2025

Dual Antiplatelet vs Monotherapy as Secondary Prevention for Myocardial Infarction in Coronary Artery Disease

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Abstract

Introduction: Coronary artery disease (CAD) is the leading cause of death globally, with myocardial infarction (MI) being the biggest contributor. While aspirin monotherapy is standard for preventing ischemic events in CAD patients, dual antiplatelet therapy (DAPT) combining aspirin with P2Y12 inhibitors may offer greater efficacy. This review examines whether DAPT reduces MI incidence compared to aspirin monotherapy (AM), weighing the benefits against potential bleeding risks to guide optimal treatment strategies.

Methods: Inclusion criteria included studies in English, published between 2019 and 2024, randomized controlled trials (RCTs), systematic reviews, and meta-analyses. The following key terms we used in the PubMed database, "Platelet Aggregation Inhibitors" AND "Aspirin" AND "Myocardial Infarction" AND "Coronary Artery Disease" along with Boolean operators.

Results: Five studies met the inclusion criteria for this review, comprising four randomized control trials (RCTs) and one meta-analysis.

Discussion: DAPT with aspirin significantly reduces the incidence of myocardial infarction in adults with coronary artery disease compared to aspirin monotherapy. This is evident in high-risk groups such as those with diabetes and a history of PCI. However, DAPT also increases the risk of major bleeding, requiring careful patient selection and monitoring. Overall, while DAPT is beneficial for reducing MI, its use should be adjusted to the patient's risk profile, with ongoing research required to improve these strategies.

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INTRODUCTION

Coronary artery disease (CAD) remains the leading cause of mortality and morbidity worldwide. It is estimated that 17.9 million people died from coronary vascular disease (CVD) in 2019 illustrating 32% of global deaths with 85% due to myocardial infarction and strokes.[1] In the United States (US), CAD was the main cause of CVD death at 41.2% in 2020, followed by stroke at 17.3%, and other cardiovascular diseases making up 40% combined.[2] Acute myocardial infarction (MI) is one of the leading causes of death in developed countries with a prevalence of 3 million people worldwide. More than 1 million deaths occur from an MI in the US annually, emphasizing the need for effective secondary prevention strategies to improve patient outcomes.[3]

The pathophysiology of CAD involves the rupture of an atherosclerotic plaque. This initiates an inflammatory response of monocytes and macrophages, promoting thrombus formation and platelet aggregation. This causes a reduction of blood flow and oxygen supply to the myocardium. The inability to produce ATP in the mitochondria triggers an ischemic cascade and leads to apoptosis of the endocardium causing an acute MI. With antiplatelet therapy, platelet aggregation and thrombus formation are inhibited, becoming a mainstay in the prevention of ischemic events in patients with CAD.[3]

A common practice is using aspirin antiplatelet therapy for secondary prevention of MI, stroke, and CVD death in patients with CAD. However, the idea of purinergic receptor P2Y, G-protein coupled, 12 protein (P2Y12) inhibitors, such as clopidogrel and ticagrelor, has generated interest in investigating dual antiplatelet therapy (DAPT) as secondary prevention in ischemic events compared to aspirin monotherapy. DAPT includes aspirin combined with P2Y12 inhibitors. P2Y12 inhibitors block Adenosine diphosphate (ADP) receptors and aspirin inhibits cyclooxygenase (COX) enzymes preventing the expression of Glycoprotein IIb/IIIa (GP IIb/IIIa)

on platelet surfaces hindering platelet aggregation.[4] DAPT targets multiple pathways of platelet formation, suggesting greater efficacy in preventing MIs and considering DAPT as a mainstay for secondary prevention of acute coronary syndromes (ACS).[5]

Due to the synergistic mechanism of antiplatelet inhibition with DAPT, it is associated with an increased risk of bleeding. By inhibiting platelet aggregation, DAPT interferes with the primary mechanism of forming a platelet plug, reducing the body's ability to clot.[6] Assessing bleeding risks includes the patient's comorbidities, age, clinical assessment tools, and laboratory tests such as complete blood count and coagulation profile.[7] Current guidelines recommend DAPT for specific durations following percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or ACS events. The decision to implement DAPT as mainstay secondary prevention of ischemic events for patients with CAD requires a thorough evaluation of the risks versus benefits in individual care plans. The optimal regimen for secondary prevention in stable CAD remains an ongoing debate.[8]

This topic is important due to the need to decrease incidences of the leading cause of death worldwide by seeking enhanced secondary prevention strategies. This review aims to synthesize recent evidence to address whether dual antiplatelet therapy with aspirin reduces the incidence of myocardial infarction compared to aspirin monotherapy in adults with coronary artery disease. This includes assessing the balance between efficacy in preventing thrombotic events and associated bleeding risks. This review seeks to guide clinicians in optimizing antiplatelet therapy in CAD to enhance patient prognosis.

METHODS

Study Selection: A review of research articles was used comparing DAPT to aspirin monotherapy (AM) in adults with CAD. The inclusion criteria required the years 2019 to 2024, randomized control trials, systematic reviews, meta-analyses, free full text, and in the English

language. Additionally, these studies involved adults diagnosed with CAD, comparing the incidence of MI using antiplatelet therapy.

Search Strategy: PubMed database was used using the search strategy, "Platelet Aggregation Inhibitors" AND "Aspirin" AND "Myocardial Infarction" AND "Coronary Artery Disease". This populated 899 results. Filters were selected on the PubMed database and this populated 50 results. Furthermore, the following Boolean search query was used in PubMed, ((("Coronary Artery Disease"[Mesh] OR "CAD"[tiab] OR "Coronary Disease"[tiab] OR "Ischemic Heart Disease"[tiab] OR "Myocardial Ischemia"[tiab]) AND ("Adult"[Mesh] OR "Adults"[tiab] OR "Middle Aged"[Mesh] OR "Elderly"[tiab] OR "Aged"[tiab])) AND (("Aspirin"[Mesh] OR "Acetylsalicylic Acid"[tiab]) AND ("Antiplatelet Therapy"[Mesh] OR "Antiplatelet Agents"[tiab] OR "Clopidogrel"[tiab] OR "Ticagrelor"[tiab] OR "Prasugrel"[tiab]))) AND ("Myocardial Infarction"[Mesh] OR "Heart Attack"[tiab] OR "MI"[tiab] OR "Incidence"[tiab])) along with inclusion criteria. This populated seven results.

Data Selection: Data from the selected articles were independently reviewed. The information collected included study design, duration, population characteristics, the type of antiplatelet agents used, and the effects on the incidence of MI. These articles included patients with CAD, diabetes, and those undergoing PCI. Due to the irrelevance of some articles, five out of the seven articles were selected due to three articles not showing relevance to myocardial infarction incidence or DAPT therapy.

RESULTS

Five articles met the inclusion criteria. This was composed of four randomized control trials (RCT) and one meta-analysis. The studies evaluated different combinations of DAPT, primarily involving ticagrelor or clopidogrel combined with aspirin versus aspirin monotherapy (AM). To evaluate each article, a systematic approach was used to analyze study designs, methodologies, control groups, outcomes, and statistical results.

Steg et al[9] conducted a double-blind RCT using 19,220 patients. The treatment groups were those over the age of 50 with stable CAD and type 2 diabetes mellitus. Patients with previous MI or stroke were excluded. The intervention involved one group to receive either ticagrelor plus aspirin DAPT or placebo plus aspirin. Eligible patients were randomly assigned to each group in a double-blind manner. The primary efficacy outcome was reduction of cardiovascular death, MI, or stroke. The primary safety outcome was major bleeding defined by the thrombolysis in myocardial infarction (TIMI) criteria. The incidence of ischemic cardiovascular events was lower in the DAPT group 7.7% compared to the placebo group 8.5% (hazard ratio [HR]: 0.90; 95% confidence ratio [CI]: 0.81 to 0.99; P = 0.04). The risk of bleeding was 2.2% in the DAPT group and 1.0% in the placebo group (HR: 2.32; 95% CI: 1.82 to 2.94; P <0.001). Ticagrelor combined with aspirin DAPT reduced ischemic cardiovascular incidence compared to placebo plus aspirin. The DAPT group had an increased risk of major bleeding compared to placebo group. No significant difference was observed between the groups for fatal bleeding (HR: 1.90; 95% CI: 0.81 to 4.15; P = 0.11).

Vranckc et al[10] conducted a RCT using 15,968 patients post-PCI. The intervention involved ticagrelor monotherapy versus DAPT with aspirin combined with clopidogrel or ticagrelor. The treatment group included ticagrelor monotherapy who received ticagrelor 90 mg twice daily for one month after PCI. The control group received DAPT with aspirin 75 to 100 mg daily combined with clopidogrel 75 mg daily or ticagrelor 90 mg twice daily for 12 months. The primary end point was the composition of death or Q-wave MI within 24 months of the start of intervention. Ticagrelor monotherapy was 3.8% and DAPT was 3.7% (HR 1.02; 95% CI: 0.88 to 1.18; P =0.81) in preventing incidence of MI. Ticagrelor monotherapy was as effective as DAPT with aspirin preventing incidence of MI at 24 months. The second end point was bleeding events between the two treatment groups. There was a reduction in bleeding events in the ticagrelor monotherapy group compared to DAPT group (HR 0.85; 95% CI: 0.73 to 0.99; P =0.04).

Yuan et al[11] conducted a meta-analysis aiming to compare the efficacy and safety of aspirin monotherapy versus clopidogrel monotherapy. The article focused on clinical outcomes such as myocardial infarction, all-cause mortality, and major bleeding. Electronic databases were searched to identify studies comparing aspirin versus clopidogrel monotherapy in patients with CAD. The data analysis was conducted using RevMan software, odds ratios (OR) and 95% CI to calculate and interpret data. A total of 5,497 patients were treated with aspirin monotherapy and 2,544 patients were treated with clopidogrel monotherapy for the years 2003 to 2011. There was a total of six RCTs that met the inclusion criteria and were used in the meta-analysis. The primary end point was the reduction of myocardial infarction, cardiovascular death, and stroke (OR: 0.99; 95% CI: 0.47-2.10; P = 0.98). There was no significant difference between aspirin and clopidogrel in reducing the incidence of myocardial infection and cardiovascular mortality in patients with CAD. The reduction of myocardial infarction specifically showed no significant difference in the occurrence of an MI (OR: 0.84; 95% CI: 0.52 to 1.36; P = 0.48). The results suggest both aspirin and clopidogrel monotherapy are similarly effective in managing adverse clinical outcomes in CAD patients.

Bhatt et al[12] conducted a RCT using ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI) trial. The study design is a phase 3 randomized, double-blinded, placebo-controlled trial conducted across 1,315 sites in 42 countries. The eligibility criteria included patients who were 50 years or older with type II diabetes, receiving anti-hyperglycemic medications for at least six months with stable CAD. They also had to have one of the following procedures, PCI, CABG, or documented angiographic stenosis of 50% or more in at least one coronary artery. The treatment groups included DAPT ticagrelor 60 mg twice daily with combined low-dose aspirin and a placebo plus aspirin group. The primary endpoint was investigating the incidence of cardiovascular death, MI, or stroke. The DAPT and placebo group resulted in 404 out of 5,558 patients (7.3%) and 480 out of

5,596 patients (8.6%) respectively to experience cardiovascular event (HR 0.85; 95% CI: 0.74 to 0.97; P = 0.013). The net clinical benefit resulted in 519 out of 5,558 patients (9.3%) in those with DAPT and 617 out of 5,596 patients (11.0%) in those with AM to experience cardiovascular event (HR 0.85; 95% CI: 0.75 to 0.95; P = 0.005). In patients with diabetes, stable coronary artery disease, and a history of previous PCI, adding ticagrelor to aspirin reduced the incidence of cardiovascular death, myocardial infarction, and stroke compared to AM.

Tomaniak et al[13] conducted RCT within the GLOBAL LEADERS framework, involving approximately 15,900 patients undergoing PCI using intention to treat method. The involved two age groups, patients younger than 75 years old and those older than 75 years of age. The intervention involved two antiplatelet strategies of one group with one month of aspirin plus ticagrelor DAPT followed by 23 months of ticagrelor monotherapy, and the reference group with 12 months of DAPT only. The primary end point was a composite of all-cause death or Q-wave MI. The statistical analysis focused on event rates, particularly in patients aged 75 and above. The primary endpoint occurred in 7.2% of elderly patients in the experimental group versus 9.4% in the reference group (HR 0.75; 95% CI: 0.58 to 0.99; P = 0.041). All cause death was lower in the experimental group (5.7% vs 7.9%; P = 0.027). There were no significant differences in bleeding rates. The effectiveness of ticagrelor monotherapy compared to the reference treatment did not vary significantly between elderly and younger patients in terms of reducing all-cause mortality or new Q-wave MI. However, among elderly patients specifically, ticagrelor monotherapy was associated with better outcomes, including lower rates of mortality and adverse events, but these benefits were not significantly different when compared to younger patients.

DISCUSSION

The investigation of DAPT with aspirin compared to AM in adults with CAD addresses a critical aspect of secondary prevention in this high-risk population. Existing literature emphasizes the benefits and disadvantages of DAPT concerning its impact on MI, one of the primary causes of

death in the United States.[2] There is heightened discussion regarding MI incidence and associated bleeding risks with DAPT in patients with CAD. This article integrates findings from key studies to provide a comprehensive understanding of the current evidence that is crucial for guiding clinical practice.

Efficacy of DAPT in Reducing Myocardial Infarction: The evidence gathered from the reviewed studies indicate a complex picture regarding the efficacy of DAPT in reducing MI incidence compared to AM. The data demonstrates that DAPT with ticagrelor and aspirin is more effective than AM in reducing ischemic cardiovascular events, including myocardial infarctions. Specifically, DAPT reduced the incidence of ischemic events to 7.7%, compared to 8.5% in patients on AM, indicating a modest but significant benefit in using DAPT to decrease ACS events.[9] Furthermore, the overall net clinical benefit was also greater with the group using DAPT at 9.3% of patients experiencing cardiovascular events versus 11.0% in the AM group.[12] This further supports evidence in DAPT reducing ACS risk. This highlights evidence of DAPT's protective effects against ischemic cardiac events due to the synergistic inhibition of platelet aggregation by P2Y12 inhibitors and aspirin.

However, Vranckx et al. (2021) and Tomaniak et al. (2020) found that ticagrelor monotherapy was as effective as DAPT preventing MI post-PCI. One study showed that ticagrelor monotherapy post-PCI was as effective as DAPT in preventing MI within 24 months (3.8% vs. 3.7% HR 1.02; 95% CI: 0.88 to 1.18; P =0.81).[10] This indicated that while DAPT is beneficial, the duration and combination of antiplatelet agents might need to be optimized to balance efficacy and safety in patients post-PCI. Additionally, the meta-analysis by Yuan et al (2019) found no significant difference between in MI incidence between aspirin and clopidogrel monotherapy, suggesting that the choice of antiplatelet agent may be less critical than previously thought for certain patient populations.

Bleeding Risks Associated with DAPT: The increased risk of bleeding with DAPT is a major concern. One study showed that there was a higher incidence of TIMI major bleeding criteria in the DAPT group compared to the placebo group (2.2% vs. 1.0% HR: 2.32; 95% CI: 1.82 to 2.94; P <0.001).[9] This finding suggest that the heightened bleeding risk emphasizes the need for careful patient selection and monitoring, especially in populations at higher risk of bleeding outcomes.

Additionally, one study noted that ticagrelor monotherapy resulted in fewer bleeding events compared to DAPT (HR 0.85; 95% CI: 0.73 to 0.99; P = 0.04).[10] This finding may suggest that monotherapy might be a safer alternative in certain clinical scenarios for preventing bleeding risk. These findings highlight the importance of individualized treatment plans that consider both thrombotic and bleeding risks.

Comparative Effectiveness of Antiplatelet Agents: One study found no significant difference in the reduction of MI and cardiovascular mortality between clopidogrel monotherapy and aspirin monotherapy in patients with stable CAD (OR: 0.99; 95% CI: 0.47-2.10; P = 0.98).[11] This may suggest that both agents are similarly effective when used as monotherapy, reinforcing the potential benefits of DAPT in targeting multiple pathways to achieve better outcomes.

Furthermore, patients who either received P2Y12 monotherapy or DAPT did not vary significantly in terms of reducing all-cause mortality or MI, and the effect was not dependent on age.[13] This supports the idea that DAPT overall offers benefits in reducing major adverse cardiovascular events in high-risk subgroups, including those with comorbidities and prior revascularization procedures. This also concludes that the effectiveness of DAPT is consistent across different age groups, meaning that age does not significantly alter the treatment's impact on mortality or MI.[13]

Clinical Application: Given the evidence, the following recommendations can be made. The patient selection for DAPT should be considered for patients at high risk of ischemic events who can tolerate the increased bleeding risk. This includes high risk groups such as patients with

diabetes, history of MI, or those undergoing PCI. The duration of DAPT should be individualized based on the patient's risk profile. Shorter durations of DAPT could be potentially beneficial for those at higher risk of bleeding. Monitoring and management should be regularly established to determine bleeding and ischemic events. Clinical tools such as risk stratification criteria for predicting risk of bleeding events and biomarkers such as coagulation profiles should be used to tailor individualized therapy and patient needs.

Limitations are an inherent aspect of any research study and can affect the validity and generalization of results. While the studies included provide valuable insights into the efficacy of DAPT compared to aspirin monotherapy, several limitations should be acknowledged. The variability in study designs, particularly the inclusion of both randomized controlled trials and a meta-analysis, introduces heterogeneity in methodology and outcomes, which could impact the comparability of results. Additionally, differences in patient populations, such as the exclusion of those with prior myocardial infarction or stroke in some studies, may limit the generalization of findings to broader clinical settings. The sample sizes, while generally large, vary across studies, which could affect the statistics of the individual analyses. Another limitation is the potential for publication bias, specifically in the meta-analysis, as studies with negative results may be underrepresented. Furthermore, the studies focused primarily on short- to medium-term outcomes (up to 24 months), leaving uncertainty regarding the long-term safety and efficacy of DAPT versus AM. These limitations should be considered when interpreting the results and applying them to patient care management.

Future research should focus on long-term outcomes with longer follow-up periods. This can help assess the sustained efficacy and safety of DAPT versus AM in reduction incidence of myocardial infarctions. Also, additional biomarkers should be developed to help identify bleeding risk and ischemic events, allowing for more personalized antiplatelet therapy. Furthermore, research can expand upon more studies involving diverse patient populations, including different

ethnic groups and with varying comorbidities to help generalize findings and help make guidelines to be used worldwide. Addressing these research gaps can enhance our understanding of the balance between efficacy and safety in antiplatelet therapy. This can also include those in various subgroups of CAD and improving overall patient outcomes in CAD management.

Conclusion: Overall, DAPT appears to offer a significant benefit in reducing MI incidence among adults with CAD. Its increased bleeding risk requires careful patient selection and management. Current evidence supports an individualized approach to antiplatelet therapy, emphasizing the need for ongoing research to optimize generalized treatment strategies and guidelines.

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