Assessment of the efficacy and safety of the abatement of antiplatelet therapy in patients with acute coronary syndrome

PhD Thesis

By

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Table of content:

1. Prologue:

1.1. Acute coronary syndrome:

Acute coronary syndrome (ACS) is a severe form of coronary heart disease (CHD) responsible for a third of deaths in individuals over 35. It includes unstable angina, non-ST elevation myocardial infarction (NSTEMI), and ST elevation myocardial infarction (STEMI), each damaging heart tissue. ACS is primarily caused by atherosclerosis, with risk factors like high blood pressure, high cholesterol, smoking, obesity, diabetes, and family history of heart disease. Treatment involves medications (antiplatelet agents, anticoagulants, beta-blockers) and procedures (PCI, CABG). PCI is a non-surgical approach for obstructive CAD, with newer antiplatelet agents like prasugrel and ticagrelor preferred over clopidogrel for reducing thrombotic events during PCI.

1.2. Myocardial ischemia–reperfusion injury:

STEMI, the most severe form of ACS, is a significant global health issue caused by prolonged myocardial ischemia from atherosclerotic plaque rupture, leading to artery blockage by a blood clot. Swift and complete restoration of blood flow, typically through primary percutaneous coronary intervention (pPCI) or thrombolytic therapy, is crucial to minimize damage,

preserve heart function, and reduce heart failure risk in STEMI cases. pPCI is preferred where available, although reperfusion can lead to reperfusion injury, complicating patient outcomes. This injury involves various pathways like cell-mediated immunity and microvascular dysfunction, influenced by factors such as left ventricular hypertrophy and diabetes. Despite advances, STEMI mortality rates remain high, necessitating further research to address reperfusion injury challenges and enhance cardio-protective strategies for improved patient outcomes.

1.3. De-esclation of antiplatelet therapy in ACS patients:

Antithrombotic therapy in ACS and PCI patients has traditionally focused on reducing ischemic events, but recent attention has shifted to the significant concern of bleeding associated with such therapy. Balancing bleeding risks against ischemic risks is crucial. Recent RCTs have shown promise in intense antithrombotic therapy for 1-3 months post-ACS/PCI, followed by de-escalation of antiplatelet therapy to manage this balance effectively. De-escalation strategies involve shortening dual antiplatelet therapy (DAPT) duration and adjusting P2Y12 inhibition post-standard DAPT. These approaches can be guided or unguided, with options like aspirin vs. P2Y12 inhibitor monotherapy and tools such as platelet function testing or genetic testing to tailor therapy and optimize outcomes.

2. AIMS:

The main aims of our studies were the following:

- Identify cardio-protective strategies against myocardial ischemia–reperfusion injury.
- Evaluate the impact of DAPT abatement strategies in patients with PCI.
- Assess the effectiveness of precision medicine approaches in individualizing P2Y12 de-escalation strategies, such as PFT guidance, genetic testing guidance, and uniform de-escalation, for ACS patients undergoing PCI.

This doctoral dissertation comprises three distinct studies. The initial investigation is based on a literature review, the second study entails a comprehensive meta-analysis of RCTs and the third study is a comprehensive literature review of clinical trials.

3. Background:

3.1. Ischemia-reperfusion injury:

The size of an infarct is influenced by both ischemia and reperfusion. Ischemia-induced damage increases with the severity and duration of blood flow reduction, while reperfusion injury peaks at a moderate level of ischemic damage. During ischemia, the lack of oxygen and nutrients can lead to cellular damage and death. Reperfusion, while necessary, can exacerbate the injury by generating reactive oxygen species, triggering inflammatory responses, and activating cell death pathways. The total tissue injury is divided into ischemia injury and reperfusion injury. In some STEMI patients, despite successful artery reopening, the 'no-reflow phenomenon' can occur due to coronary microvascular obstruction, leading to ineffective myocardial reperfusion. This is associated with capillary destruction and intramyocardial hemorrhage, and can be influenced by preexisting endothelial dysfunction or genetic predisposition.

3.2. Evaluation of the impact of DAPT abatement strategies in patients with PCI:

P2Y12 inhibitors, along with aspirin, are commonly used to reduce clotting issues in ACS patients undergoing PCI. Recent guidelines prefer prasugrel or ticagrelor over

clopidogrel due to their superior performance in reducing ischemic events, although they can increase bleeding risk and side effects, potentially affecting compliance. Patients often switch P2Y12 inhibitors during ACS treatment, as the higher clotting risk early on may outweigh bleeding risk, while in the chronic phase, the reduction in clotting risk becomes more significant than bleeding risk reduction. Strategies like uniform or guided de-escalation to a milder P2Y12 inhibitor or early aspirin discontinuation in favor of potent P2Y12 inhibitor monotherapy can address this, contributing to bleeding avoidance and economic benefits. De-escalation can also address high on-treatment platelet reactivity in many ACS patients due to genetic factors like CYP2C19 LoF alleles. Using PFT or genetic testing can enhance the safety of de-escalation by identifying higher-risk patients and selectively maintaining potent P2Y12 inhibition for them. Recent trials have aimed to test various de-escalation schemes, but often lack sufficient power to thoroughly evaluate their effectiveness and safety. A network meta-analysis showed benefit in terms of ischemic and bleeding events after switching to a less potent P2Y12 inhibitor through de-escalation or opting for potent P2Y12 monotherapy combined with aspirin discontinuation, with the latter showing a significant reduction in major bleeding risk.

3.3. Assess the effectiveness of precision medicine approaches in individualizing P2Y12 de-escalation strategies:

Platelets play a crucial role in hemostasis, becoming activated in response to damaged blood vessels or tissues through various pathways, including ADP-mediated mechanisms binding to P2Y1 and P2Y12 receptors. This activation triggers intracellular signaling pathways, leading to platelet shape change, granule secretion, and aggregation. Platelet activation involves multiple agonists like thrombin and collagen, culminating in platelet aggregation and plug formation to seal injuries. Antiplatelet therapy targets this activation to prevent clot formation, reducing the risk of heart attacks and strokes. While clopidogrel was a standard P2Y12 receptor antagonist, newer agents like prasugrel and ticagrelor offer faster action and more consistent platelet aggregation inhibition, showing superior thrombosis risk reduction in ACS patients. Personalized antiplatelet therapy based on individual characteristics is being explored to optimize treatment efficacy and safety.

Platelet function testing (PFT) is crucial for assessing clopidogrel efficacy, especially considering genetic variations in CYP2C19 activity and drug degradation issues that can lead to inadequate responses and increased clotting risks. ADP-specific PFTs, like light transmission aggregometry (LTA) and VerifyNow P2Y12 assay, help monitor antiplatelet effects. Poor clopidogrel responders may benefit from alternative medications like ticagrelor or prasugrel, with PFT guiding therapy and dosage adjustments. Genetic polymorphisms affecting clopidogrel metabolism, particularly CYP2C19 LoF alleles, can impact platelet inhibition and clinical outcomes, emphasizing the importance of personalized antiplatelet strategies for patients, especially those with ACS

undergoing PCI. Genetic polymorphisms in CYP2C19, ABCB1, and PON1 affecting clopidogrel metabolism have been studied, but their clinical relevance remains unclear. Guidelines differ on the significance of CYP2C19 LoF allele testing for PCI patients receiving clopidogrel. In this review, uniform unguided P2Y12 de-escalation strategies consistently reduce bleeding without compromising efficacy, while genetic testing-guided and PFT-guided de-escalation show no difference in bleeding or ischemic events compared to standard therapy.

4. Methods:

4.1. Evaluation of the impact of DAPT abatement strategies in patients with PCI:

This systematic review was conducted by performing a keyword-based search in PubMed (MEDLINE), EMBASE, and the Cochrane Library from January 2007 to October 2021, without any language restriction. The review included studies studies on de-escalation strategies in ACS patients post-PCI, comparing P2Y12 inhibitor monotherapy or de-escalation to framework clopidogrel versus DAPT, that met specific eligibility criteria and underwent full-text screening against the eligibility criteria outlined in the PICOS. Outcomes assessed included major adverse cardiovascular events (MACE), major bleeding, and all-cause mortality. The review utilized a network meta-analysis with a random-effects model, evaluating bias, publication bias, consistency, and heterogeneity.

Exploratory analyzes were conducted based on de-escalation strategy, population, study size, and follow-up, with calculations performed using R statistical software.

4.2. Assess the effectiveness of precision medicine approaches in individualizing P2Y12 de-escalation strategies:

A literature review conducted a computerized search in PubMed, EMBASE, and the Cochrane Library up to January 2023, using keywords like antiplatelet therapy, de-escalation, ACS, PFT, genetic testing, and individualized therapy. The review focused on RCTs with a P2Y12 de-escalation approach, including PFT and genetic testing guidance, and uniform de-escalation for ACS patients post-PCI. Studies meeting specific criteria were included. Data extraction enabled a multiple treatment analysis for various antiplatelet combinations, using a random-effects model to assess heterogeneity and rank treatments based on the P-scores method.

5. Results:

5.1. Evaluation of the impact of DAPT abatement strategies in patients with PCI:

Ten studies, encompassing 42,511 patients meeting the inclusion criteria, were included in the analysis. Of these patients, 6,359 were assigned to a P2Y12 inhibitor de-escalation strategy, and 13,062 received potent P2Y12 inhibitor monotherapy. The control group consisted of 18,540 patients on potent P2Y12 inhibitor-based DAPT, while 946 patients were on a combination of clopidogrel and aspirin. The P2Y12 inhibitor de-escalation strategy was guided by PFT in one study, genetic testing in two, and was unguided (uniform) in four studies.

Bias risk was evaluated in all the trials, revealing minimal risk across all categories of bias (Figure1).

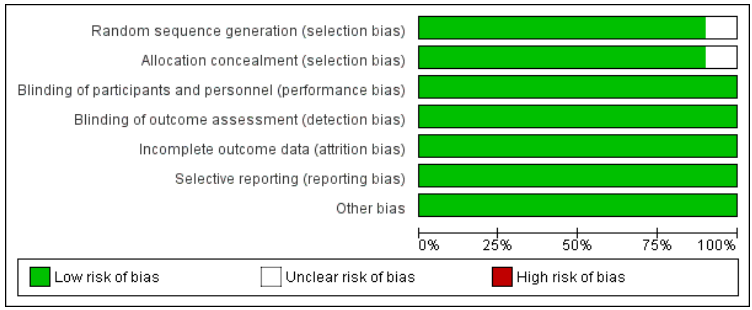


Figure 1: Assessment of bias: summarized results of the bias assessment of included trials using the Cochrane bias assessment tool.

The findings obtained through direct comparisons were consistent with those calculated using indirect comparisons.

Compared to a potent DAPT, both P2Y12 inhibitor de-escalation and P2Y12 inhibitor monotherapy significantly reduced the risk of ischemic events. P2Y12 inhibitor de-escalation led to a 24% risk reduction, and P2Y12 inhibitor monotherapy resulted in a 14% risk reduction with RR values of 0.76 (CI: 0.62-0.94) and 0.86 (CI: 0.75-0.99), respectively, both having p-values below 0.05. Major bleeding rates were similar between P2Y12 inhibitor de-escalation and the control group, with no significant differences between trials In contrast, P2Y12 inhibitor monotherapy led to a 35% reduction [RR: 0.65 (0.46, 0.91), $p < 0.05$, $I2 = 0\%$]. Differences were more pronounced when considering all bleeding events, especially minor bleeding, where both P2Y12 inhibitor de-escalation and P2Y12 inhibitor monotherapy resulted in a 36–42% reduction (Figure 2).

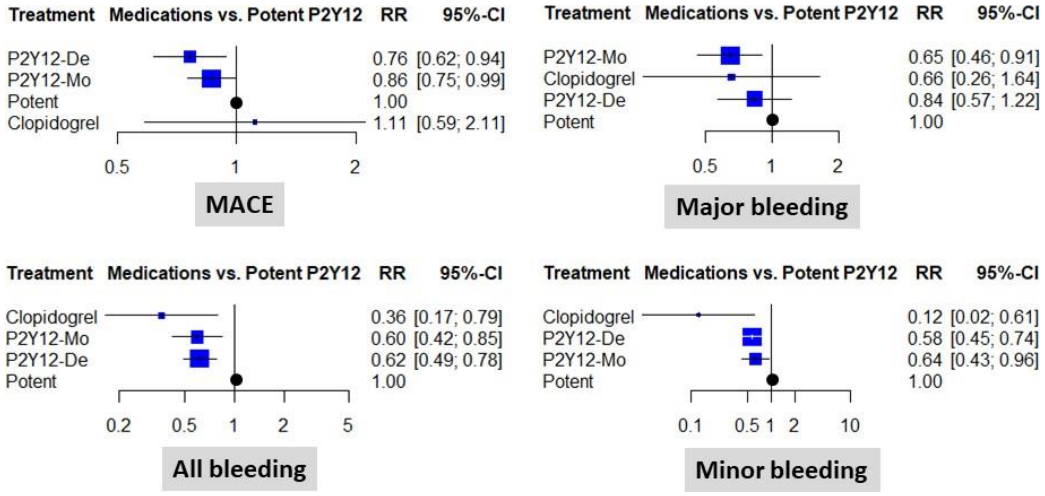


Figure 2: Clinical results of using different abatement strategies.

Upon evaluating various de-escalation strategies, a similar inclination towards risk reduction was evident. Nevertheless, it is noteworthy that none of these cases reached a statistically significant level of association. The most significant reduction was observed with uniform de-escalation, followed by the other strategies. However, in the case of PFT-guided de-escalation, no significant reduction in bleeding endpoints was noted (Figure 3).

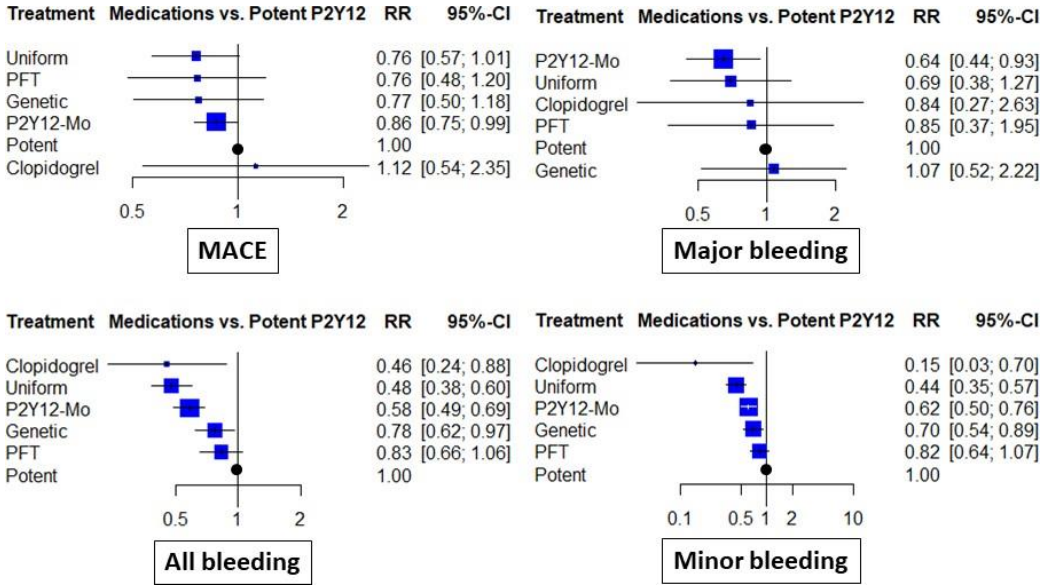


Figure 3: Clinical results of abatement strategies considering de-escalation strategies separately.

The specific elements within the combined endpoint exhibited favorable patterns, indicating reduced risks of ischemic events with de-escalation strategies, except for MI, stent thrombosis, and stroke. In the case of P2Y12

inhibitor monotherapy, there was an increased risk observed for these particular outcomes. Nevertheless, it is essential to note that none of these differences reached statistical significance (Figure 4).

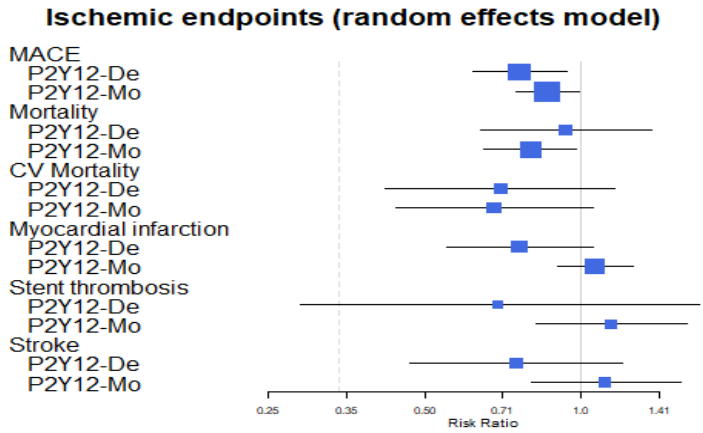


Figure 4: Results of the network analysis of ischemic endpoints.

In the treatment ranking for MACE, P2Y12 inhibitor de-escalation received the highest rank (0.92), followed by P2Y12 inhibitor monotherapy (0.62), and the lowest ranks were assigned to clopidogrel and potent P2Y12 inhibitor-based DAPT (0.24 and 0.22, respectively). Regarding major bleeding, P2Y12 inhibitor monotherapy (0.78) had a higher ranking than clopidogrel (0.67), P2Y12 inhibitor de-escalation (0.42), and potent P2Y12 inhibitor-based DAPT (0.12).

5.2. Assess the effectiveness of precision medicine approaches in individualizing P2Y12 de-escalation strategies:

In this trial, 5302 ACS patients undergoing PCI were randomly assigned to receive either the standard DAPT comprising aspirin and clopidogrel or a genotype-guided approach where CYP2C19 genotyping determined the choice of P2Y12 inhibitor. The study's results revealed that the genotype-guided therapy was as effective as standard DAPT in terms of the primary endpoint, which encompassed cardiovascular death, MI, stroke, stent thrombosis, or severe bleeding at the 12-month mark (4.0% vs. 5.9%, HR: 0.66, [95% CI: 0.43–1.02], p = 0.06). While both the rate of MACE and the net clinical benefit showed a positive trend in this trial, the anticipated reduction in major bleeding events was not significant in the trial's findings (Figure 5).

The study's findings indicated that PFT-guided de-escalation was just as effective as standard DAPT concerning the composite endpoint, which encompassed death, MI, stroke, and bleeding at the one-year mark (7% vs. 9%, p = 0.0004 for non-inferiority, HR: 0.81, [95% CI: 0.62–1.06], p-superiority = 0.12). Similar to genetic testing, there were positive trends in the rates of MACE and net clinical events. Furthermore, a noteworthy 15% reduction in the risk of major bleeding was observed. However, it is essential to note that none of these

observations reached the level of statistical significance (Figure 5).

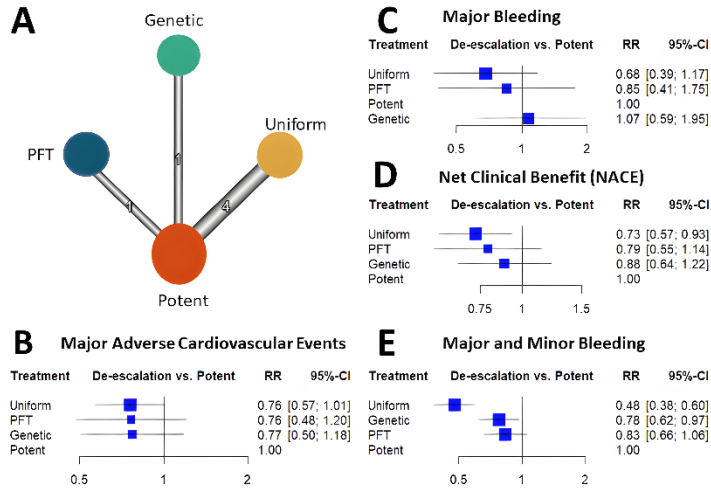
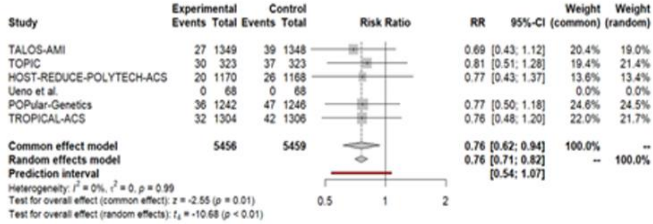


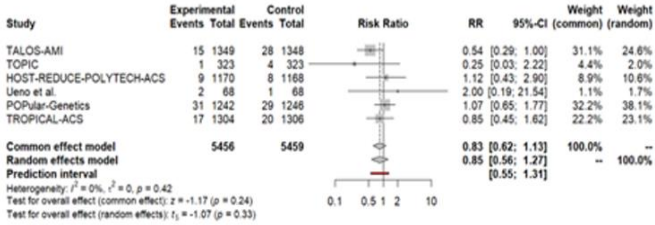
Figure 5: NMA results of randomized trials of P2Y12 de-escalation.

Among the various methods of de-escalation, uniform de-escalation demonstrated the most substantial decrease in bleeding. Genetic testing-based de-escalation followed closely in terms of effectiveness, whereas the use of PFT to guide de-escalation did not yield a noteworthy reduction in bleeding (Figure 5). These patterns of reduction were statistically significant for all instances of bleeding and minor bleeding. However, when it came to major bleeding, none of the individual de-escalation strategies or the overall assessment of de-escalation trials showed a significant reduction (Figure 6).

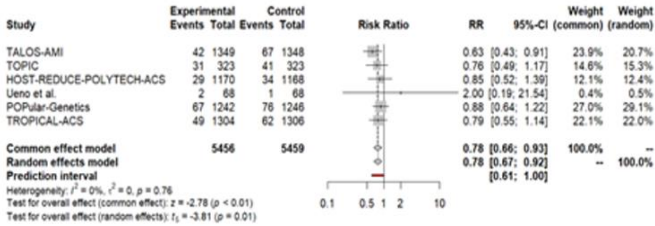
Panel A Major Adverse Cardiovascular Events



Panel B Major Bleeding



Panel C Net clinical efficacy (NACE)



Panel D Major and Minor Bleeding

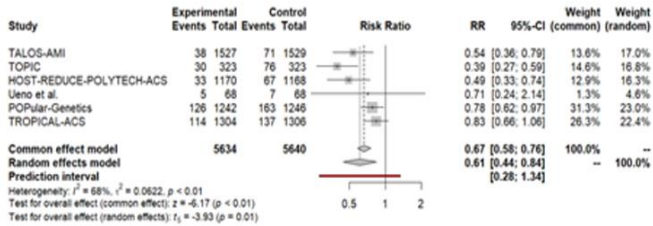
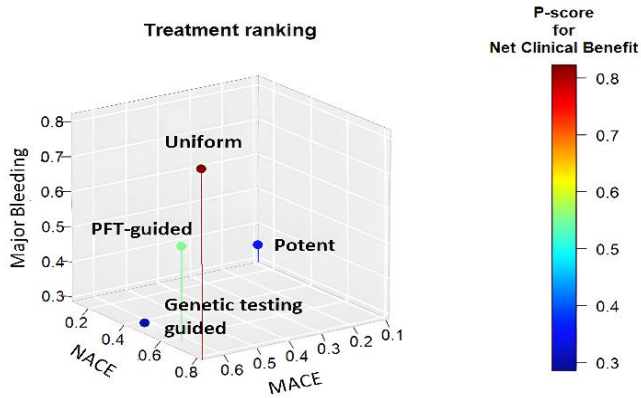


Figure 6: Forest plots depicting clinical endpoints of P2Y12 de-escalation strategies.

Despite the fact that the outcomes related to the reduction of bleeding risk fell short of expectations for de-escalation methods, there was an unexpected positive outcome. Contrary to the expected compromise of accepting a potential increase in ischemic risk, all three strategies for reducing the use of P2Y12 inhibitors resulted in a similarly lower rate of ischemic events (Figure 7).



P-score	MACE	Major Bleeding	NACE	All Bleeding
Uniform	0.67	0.82	0.82	1.00
PFT	0.63	0.56	0.64	0.55
Genetic	0.62	0.29	0.42	0.42
Potent	0.09	0.33	0.11	0.03

Figure 7: Treatment ranking of P2Y12 de-escalation strategies.

6. Discussion:

6.1. Reduction of ischemia-reperfusion injury:

Clinical studies have shown mixed results when it comes to adenosine, with some failing to demonstrate significant

improvements in infarct size or MVO. As for nitric oxide donors, other clinical trials, including the NIAMI, REOPEN-AMI, and REFLO-STEMI trials, have not shown a significant benefit in reducing infarct size or MVO in patients with STEMI. These findings suggest that intracoronary adenosine and the use of nitrite or nitroprusside may not be a routine treatment for pPCI in preventing reperfusion injury and providing a myocardial salvage and MVO during pPCI.

The METOCARD-CNIC trial found that intravenous metoprolol infusion before reperfusion decreased myocardial infarct size 1 week after anterior STEMI. However, the larger EARLY-BAMI trial failed to demonstrate metoprolol's infarct-limiting effect. Variations in timing of metoprolol administration may explain these differences. Current guidelines recommend intravenous beta-blockers, preferably metoprolol, at presentation for patients with STEMI undergoing pPCI.

Large randomized trials, TRITON-TIMI 38 and PLATO, demonstrated that third-generation P2Y12 receptor inhibitors, such as ticagrelor or prasugrel, are more effective than clopidogrel in reducing ischemic events.. The REDUCE-MVI trial showed comparable impacts on coronary microvascular dysfunction and myocardial injury between ticagrelor and prasugrel maintenance therapy following pPCI in STEMI. The ISAR REACT-5 study revealed that prasugrel, compared to ticagrelor, resulted in a reduction in ischemic risk without an increase in bleeding risk in STEMI patients undergoing pPCI, showing prasugrel’s superiority to ticagrelor.

A randomized placebo-controlled study demonstrated that in patients with STEMI who developed no-reflow phenomenon during pPCI, intracoronary administration of tirofiban significantly improved TIMI flow grade and resulted in a lower in-hospital MACE rate. The INFUSE-AMI trial showed that in patients with large anterior STEMI undergoing pPCI, infarct size measured by CMR was significantly reduced at 30 days following intracoronary administration of bolus abciximab at the site of infarct lesion. According to current guidelines, GP IIb/IIIa receptor antagonists should be considered if there is evidence of no-reflow or a thrombotic complication during pPCI.

6.2. Evaluation of the impact of DAPT abatement strategies in patients with PCI:

In this network meta-analysis, two DAPT de-escalation approaches yielded superior ischemic outcomes: transitioning to a less potent P2Y12 inhibitor and adopting potent P2Y12 monotherapy with aspirin discontinuation. Both strategies reduced bleeding risk, with P2Y12 monotherapy showing a significant decrease in major bleeding without increasing ischemic events. These findings suggest that routinely applying these strategies in the early phases of PCI for ACS patients, as per trial protocols spanning 48 hours to 3 months, could improve ischemic and bleeding outcomes.

P2Y12 inhibitor monotherapy showed significant reductions in major bleeding and adverse events, while P2Y12 inhibitor de-escalation strategies were more effective in reducing ischemic events cumulatively. Minor bleeding risk significantly decreased with de-escalation approaches, with uniform de-escalation particularly effective in reducing bleeding events. Guided de-escalation using platelet function and genetic testing showed a less pronounced reduction in bleeding. Overall, de-escalation strategies were more efficient in mitigating ischemic risk, while P2Y12 inhibitor monotherapy emerged as a safer option for reducing bleeding in ACS patients. Notably, using ticagrelor in monotherapy may offer lower ischemic risk compared to clopidogrel. The differences in pharmacodynamics and pharmacokinetics among clopidogrel, prasugrel, and ticagrelor highlight their unique mechanisms of action, with ticagrelor providing reversible inhibition without requiring metabolic activation, offering faster onset, greater potency, and more consistent response compared to clopidogrel and prasugrel.

Clopidogrel's limitation lies in its significant variability in platelet function inhibition, particularly risky for high-risk patients due to high platelet reactivity (HPR) associated with poor metabolizer CYP2C19 alleles like *2 and *3. Genetic factors and drug interactions contribute to this variability, with 15-40% of individuals considered "non-responders" or "clopidogrel-resistant," linked to increased cardiovascular risks and stent thrombosis. Strategies reducing treatment intensity have shown benefits in reducing MACE and bleeding compared to potent P2Y12-

based DAPT. While both P2Y12 inhibitor monotherapy and de-escalation strategies reduced bleeding rates similarly, genetic testing and PFT-guided de-escalation were slightly less effective, suggesting P2Y12 inhibitor monotherapy or unguided de-escalation may be preferable for minimizing bleeding risk. In terms of ischemic events, de-escalation strategies showed a trend towards a reduction, although not statistically significant in indirect comparisons.

Key clinical trials have demonstrated the superiority of prasugrel and ticagrelor over clopidogrel in ACS, showing reduced recurrent ischemic events but a slight increase in bleeding risk. Recent focus has shifted towards strategies to minimize bleeding in ACS, with this meta-analysis standing out for its exclusive inclusion of RCTs for reliability and its coverage of de-escalation from various potent P2Y12 inhibitors to clopidogrel. Studies on guided de-escalation have shown improved efficacy while maintaining safety, aligning with the findings of reduced bleeding and ischemic events. This analysis also considers aspirin monotherapy trials and evaluates different abatement strategies, including P2Y12 inhibitor monotherapy and de-escalation. Previous research supports the effectiveness of P2Y12 inhibitor de-escalation in balancing ischemic risk and bleeding in ACS patients, a trend observed in this analysis alongside a reduction in bleeding with P2Y12 inhibitor monotherapy, aligning with recent meta-analyses.

6.3. Assess the effectiveness of precision medicine approaches in individualizing P2Y12 de-escalation strategies:

This review found that uniform unguided P2Y12 de-escalation strategies consistently reduced bleeding events without compromising effectiveness, while genetic testing-guided and PFT-guided de-escalation did not show significant differences in bleeding or ischemic events compared to standard treatment. Kuno et al. conducted a comprehensive NMA analyzing various DAPT approaches, including aspirin with clopidogrel, prasugrel, and ticagrelor combinations, as well as de-escalation strategies. Their study, involving 19 RCTs and 69,746 patients, revealed that unguided de-escalation was associated with a lower MACE risk. Our analysis showed no significant difference in MACE risk between guided and unguided strategies, with all studies consistently demonstrating reduced MACE rates, primarily driven by larger patient numbers in unguided de-escalation trials. The data on ischemic events favored de-escalation strategies, while bleeding rates varied, notably differing from Kuno et al.'s grouping of trials like TROPICAL-ACS and POPULAR-GENETIC, where the latter showed increased major bleeding despite reductions in overall bleeding with genetic testing-based de-escalation.

The trials aimed for non-inferiority based on composite endpoints, with notable improvements in net clinical benefit seen with de-escalation strategies, especially in reducing bleeding events. Guided de-escalation led to

higher prasugrel use, potentially explaining less significant reductions in bleeding rates. Unguided de-escalation was most effective in reducing bleeding while maintaining efficacy but may pose a higher risk of ischemic events. The mechanistic explanation for risk reduction remains unclear, with speculation on improved patient adherence and tolerability. Genetic testing and PFT were used to assess bleeding risk, but other factors may influence bleeding events. The trials' choice of treatments based on genetics and platelet function tests, with a significant portion receiving clopidogrel, may have impacted bleeding outcomes. Uniform de-escalation studies showed advantages in MACE and NACE, with no significant reduction in major bleeding, potentially influenced by prolonged prasugrel use. PFT-guided de-escalation showed a trend in reducing major bleeding, suggesting PFT may offer more precise risk predictions than genetic testing.

7. Novel findings:

The major novel findings, based on the results from the studies mentioned previously, can be summarized as follows:

- Our review suggests that:
  - Beta-blockers, antiplatelet therapy and Glycoprotein IIb/IIIa inhibitors show improvements in myocardial ischemia-reperfusion injury.
- Our meta-analysis suggest that :
  - de-escalation of antiplatelet therapy can reduce bleeding risk without compromising the risk of MACE, which is significantly lower.
  - P2Y12 inhibitor monotherapy and P2Y12 inhibitor de-escalation exhibit differences that may influence their clinical use.
  - trials with guided de-escalation showed less expressed benefits.
- Our review suggests that:
  - the use of uniform unguided de-escalation is the most effective strategy in reducing bleeding events while maintaining efficacy.

- uniform unguided de-escalation may be associated with an increased risk of ischemic events, which can lead to serious complications and can be fatal.
- it is important to consider individual patient factors such as bleeding risk, thromboembolic risk, and patient comorbidities to select the optimal approach for DAPT abatement.

8. Scientometrics:

Scientific papers:

- Total: **11**
- English language papers: **11**

Impact factor (up to 18 January 2024 based on MTMT2):

- First author: **9.2**
- Cumulative: **36.672**

Citations (up to 18 January 2024 based on MTMT2):

- Independent: **11**
- Cumulative: **14**

9. Acknowledgements:

I would like to thank all the people who contributed in some way to the work described in this thesis and made my academic journey worthwhile.
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Lastly, I want to express my deepest gratitude to my family and friends for their belief in my abilities and support. Your encouragement played an integral role in my accomplishments. Thank you for everything. I dedicate this PhD thesis to you.