as "low", "moderate", "severe" or "critical", according to the three domains of the study: "before the intervention", "at the time of intervention" and "after the intervention"[17].

DATA ANALYSIS

The summary of the results from the primary studies was planned by meta-analysis of information, if clinical heterogeneity was low in terms of the population, interventions implemented, measured results or follow-up time, using the RevMan software (Review Manager), recommended by Cochrane with a model of random effects. If high clinical variability was identified, the plan was to summarize the information by evidence profile tables for each outcome evaluated, with no meta-analysis, differentiating the results from randomized and nonrandomized studies. Additionally, making an analysis by subgroups was proposed, according to the type of P2Y12 receptor inhibitor, the degree of thrombocytopenia, the presence of cancer and the indication of DAPT, if the collected information allowed it. Finally, in the case of finding more than 10 studies evaluating the same outcome, an analysis by funnel plot was planned, to assess the risk of publication.

RESULTS

A total of 109 studies were identified, of which 3 nonrandomized studies were included in the analysis[7,8,9]. These studies were made in the United States, Taiwan and China[7,8,9]. No randomized study was included and just one evaluated cerebrovascular outcomes. The selection process is presented in the PRISMA diagram *(Figure 1)*[18]. The characteristics of the patients included in the studies and the evaluated outcomes are presented in *Table 1*.

The three analyzed studies were observational and retrospective, analyzed patients with CAD preferably, and with DAPT based to a great extent on ASA combined with clopidogrel. The age average was similar in the three studies, around 70 years, and most of the population were men. The most frequently reported comorbidities were hypertension and diabetes mellitus. Most patients had an average of platelets between 50,000 and 150,000, so most patients had mild to moderate thrombocytopenia.



FIGURE 2.
ROBINS I tool
* Not controlled by diabetes, age, HTN; ** There is no way to evaluate the arm rate of changes; † There is a difference in the severity of thrombocytopenia between the arms of the study; # There is no way to evaluate the arm rate of change; ∫ No evaluation could be made on the effect of adhering to the intervention
C: confusion bias; **B:** bias in the selection of participants in the study; **I:** bias in the classification of interventions; **D:** bias due to deviations from the expected interventions; **MD:** bias due to missing data; **MO:** bias due to outcome measurement; **R:** bias in the selection of informed outcomes; **O:** general risk of bias

DAPT was mainly made up by aspirin and clopidogrel. Only in one study ticagrelor was used[9]. ST-segment elevation myocardial infarction was the most frequent indication for DAPT in two of the studies. One of the studies exclusively included patients with cancer, most with hematological neoplasms[9]. However, the etiology of thrombocytopenia in most was not known.

The follow-up periods in the three studies were different, with follow-ups of 5 days in-hospital for Chen et al, 30 days in Yu Ying et al, and 22 months for Iliescu, which prevented data meta-analysis given the high heterogeneity between evaluation times[7,8,9].

QUALITY EVALUATION

The quality evaluation of the studies was carried out with the ROBINS I tool, as only nonrandomized studies were found. This process is presented in *Figure 2*. In regard to the study population, in the Yu Ying Li et al group, statistically significant differences were identified in the baseline characteristics between the two groups, including gender, use of beta blockers and statins[8]. Likewise, patients in SAPT presented greater risk of bleeding in spite of the adjustment by known factors, which may have generated a confusion bias. Only in one study, the cause of thrombocytopenia was reported, understanding that its etiology could be an independent variable of mortality and higher risk of bleeding, which may lead to a confusion bias.

Two studies were classified with low risk and one study with moderate risk. The results of the risk of bias evaluation are presented in *Figure 2*.

CLINICAL OUTCOMES

Death

In *Table 2a*, mortality results are shown. Two of the studies reported mortality rates and one of them survival analysis. A lower rate of mortality and better survival were found with use of DAPT for the 2 studies that evaluated it with ASA-clopidogrel; however, estimations were imprecise. In a study evaluating the use of ASA-ticagrelor as DAPT, the mortality rate was higher with DAPT (OR 2.67; 95% CI 0.39-18.23, p = 0.5)[7].

Reinfarction

In *Table 2b*, a single study is shown to have evaluated a new ischemic myocardial event[7,8]. Similarly to mortality findings, there were less events with DAPT with ASA-clopidogrel, once again, with imprecise estimations.

New cerebrovascular event

In *Table 2c*, results are shown from the 2 studies evaluating a new cerebrovascular event[7,8]. Again, there were less cerebrovascular events with DAPT with ASA-clopidogrel compared with SAPT, and more with the ASA-ticagrelor combination.

TABLE 2A.
Evidence profiles for mortality and effectiveness. **A:** death

	DAPT			SAPT				
Study	**Events**	**Total**	**%**	**Events**	**Total**	**%**	**Measure of summary**	**Follow-up period**
Yu-Ying, 2022	8	300	2.67	9	168	5.3	HRa 0.55 (0.19-1.54) p=0.2536	30 days
Chen, 2021	3	41	7.3%	13	895	1.5%	ORa 2.67 (0.39-18.23) p=0.5	In-hospital. Median 5 days (IQR 3-7 days)
Iliescu, 2018	Survival HR 0.601 (95% CI 0.33-1.07; p = 0.087) in favor of DAPT							22 months

TABLE 2B.
Evidence profiles for mortality and effectiveness. **B:** reinfarction

	DAPT			SAPT				
Study	**Events**	**Total**	**%**	**Events**	**Total**	**%**	**Measure of summary**	**Follow-up period**
Yu-Ying, 2022	22	300	7.3	14	168	8.3	HRa 0.86 (0.41-1.81) p=0.6904	30 days

TABLE 2C.
Evidence profiles for mortality and effectiveness. **C:** new cerebrovascular event

	DAPT			SAPT				
Study	**Events**	**Total**	**%**	**Events**	**Total**	**%**	**Measure of summary**	**Follow-up period**
Yu-Ying, 2022	3	300	1	5	168	2.98	HRa 0.35 (0.07-1.68) 0.1894	30 days
Chen, 2021	4	41	9.8	24	895	2.7	ORa 2.67 (0.68-10.48) p=0.2	In-hospital. Median 5 days (IQR 3-7 days)

TABLE 3A.
Perfiles de evidencia para eventos de seguridad. **A:** Sangrado mayor

		DAPT			SAPT				
	Study	**Events**	**Total**	**%**	**Events**	**Total**	**%**	**Measure of summary**	**Follow-up period**
Major bleeding	**Yu-Ying, 2022**	18	300	6	18	168	10.6	HRa 0.66 (0.32-1.36) p=0.2573	30 days
	Chen, 2021	3	41	7.3	9	895	1	ORa 9.7 (1.57-60.4) p=0.025	In-hospital. Median 5 days (IQR 3-7 days)
	Iliescu, 2018	0	27	0	0	41	0	-	-
Total bleeding	**Chen, 2021**	3	41	7.3	11	895	1.2	ORa 6.48 (1.12-37.66) p= 0.08	In-hospital. Median 5 days (IQR 3-7 days)

TABLE 3B.
Perfiles de evidencia para eventos de seguridad. **B:** Sangrado menor

	DAPT			SAPT				
Study	**Events**	**Total**	**%**	**Events**	**Total**	**%**	**Measure of summary**	**Follow-up period**
Chen, 2021	0	41	0	2	895	0.2%	-	In-hospital. Median 5 days (IQR 3-7 days)

Major bleeding

In *Table 3a*, the results of major bleeding events are shown. In the Yu Ying study, less major and total bleeding events were found in patients with DAPT (ASA-clopidogrel), unlike the reports from Chen et al, who found more in-hospital major bleeding events in the DAPT group (ASA-ticagrelor)[8].

Minor bleeding

Only the Chen et al study evaluated minor bleeding events, finding less events in patients with DAPT, being so few that a confidence interval estimation was not possible *(Table 3b)*[7].

Hypersensitivity

Hypersensitivity events were not reported in any of the three studies.

DISCUSSION

In this systematic review, evidence available on DAPT was evaluated in comparison with SAPT or no antiplatelet therapy, in adult patients with thrombocytopenia, who were in secondary prevention for acute coronary syndrome and cerebrovascular event. It was found that there is scant information and it differs between studies. Heterogeneity could be mainly explained by the type of medication evaluated and follow-up periods, so the use of DAPT remains controversial.

Few studies were found, all of them nonrandomized, with risk of biases mainly associated to basal characteristics between groups, which may condition confusion biases. Although a tendency was observed toward a benefit with DAPT (ASA-clopidogrel) in terms of outcomes, up to now there is not enough evidence to be able to make a strong recommendation on the benefits and damages with the use of this therapy in patients with thrombocytopenia.

In the Yu Ying study, DAPT showed a tendency towards a benefit in the outcomes of death, reinfarction and new CVD, not reaching statistical significance[8]. However, in the Chen study, DAPT showed a non-significant tendency to an increase in the risk of mortality[7]. This disparity could be explained by factors such as follow-up period (quite a short period of evaluation in the Chen study), a greater risk of bleeding with ticagrelor and patients in whom a stronger P2Y12 receptor inhibitor was prescribed, then having a higher base thrombotic and mortality risk. It is for this reason that the heterogeneity found may be due to a clinical situation rather than statistical. The findings are in agreement with the recommendations by experts of preferring clopidogrel over ticagrelor in patients in high risk of bleeding, and in those with thrombocytopenia[3,13]. Besides, clopidogrel is the P2Y12 receptor inhibitor that has been most evaluated in shortened therapies for patients in high risk of bleeding[19,20,21,22]. Finally, the findings support the results of previous studies, including MATCH, where a decrease in the frequency of cerebrovascular events

was observed in DAPT with ASA-clopidogrel in patients without thrombocytopenia[23,24].

Total and major bleeding is the highest in patients with DAPT based on ticagrelor, which is in agreement with previous studies like THALES, where there were higher rates of bleeding with DAPT[25]. On the other hand, DAPT based on clopidogrel seems to be safe in the evaluated population. Previous studies like CHANCE found similar results, where there were no higher rates of bleeding with the use of DAPT, which may favor a safe use of this therapy, even in patients with high risk of bleeding[26]. In fact, in Iliescu's study, where half of patients had severe or deep thrombocytopenia, no major bleeding was documented in the arm of patients with DAPT[9].

As to minor bleeding, although it was only measured in the Chen study, there were less bleeding events with DAPT, which could be underestimated given the size of the evaluated population. Previous studies have shown that there are higher rates of minor bleeding in patients with DAPT, so in the future, studies are required that would take into account this outcome and its implications in clinical practice[27].

The greater risk of bleeding in the population with thrombocytopenia and DAPT is a consistent finding in studies and even in a meta-analysis[28]t the time of prescribing this therapy in low platelet counts. The degree of severe thrombocytopenia was minimum in the three studies, generating limitations in evidence for patients with major hematological compromise and major risk of bleeding.

Finally, there were no studies evaluating DAPT with prasugrel, so that for the time being, it shouldn't be used, as its effects are unknown in patients with thrombocytopenia in secondary prevention for ACS or CVD. Additionally, DAPT indication was exclusively evaluated in patients with ACS, so outcomes may not be extrapolated to CVD patients.

This systematic review is the first to summarize outcomes in patients receiving DAPT or SAPT associated to thrombocytopenia; however, several limitations should be acknowledged. First, in spite of what was planned, a summary with information by meta-analysis was not achieved because of the significant heterogeneity between studies. This could be explained by the difference in the degree of thrombocytopenia of participants, its etiology (with different rates of cancer) and the antiplatelet drug used for DAPT. On the other hand, the follow-up periods were different between the evaluated studies. The results could not be individualized due to the degree of thrombocytopenia, as the number of patients with severe thrombocytopenia was minimal, and outcomes were not reported in a differential way for such patients. The authors consider that it is important to evaluate by these subgroups in future summaries of information, as different clinical outcomes are expected at lower platelet counts. Finally, the number of patients with cancer was minimal, and it comes from a single study. Information on this growing population is still limited and management with DAPT should be cautious, and risks and benefits should be analyzed individually.

CONCLUSIONS

There is evidence suggesting a benefit from DAPT in patients with thrombocytopenia in secondary prevention of ACS in comparison with SAPT or no therapy. There is not enough evidence to evaluate if there is a benefit from DAPT in patients with thrombocytopenia in secondary prevention for CVD. The population with CAD may benefit from DAPT based on clopidogrel as it has proven to be safe in observational studies; however, there is no robust evidence to recommend it over ticagrelor-based therapy to decrease clinical outcomes. Finally, no evidence was found on the effectiveness or safety of prasugrel in this population.

Absence of randomized clinical trials and the scarce information in non-randomized studies with risk of significant bias shows the need for additional studies to evaluate the use of these therapies in patients with thrombocytopenia. So, for the time being, the best clinical criteria should still guide therapy.

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