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Review Article

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Challenging the efficacy and safety of clopidogrel versus aspirin monotherapy in secondary prevention of coronary artery disease: A comprehensive review

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ABSTRACT

Coronary artery disease (CAD) remains a major contributor to global morbidity and mortality, necessitating robust secondary prevention strategies. Antiplatelet therapy, particularly aspirin, has long been the cornerstone in CAD management, effectively reducing thrombotic events post-acute coronary syndrome and in patients with chronic coronary syndrome. However, aspirin's association with gastrointestinal (GI) bleeding and the emergence of alternative agents like clopidogrel have debate over the optimal monotherapy for CAD patients. Clopidogrel, a P2Y12 receptor antagonist, is increasingly considered a viable alternative, especially for patients at high risk of GI complications or aspirin intolerance. Recent clinical trials and updated guidelines have emphasized the need to reassess the roles of clopidogrel and aspirin, particularly in long-term secondary prevention. This review critically evaluates the comparative efficacy and safety of clopidogrel versus aspirin monotherapy, exploring genetic factors, bleeding risks, and the evolving role of personalized medicine. By analyzing current evidence, we provide insights into whether clopidogrel should be favored over aspirin in select populations, while highlighting the implications for future clinical practice and guideline development.

Key words: Coronary artery disease, clopidogrel, aspirin, dual-antiplatelet therapy

INTRODUCTION

Coronary artery disease (CAD) remains a leading cause of morbidity and mortality globally, necessitating effective secondary prevention strategies to mitigate adverse cardiovascular outcomes.[1-3] Antiplatelet therapy, a cornerstone in the management of CAD,[4] plays a pivotal role in preventing thrombotic events following acute coronary syndrome (ACS)[5] and in patients with chronic coronary syndrome.[6] Conventionally, aspirin has been the primary antiplatelet agent utilized in secondary prevention due to its well-established efficacy in reducing cardiovascular events.[1-3] However, aspirin's association with gastrointestinal (GI) bleeding[7] and the emergence of alternative antiplatelet agents, such as clopidogrel, have prompted ongoing debates regarding the optimal monotherapy for patients with CAD.[8] Clopidogrel, a P2Y12 receptor antagonist, offers an alternative to aspirin, particularly for patients at high risk of GI complications or those with aspirin intolerance.[9] Moreover, recent clinical trials and guidelines have raised questions about the comparative efficacy and safety of clopidogrel versus aspirin, especially in long-term monotherapy for secondary prevention.[8] The increasing focus on personalized medicine has also brought attention to genetic factors, such as CYP2C19 polymorphisms, which may influence clopidogrel's efficacy and its role in different patient populations.[10] This review critically examines the evidence comparing the efficacy and safety of clopidogrel versus aspirin monotherapy in the secondary prevention of CAD. By challenging current clinical paradigms and analyzing key trials and guideline recommendations, we aim to provide a comprehensive understanding of whether clopidogrel should be considered a superior alternative to aspirin in select patient populations. Special attention is given to the evolving role of clopidogrel in the context of contemporary cardiovascular guidelines, the duration of dual antiplatelet therapy (DAPT), and the implications for future practice.

CLINICAL CONTEXT AND BACKGROUND

Overview of CAD and Antiplatelet Therapy

CAD remains a leading cause of morbidity and mortality worldwide, characterized by the progressive narrowing of coronary arteries due to atherosclerotic plaques.[1-3] This condition significantly increases the risk of myocardial infarction (MI) and other cardiovascular events. The basis of CAD management is antiplatelet therapy, which aims to reduce the risk of thrombosis and subsequent cardiovascular events.[4-6]

Historical Perspective: Aspirin in Secondary Prevention

Aspirin has long been established as the standard antiplatelet therapy for the secondary prevention of CAD. Landmark studies, including the ISIS-2 trial,[11] demonstrated that aspirin significantly reduces the risk of recurrent MI and mortality, in patients with a history of MI. Despite its efficacy, aspirin's benefit is often accompanied by an increased risk of GI bleeding, necessitating careful patient selection and management.[7]

Emergence of Clopidogrel and Its Clinical Rationale

Clopidogrel, a thienopyridine P2Y12 inhibitor, emerged as a significant advancement in antiplatelet therapy following the CURE trial.[12] This trial demonstrated that clopidogrel, in combination with aspirin, reduced the risk of cardiovascular events compared to aspirin alone in patients with ACS.[12] Unlike aspirin, clopidogrel targets the P2Y12 receptor on platelets, providing a different mechanism of action that enhances its efficacy in certain patient populations.[9]

Comparative Efficacy of Clopidogrel and Aspirin

Recent studies comparing clopidogrel to aspirin in monotherapy for secondary prevention reveal nuanced outcomes. For instance, the clopidogrel versus aspirin in patients at risk of ischemic event (CAPRIE) demonstrated that clopidogrel reduced the risk of cardiovascular events compared to aspirin in patients with atherosclerotic disease.[13] However, the relative benefit varies based on patient-specific factors, including genetic variations and comorbidities.[10] Particularly, the research found that clopidogrel monotherapy was as effective as aspirin in preventing major adverse cardiovascular events (MACE) with a comparable safety profile, thereby challenging the traditional preference for aspirin.[5]

MONOTHERAPY WITH P2Y12 INHIBITORS: CURRENT EVIDENCE

Recent Clinical Trials and Landmark Studies

In recent years, several landmark studies have reassessed the role of P2Y12 inhibitors in monotherapy. The TWILIGHT trial highlighted that clopidogrel monotherapy, after a period of DAPT, was non-inferior to continued DAPT in preventing MACE while significantly reducing bleeding risk.[14] The study demonstrated a reduction in bleeding complications with clopidogrel monotherapy compared to DAPT.[14] Similarly, the HOST-EXAM trial confirmed the benefits of clopidogrel monotherapy in patients with stable CAD, emphasizing its potential as a viable alternative to aspirin in specific contexts.[15]

Impact of Genetic Variations on Clopidogrel Efficacy

Genetic variations, particularly in the CYP2C19 gene, play a crucial role in clopidogrel's effectiveness. Individuals with loss-of-function alleles may experience reduced clopidogrel activation and therapeutic efficacy.[16] The CHARISMA reported that patients with these genetic variants had a higher incidence of adverse cardiovascular outcomes when treated with clopidogrel.[17] Personalized medicine approaches, including genetic testing, can guide treatment decisions and optimize therapeutic outcomes by tailoring antiplatelet therapy to individual genetic profiles.

SAFETY CONSIDERATIONS AND SIDE EFFECTS

Risk of GI Bleeding: Aspirin Versus Clopidogrel

GI bleeding is a significant concern with antiplatelet therapy. The GI bleeding risk associated with aspirin is well-documented, with studies such as the study showing the incidence of major GI bleeding in aspirin-treated patients.[18] Clopidogrel, while associated with a lower bleeding risk compared to aspirin, still poses a significant concern, particularly in combination with other medications or in patients with pre-existing GI conditions.[19] The PEGASUS-TIMI 54 trial reported a lower rate of major GI bleeding with clopidogrel compared to aspirin, but the overall safety profile remains a critical consideration in therapy selection.[20]

Landmark Studies and Current Safety Data

Recent studies have refined our understanding of safety profiles. In a meta-analysis of 28 studies involving 131,412 patients, concomitant use of proton pump inhibitors (PPIs) with clopidogrel was associated with an increased risk of MACE (relative risk [RR] 1.30; 95% confidence interval [CI] 1.15–1.48; $P < 0.001$) and MI (RR 1.43; 95% CI 1.25–1.64; $P < 0.001$). Pantoprazole (RR 1.31) and lansoprazole (RR 1.35) specifically increased MACE risk, while rabeprazole did not show a significant association (HR 1.32; $P = 0.40$). Overall, post-percutaneous coronary intervention (PCI) patients on clopidogrel and PPIs had a higher risk of MACE and MI, except with rabeprazole.[21] The study found that combining PPIs with clopidogrel raised the risk of major cardiovascular events and heart attacks, particularly with pantoprazole and lansoprazole. Rabeprazole was the only PPI that did not significantly increase this risk. Careful PPI selection is crucial for safety in patients on clopidogrel.[21]

Role of PPIs: Recommendations and Evidence

PPIs are recommended for patients at high risk of GI bleeding undergoing antiplatelet therapy. The 2023 European Cardiology

Society (ESC) guidelines emphasize the use of PPIs, such as pantoprazole, over omeprazole due to potential interactions with clopidogrel metabolism.[22] The latest evidence supports this recommendation, demonstrating that pantoprazole, lansoprazole, and dexlansoprazole do not inhibit CYP2C19 to the same extent as omeprazole, thereby preserving clopidogrel's efficacy while minimizing bleeding risks.[23]

UPDATES FROM RECENT ESC GUIDELINES (2023 AND 2024)

DAPT in Contemporary Practice

The ESC guidelines (2023)[22] and recent updates (2024)[24] emphasize a tailored approach to DAPT duration based on individual patient risk profiles. For patients with ACS, a shorter duration of 6–12 months is recommended, whereas longer durations may be necessary for those with high-risk features.[25] The OPT-BIRISK supports a more individualized approach, suggesting that extending DAPT beyond 1 year (9–12 months) can be beneficial in high-risk populations but may increase bleeding risk in others.[26]

Implications for Personalized Medicine and Future Guidelines

Personalized medicine is becoming increasingly integral in antiplatelet therapy. The integration of genetic testing, risk stratification, and patient-specific factors into clinical practice is expected to refine treatment strategies and enhance outcomes. Future guidelines are likely to continue evolving, incorporating new evidence and technological advancements to optimize antiplatelet therapy for diverse patient populations.

DISCUSSION AND FUTURE DIRECTIONS

Challenges and Controversies in Antiplatelet Therapy

Despite advancements, antiplatelet therapy remains fraught with challenges. Controversies exist regarding the optimal duration of DAPT, the role of newer P2Y12 inhibitors, and the impact of genetic variations on therapy outcomes. Balancing efficacy and safety continue to be a significant challenge, necessitating ongoing research and clinical trials.

Potential Shifts in Clinical Practice Based on New Evidence

Recent evidence suggests a shift toward personalized approaches in antiplatelet therapy, with an emphasis on tailored treatment strategies based on genetic and clinical risk factors.[27] The potential for clopidogrel monotherapy to replace aspirin in certain contexts represents a significant shift in clinical practice, reflecting the need for individualized patient care.

In the clinical management of patients undergoing PCI, ensuring comprehensive safety, particularly in relation to bleeding risk, is paramount. Two key tools, the academic research consortium high bleeding risk (ARC-HBR) criteria, and the PRECISE-DAPT score, are commonly employed to predict bleeding complications, especially in patients receiving DAPT. The ARC-HBR criteria stratify risk based on major and minor clinical factors, while the PRECISE-DAPT score utilizes a simplified five-variable model, incorporating age, creatinine clearance, hemoglobin levels, white blood cell count, and previous bleeding history. Both tools demonstrate strong predictive performance, with areas under the curve ranging from 0.75 to 0.82 for 1-year bleeding outcomes, making them effective in identifying patients at high risk for major bleeding and all-cause mortality. High-risk patients, typically defined by an ARC-HBR score of ≥ 2 or a PRECISE-DAPT score >24, are more likely to experience significant bleeding and may benefit from shorter DAPT durations or alternative antithrombotic strategies. In contrast, low-risk patients can continue standard therapy but require ongoing monitoring for potential risk changes.

Importantly, both scoring systems have limitations, particularly in different ethnic populations, such as "East Asians," who may exhibit unique bleeding and thrombotic profiles. Thus, while these tools are essential for guiding treatment, they should be integrated with individualized clinical decision-making, taking into account patient-specific factors such as renal function, anemia, and procedural complexity, to optimize safety and outcomes.[28]

Recommendations for Future Research and Clinical Trials

Future research should focus on the long-term outcomes of clopidogrel monotherapy versus aspirin, the impact of genetic variations on therapy efficacy, and the development of novel antiplatelet agents. Clinical trials should aim to address existing gaps in knowledge, including optimal therapy duration and strategies to minimize bleeding risks while maximizing cardiovascular protection.

CONCLUSION

The comparative efficacy and safety of clopidogrel and aspirin in secondary prevention of CAD remain subjects of ongoing debate. While aspirin has been the traditional agent of choice, recent evidence suggests that clopidogrel offers a compelling alternative, particularly for patients at higher risk of GI bleeding or those with aspirin intolerance. Clinical trials, such as CAPRIE and HOST-EXAM, have demonstrated comparable cardiovascular outcomes between the two agents, with clopidogrel showing a reduced risk of bleeding complications in certain populations. Furthermore, the influence of genetic variations, such as CYP2C19 polymorphisms, on clopidogrel efficacy, underscores the growing importance of personalized medicine in antiplatelet therapy. As personalized approaches and tailored treatment strategies continue to evolve, clopidogrel monotherapy may emerge as a preferred option in specific clinical scenarios. Future research should focus on refining the duration of DAPT and further elucidating the long-term benefits and risks of clopidogrel versus aspirin, particularly in light of genetic testing and contemporary guideline updates.

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