REVIEW ARTICLE

Present Use of Aspirin as an Antithrombotic Agent: Current or Outdated Drug?

Uso actual de la aspirina como agente antitrombótico: ¿droga vigente u obsoleta?

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ABSTRACT

Background: Acetylsalicylic acid, or aspirin, is one of pharmacological tools most widely used in the care of cardiovascular patients. For years, it has been widely used in primary and secondary prevention to reduce cardiovascular risk.
Aspirin utilization has been questioned in recent times, with new trials in different scenarios of cardiovascular disease, such as peripheral vascular disease, stroke, primary prevention in the context of modern medical treatment, or in patients with acute coronary syndrome and concomitant need for anticoagulation. In turn, new studies question the need to maintain aspirin for 12 months together with a thienopyridine after an acute coronary syndrome, suggesting shorter regimens.
In this review, we evaluate the evidence behind the current indications for aspirin use in different clinical scenarios and provide recommendations on a case-by-case basis.

Key word: Aspirin - Prevention - Evidence

RESUMEN

Introducción: El ácido acetilsalicílico, o aspirina, es una de las herramientas farmacológicas más usadas en el cuidado de los pacientes cardiovasculares. Durante años se utilizó ampliamente en prevención primaria y secundaria para disminuir el riesgo cardiovascular. En los últimos tiempos su uso ha sido cuestionado, con nuevos ensayos en diferentes escenarios dentro de la patología cardíaca, como la enfermedad vascular periférica, el accidente cerebrovascular, la prevención primaria en el contexto del tratamiento médico moderno, o en el paciente con un síndrome coronario agudo y necesidad concomitante de anticoagulación. A su vez, nuevos estudios cuestionan la necesidad de mantener la aspirina durante 12 meses junto a una tienopiridina luego de un síndrome coronario agudo, y proponen esquemas abreviados.
En esta revisión, evaluamos la evidencia detrás de las indicaciones actuales del uso de aspirina en diferentes escenarios clínicos, y formulamos recomendaciones en cada uno de los casos.

Palabras clave: Aspirina - Prevención - Evidencia

INTRODUCTION

The use of acetylsalicylic acid, aspirin, began almost 200 years ago, initially as an antipyretic agent. Yet, its antithrombotic properties were discovered around 1960. (1) The main mechanism of action, which confers its antiplatelet effect, involves interfering with the production of agents that promote platelet aggregation, mainly thromboxane A2 (TXA2). Aspirin inhibits both cyclooxygenase 1 and 2 (COX-1 and COX-2) but is more potent in blocking COX-1 than COX-2, thus inhibiting the synthesis of prostacyclins and TXA2 from arachidonic acid. (2) As a result, TXA2-induced platelet aggregation and vasoconstriction are significantly reduced.

Over the past 20 years, we have witnessed several changes in the trend for the use of aspirin in the cardiology field. The molecule shifted from protecting against the occurrence of myocardial infarction (MI) (3) to being indicated only in selected cases. On the other hand, in the setting of dual antiplatelet therapy in acute coronary syndromes, the questionable indication of aspirin for 12 months has changed to considering discontinuation after 3 months and continuing with P2Y12 inhibitors monotherapy. In the scenario

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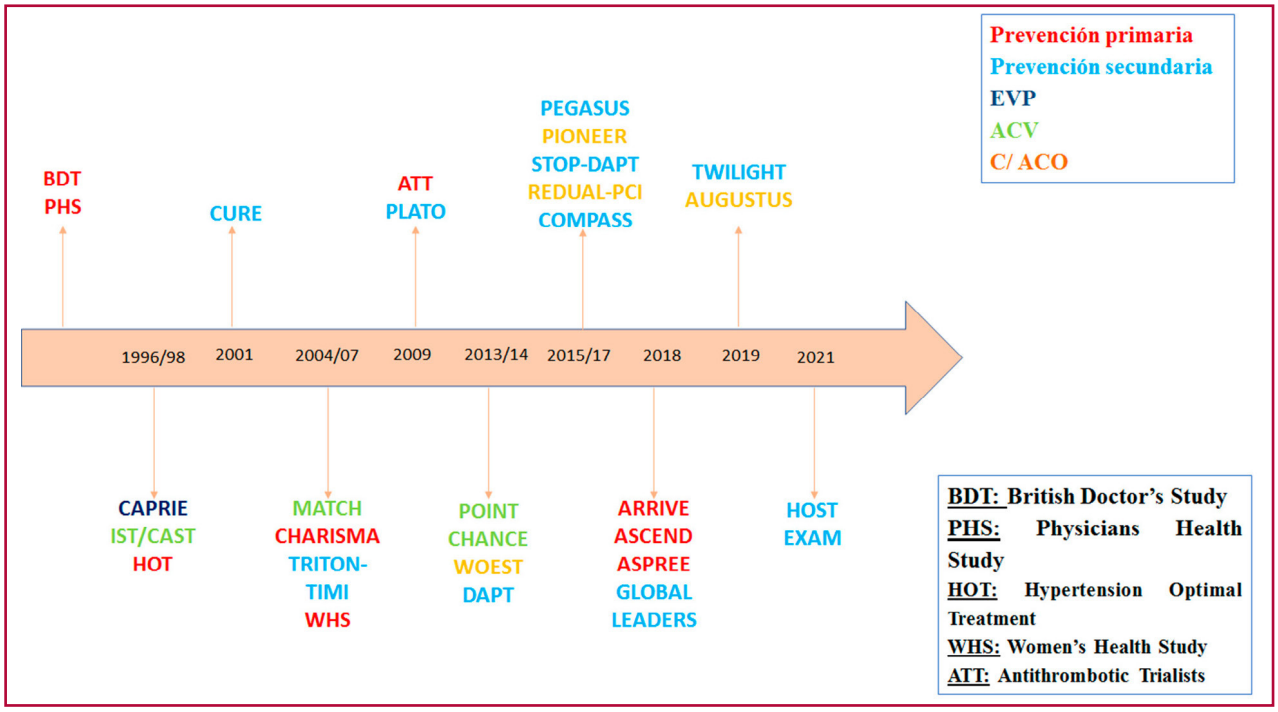

PVD: peripheral vascular disease. OAC: oral anticoagulant.

Table 1. Timeline of the main clinical trials of aspirin use. BDT: British Doctor's Study. PHS: Physicians Health Study. HOT: Hypertension Optimal Treatment. WHS: Women's Health Study. ATT: Antithrombotic Trialists.

of combination therapies with anticoagulants in patients with atrial fibrillation, aspirin moved from being part of a standard triple therapy regimen to being the first drug to be discontinued from the combination, while dual regimens are preferred due to excessive bleeding with no apparent benefits. (Figure 1)

The aim of this review is to present the rationale behind these trends, discussing the design and results of the trials involved in these decisions.

Primary prevention

The main evidence for the benefit of aspirin in primary prevention patients came from a meta-analysis published in 2009, (4) which included 6 randomized trials and 95 000 low cardiovascular risk patients. This meta-analysis showed a 12% reduction in the risk of major cardiovascular events, but the absolute risk reduction was of only 0.06%, mainly driven by a reduction in non-fatal MI. The event rate was very low in both groups (0.51% aspirin group, 0.57% placebo group), and the number of patients needed to treat to prevent an event was of 1666. In contrast, the use of aspirin significantly increased the risk of bleeding in these patients by 54% (relative risk), but once again the number of events was very low: 0.10% of bleeding events in the aspirin arm vs. 0.07% in the placebo arm. The studies included in this meta-analysis were published between 1988 and 2005, so there was a need to perform up-to-date randomized studies, and ideally in different populations to try to identify any group of special interest; thus, 3 studies published in 2018 revisited the topic.

The ARRIVE study (5) randomized male patients > 55 years and female patients > 60 years with moderate cardiovascular risk, based on the presence of the following risk factors:

- Total cholesterol > 200mg/dL or LDL-cholesterol > 130 mg/dL in men, or > 240 mg/dL / 160 mg/dL in women.
- Cigarette smoking in the past 12 months
- HDL-cholesterol < 40 mg/dL
- Hypertension (HTN) with systolic blood pressure (SBP) >140 mm Hg or receiving medication
- Family history of cardiovascular disease

The primary endpoint was a composite outcome of MI, stroke, cardiovascular death, unstable angina, or transient ischemic attack (TIA). More than 12 000 patients were enrolled, with a mean follow-up of 5 years. There were no differences in the primary endpoint (4.29% vs. 4.48%; HR 0.96, 95% CI 0.81–1.13, p = 0.6) or in any of the individual cardiovascular events. Twenty-nine percent of the population did not complete follow-up in both arms, but the results in the per-protocol analysis did not differ, except for a reduction in non-fatal MI. Gastrointestinal bleeding events (mostly mild) were higher in the aspirin group (0.97%

vs. 0.46%; HR 2.11, 95% CI 1.36–3.28; p = 0.0007). Interestingly, despite being patients specifically selected for their risk factors to include a population with moderate cardiovascular risk, the event rate was lower than expected in both groups, because of the intensive management of these risk factors. In brief, the study found no benefit in the use of aspirin in this population, and a greater trend toward bleeding.

The ASCEND study (6) was a randomized, double-blind, multicenter study designed to evaluate the effect of aspirin vs. placebo for primary prevention in 15 480 patients with diabetes, >40 years. Aspirin reduced the incidence of the composite final endpoint (8.5% vs 9.6%; p = 0.01) but did not reduce the rate of cardiovascular mortality or all-cause mortality. The rate of bleeding events, which included intracranial, ocular and gastrointestinal bleeding, increased (4.1% vs. 3.2%; p = 0.003), with most of the excess being gastrointestinal bleeding. The number necessary to treat to prevent one cardiovascular event was 91 patients. The study was interpreted as negative by the authors, as they found no net benefit with the use of aspirin.

The ASPREE study (7) was a randomized, controlled, double-blind trial comparing aspirin vs. placebo for primary prevention of a composite endpoint of death, dementia, or persistent physical disability in patients > 70 years. There were no differences in the rate of cardiovascular events including cardiovascular death, MI and stroke. The risk of major bleeding was increased by aspirin (3.8% vs. 2.8%, p < 0.001), with most of the excess being gastrointestinal bleeding and intracranial bleeding. All-cause mortality was strikingly higher in the aspirin group (HR 1.14, 95% CI 1.01-1.29), apparently linked to increased non-cardiovascular events such as cancer.

In brief, these 3 recent trials showed similar results: some reduction in the rate of ischemic events with increased risk of bleeding and no net clinical benefit even in selected higher-risk populations. The indiscriminate use of aspirin in primary prevention seems to be strongly questioned by the evidence. In this regard, Dehmer et al. conducted a study to analyze the risks and benefits of aspirin use in primary prevention in different age groups. The model showed a net benefit when aspirin was used in patients between 40 and 59 years, when their estimated 10-year cardiovascular risk was >10%, and not in patients > 59 years. (8) Based on this information, the US Preventive Services Task Force concluded with moderate certainty that initiating aspirin use in adults 60 years or older had no net benefit. (9)

Patients with indication of oral anticoagulation

The ASPECT-2 study (10) and the WARIS trial (11) demonstrated that anticoagulants in combination with aspirin or given alone, were superior to aspirin alone in preventing ischemic events, but this benefit was counterbalanced by higher risk of bleeding. From a pharmacodynamic point of view, anticoagulation has an impact on platelet aggregation, a phenomenon demonstrated with both vitamin K antagonists and direct oral anticoagulants.

In general, all guidelines recommend against the use of aspirin for primary prevention in patients who are anticoagulated for another reason.

Aspirin for primary prevention

There is no evidence for routine use of aspirin.
The use of aspirin could be considered in patients between 40-70 years with high ischemic risk and low bleeding risk.
Its use is not recommended in patients requiring anticoagulation for other diseases.

Secondary prevention

After an acute coronary syndrome

Aspirin, in combination with an oral P2Y12 receptor inhibitor (i.e. clopidogrel, prasugrel or ticagrelor), remains a cornerstone for the treatment of patients with acute coronary syndromes (ACS). The benefit of their use at the time of acute MI and during hospitalization has not been questioned yet. The standard duration of treatment is 12 months; nevertheless, several strategies modifying this duration have been developed over the past years.

In most large trials on dual antiplatelet therapy (DAPT), treatment continued for 12 months, (12-14) following which the P2Y12 inhibitor was discontinued, and aspirin was continued for life. The benefit of DAPT is dual, by reducing the risk of stent thrombosis (ST) and the events associated with new atherosclerotic plaque rupture. However, extended duration DAPT clearly confers an increased risk of bleeding with a negative impact on patients' outcome. Therefore, strategies are constantly being sought to reduce bleeding events, without losing anti-ischemic protection. Regarding the risk of ST, the development of new devices (15, 16) has reduced the dependence on DAPT for long periods. Thinner platforms, as well as the use of less pro-inflammatory or re-absorbable polymers, allow a faster re-endothelialization, reducing the risk of ST as a result of less metal exposure. While with the first-generation of drug-eluting stents, 1 year of DAPT has been recommended to prevent late ST, with the latest-generation drug-eluting stents, DAPT duration can be significantly reduced.

On the other hand, improvements in coronary stent implantation techniques reduce the risk of complications. The correct device deployment guided by intravascular ultrasound (IVUS) (17, 18) or optical coherence tomography (OCT) (19) reduces the interventions of the treated lesion. New techniques for treating bifurcation lesions (20) with a single device or with the minimum necessary apposition of two stents also contribute to reduce events.

With the development of more potent drugs such as prasugrel and ticagrelor, monotherapy with these agents began to be considered, with discontinuation of aspirin after the acute period of the greatest thrombotic risk. The most important argument supporting their use are the studies showing that P2Y12 inhibitors can reduce TxA2 production to the same extent as aspirin, making aspirin use redundant when combined with a more potent P2Y12 inhibitor. In vitro studies also demonstrated that platelet aggregation did not change significantly when aspirin was added to a P2Y12 inhibitor. (21) Consequently, the "less-is-more" concept has been proposed to mitigate the bleeding risk of DAPT while preserving antithrombotic efficacy.

The STOP-DAPT study (22) sought to test the noninferiority hypothesis of 1-month DAPT compared with the standard 12-month DAPT for a composite endpoint of cardiovascular and bleeding events. Patients were randomly assigned to 1-month DAPT with aspirin and clopidogrel followed by monotherapy with clopidogrel or to 12-month DAPT with aspirin and clopidogrel. The results showed that 1-month DAPT was both not inferior and superior to 12-month DAPT for the primary endpoint of ischemic and bleeding events; there were no differences in the rate of ischemic events and bleeding events rate was lower. However, in the exclusive analysis of patients with ACS, monotherapy with clopidogrel failed to demonstrate noninferiority versus DAPT.

The TWILIGHT study (23) evaluated the effect of ticagrelor as monotherapy compared with ticagrelor plus aspirin in patients undergoing scheduled or urgent percutaneous coronary intervention (PCI) after overcoming the first 3 months of treatment with ticagrelor plus aspirin without complications. The primary endpoint was BARC type ≥ 2 bleeding. The incidence of the primary endpoint was 4.0% among patients in the ticagrelor plus placebo arm and 7.1% in the ticagrelor plus aspirin arm (HR 0.56, 95% CI 0.45-0.68; p <0.001). The incidence of all-cause mortality, non-fatal MI or non-fatal stroke was 3.9% in both groups. The prespecified sub-analyses in the population with acute coronary syndrome, diabetes and complex angioplasty consistently showed a reduction in bleeding events and no sign of an increase in ischemic events. The TICO study (24) used a similar strategy in 3056 ACS patients treated with drug-eluting stents in South Korea, with similar results.

The GLOBAL LEADERS trial (25) evaluated the effects of 24-month monotherapy with ticagrelor (associated with aspirin only for the first month) versus standard 12-month DAPT in 15 991 patients undergoing PCI. The primary outcome, a composite of all-cause death or non-fatal new Q-wave MI at 24 months, was similar in both study arms (3.81% vs. 4.37%; RR 0.87, CI 95% 0.75-1.01; p=0.073). BARC type 3 or 5 bleeding at 24-month follow-up was similar in both arms (2.04% vs. 2.12%; RR: 0.97, 95% CI 0.78-1.2; p = 0.77); however, a substantial lack of adherence to the experimental treatment may have affected the statistical power of the study. Death from cardiac and noncardiac causes was similar in both groups.

Another strategy may be to shorten the duration of DAPT to less than 12 months and then continue with monotherapy with aspirin. There are currently more than 20 randomized controlled trials that test different DAPT duration strategies and thus challenge the recommended 12-month standard. These studies can be grouped into two classes: those that prove the non-inferiority of reducing DAPT duration to 3 or 6 months and those that prove the superiority of extending DAPT duration beyond 12 months. In brief, the results seem to show that longer DAPT treatment is associated with a significant benefit in terms of stent related events (thrombosis) and non-stent related ischemic events (plaque accidents with clinical impact), but also with a significant increase in bleeding. On the contrary, shortening DAPT to less than 1 year is associated with a significant reduction in bleeding events, with more thrombotic events. The impact of these strategies in terms of total mortality or cardiovascular mortality remains controversial.

Aspirin in ACS

Aspirin is still necessary during the acute period (1 to 3 months).
The combination of aspirin with P2Y12 inhibitors during the first 12 months is the treatment with the best evidence available.
Aspirin could be discontinued after month 3, continuing with monotherapy with ticagrelor in patients with high bleeding risk.

Chronic coronary syndrome

Aspirin is the antiplatelet agent most widely used for secondary prevention of coronary events; the evidence is found in pooled analyses of trials conducted several decades ago, which showed benefit. The strategies evaluated nowadays to enhance long-term protection include: 1) combination of aspirin with a P2Y12 inhibitor; 2) combination with low doses of an anticoagulant; 3) replacement using a P2Y12 inhibitor as monotherapy.

The DAPT trial (26) evaluated DAPT prolongation with aspirin plus a P2Y12 inhibitor beyond 12 months after an ACS vs. conventional aspirin therapy after that period. Patients treated with drug-eluting stents were included (43% due to ACS) after having completed 12 months of treatment with clopidogrel or prasugrel, and aspirin, without presenting ischemic or bleeding events. Continuous treatment with thienopyridines, compared with placebo, reduced ST rates (0.4% vs. 1.4%; HR 0.29, 95% CI 0.17-0.48; p <0.001), as well as the composite of ischemic events (4.3% vs. 5.9%; HR 0.71, 95% CI 0.59-0.85; p <0.001). The rate of MI was significantly lower with P2Y12 inhibitor

treatment than with placebo (2.1% vs. 4.1%; HR 0.47, CI 95% 0.37-0.61,p <0.001), but the rate of moderate or severe bleeding events increased with continuous treatment (2.5% vs. 1.6%; p=0.001). The PEGASUS-TIMI 54 study (27) included patients with a history of MI > 1 year treated with aspirin, who were randomly allocated to three groups: ticagrelor at a dose of 90 mg twice daily, ticagrelor 60 mg twice daily, or placebo. Compared with placebo, the two doses of ticagrelor reduced the rate of the primary efficacy endpoint (composite of cardiovascular death, MI or non-fatal stroke) at 3 years: the incidence was 7.85% in the group that received 90 mg of ticagrelor twice daily; 7.77% in the group that received 60 mg of ticagrelor twice daily and 9.04% in the placebo group (HR for ticagrelor 90 mg versus placebo: 0.85, 95% CI 0.75-0.96, p = 0.008; HR for ticagrelor 60 mg vs. placebo: 0.84; 95% CI: 0.74-0.95; p = 0.004). TIMI major bleeding rates were higher with ticagrelor (2.60% with 90 mg and 2.30% with 60 mg) than in placebo arm (1.06%) (p <0.001 for each dose vs. placebo); the rates of intracranial bleeding or fatal bleeding in the three groups were similar: 0.63%, 0.71%, and 0.60%, respectively. Given the similar reduction of ischemic events with ticagrelor 90 mg or 60 mg, and the significant difference in bleeding events, the authors recommend the use of the 60 mg dose of ticagrelor in combination with aspirin over the 90 mg dose.

The COMPASS trial (28) compared two strategies with rivaroxaban (with and without aspirin) with chronic use of aspirin for secondary prevention of atherothrombotic events in patients with a history of stable cardiovascular disease (90.6% with coronary artery disease and 27.3% with peripheral vascular disease). Patients were randomized to rivaroxaban 2.5 mg twice daily plus aspirin, rivaroxaban 5 mg twice daily, or aspirin alone 100 mg daily. At a mean follow-up of 23 months, the primary efficacy endpoint (a composite of cardiovascular death or nonfatal stroke or MI) occurred in 4.1% of the group of patients with rivaroxaban 2.5 mg and aspirin, in 4.9% of the group of patients with rivaroxaban alone and in 5.4% of the group of patients with aspirin alone (rivaroxaban plus aspirin vs. aspirin, HR 0.76, 95% CI 0.66-0.86, p < 0.001; rivaroxaban alone vs. aspirin, HR 0.90, 95% CI 0.79-1.03, p = 0.12). The benefit was driven by the reduction in the rate of cardiovascular death and stroke, without a significant reduction in the risk of MI (although the number of MI was lower). Major bleeding was more common in the rivaroxaban plus aspirin group than in those who received aspirin alone (3.1% vs. 1.9%; HR 1.70, 95% CI 1.40-2.05, p < 0.001), due mainly to gastrointestinal bleeding, without significant differences in fatal bleeding or intracranial bleeding.

The HOST EXAM study (29) included patients who maintained dual antiplatelet therapy without clinical events for 6-18 months after percutaneous coronary intervention with drug-eluting stents. Patients were randomly assigned (1:1) to receive monotherapy with clopidogrel 75 mg once daily or aspirin 100 mg once daily for 24 months. The primary endpoint (all-cause death, non-fatal MI, stroke, ACS, and BARC type ≥ 3 bleeding) occurred in 5.7% of patients in the clopidogrel group and in 7.7% in the aspirin group (HR 0.73, 95% CI 0.59–0.90, p = 0.0035). The evaluation of events individually found no differences in non-fatal MI rate (0.7 % vs 1.0 %, p = 0.15), but the rate of stroke (0.7 % vs 1.6 %, p = 0.002) and readmissions for ACS (2.5 % vs 4.1 %, p = 0.001) were significantly different. Major bleeding was more common int the aspirin group (2% vs 1.2%).

An exploratory analysis of the GLOBAL LEADERS trial compared aspirin vs. ticagrelor during the second year of treatment. The results showed a reduction in MI (HR 0.54, 95% CI 0.35-0.87, p = 0.013) and stent thrombosis, with no differences in BARC type ≥ 3 bleeding.

Aspirin in chronic coronary syndrome

Aspirin has demonstrated benefits in reducing ischemic events.

Combination with clopidogrel or low-dose ticagrelor further reduces recurrent ischemic events at the cost of increased bleeding.

Combination with rivaroxaban 2.5 mg twice daily reduces ischemic events but increases bleeding events.

Clopidogrel and ticagrelor seem to be more effective alternatives for ischemic protection with similar bleeding risks.

Peripheral vascular disease

The 10-year risk of cardiovascular events in patients with peripheral vascular disease is twice as high as that of the general population. (30) Therefore, they represent a population that requires aggressive control of cardiovascular risk factors.

Aspirin remains the most commonly used drug to prevent events in this population. However, the main evidence supporting this recommendation comes from the Antiplatelet Trialists' Collaboration (ATT). (3) This meta-analysis found a 22% reduction in vascular events associated with antiplatelet therapy compared with the control group. However, of the 26 studies that contributed to this conclusion, only 4 included a monotherapy arm with aspirin. Of 438 vascular events contributing to the analysis, only 46 occurred in trials examining aspirin monotherapy and were published before 1990. A relatively more recent meta-analysis published by Berger et al. (31) in patients with peripheral vascular disease specifically, found RR 0.75 for the composite endpoint of MI, stroke, and cardiovascular death, but with a non-significant 95% CI (0.48 - 1.18). However, a significant reduction in the risk of non-fatal stroke (RR 0.64, 95% CI 0.42-0.99) was observed.

In asymptomatic peripheral vascular disease, the POAPAD study (32) found no benefit in aspirin use compared with placebo in diabetic patients. The same finding was reported in the population-based AAA study (33) in patients without peripheral vascular disease, but with a low ankle-brachial index.

The CAPRIE study, (34) published 26 years ago, randomized more than 19 000 patients to receive 325 mg aspirin or 75 mg clopidogrel for secondary prevention, with a composite primary endpoint of stroke, MI, or vascular death. The trial showed a statistically significant (although not clinically relevant) relative reduction of 8.7% in the clopidogrel group (absolute reduction of 0.5%). In a stratified analysis according to the predominant previous condition (stroke, MI, or peripheral vascular disease), there were no differences between aspirin and clopidogrel in patients with a history of stroke or MI. In contrast, in the group with previous peripheral vascular disease, there was a relative risk reduction of 24% in the clopidogrel group. The results of the CAPRIE study seem to indicate that clopidogrel would be more effective than aspirin in secondary prevention of new events in patients with a history of peripheral vascular disease. Thereafter, the EUCLID trial (35) compared ticagrelor vs. clopidogrel in this population and found no differences in the rate of vascular events (10.8% vs. 10.6%), or bleeding events.

There is little evidence for the use of dual antiplatelet therapy with aspirin and clopidogrel in this group of patients. In a post hoc subgroup analysis of the CHARISMA study, (36) in patients with previous peripheral vascular disease, dual antiplatelet therapy decreased the rate of non-fatal MI at the cost of a two-fold increase in the risk of major or fatal bleeding. However, because of the low number of patients, the negative result of the overall trial, and the post hoc nature of this analysis, this result should be considered as hypothesis-generating and not as a definitive conclusion.

The COMPASS study explored the benefit of dual therapy with antiplatelet therapy and anticoagulation for secondary prevention. The pre-specified COMPASS-PAD substudy, (37) randomized 7470 of these patients for secondary prevention to 3 groups: rivaroxaban 2.5mg twice daily plus aspirin 100 mg (group 1), rivaroxaban 5mg twice daily (group 2), or aspirin 100 mg (group 3). The combination therapy (group 1) significantly reduced the composite endpoint of stroke, MI or cardiovascular death, by 28% (relative risk reduction), and major adverse limb events including amputation by 46% compared with the use of aspirin alone. The use of rivaroxaban (group 2) compared with aspirin alone did not significantly reduce the composite endpoint but reduced major adverse limb events by 33%. There was an increase in major bleeding, mainly gastrointestinal bleeding, in group 1 and group 2 compared with group 3 (61% and 68%, respectively).

In a similar vein to the COMPASS trial, the VOYAGER-PAD study (38) evaluated the use of rivaroxaban 2.5mg twice daily plus aspirin in patients with peripheral vascular disease immediately after revascularization and demonstrated a 24% reduction in the composite endpoint of acute limb ischemia, major amputation, MI, stroke or cardiovascular death, mainly due to a reduction in acute vascular events (limb ischemia and amputations). This was counterbalanced in part by a 42% increase in major bleeding events.

Aspirin in patients with coronary event and need for anticoagulation

The indication of aspirin comes from experience rather than from evidence.
The use of clopidogrel instead of aspirin could be considered, based on the evidence available.
Combination with rivaroxaban 2.5 mg twice daily reduces ischemic events, especially limb events, at the cost of increasing bleeding events.

Ischemic stroke

The use of aspirin following a stroke or transient ischemic attack (TIA) was initially evaluated in two large-scale trials performed in 1997, the IST trial (39) and the CAST trial (40). Aspirin significantly reduced stroke recurrence, and even cardiovascular death, which provided the starting point for the routine use of aspirin following ischemic stroke.

In 2009 an ATT meta-analysis (41) encompassing 10 trials demonstrated that long-term use of aspirin reduced vascular events, nonfatal AMI, coronary events, and recurrence of stroke, but increased the risk of hemorrhagic stroke and gastrointestinal bleeding, with a favorable benefit-risk profile. (42)

As for the dose to be used, another analysis conducted by the same group (3) found no benefit in trials using < 75 mg of aspirin daily, but higher doses produced benefit. As the risk of bleeding increases with higher doses, the dose generally used ranges between 75-150mg, the most frequent being 100mg. Dual antiplatelet therapy with aspirin and clopidogrel did not reduce vascular events in the subgroup of patients admitted for stroke in the CAPRIE study, as well as in the MATCH study (43), SPS3 study (44) and CHARISMA study, but increased bleeding events. The CARESS study (45) found a reduction in the incidence of cerebral microembolism detected by transcranial Doppler ultrasound, with the use of dual antiplatelet therapy in patients with symptomatic carotid stenosis.

However, dual antiplatelet therapy was initiated later after the index event in all these trials. Two trials which started dual antiplatelet therapy within 12-24 h of the index event, the POINT trial (46) and the CHANCE trial (47), demonstrated a reduction in cardiovascular events, primarily stroke recurrence, but little increase in bleeding, especially non-fatal events. The

CHANCE study was conducted in China, and evaluated patients with minor stroke or TIA, with a regimen of aspirin plus clopidogrel for 21 days and then clopidogrel monotherapy until day 90. A reduction of 32% in rate of recurrent ischemic or hemorrhagic stroke was observed, with no difference in the rate of moderate and severe bleeding events at 90 days. The POINT study, conducted in many countries, demonstrated a 25% reduction in the composite endpoint of stroke, MI or vascular death using the same regimen, with a twofold increase in major bleeding events (0.9% vs. 0.4%).

The evidence shows that the greatest risk of recurrent ischemic events occurs within 30 days after stroke, while the risk of bleeding increases primarily between 30-90 days; thus, there seems to be a benefit of early initiation of dual antiplatelet therapy for a limited period.

Ticagrelor has been evaluated in this setting in the SOCRATES study (48), in which patients were randomly assigned to receive ticagrelor or aspirin for 90 days after a mild or moderate stroke, with no benefit in terms of reduction of ischemic events. The THALES study (49) included 11 016 patients who were randomly assigned to receive ticagrelor-aspirin or aspirin alone after a mild or moderate stroke for 30 days. The combination therapy reduced the composite endpoint of death or recurrent stroke by 17%. Severe bleeding occurred in 0.5% in the ticagrelor–aspirin group and in 0.1% in the aspirin group ($p = 0.001$).

According to previously stated, the use of dual antiplatelet therapy for 90 days after stroke is currently endorsed only in the presence of fixed intracranial stenosis, defined as severe stenosis (70-99%) of a major intracranial artery. (50) In patients with minor stroke or high-risk TIA, dual antiplatelet therapy with aspirin and clopidogrel is recommended during the first 21 days after the event.

In case of ischemic stroke secondary to arterial dissection, initial management is usually medical, while surgery and angioplasty are recommended for selected cases. Anticoagulation is widely used. (51, 52) However, this treatment has not been validated in randomized controlled trials. Therefore, anticoagulation or antiplatelet therapy with platelet inhibitors (aspirin, clopidogrel or the combination of aspirin and dipyridamole) are the recommended therapies for patients with cerebral artery dissections. (53, 54) In the case of anticoagulation, the use of vitamin K antagonists is recommended for 3 to 6 months with a target INR between 2-3. In patients with intracranial dissections, the use of antiplatelet therapy (aspirin) is prioritized over anticoagulation due to the higher risk of bleeding with anticoagulants. There is little evidence to recommend the use of direct anticoagulants in dissections of the cerebral arteries.

In conclusion, the current management of antiplatelet therapy in ischemic stroke is as follows:

- Antiplatelet therapy should be started early after the diagnosis of an ischemic cerebrovascular event, even if the etiological workup has not been completed.
- Low-risk TIA patients (ABCD2 score < 4): aspirin monotherapy.
- High-risk TIA patients (ABCD2 score ≥ 4): dual antiplatelet therapy with aspirin (loading dose of 160 to 325 mg followed by 75 to 100 mg) plus clopidogrel (loading dose of 300 mg followed by 75 mg/day) for the first 21 days after the event. Early initiation within 12-24 hours following the event.
- Minor stroke patients (NIHSS ≤ 5): dual antiplatelet therapy with aspirin plus clopidogrel for the first 21 days following the event.
- Stroke patients (NIHSS > 5): aspirin monotherapy.
- Patients with TIA or ischemic stroke secondary to extracranial dissections (common carotid artery, extracranial internal carotid artery, and vertebral artery in segments V1, V2 or V3), anticoagulation or antiplatelet therapy for 3-6 months is recommended.
- For patients with intracranial dissection with stroke or TIA without subarachnoid hemorrhage, the use of antiplatelet therapy is recommended over anticoagulation due to the higher risk of bleeding in this type of dissection.

Aspirin in stroke

The evidence for monotherapy demonstrates reduction in the rate of ischemic recurrences with net benefit in terms of bleeding risk. Early initiation after the diagnosis is recommended.
Combination therapy with clopidogrel in highrisk TIA patients and minor stroke patients within the first 21 days produces further reduction in thrombotic events at the cost of increasing bleeding events, and should be initiated early.
In selected patients, replacement of clopidogrel by ticagrelor confers greater protection, but at the cost of greater risk of bleeding.

Patients with a coronary event requiring anticoagulation

For many years, the standard of care for patients with a coronary event and need for anticoagulation was the triple regimen with aspirin, clopidogrel and vitamin K antagonists (VKA). The disadvantage of this combination has been the high rate of associated bleeding events. For this reason, strategies have been developed over the last 10 years to reduce these events. In the WOEST study, (55) the use of dual therapy with VKA and clopidogrel was associated with a reduction in bleeding events compared with triple therapy (any bleeding 19.4% vs 44.4% with triple therapy, HR 0.36, 95% CI 0.26-0.50, $p < 0.0001$), with no differences in ischemic events. The advent of direct oral anticoagulants (DOACs) resulted in the development of trials in this setting, which showed a benefit in terms of reduc-

tion of bleeding events when a VKA was replaced by a DOAC. In most of these studies, the use of aspirin in the DOAC arm (56-58) was limited to the length of hospital stay, and its use after hospitalization was associated with increased bleeding events. The AUGUSTUS study analyzed the outcome of patients with DOACs or VKAs who received aspirin. (56) The use of aspirin during the first 30 days was associated with a reduction in ischemic events and an increase in bleeding events. However, after 30 days, the use of aspirin had no impact on ischemic events and still increased bleeding events. Considering that the greatest risk of stent thrombosis or a new plaque rupture occurs within the first 30 days, it seems reasonable to think that in selected high-risk patients, the use of aspirin for the first 30 days may provide benefit.

Aspirin in peripheral artery disease

The evidence for its use in the hyperacute stage of the coronary event is not questioned.
The combination of clopidogrel and DOACs could be sufficient in most patients after discharge.
In selected patients, aspirin could be added during the first month.

CONCLUSIONS

Aspirin remains a useful tool to prevent recurrent cardiovascular events. Nevertheless, the current evidence shows that the scenarios in which aspirin is really effective are not as broad as we previously believed. The tendency is not to use aspirin in primary prevention, except for specific cases, and to reduce the time of its use in patients who simultaneously receive dual antiplatelet therapy or anticoagulation. Understanding the scenarios in which aspirin is really useful, and those in which it is harmful, will help us optimize the treatment of our patients.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

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REFERENCES

1. Weiss HJ, Aledort LM. Impaired platelet-connective-tissue reaction in man after aspirin ingestion. Lancet. 1967;2(7514):495-7. https://doi.org/10.1016/s0140-6736(67)91658-3.
2. Awtry EH, Loscalzo J. Aspirin. Circulation. 2000;101:1206-18. https://doi.org/10.1161/01.cir.101.10.1206.
3. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86. https://doi.org/10.1136/bmj.324.7329.71.
4. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-60. https://doi.org/10.1016/S0140-6736(09)60503-1.
5. Gaziano JM, Brotons C, Coppolecchia R, Cricelli C, Darius H, Gorelick PB, et al.. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet 2018;392:1036-46. https://doi.org/10.1016/S0140-6736(18)31924-X.
6. ASCEND Study Collaborative Group, Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, et al. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. N Engl J Med 2018;379:1529-39. 10.1056/NEJMoa1804988.
7. McNeil JJ, Nelson MR, Woods RL, Lockery JE, Wolfe R, Reid CM, et al; ASPREE Investigator Group. Effect of Aspirin on All-Cause Mortality in the Healthy Elderly. N Engl J Med 2018;379:1519-28. https://doi.org/10.1056/NEJMoa1803955.
8. Dehmer SP, O'Keefe LR, Evans CV, Guirguis-Blake JM, Perdue LA, Maciosek MV. Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: Updated Modeling Study for the US Preventive Services Task Force. JAMA 2022 ;327:1598-607. https://doi.org/10.1001/jama.2022.3385.
9. Preventive Services Task Force, Davidson KW, Barry MJ, Mangione CM, Cabana M, Chelmow D, Coker TR, et al.. Aspirin Use to Prevent Cardiovascular Disease: US Preventive Services Task Force Recommendation Statement. JAMA 2022;32:1577-84. https://doi.org/10.1001/jama.2022.4983..
10. van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE; Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) Research Group. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet 2002;360:109-13. 10.1016/S0140-6736(02)09409-6.
11. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med. 2002;347:969-74. https://doi.org/10.1056/NEJMoa020496.
12. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502. https://doi.org/10.1056/NEJMoa010746 .
13. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al; PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57. https://doi.org/10.1056/NEJMoa0904327.
14. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15. https://doi.org/10.1056/NEJMoa0706482.
15. Serruys PW, Farooq V, Kalesan B, de Vries T, Buszman P, Linke A, et al,. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, noninferiority trial. JACC Cardiovasc Interv. 2013;6:777-89. https://doi.org/10.1016/j.jcin.2013.04.011.
16. Maupas E, Lipiecki J, Levy R, Faurie B, Karsenty B, Moulichon ME, et al. Safety and efficacy outcomes of 3rd generation DES in an all-comer population of patients undergoing PCI: 12-month and 24-month results of the e-Biomatrix French registry. Catheter Cardiovasc Interv 2017;90:890-7. https://doi.org/10.1002/ccd.27081..
17. Gao XF, Ge Z, Kong XQ, Kan J, Han L, Lu S, et al; ULTIMATE Investigators. 3-Year Outcomes of the ULTIMATE Trial Comparing Intravascular Ultrasound Versus Angiography-Guided Drug-Eluting Stent Implantation. JACC Cardiovasc Interv 2021;14:247-57. https://doi.org/10.1016/j.jcin.2020.10.001.
18. Darmoch F, Alraies MC, Al-Khadra Y, Moussa Pacha H, Pinto DS, Osborn EA. Intravascular Ultrasound Imaging-Guided Versus Coronary Angiography-Guided Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis. J Am Heart Assoc 2020;9:e013678. https://doi.org/10.1161/JAHA.119.013678. .
19. Kuku KO, Ekanem E, Azizi V, Melaku G, Bui A, Meirovich YF,

Dheendsa A, Beyene S, Hideo-Kajita A, Lipinski MJ, Waksman R, Garcia-Garcia HM. Optical coherence tomography-guided percutaneous coronary intervention compared with other imaging guidance: a meta-analysis. Int J Cardiovasc Imaging 2018;34:503-13. https://doi.org/10.1007/s10554-017-1272-2.

20. Di Gioia G, Sonck J, Ferenc M, Chen SL, Colaiori I, Gallinoro E, et al. Clinical Outcomes Following Coronary Bifurcation PCI Techniques: A Systematic Review and Network Meta-Analysis Comprising 5,711 Patients. JACC Cardiovasc Interv 2020;13:1432-44. https://doi.org/10.1016/j.jcin.2020.03.054.

21. Armstrong PC, Leadbeater PD, Chan MV, Kirkby NS, Jakubowski JA, Mitchell JA, et al. In the presence of strong P2Y12 receptor blockade, aspirin provides little additional inhibition of platelet aggregation. J Thromb Haemost 2011;9:552-61. https://doi.org/10.1111/j.1538-7836.2010.04160.x.

22. Natsuaki M, Morimoto T, Yamamoto E, Shiomi H, Furukawa Y, Abe M, et al. One-year outcome of a prospective trial stopping dual antiplatelet therapy at 3 months after everolimus-eluting cobalt-chromium stent implantation: ShortT and OPtimal duration of Dual AntiPlatelet Therapy after everolimus-eluting cobalt-chromium stent (STOPDAPT) trial. Cardiovasc Interv Ther 2016;31:196-209. https://doi.org/10.1007/s12928-015-0366-9.

23. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. N Engl J Med. 2019;381:2032-42. https://doi.org/10.1056/NEJMoa1908419.

24. Hong SJ, Cho YH, Yun KH, Kim YH, Suh Y, Cho JY, et al; TICO Investigators. Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome: The TICO Randomized Clinical Trial. JAMA 2020;323:2407-16. 10.1001/jama.2020.7580.

25. Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, et al; GLOBAL LEADERS Investigators. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392:940-9. 10.1016/S0140-6736(18)31858-0..

26. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG,; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155-66. https://doi.org/10.1056/NEJMoa1409312.

27. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372:1791-800. https://doi.org/10.1056/NEJMoa1500857.

28. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O,et al; COMPASS Investigators. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med 2017;377:1319-30. https://doi.org/10.1056/NEJMoa170911829.

29. Koo BK, Kang J, Park KW, Rhee TM, Yang HM, Won KB, et al; HOST-EXAM investigators. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. Lancet 2021;397:2487-96. https://doi.org/10.1016/S0140-6736(21)01063-1.

30. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008;300:197-208. https://doi.org/10.1001/jama.300.2.197.

31. Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. JAMA 2009;301:1909-19. https://doi.org/10.1001/jama.2009.623. .

32. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, et al; Prevention of Progression of Arterial Disease and Diabetes Study Group; Diabetes Registry Group; Royal College of Physicians Edinburgh. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ. 2008 ;337:a1840. https://doi.org/10.1136/bmj.a1840.

33. Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, et al; Aspirin for Asymptomatic Atherosclerosis Trialists. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA 2010;303:841-8. 10.1001/jama.2010.221..

34. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348:1329-39. https://doi.org/10.1016/s0140-6736(96)09457-3.

35. Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P; EUCLID Trial Steering Committee and Investigators. Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. N Engl J Med 2017;376:32-40. https://doi.org/10.1056/NEJMoa1611688.

36. Cacoub PP, Bhatt DL, Steg PG, Topol EJ, Creager MA; CHARISMA Investigators. Patients with peripheral arterial disease in the CHARISMA trial. Eur Heart J 2009;30:192-201. https://doi.org/10.1093/eurheartj/ehn534..

37. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P; COMPASS Investigators. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet 2018;391:219-29. https://doi.org/10.1016/S0140-6736(17)32409-1.

38. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, et al. Rivaroxaban in Peripheral Artery Disease after Revascularization. N Engl J Med 2020;382:1994-2004. https://doi.org/10.1056/NEJMoa2000052.

39. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet 1997;349:1569-81.

40. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet 1997;349:1641-9.

41. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-60. https://doi.org/10.1016/S0140-6736(09)60503-1.

42. Hackam DG, Spence JD. Antiplatelet Therapy in Ischemic Stroke and Transient Ischemic Attack. Stroke 2019;50:773-8. https://doi.org/10.1161/STROKEAHA.118.023954.

43. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al; MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364:331-7. https://doi.org/10.1016/S0140-6736(04)16721-4.

44. SPS3 Investigators, Benavente OR, Hart RG, McClure LA, Szychowski JM, Coffey CS, Pearce LA. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. N Engl J Med. 2012;367:817-25. 10.1056/NEJMoa1204133. .

45. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, Ringelstein EB. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. Circulation 2005;111:2233-40. https://doi.org/10.1161/01.CIR.0000163561.90680.1C.

46. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ; Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, and the POINT Investigators. Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. N Engl J Med 2018;379(3:215-225. https://doi.org/10.1056/NEJMoa1800410..

47. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 2013;369:11-9. https://doi.org/10.1056/NEJMoa1215340.

48. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR; SOCRATES Steering Committee and Investigators. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. N Engl J Med 2016;375:35-43. https://doi.org/10.1056/NEJ-

Moa1603060.
49. Johnston SC, Amarenco P, Denison H, Evans SR, Himmelmann A, James S; THALES Investigators. Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA. N Engl J Med 2020;383:207-17. https://doi.org/10.1056/NEJMoa1916870.
50. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. Stroke 2021;52:e364-e467. https://doi.org/10.1161/STR.0000000000000375..
51. Cimini N, D'Andrea P, Gentile M, Berletti R, Ferracci F, Candeago RM, et al. Cervical artery dissection: a 5-year prospective study in the Belluno district. Eur Neurol 2004;52:207-10. https://doi.org/10.1159/000082037.
52. Menon RK, Markus HS, Norris JW. Results of a UK questionnaire of diagnosis and treatment in cervical artery dissection. J Neurol Neurosurg Psychiatry 2008;79:612. https://doi.org/10.1136/jnnp.2007.127639.
53. Biller J, Sacco RL, Albuquerque FC, Demaerschalk BM, Fayad P, Long PH, et al.; American Heart Association Stroke Council. Cervical arterial dissections and association with cervical manipulative therapy: a statement for healthcare professionals from the american heart association/american stroke association. Stroke 2014;45:3155-74. https://doi.org/10.1161/STR.0000000000000016.
54. Debette S, Mazighi M, Bijlenga P, Pezzini A, Koga M, Bersano A, et al. ESO guideline for the management of extracranial and intracranial artery dissection. Eur Stroke J 2021;6:XXXIX-LXXX-VIII. https://doi.org/10.1177/23969873211046475
55. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, et al; WOEST study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet 2013;381:1107-15. https://doi.org/10.1016/S0140-6736(12)62177-1..
56. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R; AUGUSTUS Investigators. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. N Engl J Med 2019;380:1509-24. https://doi.org/10.1056/NEJMoa1817083.
57. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. N Engl J Med 2016;375:2423-34. 10.1056/NEJMoa1611594
58. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al; RE-DUAL PCI Steering Committee and Investigators. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. N Engl J Med 2017;377:1513-24. https://doi.org/10.1056/NEJMoa1708454.