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:

List of abbreviations:

ACS: acute coronary syndrome

ADP: adenosine diphosphate

BARC: Bleeding Academic Research Consortium

CABG: coronary artery bypass grafting

CAD: coronary artery disease

CHD: coronary heart disease

CI: confidence interval

CMR: cardiac magnetic resonance

CYP: cytochrome P450

DAPT: dual antiplatelet therapy

DES : drug-eluting stent

HPR: high on-treatment platelet reactivity

HR: hazard ratio

LTA: light transmission aggregometry

LoF: loss of function

MACE: major adverse cardiovascular events

MeSH: medical subject heading

MI: myocardial infarction

MVO: microvascular obstruction

NACE: net adverse clinical events

NMA: network meta-analysis

NSTEMI: non-ST elevation myocardial infarction

PCI: percutaneous coronary intervention

PFT: platelet function test

PICOS: population, intervention, comparison, outcomes and study

PLATO: Platelet inhibition and patient outcomes

PRISMA: preferred reporting items for systematic reviews and meta-analyses

PROSPERO: International Prospective Register of Systematic Reviews

PRU : P2Y12 reaction unit

RCT: randomized controlled trial

RR: risk ratio

STEMI: ST elevation myocardial infarction

SUCRA: surface under the cumulative ranking

TOPIC: timing of platelet inhibition after acute coronary syndrome

TRITON TIMI-38: Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction

1. Prologue:

1.1. Acute coronary syndrome:

Acute coronary syndrome (ACS) is a type of coronary heart disease (CHD) that is responsible for one-third of total deaths in people older than 35. ACS involves three stages of coronary artery disease (CAD) that damage or destroy heart tissue, which are: unstable angina, non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI). The specific stage depends on where blood flow to the heart is blocked, in unstable angina and NSTEMI, the obstruction to flow is typically incomplete, whereas in STEMI, it is complete.[1] ACS is caused primarily by atherosclerosis, which is the build-up of plaque in the arteries. Risk factors for ACS include high blood pressure, high cholesterol, smoking, obesity, diabetes, and a family history of heart disease.

ACS can be treated with medications, such as antiplatelet agents, anticoagulants, and beta-blockers, as well as invasive procedures, such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).[2]

PCI is a non-surgical technique for treating obstructive CAD, including unstable angina. Despite the benefits of PCI in reducing major cardiovascular events, the risk of thrombotic complications remains an important concern. Aspirin, in combination with clopidogrel, prevents major thrombotic events in patients undergoing PCI and has been the standard of care for more than a decade, but preference is now being given to prasugrel and ticagrelor, two antiplatelet agents that are more potent and more rapidly active than clopidogrel.[3]

1.2. Myocardial ischemia–reperfusion injury:

STEMI is the most severe form of ACS and is a major global health concern. It occurs due to prolonged and severe myocardial ischemia, usually caused by the rupture or erosion of an atherosclerotic plaque in a coronary artery, leading to the formation of a blood clot that blocks the artery. Timely and complete restoration of blood flow, achieved through procedures like primary percutaneous coronary intervention (pPCI) or thrombolytic therapy, is the most effective way to minimize the damage, preserve heart function, and reduce the risk of heart failure in STEMI patients.[4] pPCI is preferred over thrombolytic therapy where facilities are available. However, the restoration of blood flow, while crucial, can also cause additional damage known as reperfusion injury, which can worsen the prognosis for STEMI patients.[5]

Reperfusion injury is a complex phenomenon involving multiple pathways, including the role of cell-mediated immunity, microvascular dysfunction, and the influence of various factors such as left ventricular hypertrophy, diabetes mellitus, and chronic ischemia.[6] Despite the advances in reperfusion therapies, the mortality rate remains relatively high, and further research is needed to address the challenges posed by reperfusion injury and to bring promising cardio-protective strategies to clinical practice. Therefore, while reperfusion therapies are essential for saving the heart muscle from dying, they also present challenges that need to be addressed to improve outcomes for STEMI patients.[7]

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

The focus of antithrombotic therapy in patients with ACS or undergoing PCI has traditionally been on reducing ischemic events, including both ischemic recurrences and local ischemic events such as stent thrombosis. However, in recent years, there has been a growing concern about the most relevant adverse event associated with antithrombotic therapy which is bleeding. This is particularly important because bleeding risks can be significant and can lead to poor outcomes. Therefore, it is essential to balance the risk of bleeding against the risk of ischemia.[8] Recent randomized controlled trials (RCT) have shown promising results for a strategy of more intense antithrombotic therapy in the first 1-3 months after ACS/PCI, followed by a de-escalation of antiplatelet therapy thereafter. This approach aims to balance the risk of ischemia and bleeding, which is a significant concern associated with antithrombotic therapy.[9]

The two main de-escalation approaches currently adopted in patients with ACS consist in the shortening of dual antiplatelet therapy (DAPT) duration and in the mitigation of P2Y12 inhibition after a short course of standard DAPT. The former may be classified according to the single antiplatelet agent used after shortening of DAPT (aspirin vs. P2Y12 inhibitor monotherapy), while the latter strategy may be classified depending on whether tools to guide the selection of P2Y12 inhibition are used or not (guided vs. unguided de-escalation).[10]
The shortening of DAPT commonly involves discontinuing the P2Y12 inhibitor before the typically recommended 3 or 6-month period post-PCI. More recently, trials and practice guidelines have considered the cessation of aspirin and the continuation of P2Y12 inhibitor monotherapy, either 1 or 3 months after ACS or PCI.[11]

De-escalation can be achieved with different antithrombotic strategies and can be either unguided or guided by platelet function or genetic tests. These two tools of guidance can be laboratory-based or point-of-care, with platelet function testing (PFT) being preferred for practical reasons such as ease of use and providing results in a timely fashion. Genetic testing allows for the identification of genetic variants, including loss of function (LoF) alleles, of the CYP2C19 gene.[12]

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 according to preclinical studies. The extent of damage from each process is related to the duration of ischemia and the level of residual blood flow during coronary occlusion. Ischemia-induced damage increases with the severity and duration of blood flow reduction, while reperfusion injury peaks at a moderate level of ischemic damage.[30]

During ischemia, the interruption of blood supply leads to tissue injury or death, which is influenced by the magnitude and duration of the ischemic stroke. The lack of oxygen and nutrients during this period can trigger a cascade of events within the affected cells, leading to energy depletion, ion imbalance, and the accumulation of toxic by-products. These processes can ultimately result in cellular damage and, in severe cases, cell death.[31] Reperfusion, while necessary to restore oxygen and nutrient delivery, can exacerbate the injury caused by ischemia and lead to irreversible damage. The restoration of blood flow can lead to the generation of reactive oxygen species, which can cause further damage to the already compromised cells.[32] Additionally, the sudden reintroduction of oxygen can trigger inflammatory responses and the activation of cell death pathways, such as apoptosis, autophagy, necrosis, and necroptosis.[33] The total tissue injury induced by ischemia-reperfusion injury is thus divided into two parts: ischemia injury and reperfusion injury, each contributing to the overall damage observed in affected tissues.[30]

In a considerable number of patients with STEMI, despite the successful reopening of the blocked artery, a condition known as the 'no-reflow phenomenon' may occur, leading to ineffective myocardial reperfusion.[34] This state is attributed to coronary microvascular obstruction (MVO), which, in its most severe forms, is associated with capillary destruction and intramyocardial hemorrhage. It is noteworthy that the presence of preexisting endothelial dysfunction or genetic predisposition can increase the susceptibility to microvascular dysfunction and the no-reflow phenomenon.[35]

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

P2Y12 inhibitors, alongside aspirin, are commonly used to reduce blood clot-related issues in patients with ACS undergoing PCI. Recent guidelines prefer prasugrel or ticagrelor over clopidogrel due to their superior performance in reducing ischemic events.[13,14] However, these potent inhibitors can also increase the risk of bleeding and side effects, potentially affecting patient compliance. Consequently, patients often switch P2Y12 inhibitors during ACS treatment.[15] Early after ACS, the higher risk of blood clotting may outweigh bleeding risk, while in the chronic phase, the reduction in clotting risk becomes more significant than the bleeding risk reduction. Strategies for managing this include uniform or guided de-escalation to a milder P2Y12 inhibitor or early discontinuation of aspirin in favor of potent P2Y12 inhibitor monotherapy. These approaches not only contribute to bleeding avoidance but may also have economic benefits, making them common practices.[16]

However, de-escalating from a potent P2Y12 inhibitor can address the problem of high response variability with clopidogrel, leading to high on-treatment platelet reactivity (HPR) in many ACS patients. Genetic factors, like CYP2C19 LoF alleles (CYP2C19*2 and *3), contribute to this variability. Patients without these alleles respond similarly to clopidogrel, ticagrelor, and prasugrel.[17] Using PFT or genetic testing can enhance the safety of de-escalation by identifying patients at a higher risk of blood clotting events and selectively maintaining potent P2Y12 inhibition for these cases.[18]

Several recent randomized trials aimed to test various abatement schemes. However, these trials often lack sufficient power to thoroughly evaluate their effectiveness and safety. Additionally, both abatement strategies are potential alternatives that can mutually exclude each other. These trials compared them to conventional long-term treatment with potent P2Y12 inhibitors, but there is limited data comparing the two abatement strategies directly. This network meta-analysis (NMA) showed benefit in terms of ischemic and bleeding events after switching to either a less potent P2Y12 inhibitor through de-escalation or opting for potent P2Y12 monotherapy combined with aspirin discontinuation, however reduction of major bleeding risk was only significant with P2Y12 monotherapy.

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

Platelets are essential for hemostasis and become activated when they encounter damaged blood vessels or tissues. Platelet activation can be initiated by various mechanisms, including pathways mediated by thrombin, collagen, and adenosine diphosphate (ADP).[19] The ADP-mediated mechanism is one of the most crucial pathways for platelet activation. ADP binds to P2Y1 and P2Y12 receptors on platelet surfaces, activating intracellular signaling pathways that cause platelets to change shape, secrete granules, and aggregate.[20] Platelet activation is a complex process that involves other agonists such as thromboxane, and collagen, leading to platelet aggregation which results in the cross-linking of adjacent platelets and the formation of a platelet plug to seal the site of injury. Targeting platelet activation with antiplatelet therapy can help prevent platelet aggregation and the formation of blood clots that may lead to heart attacks and strokes.[21]

Clopidogrel was the primary P2Y12 receptor antagonist in clinical practice for many years, but its use exhibited drawbacks such as delayed onset of action, high interindividual response variability, and high residual platelet reactivity during treatment.[22] Prasugrel and ticagrelor represent the next generation of ADP receptor antagonists with a shorter onset of action and more consistent inhibition of platelet aggregation. They have demonstrated a higher risk reduction for thrombosis compared to clopidogrel in patients with ACS in the TRITON-TIMI 38 and PLATO trials.[13,14] However, trials testing these drugs in lower-risk populations failed to prove their benefit compared to clopidogrel. Recent trials have sought to personalize antiplatelet therapy based on the patient's characteristics, adjusting antiplatelet use according to changes in risk during the clinical course.

PFT is a valuable ex vivo method for evaluating the effectiveness of clopidogrel treatment, which requires a two-step activation process in the liver to produce its active metabolite.[23] However, genetic variations in CYP2C19 activity and the esterase mediated degradation of over 60% of the drug, as well as absorption issues in critically ill patients, can lead to insufficient active metabolite production and an inadequate response to clopidogrel, increasing the risk of blood clots.[22] ADP-specific PFTs are designed to detect alterations in P2Y12-specific signaling or aggregation and may be used to monitor the achieved antiplatelet action. Various methods exist for PFT, including light transmission aggregometry (LTA), VerifyNow P2Y12 assay, and Multiplate analyzer.[24] If patients exhibit a poor response to clopidogrel, alternative antiplatelet medications such as ticagrelor or prasugrel may be more effective. PFT can also be used to monitor the effectiveness of these alternative therapies and adjust dosages as necessary.[25]

Genetic polymorphisms affecting the function of enzymes responsible for clopidogrel metabolism can lead to variable levels of clopidogrel metabolism and platelet inhibition, potentially affecting clinical outcomes.[26] Several cytochrome P450 (CYP) enzymes, including CYP2C19, are involved in clopidogrel metabolism. The most common CYP2C19 variant alleles are the LoF alleles *2 and *3, which result in reduced enzymatic activity and lower levels of active metabolite formation (Figure 1).[27] Studies have shown that carriers of CYP2C19 LoF alleles have a higher risk of recurrent ischemic events and stent thrombosis compared to non-carriers, particularly in patients with ACS undergoing PCI.[28]

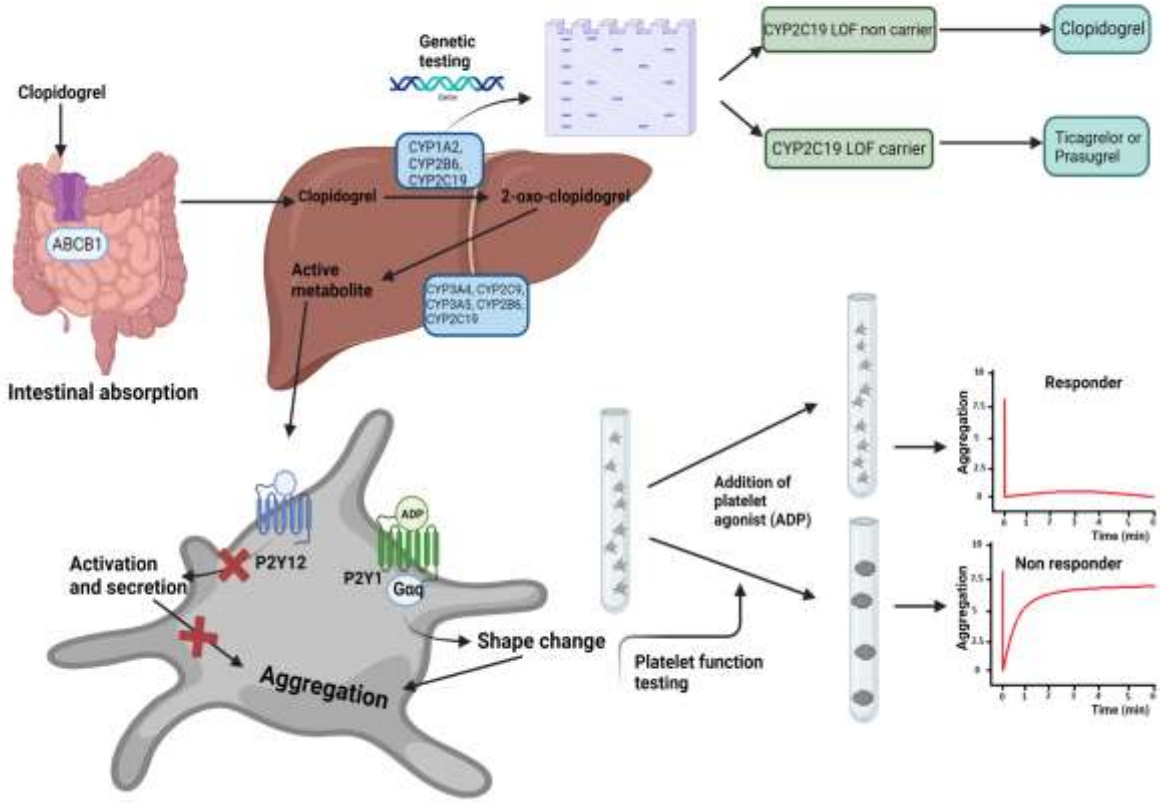


Figure 1: Genetic carrier status and the in vitro measurement of residual platelet function testing (PFT) may be used to identify patients with a higher risk for clopidogrel inefficacy.

In addition to CYP2C19, other genetic polymorphisms affecting clopidogrel metabolism have been studied, such as ABCB1 and PON1, but their clinical relevance remains unclear. The clinical significance of genetic testing for CYP2C19 polymorphisms is still under debate.[28] The 2017 American College of Cardiology/American Heart Association guidelines recommend testing for CYP2C19 LoF alleles in patients undergoing PCI who will receive clopidogrel therapy.[29] However, other guidelines, such as those from the European Society of Cardiology, do not recommend routine genetic testing due to the lack of conclusive evidence regarding its clinical utility.[5]

This review shows that uniform unguided P2Y12 de-escalation strategies have consistently shown a reduction in bleeding events without compromising efficacy while genetic testing-guided de-escalation strategies and de-escalation using PFT guidance provided results showing no difference in bleeding or ischemic events between the de-escalation group and the standard group.

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 search query included specific medical subject heading (MeSH) terms linked with Boolean operators, aiming to find articles related to CAD, ACS, or cardiovascular disease, de-escalation, and ticagrelor, prasugrel, or clopidogrel. In addition, the reference list of relevant guidelines, reviews, editorials, and studies on this topic was searched to ensure a comprehensive literature review.

The review included studies that met specific eligibility criteria, which were: (1) being clinical studies with a prospective design that included patients who received DAPT schemes for the treatment of PCI, (2) being randomized studies that compared the clinical outcomes of a group of patients with P2Y12 inhibitor-based DAPT, and (3) evaluating the benefit of P2Y12 inhibitor monotherapy or switching to clopidogrel at a predefined time point (3 months), assisted by genetic testing, PFT, or without. The articles selected in the review met specific eligibility criteria and underwent full-text screening against the eligibility criteria outlined in the PICOS framework: patients who underwent coronary stent implantation and evaluated the effect of an intervention with dual antiplatelet abatement strategy with P2Y12 inhibitor monotherapy or P2Y12 inhibitor de-escalation to clopidogrel, compared with P2Y12 inhibitor plus aspirin DAPT, on bleeding, major adverse cardiovascular events (MACE), or mortality.

The systematic review was performed in accordance with the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Healthcare Interventions[36] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021258502).

The analysis had primary and secondary outcomes. The primary efficacy outcome was the occurrence of MACE, which was defined as the composite of cardiovascular mortality, myocardial infarction (MI), and stroke. The main safety endpoints were major bleeding and all-cause mortality. Secondary outcomes included the individual components of MACE and stent thrombosis. Safety outcomes, such as the frequency of major and minor bleeding complications, were also evaluated. In the case of multiple bleeding definitions, data were extracted according to the Bleeding Academic Research Consortium (BARC) criteria, defining type 3 or type 5 as major and type 2 as minor bleeding. The Cochrane Collaboration tool was used to assess the methodological quality of the studies included in the analysis.

The rates of events with each antiplatelet treatment combination were entered as an individual study arm, and data were pooled in a multiple treatment NMA that allows integration of direct and indirect comparisons. The risk ratio (RR) and its standard error were calculated using a frequentist approach to construct an NMA model accounting for the correlated treatment effects.[37,38] A random-effects model was applied, and the estimated heterogeneity was added to the variance of each comparison. The random-effects model was chosen based on the consideration that the true preventive effect of antithrombotic treatment may vary from study to study and is influenced by the heterogeneity of the included trials. The amount of inconsistency and heterogeneity in the network were also calculated to assess the validity of the analysis.[37,39]

The effect sizes were displayed as forest plots with potent DAPT set as a reference to facilitate interpretation. A comparative ranking of the treatments was performed using the P-scores method, which is a frequentist analog of SUCRA. The P-scores method reflects the certainty that one treatment protocol is better than another.[37]

The studies included in the analysis were assessed for potential bias using the Cochrane Collaboration's bias assessment tool and a comparison-adjusted funnel plot supplemented with Eggers' test results to assess publication bias.[40] The assumption of consistency was assessed by comparing and visualizing direct and indirect evidence. Additional exploratory analyzes included stratification and subgrouping based on different de-escalation strategies, patient population, study size, and follow-up time. The calculations were performed using R statistical software package version 4.0.3,[41] using the packages "meta 4.11-0," "netmeta 1.2-0," and "gemtc 0.8-4".[42] A p-value of < 0.05 was considered statistically significant to determine the validity of the analysis.

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

In this literature review, a computerized search was conducted in the following electronic databases: PubMed (MEDLINE), EMBASE, and the Cochrane Library, limiting the search to papers until January 2023, without any language restriction. The following keywords were used: antiplatelet therapy, de-escalation, ACS, PFT, genetic testing, individualized therapy. Data was collected from articles reporting RCTs with a P2Y12 De-escalation approach, such as PFT guidance, genetic testing guidance, and uniform de-escalation, for ACS patients undergoing PCI.

The analysis involved the inclusion of studies that adhered to specific criteria: (1) RCTs, (2) studies involving patients who had undergone PCI and were administered DAPT, (3) studies that conducted a comparative analysis of the clinical outcomes among a group of patients who utilized DAPT based on P2Y12 inhibitors, (4) studies that evaluated the potential benefits of individualized or uniform de-escalation strategies for antiplatelet therapy in patients with ACS. Conversely, studies were excluded if they failed to meet any of these criteria: (1) studies that were not RCTs, (2) studies where the outcomes of interest were either not reported or could not be extracted or calculated from the published data, and (3) any duplicate publications that were identified.

In this study, the data needed for the analysis were extracted. A multiple treatment analysis was used to analyze the potential antiplatelet combinations. Each combination was entered as an individual study arm, and data were pooled to allow for integration of direct and indirect comparisons. The RR and its standard error were calculated using a frequentist approach to construct an NMA model that accounted for the correlated treatment effects. A random-effects model was applied by adding the estimated heterogeneity to the variance of each comparison using an adaptation of the DerSimonian-Laird estimator. The I^2 values, which reflect the degree of variation or inconsistency within the data, were calculated along with the Cochran's Q statistics and its associated p-value. These statistical measures helped assess the level of heterogeneity present within the network. Additionally, a comparative ranking of the treatments according to the P-scores method was performed.

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 trials involved patients who underwent coronary intervention and stent implantation following an acute coronary syndrome event, with two exceptions where patients after planned coronary intervention were also included. 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. Table 1 displays the characteristics and designs of the included RCTs. The P2Y12 inhibitor de-escalation strategy was guided by PFT in one study, genetic testing in two, and was unguided (uniform) in four studies. The trial sizes varied from 131 to 15,968 participants, and the follow-up duration ranged from 1 week to 12 months. In the Global Leaders trial, patients were followed for 24 months after coronary intervention. However, since patients received ticagrelor monotherapy or conventional DAPT during the first year and aspirin or ticagrelor monotherapy during the second year, we extracted data from the analysis conducted during the first 12 months.[43]

First author	Claassens	Cuisset	Kim	Sibbing	Pereira	Ueno	Park	Kim	Mehran	Vranckx
Publication year	2019	2017	2020	2017	2020	2016	2021	2020	2019	2018
Acronym	POPular Genetics	TOPIC	HOST-REDUCE-POLYTECH-ACS	TROPICAL-ACS	TAILOR-PCI	-	TALOS-AMI	TICO	TWILIGHT	GLOBAL LEADERS
Design	R open label	R, open label, single centre	R, open label, multi centre	R, open label, multi centre	R, open label, multi centre	R, open label, multi centre	R, open label, multi centre	R, multi centre	R, open label	R, OPEN LABEL
Number of patients	2751	646	2338	2610	5302	131	2590	3056	7119	15968
Time between PCI and randomization	48 hours	1 month	1 month	2 weeks	72 hours	At the PCI	1 month	3 months	3 months	1 month
STEMI (%)	100	40	14	55	22	48	54	36	0	13
NSTEACS (%)	0	60	85.2	44	59	52	46	64	30	34
UAP (%)	0	NA	60	0	30	39	0	31.	70	13
CCS (%)	0	0	0	0	18	47	0	0	35	47
Clopidogrel (Experimental/Control) (%)	60.6/7.0	100/0	-	100/0	15/99	100/0	100/0	36/33	-	53/53.2
Prasugrel (Experimental/Control) (%)	1 / 2.3	56/59	100/100	0/100	-	0/100	-	-	-	-
Ticagrelor (Experimental/Control) (%)	38.1/90.5	44/42	-	-	85/1	-	0/100	73/70	0/100	47/46.8
Study group Type	P2Y12-De	P2Y12-De	P2Y12-De	P2Y12-De	P2Y12-De	P2Y12-De	P2Y12-De	P2Y12-Mo	P2Y12-Mo	P2Y12-Mo
Definition of bleeding (Primary/Secondary)	PLATO/BARC	TIMI/BARC	BARC	BARC	BARC/TIMI	BARC/TIMI	BARC	TIMI	BARC/TIMI,GUSTO,ISTH	BARC
End point	Bleeding, MACE, ST, TVR	Bleeding, UREV, MACE	Bleeding, TVR, MACE, ST	Bleeding, MACE, UREV, ST	CVD, MI, ST, Stroke, SRI	PRU	CVD, MI, Stroke, Bleeding	Major bleeding, Death, MI, ST, TVR, Stroke	Bleeding, MI, Stroke, Death	Q-wave MI, Death
Follow-up, months	12	12	12	12	12	1,5	12	12	12	24
Age (mean ± SD)	61.7±11.3	60.0 ±10.2	58.8 (9.0)	58.7 (10.2)	62 (21-95)	68.8 ± 10.3	60 ± 11	61(11)	65.01±10.3	64.5±10.3
Female, N (%)	317(25.5)	114(18)	251(10.75)	2052(78.5)	1738 (32.78)	32 (24,4)	454 (16.8)	628 (20.5)	1698 (23.8)	3714 (23.2)
DM, N (%)	288(11.6)	177(27)	990(42.3)	527(20)	1938 (36.55)	53 (40.5)	731 (27.2)	835(27)	2620(36.8)	4038 (25.3)
Smoking, N (%)	1127(45.8)	286(44)	838(71.7)	1182(45)	1752 (33.04)	NR	-	1142(37)	1548(21.7)	4169 (26.2)
HTN, N (%)	1032(41.4)	313(48)	1476(63.1)	1599(61.5)	4409 (83.15)	89 (67.9)	1318 (48.9)	1541(50.5)	5154(72.4)	11705 (73.6)
DES, N (%)	NR	585(91)	2338(100)	2005(77)	NR	NR	-	NR	NR	19415 (94.6)
PCI approach (%)	NR	Femoral (4) Radial(96)	NR	NR	NR	NR	Femoral (49.4) Radial (49.4)	NR	NR	Femoral (26) Radial (74)

Table 1: describes the main characteristics of the included studies.

R randomized, *ACS* acute coronary syndrome, *BARC* Bleeding Academic Research Consortium Criteria, , *DES* drug-eluting stent, *DM* diabetes mellitus, *HTN* Hypertension, *LD* loading dose, *MD* maintenance dose, *MACE* major adverse cardiac events, *NR* not reported,, *O* observational study, *R* retrospective, *SD* standard deviation, *ST* stent thrombosis, *TIMI* Thrombolysis In Myocardial Infarction, *TVR* target vessel revascularization, *UREV* urgent revascularization, *PLATO* Platelet Inhibition and Patient Outcomes, *MI* Myocardial infarction, *SRI* Severe Recurrent Ischemia, *PRU* P2Y12 Reaction Unit, *STEMI* ST-segment elevation MI, *NSTEACS* non-ST-segment elevation acute coronary syndrome, *UAP* unstable angina pectoris, *CCS* chronic coronary syndrome, *De* de-escalation, *Mo* monotherapy.

Three trials implemented strategies for the selective de-escalation of P2Y12 inhibitors. Among these trials, the POPular Genetics trial[17] and the TAILOR-PCI[44] trial utilized genetic testing through TaqMan assays. In the POPular Genetics trial, individuals carrying the LoF CYP2C19 allele were administered either ticagrelor or prasugrel (comprising 49% of the participants), while those without the allele (CYP2C19*1/1) received clopidogrel (making up 51% of the participants). In the TAILOR-PCI trial, patients identified as having CYP2C19*2 or *3 LoF alleles (referred to as CYP2C19 LoF carriers) were prescribed ticagrelor for ongoing therapy or prasugrel if ticagrelor was not well-tolerated. Non-carriers or individuals with inconclusive test results were prescribed clopidogrel.

In the TROPICAL-ACS trial[18], they implemented a treatment plan for reducing platelet function based on testing. Patients in the group where they reduced P2Y12 inhibitor treatment received a treatment regimen after leaving the hospital. This regimen involved taking prasugrel for one week at either 10 or 5 mg per day, followed by one week of clopidogrel at 75 mg per day. Additionally, they measured platelet function while the patients were on clopidogrel two weeks after being discharged from the hospital. This approach was guided by PFT.

Bias risk was evaluated in all the trials, revealing minimal risk across all categories of bias (Figure 2 and 3).

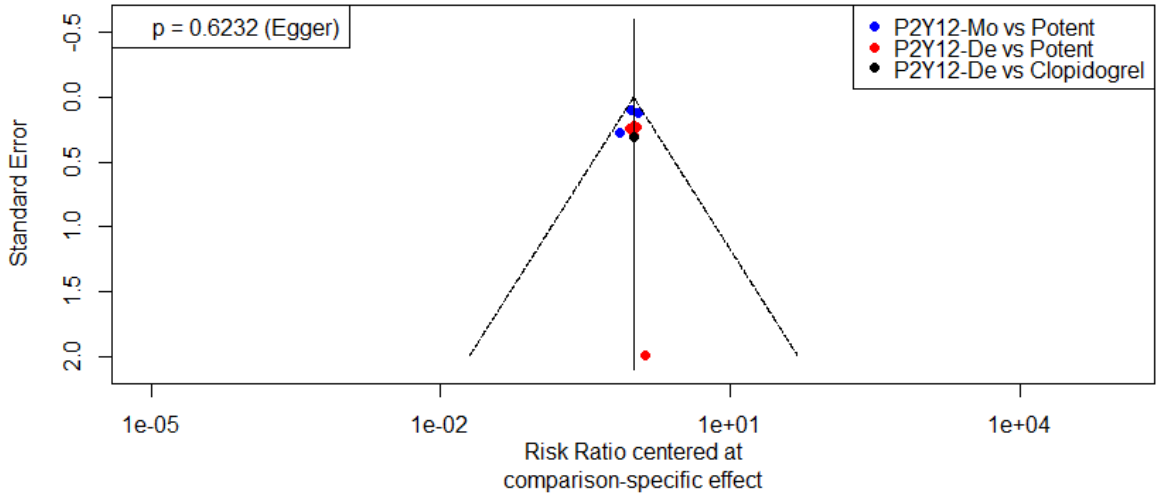
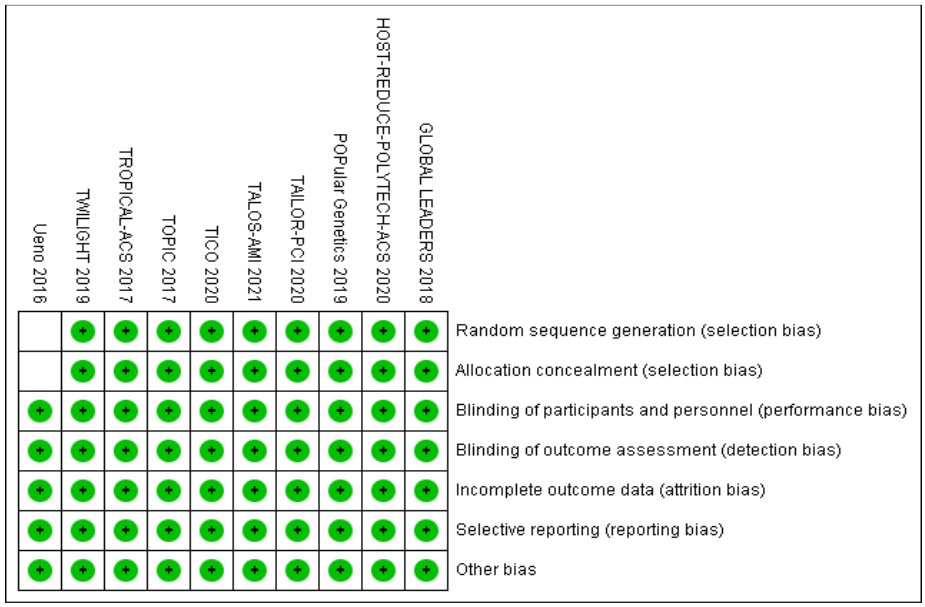


Figure 2: Assessment of publication bias. Comparison-adjusted funnel plot showed no signs of important publication bias. *Abbreviations*: P2Y12-De; P2Y12 inhibitor de-escalation, P2Y12-Mo; potent P2Y12 inhibitor monotherapy.



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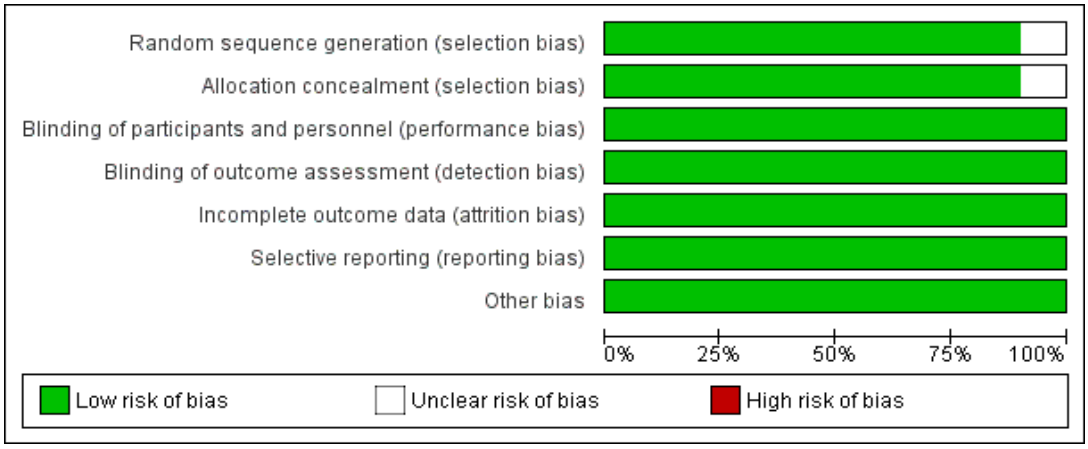
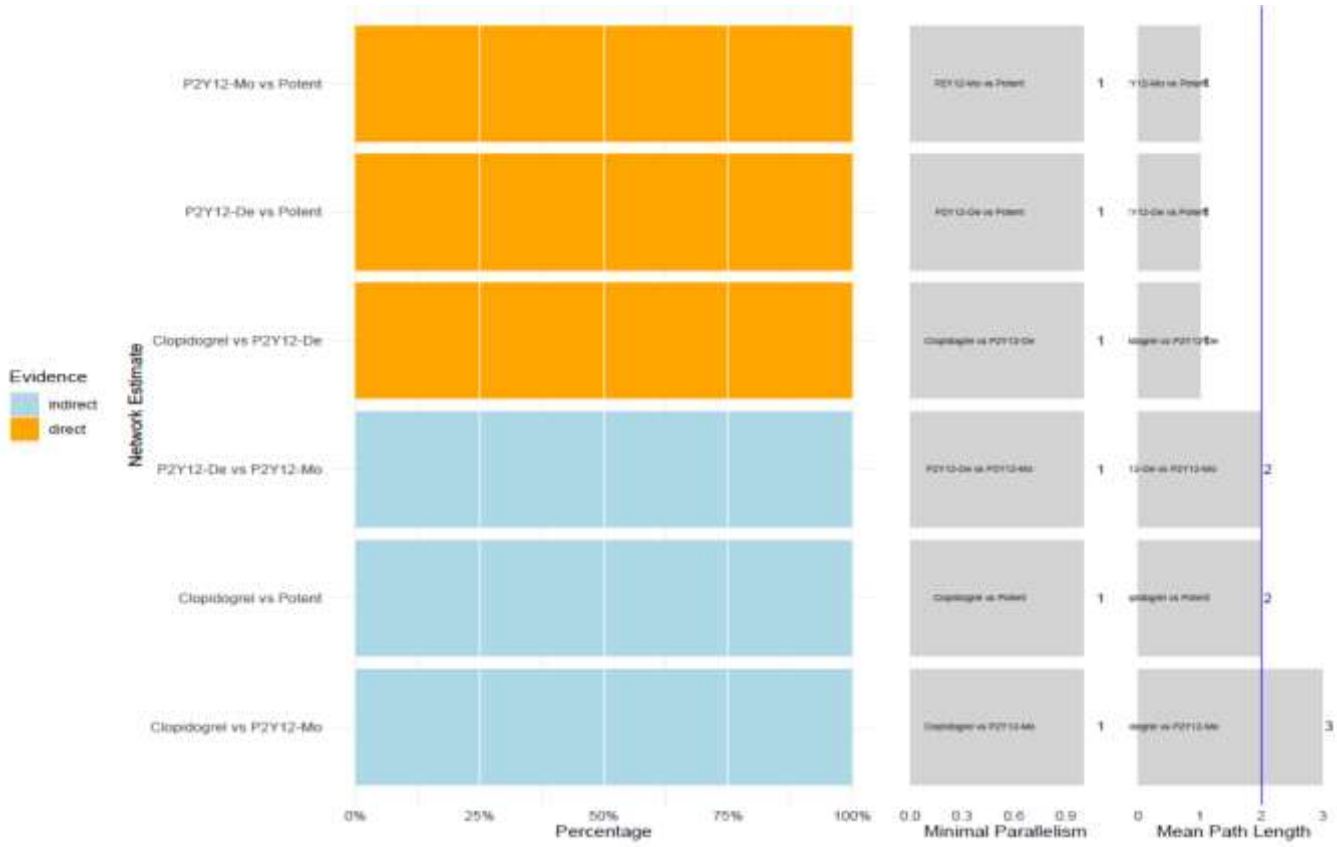


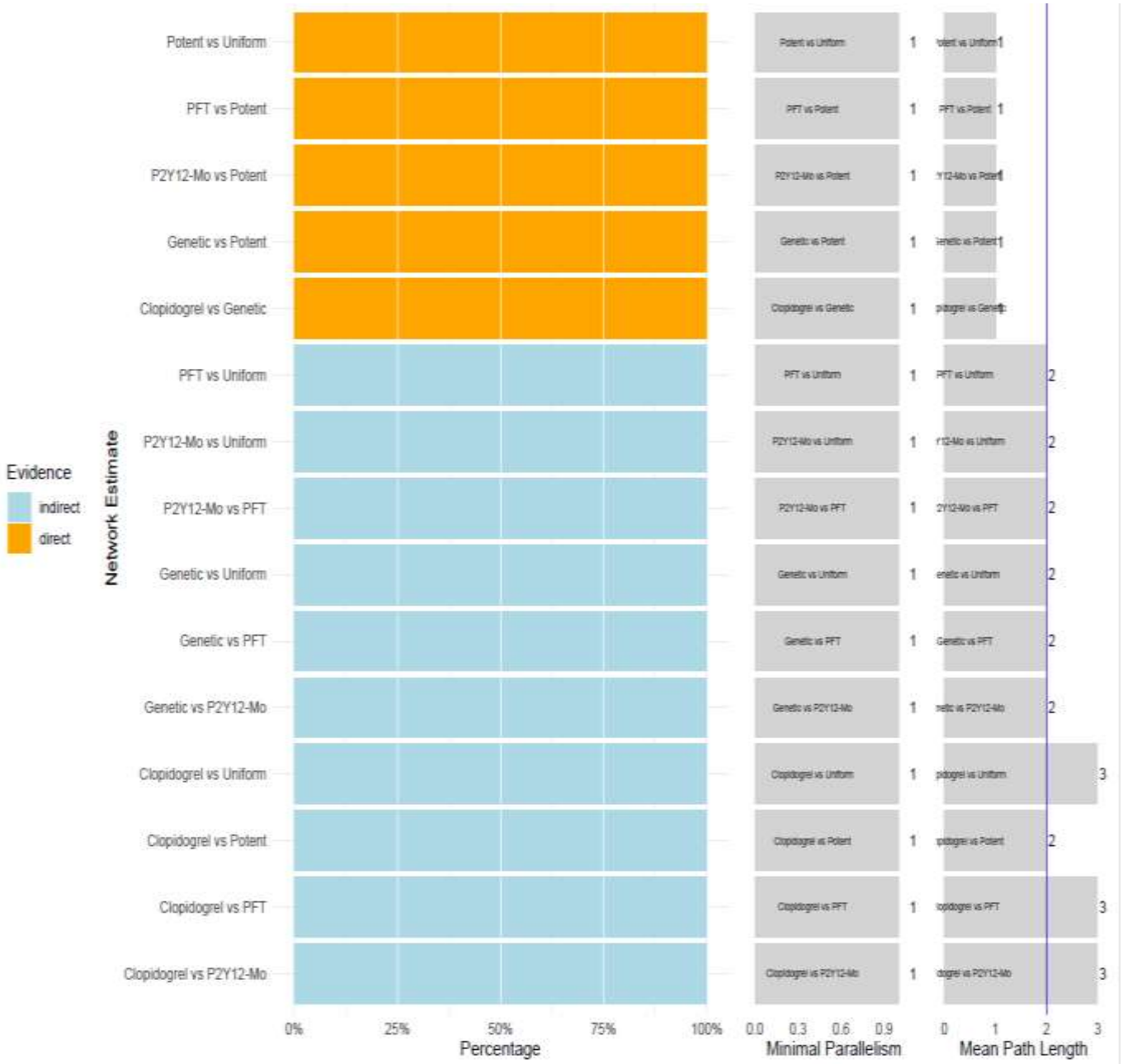
B

Figure 3: Assessment of bias. The chart shows the individual (Panel A) and the summarized results (Panel B) of the bias assessment of included trials using the Cochrane bias assessment tool. Of note is that in none of the studies was complete treatment blinding implemented, however, as the outcome was not directly influenced per the Cochrane Collaboration user instructions we evaluated detection bias as low risk of bias.
No blinding or incomplete blinding was evaluated.

The findings obtained through direct comparisons were consistent with those calculated using indirect comparisons (Figure 4).



Panel A



Panel B

Figure 4: Visualizing direct and indirect evidence in the entire network (Panel A) and in subgroups according to de-escalation strategies (Panel B). The proportion of direct and indirect evidence used to estimate each comparison is depicted. The plot also provides two additional metrics: the minimal parallelism and mean path length of each estimated comparison. According to König, Krahn, and Binder (2013), a mean path length > 2 means that a comparison estimate should be interpreted with caution.

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. These results showed consistency within the study designs ($p = 0.91$) and low variability between different study designs ($I^2 = 0\%$, ranging from 0.0% to 17.6%). Major bleeding rates were similar between P2Y12 inhibitor de-escalation and the control group, with no significant differences between trials [RR: 0.84 (0.57, 1.22)]. 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 5).

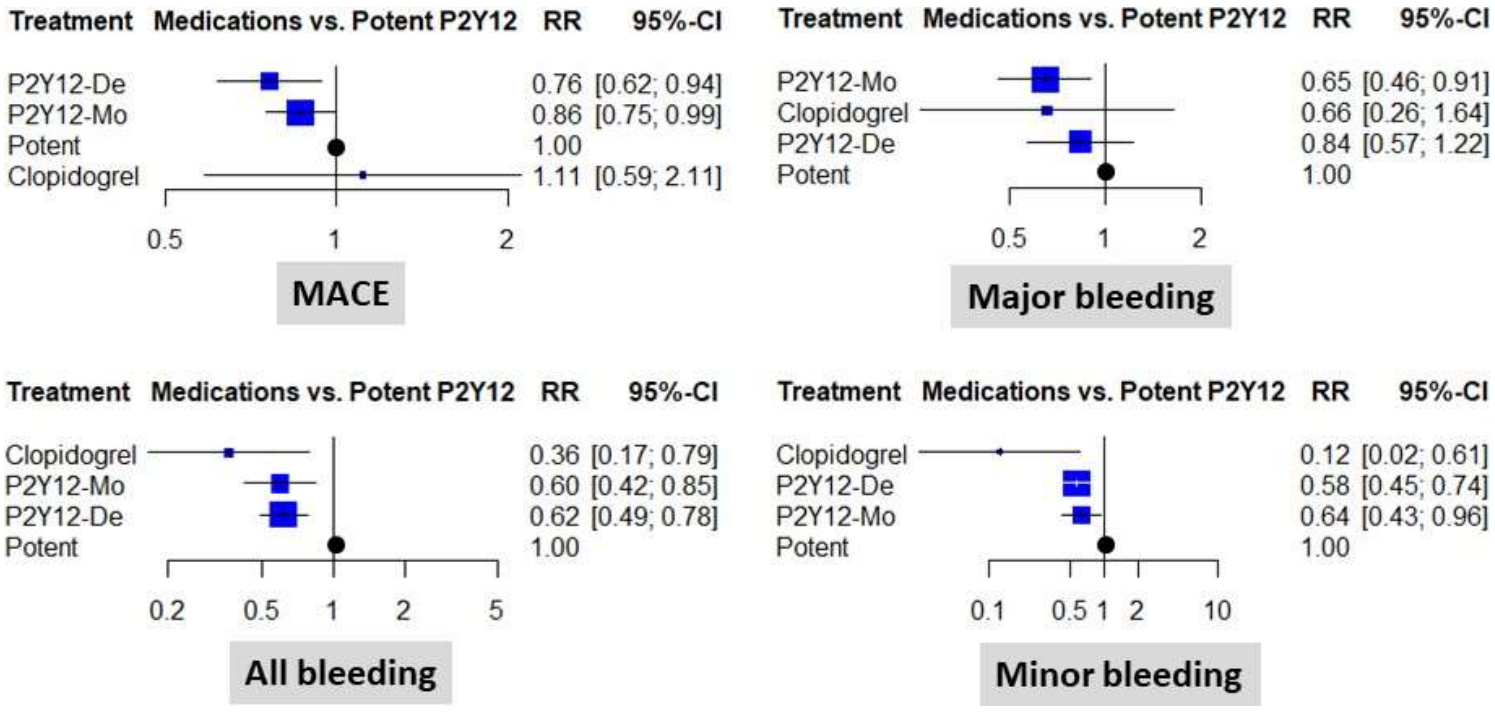


Figure 5: Clinical results of using different abatement strategies. The forest plots depict the results of the network meta-analysis (NMA) computed based on direct and indirect comparisons as risk ratio (RR) and 95% confidence intervals (95% CI). Data are presented as compared to the potent P2Y12 inhibitor-based dual antiplatelet therapy (DAPT) (marked as "Potent). MACE, major adverse cardiovascular events; P2Y12-De, P2Y12 inhibitor de-escalation; P2Y12-Mo, potent P2Y12 inhibitor monotherapy; Clopidogrel, clopidogrel based DAPT.

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 6).

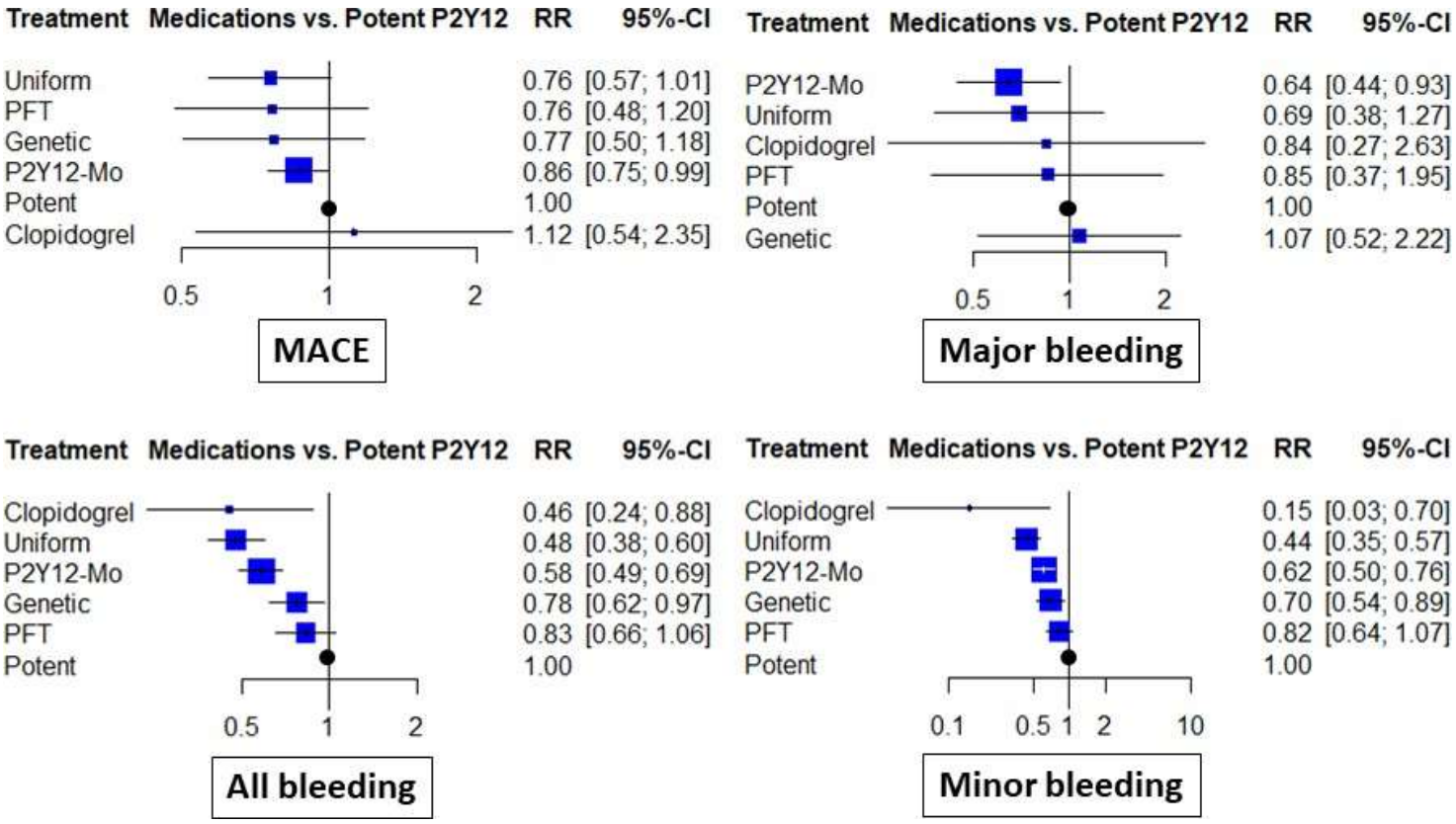


Figure 6: Clinical results of abatement strategies considering de-escalation strategies separately. The forest plots depict the RR and 95% CI achieved with the abatement strategies compared to the potent P2Y12 inhibitor-based DAPT for MACE, all bleeding (including major and minor events), as well as major bleeding and minor bleeding. In these analyses, de-escalation strategies were considered separate subgroups based on the use of genetic or platelet-function testing (PFT) guidance or uniform de-escalation. P2Y12-Mo, potent P2Y12 inhibitor monotherapy; Clopidogrel, clopidogrel based DAPT.

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 7).

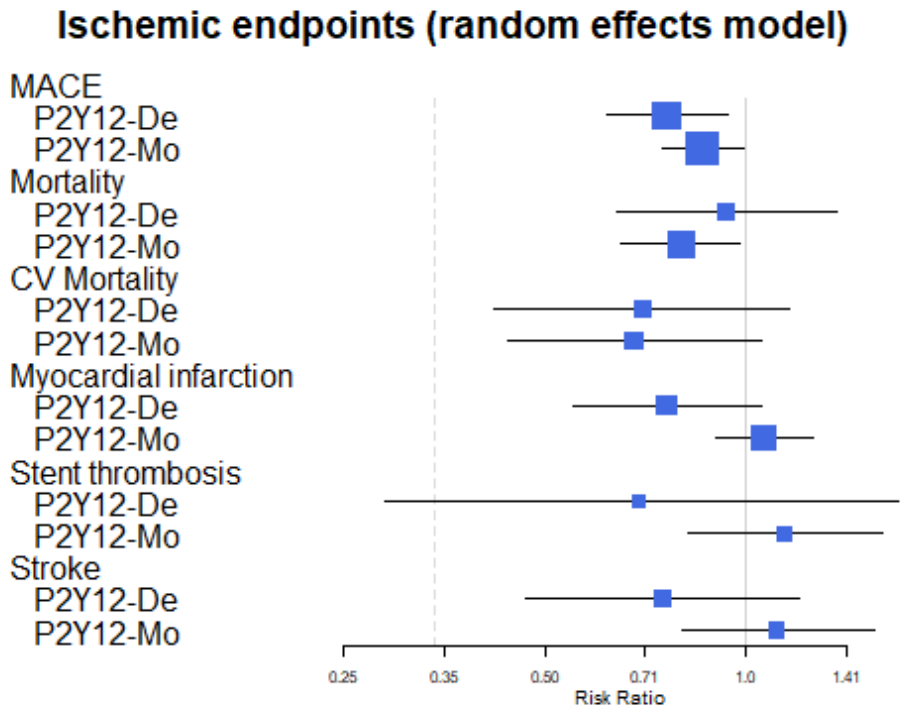


Figure 7: Results of the network analysis of ischemic endpoints. The forest plot depicts RR and 95% CI with the abatement strategies compared to the potent P2Y12 inhibitor based DAPT.

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).

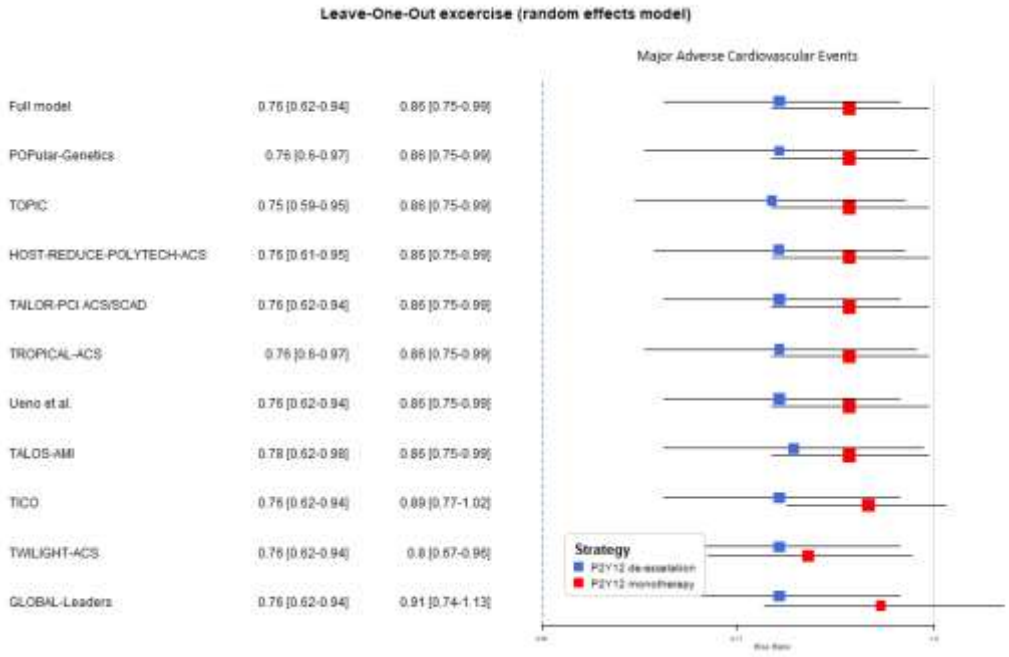
In every comparison between de-escalation and monotherapy, the effect estimates did not reach statistical significance. Yet, when examining specific subgroups of de-escalation strategies, it was found that uniform de-escalation produced estimates similar to monotherapy. However, the rates of both minor and major bleeding were significantly higher in the uniform de-escalation subgroup compared to monotherapy (Table 2).

	De-escalation	*Genetic*	*PFT*	*Uniform*
MACE	0.88 (0.68; 1.13)	0.89 (0.57; 1.39)	0.88 (0.55; 1.42)	0.88 (0.64; 1.21)
All Bleeding	1.03 (0.68; 1.57)	**1.33 (1.00; 1.75)**	**1.43 (1.06; 1.91)**	0.82 (0.62; 1.09)
CV Death	1.04 (0.53; 2.02)	1.34 (0.49; 3.63)	1.15 (0.39; 3.39)	0.80 (0.33; 1.96)
MI	0.71 (0.50; 1.03)	0.69 (0.37; 1.27)	0.81 (0.46; 1.42)	0.64 (0.35; 1.17)
Stroke	0.67 (0.38; 1.19)	0.66 (0.25; 1.72)	0.39 (0.10; 1.55)	0.76 (0.39; 1.50)
Mortality	1.17 (0.76; 1.80)	1.26 (0.65; 2.45)	1.15 (0.50; 2.68)	1.10 (0.60; 2.04)
Stent Thrombosis	0.61 (0.24; 1.56)	0.59 (0.09; 3.61)	0.58 (0.09; 3.60)	0.63 (0.17; 2.27)
Major Bleeding	1.29 (0.78; 2.14)	1.67 (0.74; 3.78)	1.33 (0.53; 3.29)	1.08 (0.53; 2.20)
Minor Bleeding	0.90 (0.56; 1.44)	1.13 (0.82; 1.56)	1.33 (0.96; 1.86)	0.72 (0.52; 0.99)

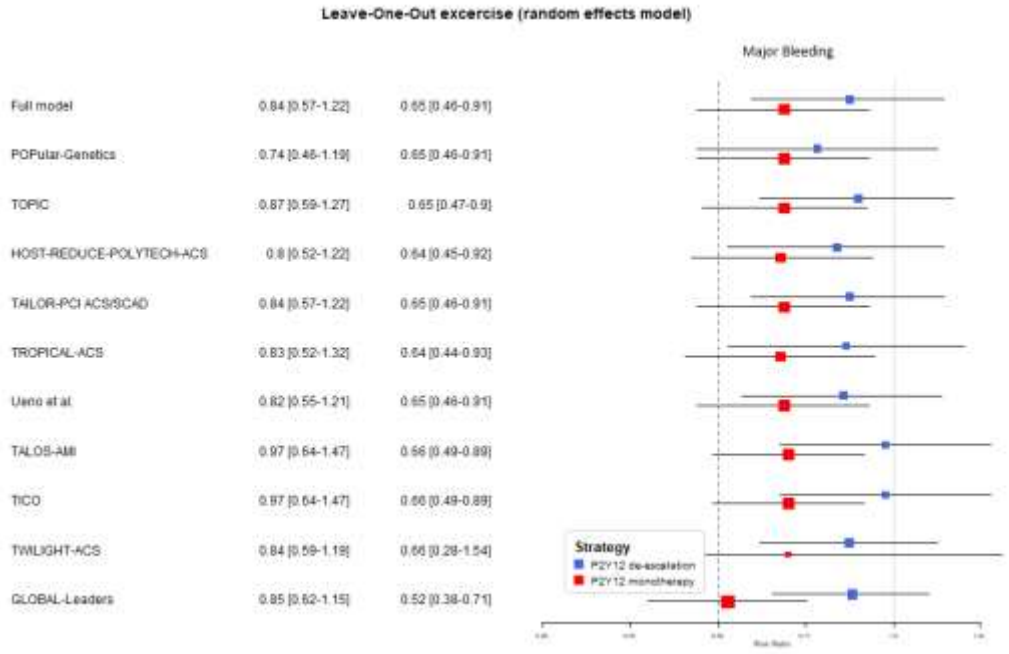
Table 2: Results of the analyses of subgroups of de-escalation strategies. The table depicts risk ratio and 95% CI of the different subgroups of de-escalation strategies results compared with uniform de-escalation. Abbreviations: MACE: major adverse cardiovascular events, MI: myocardial infarction, PFT: platelet function test.

The leave-one-out sensitivity exercises did not reveal any indication of individual studies having an excessive influence on the network (Figure 8).

Additionally, the consistency of the findings was supported by further subgroup analyses (Figure 9).

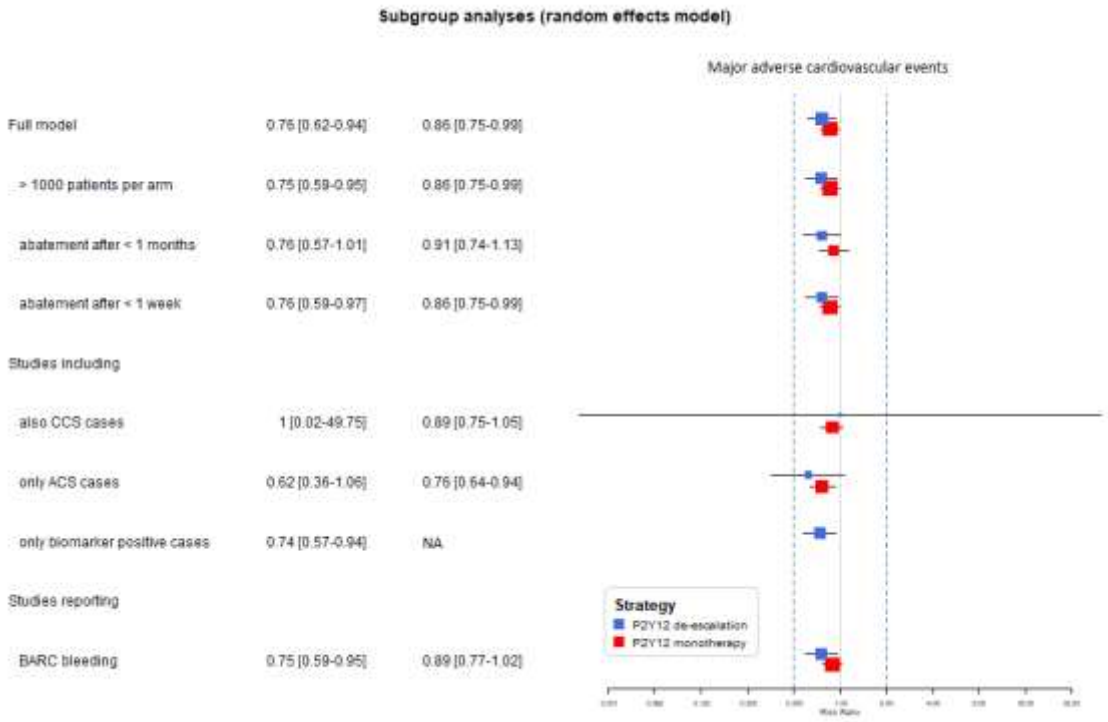


A

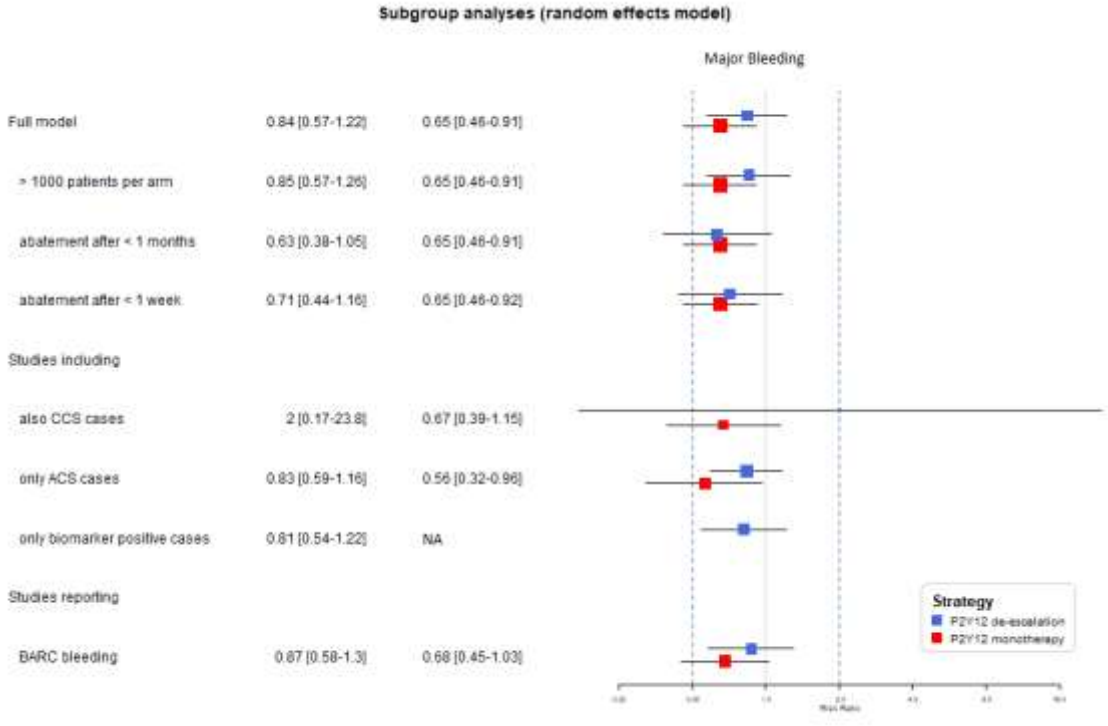


B

Figure 8: Results of the leave- one-out sensitivity exercises. The forest plots depict the results of the random effect network analyses of the risk of MACE (Panel A) and major bleeding (Panel B). Data are presented as relative risk and 95% confidence interval (RR [95%CI]) compared to the potent P2Y12 inhibitor based DAPT in the full model and in analyses performed with individual studies ignored.



A



B

Figure 9: Results of the subgroup analysis. The forest plots depict the results of the random effect network analyses of the risk of MACE (Panel A) and major bleeding (Panel B). Data are presented as relative risk and 95% confidence interval (RR [95%CI]) compared to the potent P2Y12 inhibitor based DAPT. *Abbreviations*: CCS: chronic coronary syndrome, ACS: acute coronary syndrome, NA: not available, BARC: Academic Research Consortium bleeding definition.

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

Genetic testing can be employed to pinpoint individuals who may not have a favorable response to clopidogrel, which could have lasting consequences for their risk of ischemic events. Nevertheless, the selective use of potent P2Y12 inhibitors in those with loss-of-function genetic variants did not yield better clinical outcomes.[45,46] The TAILOR-PCI trial implemented a strategy based on carrier status, aiming to de-escalate treatment. 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) (Table 3).[44] 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 10).

Study	TALOS-AMI trial	HOST-REDUCE-POLYTECH-ACS	TAILOR-PCI	TOPIC	TROPICAL-ACS	-
First author	Park	Kim	Pereira	Cuisset	Sibbing	Ueno
Publication year	2021	2020	2020	2017	2017	2016
Number of patients	2,697	2,338	5,302	646	2,610	131
De-escalation strategy	Uniform unguided de-escalation	Uniform unguided de-escalation	Genotype – guided therapy	Uniform unguided de-escalation	Guided by platelet function testing	Uniform unguided de-escalation
Primary outcome	NACE (CVD+MI+Stroke+ Bleeding)	NACE (Death+MI+ST+SRI +Bleeding)	CVD+MI+ST+ RR+Stroke	CVD+UR+ Stroke +Bleeding	CVD+MI+ Stroke+ Bleeding	PRU
Definition of bleeding (Primary/Secondary)	BARC	BARC	BARC/TIMI	TIMI/BARC	BARC	BARC/TIMI
Treatment used before de-escalation	Ticagrelor + Aspirin	Prasugrel + Asprin	Ticagrelor + Aspirin	Ticagrelor or Prasugrel + Aspirin	Prasugrel + Aspirin	Prasugrel + Aspirin
Treatment used after de-escalation	Clopidogrel + Aspirin	Prasugrel + Aspirin	Clopidogrel + Aspirin	Clopidogrel + Aspirin	Clopidogrel + Aspirin	Clopidogrel + Aspirin
Clopidogrel (Experimental/ Control) (%)	100/0	-	15/99	100/0	100/0	100/0
Prasugrel (Experimental/ Control) (%)	0/100	100/100	-	56/59	0/100	0/100
Ticagrelor (Experimental/ Control) (%)	0/100	-	85/1	44/42	-	-
Result	Significant decrease in bleeding risk	Reduced risk of NACE	No significant results	Reduced risk of bleeding	No significant results	Increase in PRU

Table 3: Describes the main characteristics of the de-escalation studies. Abbreviations: *BARC:* Bleeding Academic Research Consortium Criteria, *NACE:* net adverse clinical events, *ST:* stent thrombosis, *TIMI:* Thrombolysis In Myocardial Infarction, *PLATO:* Platelet Inhibition and Patient Outcomes, *MI:* Myocardial infarction, *PRU:* P2Y12 Reaction Unit, *SRI:* Severe Recurrent Ischemia, *CVD:* cardiovascular death, *UR:* urgent revascularization.

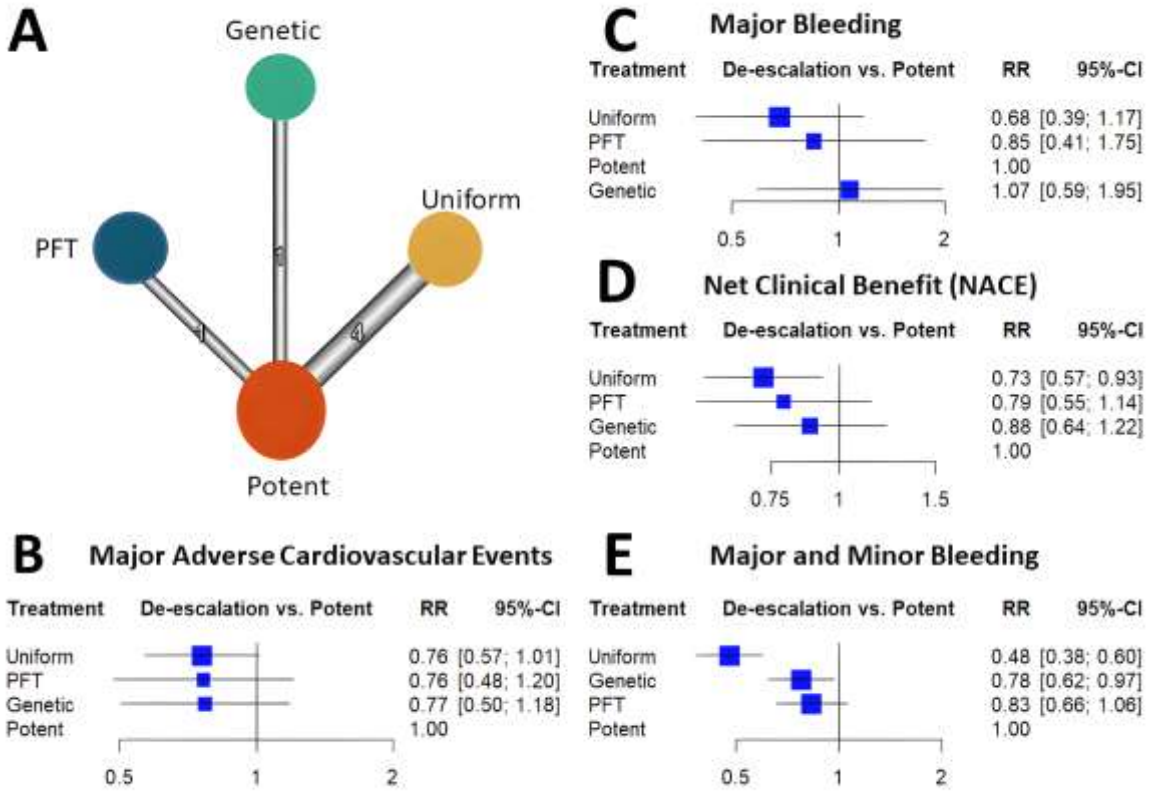


Figure 10: NMA results of randomized trials of P2Y12 de-escalation. Network graph depicts the available trial information. Nodes are proportional with the number of patients included and edges are proportional with the number of studies performed (Panel (**A**)). Forest plots depict the results of NMA showing the RR and its 95% CI compared to the control arm using long-term potent P2Y12 inhibition. MACE is defined as composites of cardiovascular mortality, MI, and stroke. NACE is defined as composite of MACE and major bleeding (Panel (**B**–**E**)).

In the TROPICAL-ACS trial, PFT-based P2Y12 de-escalation strategy was used. The study conducted a randomization of 2610 ACS patients undergoing PCI. They were divided into two groups: one received standard DAPT consisting of aspirin and prasugrel, while the other followed a de-escalation strategy guided by PFT. In the de-escalation group, patients initially received prasugrel for one week, followed by clopidogrel for another week. The decision for long-term P2Y12 inhibitor treatment was contingent on the results of the ADP-specific platelet function assay. Those with acceptable residual platelet reactivity continued with clopidogrel, whereas individuals with high reactivity were switched back to prasugrel. This latter group constituted 38.8% of the de-escalation arm.[47]

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 10).

Among the trials with uniform P2Y12 de-escalation strategy, the TOPIC trial, which stands for the study testing responsiveness to platelet inhibition on chronic antiplatelet treatment for ACS, 646 patients with ACS who were on DAPT were randomly assigned to either switch to clopidogrel or continue with the newer P2Y12 inhibitor one month after undergoing PCI. The study's primary outcome, which included cardiovascular death, MI, stroke, or stent thrombosis, was observed in 26.3% of patients who did not switch and 13.4% of those who switched (HR: 0.48, [95% CI: 0.34–0.68], p < 0.01). There were no significant differences in terms of ischemic events between the two groups, but bleeding events occurred in 4.0% of patients in the switched DAPT group and 14.9% in the unswitched DAPT group (HR: 0.30, [95% CI: 0.18–0.50], p < 0.01).[48]

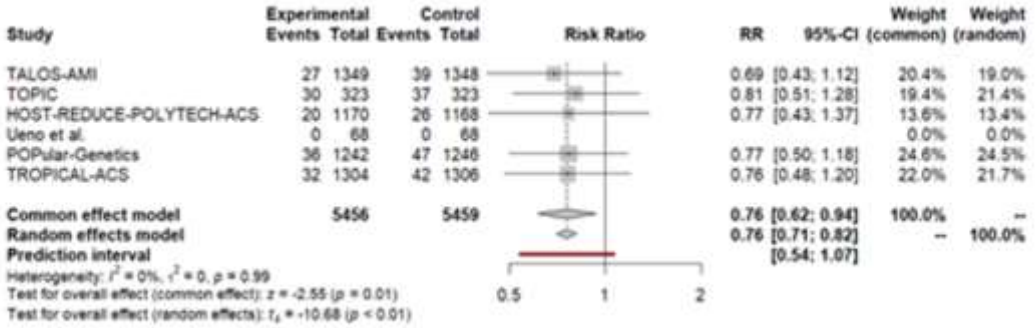
In the HOST-REDUCE-POLYTECH-ACS trial, 2338 patients with ACS who were on DAPT were randomly assigned to either maintain their current prasugrel dose of 10 mg or receive a reduced dose of prasugrel at 5 mg. The trial's primary endpoint, which consisted of a combination of cardiovascular death, MI, definite stent thrombosis, or ischemic stroke, was observed in 7.2% of patients in the de-escalation group and 10.1% of patients in the standard care group (p -noninferiority < 0.0001, HR: 0.70, [95% CI: 0.52–0.92], p-equivalence = 0.012). Importantly, there was no heightened risk of ischemic events in the de-escalation group compared to the conventional group (HR: 0.76, [95% CI: 0.40–1.45], p = 0.40), and the incidence of bleeding events was significantly reduced (HR: 0.48, [95% CI: 0.32–0.73], p = 0.0007).[49]

In the TALOS-AMI trial, 2697 patients who were on DAPT were randomly assigned to either switch to clopidogrel with aspirin or continue DAPT with ticagrelor. The trial's primary outcome, which included net adverse clinical events (NACE) such as cardiovascular death, MI, stroke, and BARC 3 or 5 bleeding, was observed in 4.7% of patients in the de-escalation group and 8.3% of patients in the control group (HR: 0.58, [95% CI: 0.38–0.87], p = 0.009). Importantly, there was a significant reduction in bleeding events (HR: 0.52, [95% CI: 0.35–0.77], p = 0.001), and there was no increase in the occurrence of ischemic events.[50]

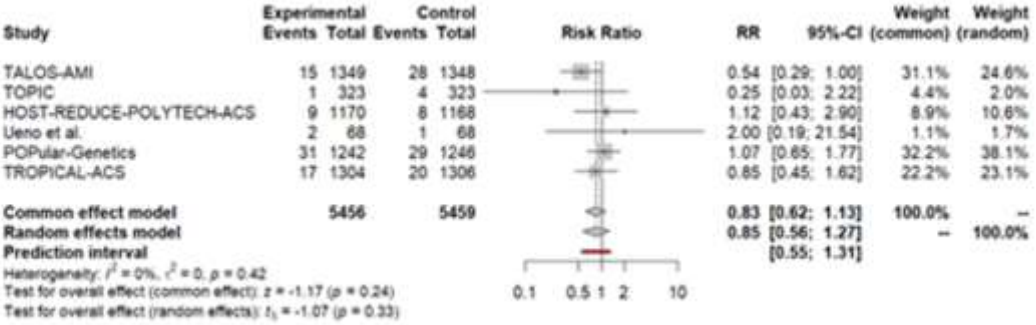
Ueno et al conducted a randomization of 136 patients with ACS who were on DAPT. They were assigned to either transition to clopidogrel with aspirin or maintain DAPT with prasugrel. The main outcome of interest was the average P2Y12 reaction unit (PRU) at week 6. Notably, the PRU was significantly lower in the group that continued with their initial treatment compared to the group that switched (140.7 versus 183.0, respectively; p = 0.001).[51]

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 10). 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 11).

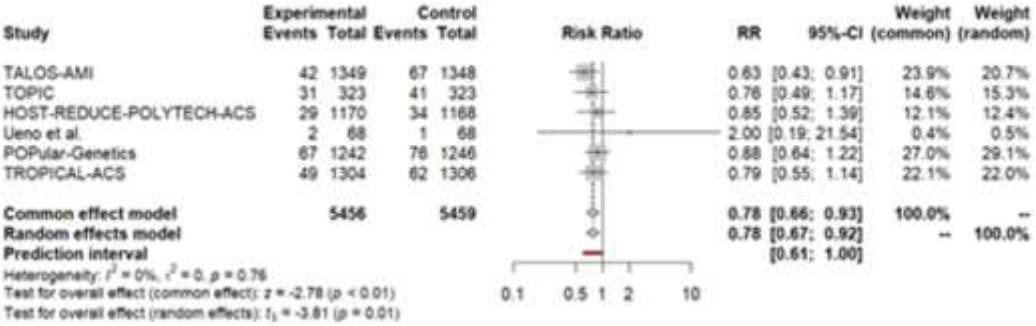
Panel A Major Adverse Cardiovascular Events



Panel B Major Bleeding



Panel C Net clinical efficacy (NACE)



Panel D Major and Minor Bleeding

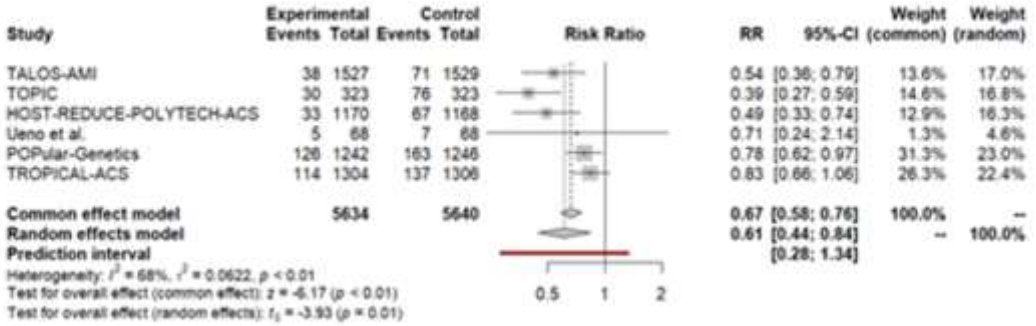
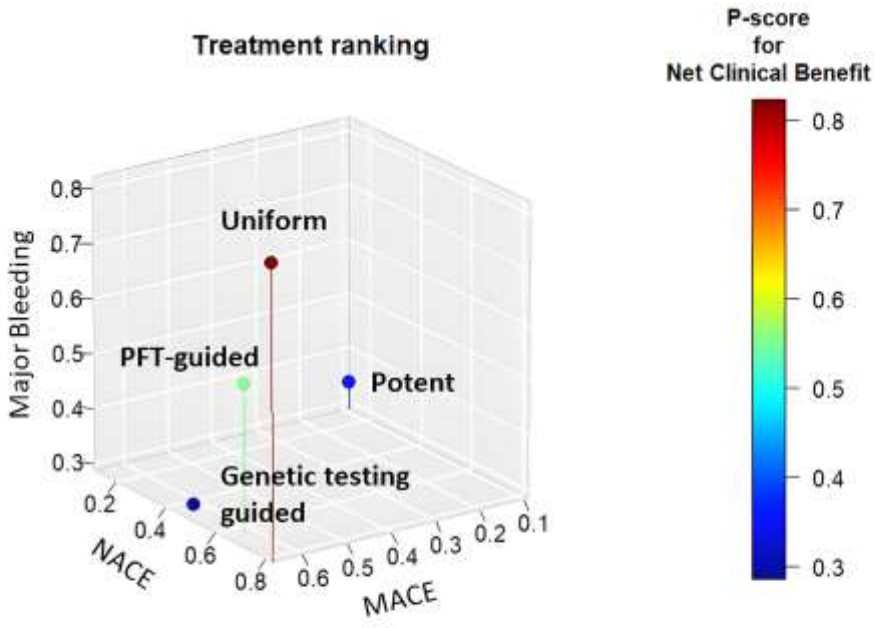


Figure 11: Forest plots depicting clinical endpoints of P2Y12 de-escalation strategies. Panels depict the relative risk of MACE (Panel (**A**)), major bleeding (Panel (**B**)), NACE (Panel (**C**)), and all bleeding defined as major and minor bleeding events (Panel (**D**)).

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 12). Although these trials were not originally designed to specifically evaluate these endpoints, a cumulative analysis involving over 10,000 randomly assigned patients revealed a highly significant 24% decrease in MACE without significant variations among the trials. Likewise, in analyzes assessing the overall clinical benefit, a notable 22% decrease in the risk of adverse events was observed (Figure 11).



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 12: Treatment ranking of P2Y12 de-escalation strategies. The scatterplot depicts the treatment ranking with regard to the risk of MACE, major bleeding, and NACE. Uniform de-escalation was ranked first in all analyses.

6. Discussion:

6.1. Reduction of ischemia-reperfusion injury:

Adenosine, known for its vasorelaxant effect and potential anti-inflammatory and platelet inhibition properties, may improve myocardial microcirculation and protect against reperfusion injury.[32] However, clinical studies have shown mixed results, with some failing to demonstrate significant improvements in infarct size or MVO.[71] Other preclinical studies suggest that nitric oxide donors may mitigate myocardial reperfusion injury.[30] Nevertheless, 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.[72–74] 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.

In preclinical models, metoprolol administration before reperfusion during MI has been shown to reduce infarct size and MVO.[34] The METOCARD-CNIC trial found that intravenous metoprolol infusion before reperfusion decreased myocardial infarct size 1 week after anterior STEMI.[75] However, the larger EARLY-BAMI trial failed to demonstrate metoprolol's infarct-limiting effect.[76] 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.[5]

Platelet P2Y12 receptor inhibitors, such as prasugrel and ticagrelor, have shown superiority over clopidogrel in reducing ischemic events in patients undergoing PCI for the entire spectrum of ACS. Large randomized trials, TRITON-TIMI 38 and PLATO, demonstrated that these third-generation P2Y12 receptor inhibitors are more effective than clopidogrel in reducing ischemic events.[77,78] The ATLANTIC trial found that prehospital administration of ticagrelor did not improve pre-PCI coronary reperfusion in patients with ongoing STEMI.[79] The REDUCE-MVI trial showed comparable impacts on coronary microvascular dysfunction and myocardial injury between ticagrelor and prasugrel maintenance therapy following pPCI in STEMI.[80] 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.[81] However, the PITRI trial may clarify whether intravenous cangrelor administration prior to reperfusion in STEMI patients would reduce acute infarct size and MVO, as assessed by cardiac magnetic resonance (CMR).[82]

Glycoprotein IIb/IIIa inhibitors have been proposed to improve microvascular perfusion by decreasing the incidence of thrombotic events such as distal embolization. The On-TIME-2 study showed that prehospital initiation of bolus tirofiban improved ST-segment resolution before and one hour after pPCI, while angiographic correlates of MVO were unaffected. 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.[83] 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.[84] 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.[5]

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

In this NMA examining strategies for de-escalating DAPT, we observed that two approaches yielded superior results in terms of ischemic outcomes. These approaches included transitioning to a less potent P2Y12 inhibitor as part of a P2Y12 inhibitor de-escalation strategy and adopting potent P2Y12 monotherapy coupled with discontinuation of aspirin. Both strategies also demonstrated benefits in reducing the risk of bleeding; however, a significant reduction in major bleeding was only evident in the case of P2Y12 monotherapy.

Both strategies, involving P2Y12 inhibitor de-escalation and P2Y12 inhibitor monotherapy, demonstrated advantages. However, our analysis also uncovered noteworthy distinctions with potential practical implications. While both strategies lowered the overall risk of bleeding, only P2Y12 inhibitor monotherapy, and not the de-escalation schemes, showed a significant reduction in major bleeding events. Importantly, our analysis suggests that this benefit is not offset by a higher risk of ischemic events. Nevertheless, individual trials demonstrated favorable trends, with significant reductions only becoming apparent when the data were cumulatively analyzed. These findings suggest that the routine adoption of these strategies in the early phases of PCI for patients with ACS could be beneficial. When applied in line with the trial protocols, which typically span from 48 hours to 3 months, these strategies have the potential to improve both ischemic and bleeding risk outcomes.

While P2Y12 inhibitor monotherapy demonstrated a noteworthy reduction in both major bleeding and adverse events, the outcomes associated with P2Y12 inhibitor de-escalation strategies exhibited different patterns. These strategies appeared to be more effective in cumulatively reducing the risk of ischemic events, with favorable trends. However, only minor bleeding risk showed a significant reduction with these approaches. All three P2Y12 inhibitor de-escalation strategies produced a similarly lower rate of ischemic events, with uniform de-escalation being particularly effective in reducing bleeding events. In contrast, guided de-escalation using platelet function and genetic testing showed a less pronounced reduction in bleeding endpoints. Consequently, P2Y12 inhibitor de-escalation strategies appear to be more efficient in mitigating ischemic risk, whereas P2Y12 inhibitor monotherapy emerges as a safer option for reducing bleeding in patients with ACS. It's worth noting that using ticagrelor in the P2Y12 inhibitor monotherapy strategy may offer a lower ischemic risk compared to clopidogrel.[52]

The three oral P2Y12 inhibitors currently used in patients with ACS and PCI exhibit significant differences in both pharmacodynamics and pharmacokinetics. Clopidogrel and prasugrel are prodrugs that undergo conversion into their active metabolites through hepatic CYP450 enzymes.[49] This activation process is faster and more efficient in the case of prasugrel, and the resulting active metabolite from both compounds irreversibly inhibits the P2Y12 receptor on platelets.[53] On the other hand, ticagrelor achieves reversible inhibition of ADP binding to the P2Y12 receptor in a non-competitive manner. Notably, ticagrelor is an active drug that does not require in vivo biotransformation[54]. In comparison to clopidogrel, both alternatives offer quicker onset of action, greater potency, and less variability in response.[55]

One of the primary limitations associated with clopidogrel is the substantial interindividual variability in platelet function inhibition it produces, which serves as a significant risk marker, especially among high-risk patients.[22] High platelet reactivity (HPR) can be identified through PFT and is more prevalent among individuals who carry mutations in cytochrome enzymes involved in thienopyridine metabolism. These mutations encompass CYP2C19 alleles like the LoF CYP2C19*2 and 3 alleles, classifying carriers with two non-functional copies of the CYP2C19 gene as CYP2C19 poor metabolizers. Such individuals exhibit reduced clopidogrel efficacy. Conversely, there are variations such as the CYP2C19 gain-of-function allele, which is found in rapid clopidogrel metabolizers. Due to genetic factors and the potential for drug interactions, there exists a substantial degree of interindividual variability in the response to clopidogrel.[56] Depending on the criteria used, approximately 15-40% of individuals are considered "non-responders" or "clopidogrel-resistant," characterized by high residual platelet aggregation. Extensive evidence underscores the association between high platelet reactivity, despite clopidogrel treatment, and an increased risk of cardiovascular events and stent thrombosis. Conversely, lower levels of residual platelet aggregation are linked to a higher incidence of bleeding complications.[57]

While strategies aimed at reducing treatment intensity led to a decrease in MACE and bleeding when compared to potent P2Y12-based DAPT, indirect comparisons between P2Y12 inhibitor monotherapy and de-escalation strategies only provided preliminary insights to aid decision-making. The reduction in bleeding rates was similar between these two options, but subgroup analyzes revealed that genetic testing and PFT-guided de-escalation strategies were somewhat less effective compared to P2Y12 inhibitor monotherapy in this regard. This implies that if the primary concern is reducing bleeding risk, P2Y12 inhibitor monotherapy or unguided de-escalation may be more favorable choices. On the other hand, when it comes to indirect comparisons of the incidence of ischemic events, there was a tendency towards an 11–12% reduction with P2Y12 inhibitor de-escalation strategies, although these differences did not reach statistical significance.

The pivotal clinical trials establishing the superiority of prasugrel and ticagrelor over clopidogrel in ACS revealed a reduction in recurrent ischemic events but a slight increase in bleeding risk.[58] Recent emphasis has been placed on strategies to reduce bleeding in ACS.[54,59] This meta-analysis differs from others in several ways. Unlike Guo et al.[60], we exclusively included RCTs to enhance reliability and excluded observational studies due to their inherent biases. While Angiolillo et al[61]. focused solely on de-escalation from ticagrelor to clopidogrel, our analysis encompasses de-escalation from various potent P2Y12 inhibitors to clopidogrel.
Several studies have explored the outcomes and benefits of guided de-escalation. Galli et al[62]. found that guided de-escalation improved efficacy outcomes while maintaining safety.[63] Tavenier et al.[64] suggested that both guided and unguided de-escalation were associated with reduced bleeding and ischemic events, which aligns with our findings. Notably, this analysis includes trials involving aspirin monotherapy, which was excluded in another meta-analysis. Additionally, we evaluate various abatement strategies, including P2Y12 inhibitor monotherapy and de-escalation.

To date, numerous RCTs have explored the optimal duration of DAPT following drug-eluting stent (DES) implantation, comparing various lengths (e.g., 3, 6, 12, 24, or 30 months). These investigations have assessed the trade-off between prolonged DAPT, which may increase bleeding risk, and its potential to reduce recurrent MI and stent thrombosis.[65,66] D'Ascenzo et al., in a NMA of these trials, highlighted that the choice of stent type also influences adverse event risk alongside DAPT duration. However, there is limited data directly comparing different DAPT durations in patients treated with various generations of DES or bioresorbable scaffolds.[67]

Previous analyses, consistent with our findings, have indicated that P2Y12 inhibitor de-escalation can mitigate both ischemic risk and bleeding in patients with ACS. We have expanded upon these insights, observing a similar reduction in the P2Y12 inhibitor monotherapy trial. Moreover, our analysis facilitates a comparison of these two strategies. Our results align with recent meta-analyses by Laudani et al.[68] and Ullah et al.[69], where P2Y12 inhibitor de-escalation was associated with a decrease in ischemic risk, and P2Y12 inhibitor monotherapy was linked to a reduction in bleeding.

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

This review revealed that employing uniform unguided P2Y12 de-escalation strategies consistently led to a reduction in bleeding events without compromising effectiveness. In contrast, genetic testing-guided de-escalation and de-escalation guided by PFT did not exhibit any discernible differences in bleeding or ischemic events when compared to the standard treatment group.

Kuno and colleagues conducted an extensive NMA with the objective of evaluating the effectiveness and safety of various DAPT approaches. Their broader inclusion criteria allowed for a larger pool of trials with less strict de-escalation requirements. This analysis encompassed data from 19 RCTs involving a total of 69,746 patients, assessing six distinct DAPT strategies. These strategies included combinations of aspirin with clopidogrel, low-dose prasugrel, standard-dose prasugrel, and ticagrelor, as well as unguided de-escalation and guided de-escalation strategies.[70] Kuno et al.'s findings were consistent and demonstrated that unguided de-escalation was linked to a reduced risk of MACE when compared to DAPT regimens. Our subsequent analyzes found no significant difference in MACE risk between guided and unguided strategies. However, all studies consistently showed reductions in MACE that reached statistical significance, primarily driven by the larger cumulative number of patients included in unguided de-escalation trials.

While the results concerning ischemic events indicated a comparable advantage for de-escalation strategies, whether guided or not, the data on bleeding rates presented a more varied picture. It is important to note a crucial difference between our analysis and that of Kuno et al. Specifically, Kuno et al. grouped the TROPICAL-ACS[18] and POPULAR-GENETIC[17] trials within the same category. Notably, the POPULAR-GENETIC trial exhibited a significant increase in major bleeding, even though it showed substantial reductions in both major and minor bleeding with genetic testing-based de-escalation. The underlying reasons for this marked difference in major bleeding rates remain unexplained. In light of this inconsistency, we believe it is justified not to group these two trials together.[70]

The primary objective of the trials was to establish non-inferiority based on composite endpoints, and none of the trials were originally designed to detect distinctions in MACE or major bleeding. However, the study demonstrated a noteworthy enhancement in net clinical benefit associated with de-escalation strategies. Both guided de-escalation approaches resulted in a higher utilization of prasugrel treatments in the de-escalation arm, potentially explaining the less pronounced reductions in major and minor bleeding rates. Unguided de-escalation appears to be the most effective strategy in reducing bleeding events while maintaining efficacy, but it may be associated with an increased risk of ischemic events, which can lead to serious complications and can be fatal.

The precise mechanistic explanation for the risk reduction remains elusive. It has been conjectured that the decrease in these bothersome events, along with the findings related to minor bleeding rates, might have contributed to a more tolerable treatment regimen with improved patient adherence. However, whether this hypothetical increase in adherence translates to the observed clinical benefit remains uncertain. The incidence of bleeding events may also be influenced by additional factors. Both genetic testing and PFT were incorporated into the de-escalation strategies to implement pharmacokinetic-based risk assessment for identifying patients at the highest risk. Nevertheless, The rate of bleeding events may also be influenced by other factors.

The strategies we used to decide which patients receive which treatment, based on their genetics and platelet function tests, resulted in approximately 40% of patients receiving clopidogrel. This choice might explain why the trials did not observe as significant a decrease in bleeding as initially expected. For instance, among individuals with heart issues who have access to more potent antiplatelet medications, continuing clopidogrel therapy may yield similar results. However, these tests are less reliable when it comes to predicting who might experience problems, which could explain why the trials produced varying results.

The cumulative analyses of studies examining the de-escalation of P2Y12 inhibitor treatment revealed significant benefits in terms of MACE, NACE, and the combination of major and minor bleeding. Among these, the uniform de-escalation studies showed slightly greater advantages. Nevertheless, when it came to major bleeding, there was no statistically significant reduction observed. Major bleeding incidents appeared to be less frequent in the uniform de-escalation studies, followed by strategies guided by PFT, and finally, those guided by genetic testing, which exhibited a less pronounced trend in reducing major bleeding. These outcomes might be linked to the extended use of prasugrel in the de-escalation groups, accounting for 40% of both PFT and genetic testing-guided de-escalation. Such prolonged use could have impacted clinical outcomes, particularly with regard to bleeding events. Furthermore, these findings suggest that assessing risk using PFT may offer more precise predictions compared to evaluating metabolizer status.

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. Nevertheless, the implementation of effective cardioprotective strategies in clinical practice remains an unmet medical need.
- 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. P2Y12 inhibitor monotherapy results in a reduction of both major and minor bleeding, while ischemic risk reduction was less expressed. The de-escalation strategy was quite the opposite, as there was no difference in major bleeding between this strategy and the control; however, ischemic risk was strongly reduced.
  - Trials with guided de-escalation showed less expressed benefits. Nevertheless, in selected patients with high-ischemic risk, these strategies may still offer a safe alternative compared to the long-term potent P2Y12 inhibitor DAPT.
- our review suggests that:
  - the use of uniform unguided de-escalation is the most effective strategy in reducing bleeding events while maintaining efficacy.
  - although genetic testing-guided de-escalation strategies and de-escalation using PFT guidance provided results showing no difference in bleeding or ischemic events between the de-escalation group and the standard group, 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.

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9. 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**

9.1. Topic-related scientific articles

- El Alaoui El Abdallaoui O, Tornyos D, Lukács R, Komócsi A: Abatement of potent P2Y12 anatgonist-based dual antiplatelet therapy after coronary intervention: A network meta-analysis of randomized controlled trials; DOI: 10.3389/fcvm.2022.1008914

  FRONTIERS IN CARDIOVASCULAR MEDICINE (2023)

  IF : 3.6 **Q1**

- El Alaoui El Abdallaoui O, Tornyos D, Lukács R, Szabó D, Komócsi A: Individualized or uniform de-escalation strategies for antiplatelet therapy in acute coronary syndrome: A review of clinical trials with platelet function testing and genetic testing-based protocols; DOI: 10.3390/ijms24109071

  INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES (2023)

  IF: 5.6 **Q1**

- El Alaoui El Abdallaoui O, Komócsi A, Szokodi I: Cardioprotective strategies against myocardial ischemia–reperfusion injury.

SPORT- ÉS EGÉSZSÉGTUDOMÁNYI FÜZETEK (2024)

CUMULATIVE IMPACT FACTOR: 9.2

9.2. Non-topic-related scientific articles

- Szapáry L, Tornyos D, Kupó P, Lukács R, El Alaoui El Abdallaoui O, Komócsi A: Combination of antiplatelet and anticoagulant therapy, component network meta-analysis of randomized controlled trials. DOI: 10.3389/fcvm.2022.1036609

FRONTIERS IN CARDIOVASCULAR MEDICINE (2022)

IF : 3.6 **Q1**

- Tornyos D, Meuer M, Lukács R, El Alaoui El Abdallaoui O, Kupó P, Faludi R, Komócsi A: Cardiovascular outcomes in patients treated with sodium-glucose transport protein 2 inhibitors, a network meta-analysis of randomized trials. DOI: 10.3389/fcvm.2022.1041200

FRONTIERS IN CARDIOVASCULAR MEDICINE (2022)

IF: 3.6 **Q1**

- Tornyos D, Komócsi A, Bálint A, Kupó P, El Alaoui El Abdallaoui O, Szapáry L, Szapáry LB: Antithrombotic therapy for secondary prevention in patients with stroke or transient ischemic attack: A multiple treatment network meta-analysis of randomized controlled trials. DOI: 10.1371/journal.pone.0273103

PLOS ONE (2022)

IF: 3.7 **Q1**

- Bálint A, Tornyos D, El Alaoui El Abdallaoui O, Kupó P, Komócsi A: Network meta-analysis of ticagrelor for stroke prevention in patients at high risk for cardiovascular or cerebrovascular events. DOI: 10.1161/STROKEAHA.120.032670

  STROKE (2021)

  IF: 10.170 **Q1**

- Bálint A, Kupó P, Tornyos D, El Alaoui El Abdallaoui O, Jánosi A, Komócsi A: Oral anticoagulation and outcomes in patients with acute myocardial infarction: Insights from the Hungarian Myocardial Infarction Registry. DOI: 10.1111/ijcp.14179

  INTERNATIONAL JOURNAL OF CLINICAL PRACTICE (2021)

  IF: 3.149 **Q2**

- Tornyos D, Bálint A, Kupó P, El Alaoui El Abdallaoui O, Komócsi A: Antithrombotic therapy for secondary prevention in patients with non-cardioembolic stroke or transient ischemic attack: A systematic review. DOI: 10.3390/life11050447

  LIFE-BASEL (2021)

  IF: 3.253 **Q2**

- Salah M, El Alaoui El Abdallaoui O, Zeroual A, Acharjee N, Idrissi ME: Insights into a new discovery of SARS-CoV-2 inhibitor activated through Chloroquine derivatives. DOI: 10.5267/j.ccl.2023.8.010

  CURRENT CHEMISTRY LETTERS (2024)

  IF: 0 **Q3**

CUMULATIVE IMPACT FACTOR: 27.472

9.3. Non-topic-related abstracts published in scientific journals:

- Bálint A, Kupó P, Tornyos D, El Alaoui El Abdallaoui O, Jánosi A, Komócsi A, Oral anticoagulation and outcomes in patients with acute myocardial infarction: Insights from the Hungarian Myocrdial Infarction Registry.

  Medical Conference for PhD Students and Experts of Clinical Sciences 2021: Book of Abstracts pp 41-41 ISBN: 9789634296539

9.4. Oral presentations:

- 2024.04.19. Oumaima El Alaoui El Abdallaoui, András Komócsi: Abatement of potent P2Y12 antagonist based dual antiplatelet therapy after coronary intervention in patients with diabetes: A systematic review.
  National and International Interdisciplinary Grastyán Conference (Grastyán 100). Pécs.

9.5. Poster presentations:

- 2023.11.02. Oumaima El Alaoui El Abdallaoui, Dániel Tornyos, Réka Lukács, András Komócsi: Impact of Dual Antiplatelet Therapy Abatement Strategies in Patients Undergoing Coronary Intervention : A Systematic Review and Network Meta-Analysis. EuroCVP 2023 – The annual meeting on advances in cardiovascular pharmacotherapy. Florence.
- 2023.11.23. Oumaima El Alaoui El Abdallaoui, Dániel Tornyos, Réka Lukács, András Komócsi: Impact of Dual Antiplatelet Therapy Abatement Strategies in Patients Undergoing Coronary Intervention : A Systematic Review and Network Meta-Analysis. ISCP 2023 – 28th International Society of cardiovascular pharmacotherapy. Seoul.
- 2024.05.02. Oumaima El Alaoui El Abdallaoui, András Komócsi: Abatement of potent P2Y12 antagonist based dual antiplatelet therapy after coronary intervention in patients with diabetes: A systematic review.
  Society for Cardiovascular Angiography and Interventions (SCAI) 2024 Scientific Sessions. Long Beach.

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11. Appendix

Articles related to the thesis

frontiers | Frontiers in Cardiovascular Medicine

TYPE Systematic Review
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Front. Cardiovasc. Med. 9:1008914.
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Abatement of potent P2Y12 antagonist-based dual antiplatelet therapy after coronary intervention: A network meta-analysis of randomized controlled trials

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Introduction: Dual antiplatelet therapy (DAPT) including prasugrel or ticagrelor is recommended in patients with acute coronary syndromes (ACS) treated with coronary intervention (PCI). Acknowledging the importance of bleeding, multiple trials tested abatement schemes including uniform or guided de-escalation from the potent P2Y12 inhibitor (P2Y12-De) or P2Y12 inhibitor monotherapy (P2Y12-Mo) with heterogeneous results. We aimed to perform a systematic review and network meta-analysis of the impact of DAPT abatement strategies in patients with PCI.

Methods: Electronic databases were searched for relevant randomized clinical studies evaluating clinical outcomes of patients after PCI. The rate of adverse events was evaluated using a frequentist network metanalysis. The random-effects model was used to combine risk estimates across trials and risk ratio (RR) with 95% confidence intervals (95% CIs) served as summary statistics. The primary endpoints of interest were the rate of major cardiac adverse events (MACE, defined as the composite of cardiovascular mortality, myocardial infarction and stroke) and bleeding.

Results: Ten studies were identified randomizing 42511 patients. 6359 switched to the P2Y12-De and 13062 switched to the P2Y12-Mo. The risk of MACE, reflected a 24% reduction in the P2Y12-De and a 14% in the P2Y12-Mo in comparison with the DAPT strategy using potent P2Y12 inhibitors (RR: 0.76 [0.62, 0.94], and RR: 0.86 [0.75, 0.99], $p < 0.05$ both). A 35% risk reduction of major bleeding was seen with monotherapy (RR: 0.65 [0.46, 0.91],) contrasting the de-escalation trials where this effect was not significant (RR: 0.84 [0.57, 1.22]). All bleeding and minor bleeding events were reduced with both strategies. Indirect P2Y12-Mo versus P2Y12-De comparisons exhibited them as similar alternatives without significant differences.

Conclusion: Our analysis suggests that both P2Y12-De and P2Y12-Mo reduce ischemic events and bleeding among PCI-treated ACS patients. Ischemic benefit was more expressed with P2Y12-De, however, reduction of major bleeding was only significant with P2Y12-Mo strategy.

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Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021258502, identifier CRD42021258502.

KEYWORDS

ticagrelor, prasugrel, network meta-analysis, coronary intervention, P2Y12 de-escalation therapy

Introduction

P2Y12 inhibitors are routinely administrated, in addition to aspirin, to reduce thrombotic complications of patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). Recent guidelines support the preferential use of the potent inhibitors, prasugrel or ticagrelor, as they showed a better reduction of ischemic events in their respective pivotal trials, as compared to the less effective clopidogrel (1, 2). However, these benefits come with disadvantages such as a higher risk of bleeding or side effects that may undermine patient compliance. Therefore, as observational data reflect, P2Y12 inhibitors are frequently switched during treatment in patients with ACS (3). Early after an ACS event, the higher thrombotic risk may outweigh the bleeding risk, whereas, during the chronic phase, the decrease in thrombotic risk is more pronounced than that in the bleeding risk. Abatement strategies include uniform or guided de-escalation to a less potent P2Y12 inhibitor or early cessation of aspirin and the use of potent P2Y12 inhibitor monotherapy. In addition to the pharmacological contribution to bleeding avoidance strategies, these schemes may offer potential economic benefits and, thus, are commonly practiced (4).

Nevertheless, de-escalation of antiplatelet therapy from a potent P2Y12 inhibitor may account for the large response variability of clopidogrel and the consequential issue of high on-treatment platelet reactivity (HPR), which appears in a substantial proportion of patients with ACS. Part of this response variation is explainable by genetic variations, such as the CYP2C19*2 and CYP2C19*3 loss-of-function alleles. In patients without these alleles, clopidogrel has shown a similar efficacy to those of ticagrelor and prasugrel (5). Platelet function testing (PFT) or genetic testing may, thus, make de-escalation safer by identifying patients with characteristics exposing them to an increased risk of thrombotic events and selectively maintaining potent P2Y12 inhibition for these cases (6).

Recently, multiple randomized trials were performed to test different abatement schemes. However, these were typically underpowered in order to accurately assess the efficacy and safety. Moreover, both strategies represent a potentially mutually exclusive alternative. They were tested against conventional long-term potent P2Y12 inhibitor-based DAPT treatment; however, data is lacking regarding their comparison. We aimed to evaluate the clinical outcomes of P2Y12 inhibitor de-escalation and P2Y12 inhibitor monotherapy compared with continuation of DAPT in patients treated with PCI, as well as to perform a systematic review and network meta-analysis in order to achieve greater statistical power and more precise effect estimates of the impact of DAPT abatement strategies in patients undergoing coronary intervention.

Methods

Search strategy

This systematic review was performed as per the standards outlined in the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Healthcare Interventions (7) and was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021258502).

The data that support the findings of this analysis are available from the corresponding author upon reasonable request.

Study selection

A keyword-based search for relevant articles was performed in PubMed (MEDLINE), EMBASE, and the Cochrane Library from January 2007 to October 2021. No language restriction was used. The query included the following medical subject heading (MeSH) terms which were linked with Boolean operators: "coronary artery disease" [MeSH] OR "acute coronary syndrome" [MeSH] OR "cardiovascular disease" [MeSH] AND "de-escalation" [MeSH] AND "ticagrelor" [MeSH] OR "prasugrel" [MeSH] OR "clopidogrel" [MeSH]. Furthermore,

Abbreviations: ACS, Acute coronary syndrome; BARC, Bleeding Academic Research Consortium; DAPT, Dual antiplatelet therapy; HPR, High on-treatment platelet reactivity; MACE, major adverse cardiac events; NMA, network meta-analysis; 95% CIs, 95% confidence intervals; PCI, Percutaneous coronary intervention; PFT, Platelet function testing; RR, Risk ratio.

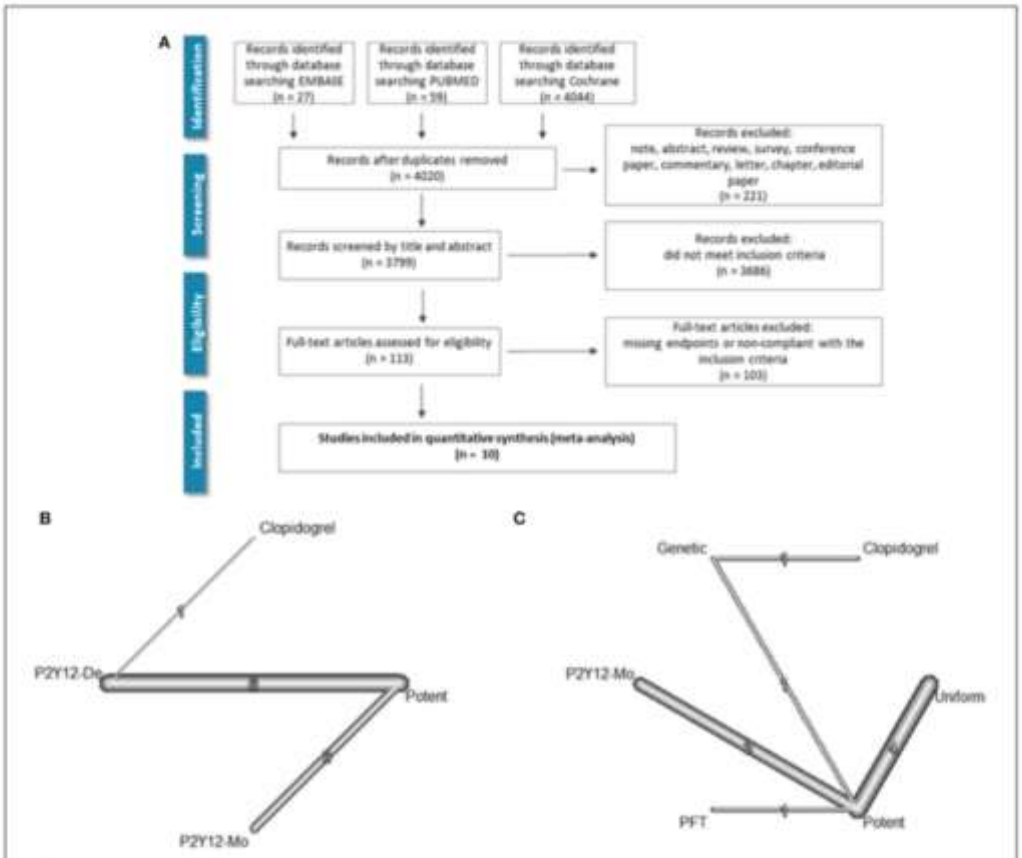

FIGURE 1
Literature search and evidence network. PRISMA flowchart of the literature search is shown in **(A)**. **(B)** Depicts the evidence network as a network of P2Y12 de-escalation (P2Y12-De), potent P2Y12 monotherapy (P2Y12-Mo), and dual antiplatelet therapy controls (i.e., DAPT with potent P2Y12 inhibitors (potent) or with clopidogrel). In **(C)**, the network with subgrouping of de-escalation strategies is presented. De-escalation studies used three strategies either switching back to less potent P2Y12 inhibitor in every patient (uniform) or only selective de-escalation based on platelet function (PFT) or genetic characteristics (genetic).

we searched the reference list of relevant guidelines, reviews, editorials, and studies on this topic. The literature screening process is summarized in Figure 1A.

Studies were considered eligible if they fulfilled all the following criteria: (1) Clinical studies with a prospective design, including patients who received DAPT schemes for the treatment of percutaneous coronary intervention. (2) Randomized studies comparing the clinical outcomes of a group of patients with P2Y12 inhibitor-based dual antiplatelet therapy. (3) Studies that evaluate the benefit of P2Y12 inhibitor monotherapy or switching to clopidogrel at a predefined time point (≤3 months), assisted by genetic testing, platelet function testing, or without.

Quality assessment and endpoints

Two investigators (O.A.A and D.T) independently evaluated the titles and abstracts of all citations, in line with the PICOS criteria; any discrepancies were resolved by a third investigator (A.K.).

Articles, that met predefined eligibility criteria, were chosen for full-text screening and were reviewed by the two investigators against the eligibility criteria outlined in the PICOS framework: Patients who underwent coronary stent implantation (P), whether an intervention with dual antiplatelet abatement strategy with P2Y12 inhibitor monotherapy or P2Y12 inhibitor de-escalation to clopidogrel (I), compared with P2Y12

inhibitor plus aspirin dual antiplatelet therapy (C) has a favorable effect on bleeding, or major adverse cardiovascular events (MACE) or mortality (O).

The primary efficacy outcome of our analysis was the occurrence of MACE, defined as the composite of cardiovascular mortality, MI, and stroke. Major bleeding and all-cause mortality were assessed as main safety endpoints. Secondary outcomes included the individual components of MACE and stent thrombosis, defined according to the ARC criteria. Furthermore, safety outcomes, such as the frequency of major and minor bleeding complications, were also evaluated. In the case of the availability of multiple bleeding definitions, we extracted data according to the Bleeding Academic Research Consortium (BARC) criteria, defining type 3 or type 5 as major and type 2 as minor bleeding. The data were extracted, and the endpoints of interest were collected up to the 1st year after the coronary intervention.

The methodological qualities of the studies were also assessed using the Cochrane Collaboration tool for assessing the quality of RCTs.

Data analysis

We pre-specified the use of multiple treatment network meta-analysis (NMA). The rates of events with each antiplatelet treatment combination were entered as an individual study arm, and data were pooled in a multiple treatment NMA that allows integration of direct and indirect comparisons. We calculated the risk ratio (RR) and its standard error using a frequentist approach to construct an NMA model accounting for the correlated treatment effects (8, 9). A random-effects model was applied by adding the estimated heterogeneity to the variance of each comparison, using an adaptation of the DerSimonian–Laird estimator. The random-effects model was chosen based on the consideration that the true preventive effect of antithrombotic treatment may vary from study to study and is influenced by the heterogeneity of the included trials. Values of I^2 representing the amount of inconsistency, and Cochran's Q statistic and its corresponding p-value measuring the heterogeneity in the network were also calculated (8, 10).

Effect sizes are depicted as forest plots with potent dual antiplatelet therapy set as a reference. Furthermore, a comparative ranking of the treatments according to the P-scores method [a frequentist analog of SUCRA (Surface Under the Cumulative Ranking curve) was also performed (9)].

We appraised potential bias in the individual studies using the Cochrane Collaborations' bias assessment tool. To assess publication bias, a comparison-adjusted funnel plot supplemented with Eggers' test results was used (11).

The assumption of consistency; that the direct evidence for the effect size between two treatments in a network does not differ from the indirect evidence, was assessed by comparing and visualizing direct and indirect evidence.

Additional exploratory analyses included stratification and subgrouping based on the different de-escalation strategies and the included patient population, study size, and follow-up time.

Calculations were performed using R statistical software package version 4.0.3 (12), using the packages "meta 4.11-0," "netmeta 1.2-0," and "gemtc 0.8-4" (13). A p-value of < 0.05 was considered to represent statistical significance.

Results

Ten studies that included 42,511 patients met the inclusion criteria. Among the included patients, 6,359 were randomized to a P2Y12 inhibitor de-escalation strategy, while 13,062 received potent P2Y12 inhibitor monotherapy. The included trials randomized patients treated with coronary intervention and stent implantation after an acute coronary syndrome event except for two studies where patients after a planned coronary intervention were also included. Potent P2Y12 inhibitor-based dual antiplatelet therapy control involved 18,540 cases while clopidogrel and aspirin combination involved 946. The characteristics and design of the included RCTs are shown in Table 1. The P2Y12 inhibitor de-escalation strategy was guided based on platelet function testing in two studies, based on genetic testing in two, and unguided, uniform in four. The size of the trials ranged from 131 to 15,968 participants, and the follow-up time was from 1 week to 12 months. The Global Leaders trial followed patients for 24 months after coronary intervention; however, as the patient received ticagrelor monotherapy or conventional DAPT during the 1st year, while during the 2nd-year, patients in the control received aspirin and in the experimental arm ticagrelor monotherapy, we extracted data from the first 12 months landmark analysis.

Three trials used selective P2Y12 inhibitor de-escalation strategies. Among these, the POPular Genetics trial (5) and the TAILOR-PCI trial (14) used genetic testing with TaqMan assays. In the POPular Genetics trial, carriers of the loss-of-function CYP2C19 allele were treated with ticagrelor or prasugrel (49%), whereas non-carriers (CYP2C19*1/*1) received clopidogrel (51%). In the TAILOR-PCI trial, patients identified as possessing CYP2C19*2 or *3 LOF alleles (CYP2C19 LOF carriers) were prescribed ticagrelor for maintenance therapy or prasugrel for patients who did not tolerate ticagrelor, and non-carriers or those with inconclusive results were prescribed clopidogrel.

In the TROPICAL-ACS trial (6), a platelet-function testing-based de-escalation treatment algorithm was applied. Patients in the P2Y12 inhibitor de-escalation group received a post-discharge treatment consisting of 1-week prasugrel treatment (10 or 5 mg per day) followed by 1 week of clopidogrel treatment (75 mg per day) and a platelet function measurement (on

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TABLE 1 Main characteristics of the included studies.

First author	Claassens	Cuisset	Kim	Sibbing	Pereira	Ueno	Park	Kim	Mehran	Vranckx
Publication year	2019	2017	2020	2017	2020	2016	2021	2020	2019	2018
Acronym	POPular Genetics	TOPIC	HOST-REDUCE-POLYTECH-ACS	TROPICAL-ACS	TAILOR-PCI	-	TALOS-AMI	TICO	TWILIGHT	GLOBAL LEADERS
Design	R, open label	R, open label, single center	R, open label, multi-center	R, open label, multi-center	R, open label, multi-center	R, open label, multi-center	R, open label, multi-center	R, multi-center	R, open label	R, OPEN LABEL
Number of patients	2,751	646	2,338	2,610	5,302	131	2,590	3,056	7,119	15,968
Time between PCI and randomization	48 h	1 month	1 month	2 weeks	72 h	At the PCI	1 month	3 months	3 months	1 month
STEMI (%)	100	40	14	55	22	48	54	36	0	13
NSTEACS (%)	0	60	85.2	44	59	52	46	64	30	34
UAP (%)	0	NA	60	0	30	39	0	31.	70	13
CCS (%)	0	0	0	0	18	47.	0	0	35	47
Clopidogrel (experimental/control; %)	60.6/7.0	100/0	-	100/0	15/99	100/0	100/0	36/33	-	53/53.2
Prasugrel (experimental/control; %)	1 / 2.3	56/59	100/100	0/100	-	0/100	-	-	-	-
Ticagrelor (experimental/control; %)	38.1/90.5	44/42	-	-	85/1	-	0/100	73/70	0/100	47/46.8
Study group type	P2Y12-De	P2Y12-De	P2Y12-De	P2Y12-De	P2Y12-De	P2Y12-De	P2Y12-De	P2Y12-Mo	P2Y12-Mo	P2Y12-Mo
Definition of bleeding (primary/secondary)	PLATO/BARC	TIMI/BARC	BARC	BARC	BARC/TIMI	BARC/TIMI	BARC	TIMI	BARC/TIMI, GUSTO, and ISTH	BARC
End point	Bleeding, MACE, ST, and TVR	Bleeding, UREV, and MACE	Bleeding, TVR, MACE, and ST	Bleeding, MACE, UREV, and ST	CVD, MI, ST, stroke, and SBI	PBU	CVD, MI, stroke, and bleeding	Major bleeding, death, MI, ST, TVR, and stroke	Bleeding, MI, stroke, and death	Q-wave MI, and death
Follow-up, months	12	12	12	12	12	15	12	12	12	24
Age (mean ± SD)	61.7 ± 11.3	60.0 ± 10.2	58.8 (9.0)	58.7 (10.2)	62 [21–95]	68.8 ± 10.3	60 ± 11	61 (11)	65.01 ± 10.3	64.5 ± 10.3
Female, *N* (%)	317 (25.5)	114 (18)	251 (10.75)	2,052 (78.5)	1,738 (32.78)	32 (24.4)	454 (16.8)	628 (20.5)	1,698 (23.8)	3,714 (23.2)
DM, *N* (%)	288 (11.6)	177 (27)	960 (42.3)	527 (20)	1,930 (36.55)	53 (40.5)	731 (27.2)	835 (27)	2,620 (36.8)	4,038 (25.3)

(Continued)

10.3389/fcvm.2022.1008914

TABLE 1 (Continued)

First author	Claassens	Cuisset	Kim	Sibbing	Pereira	Ueno	Park	Kim	Mehran	Vranckx
Smoking, *N* (%)	1,127 (45.8)	286 (44)	838 (71.7)	1,182 (45)	1,752 (33.04)	NR	-	1,142 (37)	1,548 (21.7)	4,169 (26.2)
HTN, *N* (%)	1,032 (41.4)	313 (48)	1,476 (63.1)	1,599 (61.5)	4,409 (83.15)	89 (67.9)	1,318 (48.9)	1,541 (50.5)	5,154 (72.4)	11,705 (73.6)
DES, *N* (%)	NR	585 (91)	2,338 (100)	2,005 (77)	NR	NR	-	NR	NR	19,415 (94.6)
PCI approach (%)	NR	Femoral (4) Radial (96)	NR	NR	NR	NR	Femoral (49.4) Radial (49.4)	NR	NR	Femoral (26) Radial (74)

R, randomized; ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium Criteria; DES, drug-eluting stent; DM, diabetes mellitus; HTN, hypertension; LD, loading dose; MD, maintenance dose; MACE, major adverse cardiac events; NR, not reported; O, observational study; R, retrospective; SD, standard deviation; ST, stent thrombosis; TIMI, Thrombolysis in Myocardial Infarction; TVR, target vessel revascularization; UREV, urgent revascularization; PLATO, Platelet Inhibition and Patient Outcomes; MI, Myocardial infarction; SRI, Severe Recurrent Ischemia; PRU P2Y12, Reaction Unit.; STEMI ST, segment elevation MI; NSTEACS, non-ST-segment elevation acute coronary syndrome; UAP, unstable angina pectoris; CCS, chronic coronary syndrome; De, de-escalation; Mo, monotherapy.

clopidogrel) 2 weeks after hospital discharge (PFT-guided de-escalation group). The network of evidence, both regardless of, and with regard to the applied de-escalation strategies, is depicted in Figures 1B, C.

The risk of bias was assessed for all the trials, showing a minimal risk in all biases. The results derived from direct comparisons were identical to those computed with the help of indirect comparisons (Supplementary Figures 1–3).

When compared to a potent dual antiplatelet strategy, both P2Y12 inhibitor de-escalation and P2Y12 inhibitor monotherapy were associated with a significant ischemic risk reduction. The estimated cumulative effect reached a 24% risk reduction with P2Y12 inhibitor de-escalation and a 14% risk reduction with P2Y12 inhibitor monotherapy [RR: 0.76 (0.62, 0.94), $p < 0.05$, and RR: 0.86 (0.75, 0.99), $p < 0.05$, respectively]. The results were consistent without important heterogeneity ($p = 0.91$ within designs), and the I^2 test showed low levels of inconsistency (between designs): $I^2 = 0\%$ (0.0%; 17.6%) (Figure 2).

When different de-escalation strategies were considered, a similar tendency for risk reduction was observed; however, this association did not reach the level of statistical significance in any case (Figure 3).

Individual components of the composite endpoint showed beneficial trends, with a lower risk of ischemic events in the abatement strategies except for the risk of myocardial infarction, stent thrombosis, and stroke. These showed an increased risk after P2Y12 inhibitor monotherapy; however, none of these differences reached the level of statistical significance (Supplementary Figure 4).

Treatment ranking gave the highest rank to P2Y12 inhibitor de-escalation (0.92), followed by P2Y12 inhibitor monotherapy (0.62), and the lowest to the clopidogrel or potent P2Y12 inhibitor-based dual antiplatelet therapy (0.24 and 0.22, respectively) in terms of MACE. P2Y12 inhibitor monotherapy (0.78) ranked higher than clopidogrel (0.67) and P2Y12 inhibitor de-escalation (0.42) as well as potent P2Y12 inhibitor-based-dual antiplatelet therapy (0.12) in terms of major bleeding.

Major bleeding rates were similar between P2Y12 inhibitor de-escalation and the control, without major differences among trials [RR: 0.84 (0.57, 1.22)]; however, P2Y12 inhibitor monotherapy resulted in a 35% reduction [RR: 0.65 (0.46, 0.91), $p < 0.05$, $I^2 = 0\%$]. Differences were more expressed in the analyses of all bleeding events and were substantially influenced by minor bleeding. Both P2Y12 inhibitor de-escalation and P2Y12 inhibitor monotherapy resulted in a 36–42% reduction (Figure 2). The most expressed reduction was observed for uniform de-escalation, followed by the other strategies. In the case of PFT-guided de-escalation, no bleeding endpoint was significantly reduced (Figure 3).

Each comparison between de-escalation and monotherapy resulted in an effect estimate that did not reach the level

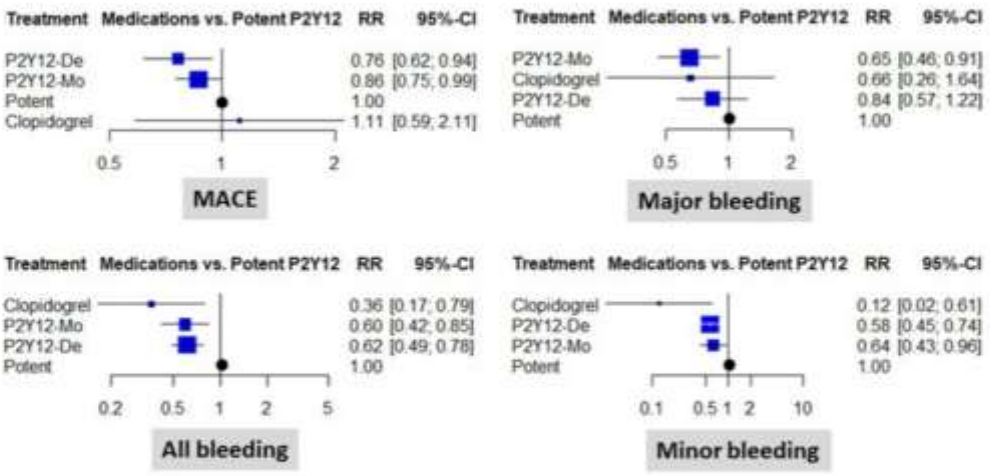

FIGURE 2
Clinical results of using different abatement strategies. The forest plots depict the results of the network meta-analysis computed based on direct and indirect comparisons as risk ratio (RR) and 95% confidence intervals (95% CI). Data are presented as compared to the potent P2Y12 inhibitor-based dual antiplatelet therapy (marked as "Potent"). MACE, major adverse cardiovascular events; P2Y12-De, P2Y12 inhibitor de-escalation; P2Y12-Mo, potent P2Y12 inhibitor monotherapy; Clopidogrel, clopidogrel based DAPT.

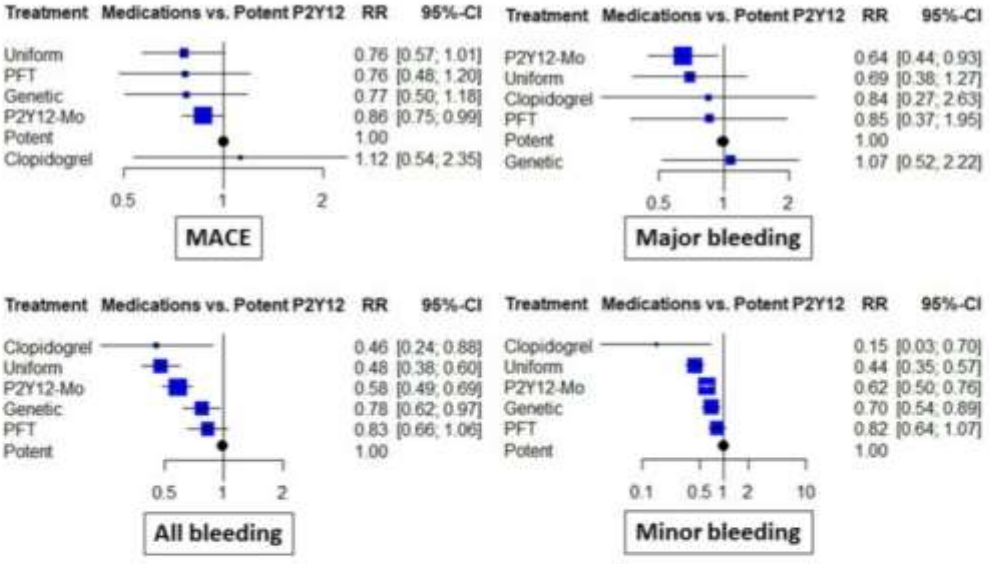

FIGURE 3
Clinical results of abatement strategies considering de-escalation strategies separately. The forest plots depict the risk ratio (RR) and 95% confidence interval (95% CI) achieved with the abatement strategies compared to the potent P2Y12 inhibitor-based dual antiplatelet therapy for major adverse cardiovascular events (MACE), all bleeding (including major and minor events), as well as major bleeding and minor bleeding. In these analyses, de-escalation strategies were considered separate subgroups based on the use of genetic or platelet-function (PFT) testing guidance or uniform de-escalation. P2Y12-Mo, potent P2Y12 inhibitor monotherapy; Clopidogrel, clopidogrel based DAPT.

10.3389/fcvm.2022.1008914

of statistical significance. When considering, however, the different subgroups of de-escalation strategy results, with uniform de-escalation, the estimates were similar to that of monotherapy, while the rates of minor and major bleeding were significantly higher than that for monotherapy (Supplementary Table 1).

Leave-one-out sensitivity exercises did not show any signal of individual studies having excessive influence in the network (Supplementary Figure 5). Further subgroup analyses supported the consistency of the findings (Supplementary Figure 6).

Discussion

In this network meta-analysis of DAPT abatement strategies, we found that both switching to a less potent P2Y12 inhibitor, with a P2Y12 inhibitor de-escalation strategy, or using potent P2Y12 monotherapy with aspirin cessation, were associated with better results with regard to the ischemic endpoints. Benefits in terms of bleeding risk reduction were also associated with both strategies; however, reduction of major bleeding was only significant with P2Y12 monotherapy.

Bleeding events represent an important Achilles' heel of adjunctive pharmacotherapy after coronary interventions. To improve prognosis, bleeding avoidance strategies are widely applied and include both pharmacological and non-pharmacological approaches. The benefits of intensified antiplatelet therapy were demonstrated in cases with the highest ischemic risks as well as in the timeframe closest to the intervention. However, as time passes, this advantage may be overweighted by the cumulative risk of bleeding. Multiple trials were conducted to test alternative protocols, with the potential to attenuate long-term bleeding risk. In a comprehensive analysis of these recent studies, we found that abatement from a potent P2Y12 inhibitor-based dual antiplatelet treatment was associated with an important reduction of bleeding events in patients treated with PCI. Both strategies, with de-escalation of P2Y12 inhibitor and P2Y12 inhibitor monotherapy, showed advantages; however, the analysis also explored important differences which have potential practical implications. While both strategies reduced the risk of all bleeding, P2Y12 inhibitor monotherapy, but not P2Y12 inhibitor de-escalation schemes, was associated with a significant reduction of major bleeding events. Our analysis also suggests that this benefit is not counterbalanced with a higher risk of ischemic events. Nonetheless, the individual trials showed only beneficial trends; this was associated with a significant reduction only in the cumulative analyses. These findings suggest routine use of abatement in patients with ACS undergoing PCI in the early phase. If applied according to the trials, i.e., between 48 h and 3 months, these strategies could be beneficial in terms of improvement of ischemic and bleeding risk.

The three oral P2Y12 inhibitors currently used in patients with ACS and PCI exhibit important pharmacodynamic and pharmacokinetic differences. Clopidogrel and prasugrel are prodrugs that are transformed into their active metabolites by hepatic cytochrome P450 enzymes (15). This activation step is faster and more effective in the case of prasugrel, and the active metabolite of both substances irreversibly inhibits the P2Y12 receptor on platelets. Ticagrelor reversibly inhibits the binding of ADP to the P2Y12 receptor in a non-competitive manner. Ticagrelor is an active drug that does not require *in vivo* biotransformation (16). Compared with clopidogrel, both alternatives have faster onsets, are more potent, and have less response variabilities (17).

One of the main limitations of clopidogrel is that the achieved platelet function inhibition reflects high-interindividual variability, which, among high-risk patients, also represents an important risk marker (18). High-platelet reactivity can be verified with the help of platelet function testing and is present in a higher frequency among mutation carriers of cytochrome enzymes involved in thienopyridine metabolism. These include CYP2C19 mutant alleles such as loss-of-function CYP2C19*2 and *3 alleles. Carriers of these two non-functional copies of the CYP2C19 gene are classified as CYP2C19 poor metabolizers and are characterized by a reduced efficacy of clopidogrel. Other variations include the CYP2C19*17 gain-of-function allele, which can be found in rapid clopidogrel metabolizers. Due to genetics and the high rate of potential drug interactions, there is large interindividual variability in response to clopidogrel, and 15–40% of individuals, depending on the criteria used, are considered "non-responders," or "clopidogrel-resistant," with high residual platelet aggregation. There is a vast amount of evidence indicating that high-platelet reactivity, despite clopidogrel treatment, is a risk factor for cardiovascular events and stent thrombosis, while lower levels of residual platelet aggregation are associated with a higher frequency of bleeding complications (19).

While P2Y12 inhibitor monotherapy was associated with a significant reduction of both major bleeding and adverse events, the effects of P2Y12 inhibitor de-escalation strategies were different. The cumulative ischemic risk reduction was more expressed with these strategies; however, despite favorable tendencies, only the risk of minor bleeding was significantly reduced. All three P2Y12 inhibitor de-escalation strategies resulted in a similarly lower rate of ischemic events; the reduction of bleeding events was most associated with uniform de-escalation. Guided de-escalation with platelet function genetic testing showed less expressed reduction of the bleeding endpoints.

Therefore, P2Y12 inhibitor de-escalation strategies seem to be more efficient in decreasing ischemic risk, while P2Y12 inhibitor monotherapy is a safer strategy for reducing bleeding

10.3389/fcvm.2022.1008914

in patients with ACS. However, using ticagrelor in the P2Y12 inhibitor monotherapy strategy could lead to lower ischemic risks than clopidogrel (20).

While abatement strategies reduced the rate of MACE and bleeding compared to potent P2Y12-based DAPT, indirect comparisons of P2Y12 inhibitor monotherapy and de-escalation only explored signals that may guide decision-making. The reduction of bleeding was similar between the two alternatives; however, subgroup analyses showed that genetic testing and platelet function test-guided de-escalation strategies lagged behind P2Y12 inhibitor monotherapy. This suggests that if bleeding reduction is the main interest, P2Y12 inhibitor monotherapy or unguided de-escalation may offer better alternatives. In indirect comparisons of the rate of ischemic events, however, a tendency for an 11–12% reduction with P2Y12 inhibitor de-escalation strategies was observed; these differences did not reach the level of statistical significance. Thus, more data is required to inform ischemic risk reduction-based decision-making.

Both pivotal clinical trials verifying the benefits of prasugrel and ticagrelor over clopidogrel in ACS showed a reduction of recurrent ischemic events with more effective P2Y12 inhibition but counterbalanced with some degree increase of bleeding risk. The importance of bleeding reduction strategies in ACS was recently emphasized (20, 21). Moreover, because of the publication of alternative antiplatelet protocols, multiple meta-analyses were published. Our meta-analysis differs from these in several aspects (22). Guo et al. (23) included in their meta-analysis both randomized and observational studies. In addition to updating the literature search to include the latest trials, we restricted our inclusion criteria to randomized controlled studies. As observational trials suffer from multiple downsides due to inclusion bias, we considered excluding them to improve the robustness of our analysis. Angiolillo et al. (24) included in their meta-analysis only studies of de-escalation from ticagrelor to clopidogrel, while our meta-analysis also includes de-escalation from both potent P2Y12 inhibitors to clopidogrel. A number of studies focused on the outcomes and benefits of guided de-escalation. Galli et al. (25) found that guided de-escalation improved both composite and individual efficacy outcomes and that it is associated with the most favorable balance between safety and efficacy (26). Tavenier et al. (27) presented results that suggest that both guided and unguided de-escalation were associated with lower rates of bleeding and ischemic events, which aligns with our results. However, the latter meta-analysis excluded aspirin monotherapy trials, which were included in this meta-analysis. Furthermore, with the inclusion of trials testing P2Y12 inhibitor monotherapy and P2Y12 inhibitor de-escalation, our analysis enables the comparison of different abatement strategies.

Thus, far, many randomized controlled trials have investigated the optimal duration of DAPT and meta-analyses comparing different DAPT lengths (3, 6, 12, 24, or 30 months) following DES implantation. The association of prolonged DAPT with an increased bleeding risk, along with a potential reduction of recurrent myocardial infarction (MI) and ST, has been assessed. In an NMA of these trials, D'Ascenzo et al. found that the type of stent impacts the risk of adverse events in addition to DAPT duration. However, there is limited data that directly compare different DAPT durations in patients treated with different generation DES or bioresorbable scaffolds.

Earlier analyses in line with our results reported that P2Y12 inhibitor de-escalation reduces ischemic risk and bleeding in patients with ACS. We extended these observations, with a similar reduction observed in the P2Y12 inhibitor monotherapy trial. Our analysis also enabled comparison of the two strategies. Our results align with the outcomes of the recent meta-analyses by Laudani et al. (28) and Ullah et al. (29), where P2Y12 inhibitor de-escalation decreased ischemic risk, and P2Y12 inhibitor monotherapy decreased bleeding.

Limitations

This meta-analysis has some limitations such as differences in the definition and adjudication of clinical outcomes, diverse follow-up duration, and inconsistency in the timing of switching. Also, few trials were identified, and the low number of events was a typical characteristic of the included studies. Not all studies restricted their inclusion to patients with ACS; however, when relative risk measures are used, differences in absolute risk are less influential to a network. Thus, neither exclusion nor subgroup analyses reflected an important influence attributable to the inclusion of a lower-risk population. We still support the need for adequately powered RCTs to evaluate de-escalation and to further elucidate the role of risk stratification, including potential genetic and PFT characteristics, before applying antiplatelet abatement. It is important to underline that several treatment combinations were not directly compared in specifically designed trials, and thus, an important part of the effect estimates are only based on indirect comparisons. Furthermore, the inclusion of multiple treatment options may also weaken the consistency of the analysis. Thus, the results should be interpreted as observational and only hypothesis-generating.

A new randomized study, the ELECTRA-SIRIO 2 study, which is still underway, aims to evaluate the safety and efficacy of two ticagrelor-based de-escalation antiplatelet strategies in patients with ACS. The results of this study could help inform and confirm the benefits of de-escalation.

Despite these limitations, this systematic review, with a meta-analysis, provides robust evidence evaluating the risks and benefits of abatement strategies.

Conclusion

Our findings suggest that the abatement of antiplatelet treatment gives better results in terms of the bleeding risk, without compromising the major adverse cardiovascular events risk, which turns out to be significantly lower. P2Y12 inhibitor monotherapy and P2Y12 inhibitor de-escalation exhibit differences that may influence their clinical use. P2Y12 inhibitor monotherapy resulted in a reduction of both major and minor bleeding, while ischemic risk reduction was less expressed. The de-escalation strategy was quite the opposite, as there was no difference in major bleeding between this strategy and the control; however, ischemic risk was strongly reduced. Despite their plausible background data, trials with guided de-escalation showed less expressed benefits. It is of note that, in selected patients with high-ischemic risk, these strategies may still offer a safe alternative compared to the long-term potent P2Y12 inhibitor DAPT.

Impact on daily practice

Dual antiplatelet therapy, using a potent P2Y12 inhibitor in patients with acute coronary syndrome receiving percutaneous coronary intervention, maintained for up to 12 months is a guideline-recommended therapy.

Alternative abatement schemes may improve safety outcomes such as major bleeding, without increasing the frequency of ischemic endpoints, creating an optimal balance between bleeding and ischemic complications.

P2Y12 inhibitor monotherapy significantly reduced both major and minor bleeding, while with P2Y12 inhibitor de-escalation, only minor bleeding risk was reduced. Both strategies also significantly reduced the rate of ischemic complications.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

OE and DT performed the literature search and the data extraction. DT and AK performed the statistical analysis. All authors participated in the conception and drafting the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1008914/full#supplementary-material

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Review

Individualized or Uniform De-Escalation Strategies for Antiplatelet Therapy in Acute Coronary Syndrome: A Review of Clinical Trials with Platelet Function Testing and Genetic Testing-Based Protocols

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Abstract: This comprehensive literature review assessed the effectiveness of precision medicine approaches in individualizing P2Y12 de-escalation strategies, such as platelet function testing guidance, genetic testing guidance, and uniform de-escalation, for acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI). Analyzing six trials with a total of 13,729 patients, the cumulative analyses demonstrated a significant reduction in major adverse cardiac events (MACE), net adverse clinical events (NACE), and major and minor bleeding events with P2Y12 de-escalation. Specifically, the analysis found a 24% reduction of MACE and a 22% reduction of adverse event risk (relative risk (RR) 0.76, 95% confidence interval (CI): 0.71–0.82, and RR: 0.78, 95% CI 0.67–0.92, respectively). Reductions in bleeding events were highest with uniform unguided de-escalation, followed by guided de-escalations, while ischemic event rates were similarly lower across all three strategies. Although the review highlights the potential of individualized P2Y12 de-escalation strategies to offer a safer alternative to the long-term potent P2Y12 inhibitor-based dual antiplatelet therapy, it also indicates that laboratory-guided precision medicine approaches may not yet offer the expected benefits, necessitating further research to optimize individualized strategies and evaluate the potential of precision medicine approaches in this context.

Keywords: antiplatelet therapy; de-escalation; acute coronary syndrome; platelet function testing; genetic testing; individualized therapy

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1. Introduction

Acute coronary syndrome (ACS) encompasses a spectrum of conditions characterized by a sudden decrease in blood flow to the heart, which can be life-threatening and necessitate prompt medical intervention to restore blood supply, prevent myocardial damage, and address potential complications such as ischemia and arrhythmia [1]. Antiplatelet therapy is a critical component in the management of ACS, as it inhibits the formation and progression of blood clots that may obstruct coronary arteries. For most cases of ACS, mechanical reperfusion through balloon dilation and stent implantation in the affected coronary arteries is the preferred treatment approach, with antiplatelet therapy playing a key role in preventing thrombosis at the intervention site [2].

Nonetheless, antiplatelet therapy carries some risks, with bleeding complications and MACE occurring in up to 5% and 5.8% of patients, respectively [3,4]. Consequently, it is vital to strike a balance between the benefits and risks of antiplatelet therapy in ACS patients. In recent years, several de-escalation strategies involving platelet function testing (PFT) and genetic testing-based protocols have been developed to minimize bleeding risk

while preserving the effectiveness of antiplatelet therapy. This article reviews the current evidence on individualized or uniform de-escalation strategies for antiplatelet therapy in ACS patients, with an emphasis on the role of PFT and genetic testing-based protocols in informing treatment decisions.

2. Pathophysiological Background

Platelets play a vital role in hemostasis. They become activated upon encountering damaged blood vessels or tissues. Various mechanisms can initiate platelet activation, including pathways mediated by thrombin, collagen, and adenosine diphosphate (ADP) [5].

The ADP-mediated mechanism is one of the most crucial pathways for platelet activation. ADP binds to P2Y1 and P2Y12 receptors on platelet surfaces, activating intracellular signaling pathways that cause platelets to change shape, secrete granules, and aggregate [6].

The P2Y1 receptor is responsible for inducing rapid calcium influx into the platelet, leading to shape change and granule secretion after it is linked to Gαq. The P2Y12 receptor is involved in platelet aggregation by activating the integrin alpha IIb beta 3 on the platelet surface and completing the ADP-dependent platelet aggregation response initiated by P2Y1 as well as the ADP-dependent amplification of platelet aggregation induced by other agents such as Gq-coupled serotonin receptors, Gq and G12/13-coupled TXA2 and PAR-1 receptors, immune complexes, or when platelets are activated by collagen through the GPVI/tyrosine kinase/PLCγ2 pathway. This process results in the cross-linking of adjacent platelets and the formation of a platelet plug to seal the site of injury [7].

Platelet activation is a complex process that involves other agonists such as thrombin, thromboxane, and collagen. Targeting platelet activation with antiplatelet therapy can help prevent platelet aggregation and the formation of blood clots that may lead to heart attacks and strokes. Combining antiplatelet treatments that block multiple signaling pathways, such as aspirin and a P2Y12 inhibitor, is often used in high-risk patients, including those with ACS and following coronary intervention. Additionally, protease-activated receptor-1 (PAR-1) inhibition has been investigated as an alternative treatment option [8]. Vorapaxar, a PAR-1 inhibitor, has been a significant focus of drug development. Studies involving these drugs have demonstrated some success; however, concerns about increased bleeding risk have overshadowed their positive results [9,10].

Clopidogrel was the primary P2Y12 receptor antagonist in clinical practice for many years, but its use exhibited drawbacks such as delayed onset of action, high interindividual response variability, and high residual platelet reactivity during treatment. This was associated with an increase in ischemic events such as stent thrombosis, primarily among high-risk patients with ACS [11].

Prasugrel and ticagrelor represent the next generation of ADP receptor antagonists with a shorter onset of action and more consistent inhibition of platelet aggregation. They have demonstrated a higher risk reduction for thrombosis compared to clopidogrel in patients with ACS in the TRITON-TIMI 38 and PLATO trials [12,13]. However, trials testing these drugs in lower-risk populations failed to prove their benefit compared to clopidogrel. Notably, while the benefits of more potent antiplatelet therapy are more pronounced during the earliest weeks after intervention, bleeding events accumulate during long-term antiplatelet treatment. As both ischemic and bleeding events pose significant prognostic risks for patients with ACS, recent trials have sought to personalize antiplatelet therapy based on these characteristics, adjusting antiplatelet use according to changes in risk during the clinical course.

3. Role of Platelet Function Testing in Assessing P2Y12 Inhibitor Therapy

PFT is a valuable ex vivo method for evaluating the effectiveness of clopidogrel treatment [14]. Clopidogrel, a prodrug, requires a two-step activation process in the liver to produce its active metabolite. The absorbed clopidogrel competes with other substrates for the limited metabolic capacity of the liver enzyme CYP2C19 and is subject to non-specific inactivation by plasma esterases. Genetic variations in CYP2C19 activity and the esterase-

mediated degradation of over 60% of the drug, as well as absorption issues in critically ill patients, can lead to insufficient active metabolite production and an inadequate response to clopidogrel, increasing the risk of blood clots [11]. ADP-specific PFTs are designed to detect alterations in P2Y12-specific signaling or aggregation and may be used to monitor the achieved antiplatelet action.

Various methods exist for PFT, including light transmission aggregometry (LTA), VerifyNow P2Y12 assay, and Multiplate analyzer. LTA, considered the most reliable method, is time-consuming and requires specialized equipment. The VerifyNow P2Y12 assay and Multiplate analyzer are faster point-of-care methods, but they have limitations in sensitivity and specificity [15].

If patients exhibit a poor response to clopidogrel, alternative antiplatelet medications such as ticagrelor or prasugrel may be more effective. PFT can also be used to monitor the effectiveness of these alternative therapies and adjust dosages as necessary [16].

The limitations of these PFT methods have been discussed extensively elsewhere [17]. PFT analyses were included in trials aiming to characterize optimal antiplatelet dosages. They are considered helpful in identifying individuals with a poor treatment response and can aid in selecting appropriate alternative treatments.

4. Genetic Background of Interindividual Response Variability by Clopidogrel

Genetic polymorphisms impacting the function of enzymes responsible for their metabolism can lead to variable levels of clopidogrel metabolism and platelet inhibition, potentially affecting clinical outcomes [18].

Several cytochrome P450 (CYP) enzymes, including CYP2C19, are involved in clopidogrel metabolism. Genetic polymorphisms affecting CYP2C19 function can result in variable levels of clopidogrel metabolism and platelet inhibition, ultimately impacting clinical outcomes [18].

The most common CYP2C19 variant alleles are the loss-of-function alleles *2 and *3, which result in reduced enzymatic activity and lower levels of active metabolite formation. In contrast, the gain-of-function allele *17 is associated with increased enzymatic activity and higher levels of active metabolite formation. Studies have shown that carriers of CYP2C19 loss-of-function alleles have a higher risk of recurrent ischemic events and stent thrombosis compared to non-carriers, particularly in patients with ACS undergoing PCI. This is likely due to decreased platelet inhibition and a lower antiplatelet effect of clopidogrel in these patients [19].

In addition to CYP2C19, other genetic polymorphisms affecting clopidogrel metabolism have been studied, such as ABCB1 and PON1, but their clinical relevance remains unclear. Rideg et al. studied the effect of various SNPs, such as Cytochrome 2C19 (CYP2C19) loss-of-function (LOF; *2, *3) and gain-of-function (GOF; *17) allelic variants, along with ABCB1 (3435 C→T and 2677 G→T/A) and paraoxonase-1 (PON-1; 192 Q→R), on post-clopidogrel platelet reactivity and clinical outcome. They found that genetic variants in CYP2C19 had a gene-dose effect on post-clopidogrel platelet reactivity, but neither ABCB1 nor PON-1 genotypes significantly influenced platelet reactivity or outcome [19] (Figure 1).

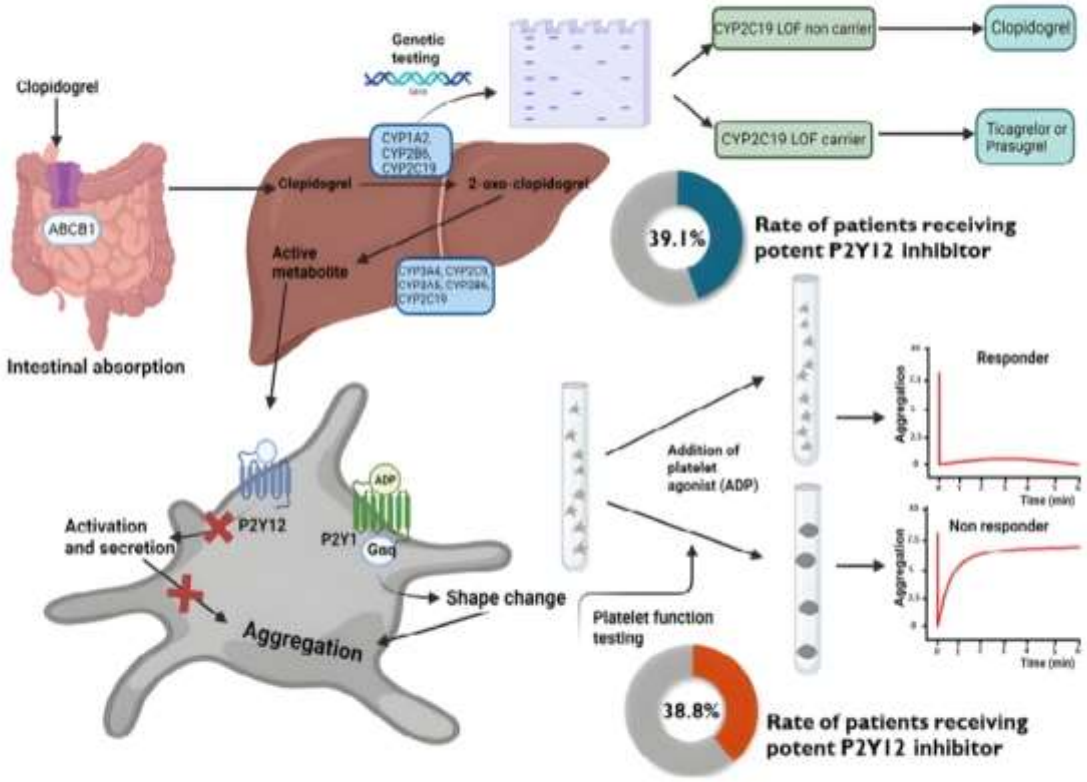


Figure 1. The metabolism of clopidogrel in the liver is genetically determined by the CYP2C19 enzyme. Genetic carrier status and the in vitro measurement of residual platelet function testing (PFT) may be used to identify patients with a higher risk for clopidogrel inefficacy. P2Y12 de-escalation trials using PFT and genetic testing-guided trials maintained long-term potent P2Y12 inhibitor treatment in the identified high-risk subset (rates in orange and blue, respectively). (Created with BioRender.com accessed on 21 April 2023).

The clinical significance of genetic testing for CYP2C19 polymorphisms is still under debate. The 2017 American College of Cardiology/American Heart Association guidelines recommend testing for CYP2C19 loss-of-function alleles in patients undergoing PCI who will receive clopidogrel therapy [20]. However, other guidelines, such as those from the European Society of Cardiology, do not recommend routine genetic testing due to the lack of conclusive evidence regarding its clinical utility. The optimal approach to genetic testing and its clinical usefulness remains to be determined.

Numerous studies have been conducted to personalize antiplatelet therapy for patients undergoing percutaneous coronary intervention (PCI). The GRAVITAS trial showed that high on-treatment platelet reactivity (HTPR), evaluated by assays such as LTA, VerifyNow, Multiplate, or VASP, is a strong marker for worse outcomes in patients after PCI [21]. However, HTPR is not the only determinant of clinical outcomes, as other clinical and procedural factors also play a role. In the POPULAR study, adding HTPR to traditional risk factors only modestly improved the overall predictive value of the model in elective patients after PCI. Nonetheless, platelet function monitoring may be useful in combining the prognostic impact of a patient's fixed clinical makeup with a potentially corrigible estimate of a drug's effect.

The ARCTIC-GENE study aimed to adjust antiplatelet therapy according to CYP2C19 genotypes, clopidogrel pharmacodynamic response, and assessed clinical outcomes in patients who underwent stent implantation. The study included 1394 patients who were genotyped for loss- and gain-of-function CYP2C19 alleles and randomized to a strategy of platelet function monitoring with drug adjustment or a conventional strategy without monitoring and drug adjustment. The study found that slow metabolizers, identified as carriers of at least one loss-of-function allele CYP2C19*2, were more likely to be poor responders to antiplatelet therapy at randomization and 14 days later. However, the study did not find any significant difference in the primary study outcome, defined as the composite of death, myocardial infarction, stent thrombosis, stroke, or urgent revascularization 1 year after stent implantation, between slow and rapid metabolizers. The study concluded that the genetic clopidogrel profile was a good marker of platelet function response but added little to the pharmacodynamic information used in the study to adjust antiplatelet therapy [22].

The POPular Genetics trial also failed to show a significant reduction in clinical endpoints with the use of genetic testing-based individualized antiplatelet strategy. The study randomized 2488 ACS patients to either standard DAPT with aspirin and clopidogrel or to CYP2C19 genotyping guided treatment. The latter group received either clopidogrel or ticagrelor based on CYP2C19 genotype. The study found no significant difference between the two groups in terms of the composite endpoint of death from cardiovascular causes, myocardial infarction, stroke (5.1% vs. 5.9%, HR: 0.89, [95% CI: 2.0–0.7]), or major bleeding at 12 months (9.8% vs. 12.5%, HR: 0.78, [95% CI: 0.61–0.98]) [23].

5. The Use of P2Y12 Inhibitors in Acute Coronary Syndrome

Coronary artery disease (CAD) is a prevalent and severe medical condition that leads to significant morbidity and mortality worldwide. ACS typically results from plaque rupture or erosion, leading to blood clot formation. PCI with stent placement is a common treatment for ACS patients. Antiplatelet medications, particularly P2Y12 inhibitors, play a crucial role in reducing the risk of recurrent ischemic events in patients undergoing PCI, but they may also increase the likelihood of bleeding [24].

Prasugrel, a third-generation thienopyridine, irreversibly inhibits the P2Y12 receptor. The TRITON-TIMI 38 trial compared prasugrel to clopidogrel in patients with ACS undergoing PCI. Prasugrel reduced the risk of the primary endpoint—a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke—compared to clopidogrel (9.9% vs. 12.1%, HR: 0.81, [95% CI: 0.73–0.90]). However, prasugrel was associated with an increased risk of major bleeding (2.4% vs. 1.8%, HR: 1.32, [95% CI: 1.03–1.68]), including fatal bleeding (0.4% vs. 0.1%, HR: 3.39, [95% CI: 1.78–6.45]) [12].

Ticagrelor is a reversible P2Y12 inhibitor with a faster onset of action than clopidogrel and does not require hepatic metabolism for activation. The PLATO trial investigated ticagrelor compared to clopidogrel in ACS patients. There was no difference in terms of the risk of the primary endpoint—PLATO major bleeding—between ticagrelor and clopidogrel treated patients (11.6 vs. 11.2%, $p = 0.43$). Ticagrelor reduced the risk of the primary endpoint—a composite of death from cardiovascular causes, myocardial infarction, stroke, and bleeding—compared to clopidogrel (7.86 vs. 8.97%, HR: 0.87, [95% CI 0.77–0.98], $p = 0.026$). However, it was associated with an increased non-CABG major bleeding (4.5 vs. 3.8%, $p = 0.02$) and non-procedure related major bleeding (3.1 vs. 2.3%, $p = 0.05$). The risk of fatal bleeding was similar between the two groups (0.3 vs. 0.3%, $p = 0.66$) [13].

The ISAR-REACT 5 trial conducted a head-to-head comparison of the two potent P2Y12 inhibitors. In this trial, the composite endpoint of cardiovascular death, myocardial infarction, or stroke showed a highly significant reduction favoring prasugrel vs. ticagrelor (HR: 1.36, [95% CI: 1.09–1.70], $p = 0.006$), and bleeding events did not differ between groups (HR: 1.12, [95% CI: 0.83–1.51], $p = 0.45$) [25].

In conclusion of all these trials, both prasugrel and ticagrelor have been shown to minimize the risk of recurrent ischemic events in ACS patients undergoing PCI compared to clopidogrel. The ISAR-REACT 5 trial directly compared prasugrel and ticagrelor, demon-

strating that prasugrel was associated with a lower risk of the primary endpoint, which included death, myocardial infarction, or stroke, compared to ticagrelor. However, the risk of bleeding (major bleeding events defined by the Bleeding Academic Research Consortium (BARC) type 3 or 5) was not significantly different between the two groups. Therefore, while prasugrel showed superior efficacy compared to ticagrelor, the risk of bleeding between the two drugs was comparable.

6. Genetic Testing-Based P2Y12 De-Escalation Strategy

Genetic testing can help identify individuals who may not respond well to clopidogrel, which could have long-term implications for their ischemic risk. However, selective use of potent P2Y12 inhibitors in loss-of-function carriers did not result in an improvement of clinical outcomes [21,22]. The TAILOR-PCI trial tested a carrier status-based de-escalation strategy. This trial randomized 5302 ACS patients undergoing PCI to either standard dual antiplatelet therapy (DAPT) with aspirin and clopidogrel or a genotype-guided strategy in which CYP2C19 genotyping was used to determine the choice of P2Y12 inhibitor. The study found that genotype-guided therapy was non-inferior to standard DAPT in terms of the primary endpoint of cardiovascular death, myocardial infarction, stroke, stent thrombosis, or severe bleeding at 12 months (4.0% vs. 5.9%, HR: 0.66, [95% CI: 0.43–1.02], $p = 0.06$) [26] (Table 1). Both the rate of major adverse cardiovascular events (MACE) and the net clinical benefit showed a beneficial trend in this trial; however, the expected lower rate of major bleeding was not reflected in the trial results (Figure 2).

Table 1. Table 1 describes the main characteristics of the de-escalation studies. Abbreviations: BARC: Bleeding Academic Research Consortium Criteria, NACE: net adverse clinical events, ST: stent thrombosis, TIMI: thrombolysis in myocardial infarction, PLATO: platelet inhibition and patient outcomes, MI: myocardial infarction, PRU: P2Y12 reaction unit, SRI: severe recurrent ischemia, CVD: cardiovascular death, UR: urgent revascularization.

Study	TALOS-AMI Trial	HOST-REDUCE-POLYTECH-ACS	TAILOR-PCI	TOPIC	TROPICAL-ACS	-
First author	Park	Kim	Pereira	Cuisset	Sibbing	Ueno
Publication year	2021	2020	2020	2017	2017	2016
Number of patients	2697	2338	5302	646	2610	136
De-escalation strategy	Uniform unguided de-escalation	Uniform unguided de-escalation	Genotype-guided therapy	Uniform unguided de-escalation	Guided by platelet function testing	Uniform unguided de-escalation
Primary outcome	NACE (CVD + MI + Stroke + Bleeding)	NACE (Death + MI + ST + SRI + Bleeding)	CVD + MI + ST + RR + Stroke	CVD + UR + Stroke + Bleeding	CVD + MI + Stroke + Bleeding	PRU
Definition of bleeding (Primary/Secondary)	BARC	BARC	BARC/TIMI	TIMI/BARC	BARC	BARC/TIMI
Treatment used before de-escalation	Ticagrelor + Aspirin	Prasugrel + Aspirin	Ticagrelor + Aspirin	Ticagrelor or Prasugrel + Aspirin	Prasugrel + Aspirin	Prasugrel + Aspirin
Treatment used after de-escalation	Clopidogrel + Aspirin	Prasugrel + Aspirin	Clopidogrel + Aspirin	Clopidogrel + Aspirin	Clopidogrel + Aspirin	Clopidogrel + Aspirin
Clopidogrel (Experimental/Control) (%)	100/0	-	15/99	100/0	100/0	100/0
Prasugrel (Experimental/Control) (%)	0/100	100/100	-	56/59	0/100	0/100
Ticagrelor (Experimental/Control) (%)	0/100	-	85/1	44/42	-	-
Result	Significant decrease in bleeding risk	Reduced risk of NACE	No significant results	Reduced risk of bleeding	No significant results	Increase in PRU

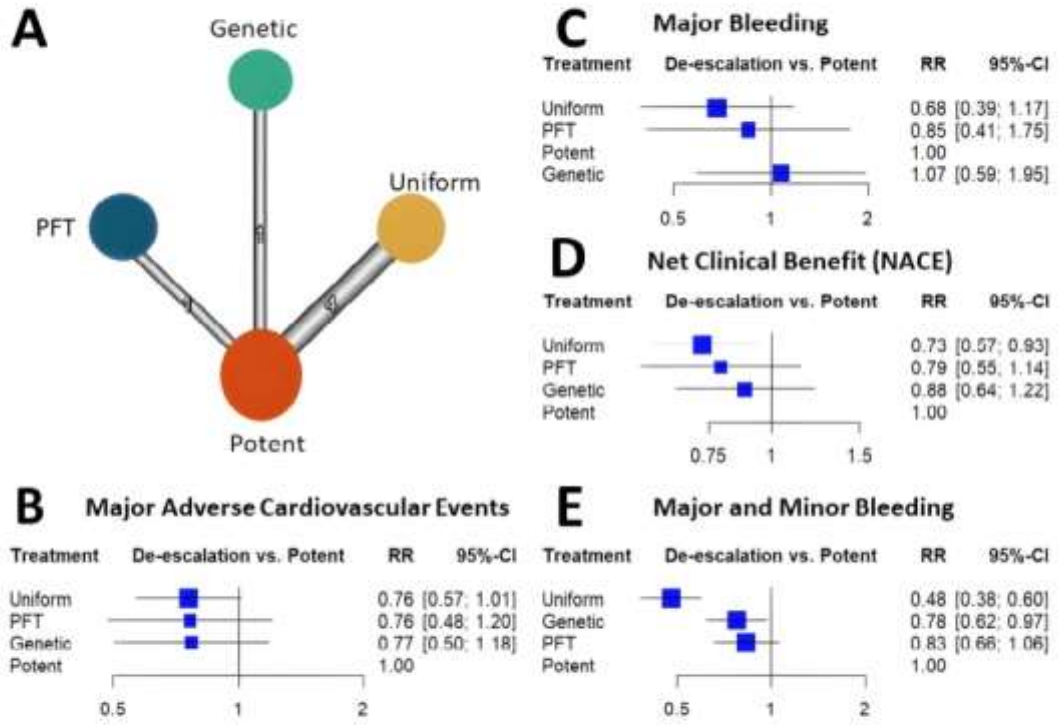


Figure 2. Network meta-analysis results of randomized trials of P2Y12 de-escalation. Network graph depicts the available trial information. Nodes are proportional with the number of patients included and edges are proportional with the number of studies performed (Panel (**A**)). Forest plots depict the results of network meta-analysis showing the risk ratio (RR) and its 95% confidence interval (95% CI) compared to the control arm using long-term potent P2Y12 inhibition. Major adverse cardiovascular events (MACE) are defined as composites of cardiovascular mortality, myocardial infarction, and stroke. Net clinical benefit (NACE) is defined as composite of MACE and major bleeding (Panel (**B**–**E**)).

7. Platelet Function Testing-Based P2Y12 De-Escalation Strategy

A randomized clinical trial investigated the feasibility and safety of a PFT-based P2Y12 de-escalation strategy in ACS patients. The study aimed to assess whether using PFT to guide P2Y12 inhibitor de-escalation could reduce bleeding complications while maintaining adequate platelet inhibition.

The TROPICAL-ACS trial randomized 2610 ACS patients undergoing PCI to either standard DAPT with aspirin and prasugrel or a de-escalation strategy guided by PFT. In the de-escalation arm, patients received prasugrel for one week followed by clopidogrel for another week. Long-term P2Y12 inhibitor treatment was determined based on the results of the ADP-specific platelet function assay. Patients with acceptable residual platelet reactivity continued clopidogrel, while those with high reactivity were switched back to prasugrel. The latter group constituted 38.8% of the de-escalation arm. The study found that PFT-guided de-escalation was non-inferior to standard DAPT with regard to the composite endpoint of death, myocardial infarction, stroke, and bleeding at 1 year (7% vs. 9%, $p = 0.0004$ for non-inferiority, HR: 0.81, [95% CI: 0.62–1.06], p-superiority = 0.12) [27].

Similar to genetic testing, the rates of MACE and net clinical events showed beneficial trends, and a 15% reduction in major bleeding risk was also observed. However, none of these reached the level of statistical significance (Figure 2).

8. Trials with Uniform P2Y12 De-Escalation Strategy

Several trials have investigated de-escalation protocols for P2Y12 treatment without considering patient-specific genetic or platelet function data. These trials compared long-term, potent DAPT to protocols that switched patients from potent inhibitors to clopidogrel after a predetermined period.

The TOPIC trial (testing responsiveness to platelet inhibition on chronic antiplatelet treatment for acute coronary syndromes) randomized 646 ACS patients on DAPT to either switch to clopidogrel or continue the newer P2Y12 inhibitor one month after PCI. The primary endpoint of cardiovascular death, myocardial infarction, stroke, or stent thrombosis occurred in 26.3% of patients in the unswitched group and in 13.4% of the switched group (HR: 0.48, [95% CI: 0.34–0.68], $p < 0.01$). No significant difference in ischemic endpoints was reported between the two groups, while bleeding occurred in 4.0% of patients in the switched DAPT and 14.9% in the unswitched DAPT group (HR: 0.30, [95% CI: 0.18–0.50], $p < 0.01$) [28].

The HOST-REDUCE-POLYTECH-ACS trial randomized 2338 ACS patients on DAPT to either continue their current P2Y12 inhibitor dose of prasugrel (10 mg) or receive a lower dose of prasugrel (5 mg). The primary endpoint of a composite of cardiovascular death, myocardial infarction, definite stent thrombosis, or ischemic stroke occurred in 7.2% of patients in the de-escalation group and 10.1% of patients in the standard care group (p-non-inferiority < 0.0001, HR: 0.70, [95% CI: 0.52–0.92], p-equivalence = 0.012). There was no increase in ischemic risk in the de-escalation group compared with the conventional group (HR: 0.76, [95% CI: 0.40–1.45], $p = 0.40$), and the risk of bleeding events was significantly decreased (HR: 0.48, [95% CI: 0.32–0.73], $p = 0.0007$) [29].

The TALOS-AMI trial randomized 2697 patients on DAPT to either undergo de-escalation to clopidogrel with aspirin or continue DAPT with ticagrelor. The primary endpoint of net adverse clinical events (NACE), including cardiovascular death, myocardial infarction, stroke, and BARC 3 or 5 bleeding, occurred in 4.7% of patients in the de-escalation group and 8.3% of patients in the control group (HR: 0.58, [95% CI: 0.38–0.87], $p = 0.009$), with a significant decrease in bleeding (HR: 0.52, [95% CI: 0.35–0.77], $p = 0.001$) and no increase in ischemic events [30].

Ueno et al. randomized 136 ACS patients on DAPT to either undergo de-escalation to clopidogrel with aspirin or continue DAPT with prasugrel. The primary endpoint was the mean P2Y12 reaction unit (PRU) at week 6, which was significantly lower in the continued group relative to the switched group (140.7 and 183.0, respectively; $p = 0.001$) [31].

9. Comparison of Approaches

Comparing the effectiveness of the three de-escalation approaches to P2Y12 de-escalation, including PFT guidance, genetic testing guidance, and uniform de-escalation without laboratory guidance, is challenging due to variations in patient populations, follow-up durations, and endpoints among the trials. Notably, none of these individual trials found a significant reduction in major bleeding, MACE, or net clinical benefit. However, their results supported that protection against ischemic events is not compromised with de-escalation compared to long-term potent P2Y12 treatment.

The risk and benefit of de-escalation related to other antiplatelet strategies were assessed in multiple recent analyses. A recent network meta-analysis aimed to compare the efficacy and safety of different approaches linking standard long-term DAPT with potent P2Y12 antagonists to strategies based on earlier aspirin cessation and potent P2Y12 inhibitor monotherapy after coronary intervention [32]. Ten randomized controlled trials with a total of 42,511 participants were included. They compared four different strategies for abating DAPT: PFT-based P2Y12 de-escalation, genetic testing-based P2Y12 de-escalation, uniform

unguided P2Y12 de-escalation, and P2Y12 monotherapy, including ticagrelor monotherapy and clopidogrel arms, which allowed a broader context to relate the efficacy and safety of abatement strategies.

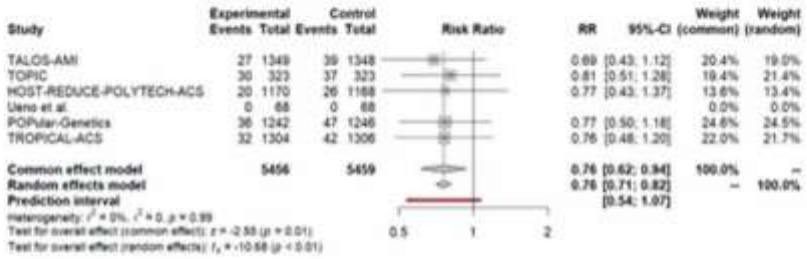
The authors found that both P2Y12 inhibitor de-escalation and P2Y12 inhibitor monotherapy reduce ischemic events and all bleeding (including major and minor events) among PCI-treated ACS patients. However, the different severity of bleeding was differently affected by the abatement strategies. With ticagrelor monotherapy, both major and minor bleeding event risk was significantly reduced, while with de-escalation, only the risk of minor bleeding was significantly reduced.

Among the de-escalation strategies, uniform de-escalation exhibited the highest reduction in bleeding, followed by genetic testing-guided de-escalation, while PFT-guided de-escalation did not show any significant reduction in bleeding (Figure 2). These trends reached significant levels for all bleeding and minor bleeding, but regarding major bleeding, none of the individual de-escalation strategies or the cumulative estimate of the de-escalation trials reflected a significant reduction (Figure 3). While results of the bleeding risk reduction remained behind expectations for de-escalation strategies, an unexpected benefit was unveiled. Contrary to the anticipated trade-off of accepting a certain increase in ischemic risk, all three P2Y12 inhibitor de-escalation strategies resulted in a similarly lower rate of ischemic events (Figure 4). As these trials were not powered to assess individual endpoints, the cumulative analysis of more than 10,000 randomized patients reflected a highly significant 24% reduction of MACE without signs of major heterogeneity among the trials. Similarly, in net clinical benefit analyses, a significant 22% reduction of adverse event risk was found (Figure 3).

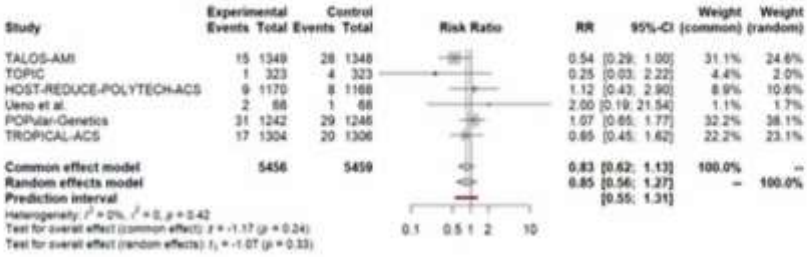
An extensive network meta-analysis conducted by Kuno et al. aimed to assess the efficacy and safety of various dual antiplatelet therapy (DAPT) approaches. The employment of broader inclusion criteria permitted a higher number of trials with less stringent requirements regarding de-escalation. The analysis incorporated 19 randomized controlled trials, totaling 69,746 patients, and evaluated six distinct DAPT strategies, including aspirin and clopidogrel, aspirin and low-dose prasugrel, aspirin and standard-dose prasugrel, aspirin and ticagrelor, as well as an unguided de-escalation strategy and guided selection strategy. Although this approach may facilitate a better understanding of de-escalation within a broader range of therapeutic options, it also carries the risk of network results being influenced or dominated by indirect comparisons. Results of Kuno et al.'s findings were in agreement, indicating that unguided de-escalation was associated with a reduced risk of major adverse cardiovascular events (MACE) when compared to DAPT regimens [33]. Our further analyses revealed no significant difference in MACE risk between guided and unguided strategies, but all studies demonstrated similar reductions that reached statistical significance due to the larger cumulative number of patients included in unguided de-escalation trials.

While ischemic event outcomes suggested a similar benefit for de-escalation with or without laboratory guidance, bleeding rates presented a more heterogeneous picture. A key distinction between our analysis and that of Kuno et al. is that the latter grouped the TROPICAL-ACS and POPULAR-GENETIC trials in the same category. The notable increase in major bleeding in the latter trial, despite significant reductions in major and minor bleeding with genetic testing-based de-escalation, remains unexplained. We believe this discrepancy justifies not grouping these two trials together.

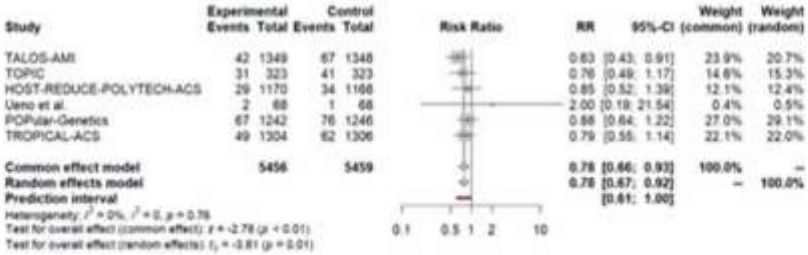
Panel A Major Adverse Cardiovascular Events



Panel B Major Bleeding



Panel C Net clinical efficacy (NACE)



Panel D Major and Minor Bleeding

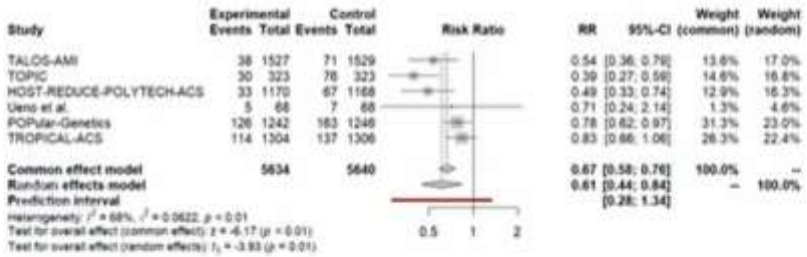
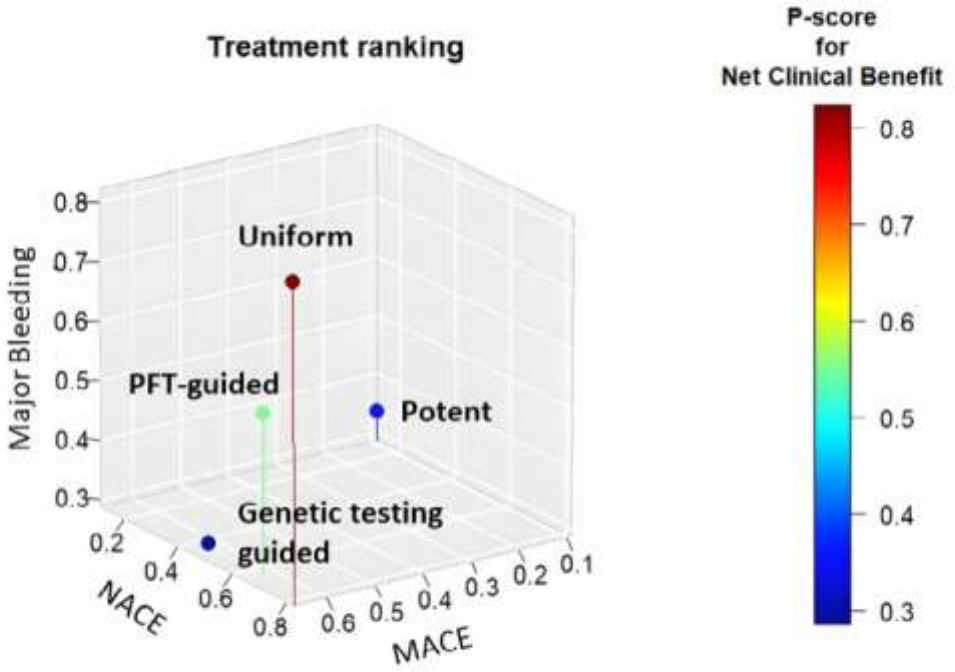


Figure 3. Forest plots depicting clinical endpoints of P2Y12 de-escalation strategies. Panels depict the relative risk of MACE (Panel (**A**)), major bleeding (Panel (**B**)), NACE (Panel (**C**)), and all bleeding defined as major and minor bleeding events (Panel (**D**). (source of data: [32]).



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 4. Treatment ranking of P2Y12 de-escalation strategies. The scatterplot depicts the treatment ranking with regard to the risk of MACE, major bleeding, and NACE. Uniform de-escalation was ranked first in all analyses.

It is essential to note that none of the trials were designed to demonstrate differences in MACE or major bleeding, but rather to establish non-inferiority based on composite endpoints. Complementing Kuno et al.'s analysis, we demonstrated a significant improvement in net clinical benefit with de-escalation strategies. We concur that both guided de-escalation approaches resulted in a higher number of prasugrel treatments in the de-escalation arm, which may explain the less pronounced reduction in major and minor bleeding rates. This observation, combined with cost and logistical concerns, renders unguided de-escalation a more attractive option [33].

We lack a clear mechanistic explanation for the risk reduction, but together with the findings of minor bleeding rate, it has been hypothesized that reduction of these nuisance events may have permitted a more tolerable treatment with higher compliance. If this hypothetical higher adherence translated to the observed clinical benefit, however, we lack conclusive data [32]. The rate of bleeding events may also be influenced by additional factors. Both genetic testing and PFT were incorporated into the de-escalation strategies to implement pharmacokinetic-based risk stratification for identifying patients at the highest

risk. However, the practical application of this strategy led to approximately 40% of patients in the individualized treatment arm receiving clopidogrel. A selection strategy resulting in a higher rate of potent treatment might be the reason why these trials' observed bleeding risk reduction fell short of expectations. It has been suggested that platelet function measurements' negative predictive values are excellent, potentially providing a valuable tool for identifying patients who can safely remain on clopidogrel therapy. For instance, in a group of ACS patients with access to more potent antiplatelet drugs, continuing clopidogrel therapy may be non-inferior to switching to prasugrel or ticagrelor. However, the positive predictive values of platelet function measurements are mostly fair or poor. While platelet function tests assess residual platelet reactivity, the connection between ischemic risk and genetic predisposition may be even weaker, which could explain the discrepancies in these trials.

Cumulative analyses of P2Y12 inhibitor de-escalation studies demonstrated significant benefits in MACE, NACE, and major + minor bleeding, with slightly greater benefits observed in the uniform studies. However, major bleeding did not show a significant reduction; it was more prevalent in uniform studies, followed by PFT de-escalation strategies, and lastly, genetic testing de-escalation, which exhibited a lesser trend of major bleeding reduction. These results might be attributed to the long-term prasugrel treatment in the de-escalation arms (40%) of both PFT and genetic testing de-escalation, which can impact clinical outcomes, particularly bleeding events. Additionally, these results suggest that risk assessment with PFT may be more precise compared to metabolizer status. Nonetheless, further studies will be necessary to support these assumptions (Figure 3).

Most trials demonstrated trends for improvement concerning these endpoints. A cumulative analysis resulted in a significant reduction in all three endpoints (Figures 2 and 3).

In summary, network analyses suggest that uniform unguided de-escalation may be an effective strategy for reducing potent P2Y12 antagonist-based DAPT after coronary intervention (Figure 4). However, this approach might be associated with an increased risk of ischemic events, as it does not consider each patient's individual bleeding and ischemic risk to select the optimal approach for DAPT abatement.

Overall, these network analyses suggest that uniform unguided de-escalation may be an effective strategy for abating potent P2Y12 antagonist-based DAPT after coronary intervention (Figure 4). However, this approach may be associated with an increased risk of ischemic events since it does not take into consideration the individual patient's bleeding and ischemic risk in order to select the optimal approach for DAPT abatement.

In conclusion, uniform unguided P2Y12 de-escalation strategies have consistently shown a reduction in bleeding events without compromising efficacy. Genetic testing-guided de-escalation strategies and de-escalation using PFT guidance provided results showing no difference in bleeding or ischemic events between the de-escalation group and the standard group (4.0% vs. 5.9% and 7% vs. 9%, respectively). Overall, the use of uniform unguided de-escalation appears to be the most effective strategy in reducing bleeding events while maintaining efficacy. However, it is important to note that uniform unguided de-escalation may be associated with an increased risk of ischemic events, that would be more difficult to manage than bleeding, since it does not take into consideration the individual patient's bleeding and ischemic risk in order to select the optimal approach for DAPT abatement, which can lead to serious complications and can be fatal. Further studies will be required to support these assumptions and to determine the most effective approach for individualized patient care.

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Cardioprotective strategies against myocardial ischemia–reperfusion injury

Kardioprotektív stratégiák a szívizom iszkémiás-reperfúziós károsodásával szemben

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Abstract

The incidence of ST-segment elevation myocardial infarction (STEMI) has demonstrated a decline in developed countries over the past two decades. However, despite widespread access to reperfusion therapy, the mortality associated with STEMI remains substantial. This review comprehensively explores the pathophysiology of acute myocardial infarction and reperfusion, encompassing the evolution of ischemic and reperfusion injuries, diverse modalities of cell death, and the resultant coronary microvascular dysfunction. Finally, we provide an in-depth discussion on efforts to translate cardioprotective drug therapies into clinical practice.

Keywords: ST-segment elevation myocardial infarction, reperfusion injury, coronary microvascular dysfunction, cardioprotection

Absztrakt

Az ST-szegment elevációval járó szívinfarktus (STEMI) előfordulása az elmúlt két évtizedben a fejlett országokban csökkenést mutatott. A reperfúziós terápiához való széles körű hozzáférés ellenére azonban a STEMI-hez kapcsolódó halálozás továbbra is jelentős. Áttekintésünk átfogóan vizsgálja az akut szívinfarktus és a reperfúzió patofiziológiáját, felölelve az iszkémiás és reperfúziós sérülések kialakulását, a sejthalál különböző módozatait és az ebből eredő koszorúér-mikrovaszkuláris diszfunkciót. Végül részletesen tárgyaljuk a kardioprotektív gyógyszeres terápiák klinikai gyakorlatba való átültetésére irányuló erőfeszítéseket.

Kulcsszavak: ST-szegment elevációs szívinfarktus, reperfúziós sérülés, koszorúér mikrovaszkuláris diszfunkció, kardioprotekció

Introduction

ST-segment–elevation myocardial infarction (STEMI) represents the upper end of the acute coronary syndrome (ACS) continuum and remains one of the most significant clinical burdens worldwide. Irreversible injury results from prolonged and severe myocardial ischemia and is typically caused by the rupture or erosion of an atherosclerotic plaque in an epicardial coronary artery. This event sets off superimposed thrombosis, resulting in the occlusion of the coronary artery, classified as Type 1 myocardial infarction (MI) (Thygesen et al., 2019). Timely and complete reperfusion, achieved by primary percutaneous coronary intervention (pPCI) or thrombolytic therapy, stands as the most effective treatment for minimizing the size of MI, preserving cardiac function, and lowering the risk of heart failure in STEMI patients. Given the accessibility of facilities, myocardial reperfusion by pPCI is the favored therapeutic strategy over thrombolysis (Byrne et al., 2023). Although reperfusion is essential to rescue ischemic myocardium from imminent infarction, it paradoxically triggers additional irreversible damage. This phenomenon, known as reperfusion injury, manifests as microvascular dysfunction and augmented infarct size, adversely influencing the short- and long-term prognosis of patients with STEMI. Several treatments demonstrating robust cardioprotection have been identified in preclinical models of acute ischemia-reperfusion injury (Heusch, 2019; Ferdinandy, 2023). Nonetheless, the implementation of these cardioprotective strategies in clinical practice is still awaited.

Ischemia-reperfusion injury

The findings from preclinical studies indicate that the size of an infarct is influenced by a combination of damage resulting from both ischemia and reperfusion. The extent of both types of injury is related to the duration of ischemia and the level of residual blood flow during coronary occlusion. Irreversible damage due to ischemia escalates with the severity and duration of blood flow reduction, whereas reperfusion injury peaks at a moderate level of ischemic damage (Heusch, 2020).

Cardiomyocyte death

During ischemia, cardiomyocyte metabolism switches from oxidative phosphorylation to anaerobic glycolysis. As ATP levels fall, the function of ATP-dependent ion pumps is disturbed. Inhibition of Na^+-K^+–ATPase results in accumulation of intracellular Na^+ and loss

of K^+. Intracellular acidosis further increases intracellular Na^+ load through activation of the Na^+–H^+ exchanger (NHE), although the extracellular acidosis that rapidly develops during ischemia begins to inhibit NHE activity. The increase in Na^+ drives the rise in intracellular Ca^{2+} by stimulating Na^+–Ca^{2+} exchanger (NCX) in the reverse-mode (Ca^{2+} in, Na^+ out). In addition, Ca^{2+} reuptake into the sarcoplasmic reticulum is impaired due to inhibition of sarcoplasmic reticulum Ca^{2+}–ATPase (Murphy & Steenbergen, 2008; Heusch, 2020; Wang et al., 2023). Substantial part of the ATP pool serves to generate mitochondrial membrane potential, which is used to take up cytosolic Ca^{2+} into the mitochondria. During reperfusion, as oxygen returns, a large burst of reactive oxygen species (ROS) occurs, which can lead to extensive oxidative damage to cells, ultimately resulting in loss of cell viability (Murphy & Steenbergen, 2008). Moreover, upon reperfusion, extracellular acidosis is quickly normalized, reactivating NHE to restore intracellular pH at the expense of further increasing intracellular Na^+. The rise in intracellular Na^+ triggers a large cytosolic Ca^{2+} overload via reverse-mode NCX (Murphy & Steenbergen, 2008). Depending on ATP levels, intracellular Na^+ concentrations, and damage to Ca^{2+} handling proteins, intracellular Ca^{2+} levels may rapidly return to normal, oscillate, or stay elevated. Ca^{2+} oscillations can trigger life threatening arrhythmias. Elevated Ca^{2+} levels can result in hypercontracture of the myofibrils. When mitochondrial membrane potential is regenerated, and intracellular Ca^{2+} is elevated, there is an additional Ca^{2+} uptake into the mitochondria. High mitochondrial Ca^{2+} levels in association with excessive ROS production triggers the opening of the mitochondrial permeability transition pore (mPTP), dissipating mitochondrial membrane potential and thereby ATP synthesis, causing swelling and rupture of mitochondria (Murphy & Steenbergen, 2008; Heusch, 2020; Wang et al., 2023).

During ischemia and reperfusion, several forms of cell death can occur in the myocardium, including necrosis, apoptosis, necroptosis and autophagy. Necrosis is often considered an uncontrolled and chaotic form of cell death. Necrotic cell death is characterized by cell swelling leading to irreversible rupture of the plasma membrane with release of cytosolic components, which result in an inflammatory response. Several interconnected events are driving necrotic cell death including cytosolic Ca^{2+} overload, excess formation of ROS, opening of mPTP, cleavage of cytoskeleton and sarcolemma by calpains, and hypercontracture-induced mechanical rupture of cardiac tissue (Murphy & Steenbergen, 2008; Heusch, 2020). Apoptosis is a regulated, energy-dependent mode of cell death, characterized by DNA fragmentation, cell shrinkage, and the formation of apoptotic bodies. Cardiomyocyte

apoptosis occurs via the intrinsic pathway, in response to DNA damage and increased ROS and cytosolic Ca^{2+} levels, or via the extrinsic pathway, in response to activation of sarcolemmal death receptors. The mPTP opening is associated with both necrotic and apoptotic cell death in myocardial ischemia-reperfusion injury. If a large number of mitochondria in a cell undergo mPTP opening, the cell loses the capacity to make ATP, which leads to cell swelling, membrane rupture and necrotic cell death through disruption of ion homeostasis. If mPTP opening is less extensive, and thereby energy production is less compromised, mitochondrial matrix swelling and rupture of the outer mitochondrial membrane leads to the release of cytochrome c into the cytosol, where it activates caspases. Because the sarcolemma remains intact in apoptotic cells, this type of cell death does not elicit an inflammatory reaction (Murphy & Steenbergen, 2008; Heusch, 2020). Necroptosis is an active, tightly regulated form of cell death. It is mediated by death receptor signaling including specific receptor-interacting kinases and shares features with necrosis and apoptosis (Heusch, 2020). Autophagy is a process that involves the lysosomal degradation and recycling of certain cellular components, in particular mitochondrial proteins (i.e. mitophagy). During ischemia-reperfusion, it can act as a survival-promoting mechanism by removing damaged proteins and inhibiting apoptosis and necroptosis. However, excessive or uncontrolled autophagy may contribute to cell death (Heusch, 2020). While the precise quantitative contribution of various cell death mechanisms to infarction remains unclear, the distinct regulated modes of cell death could offer specific targets for pharmacological cardioprotection.

Coronary microvascular injury

In a significant proportion of patients with STEMI, despite successful recanalization of the infarct-related artery, pPCI fails to achieve effective myocardial reperfusion, a condition called 'no-reflow phenomenon' (Niccoli et al., 2019). This state is due to the occurrence of coronary microvascular obstruction (MVO). During ischemia-reperfusion, dysfunction in the coronary microcirculation, which includes vessels with a diameter of less than 200 µm, ensues due to increased capillary permeability and edema. This dysfunction is further characterized by impaired vasomotion resulting from damage to the endothelial and vascular smooth muscle, the release of substances eliciting vasoconstriction, and stasis involving aggregates of platelets, leukocytes, and erythrocytes within the microcirculation. Apart from the events associated with ischemia-reperfusion, a significant portion of clinically observed

MVO is attributable to the distal coronary microembolization of atherosclerotic debris or thrombotic material. In its most severe forms, MVO is associated with the destruction of capillaries and the occurrence of intramyocardial hemorrhage (Heusch, 2019). Of note, the presence of preexisting endothelial dysfunction or genetic predisposition, increases the susceptibility to microvascular dysfunction and no-reflow (Ndrepepa & Kastrati, 2023).

MVO is characterized by its dynamic nature, evolving gradually over hours following the restoration of coronary blood flow and persisting for days to weeks. Consequently, the diagnostic accuracy of any diagnostic method employed to detect MVO relies on the extent and severity of the MVO, as well as the timing of the examination (Ndrepepa & Kastrati, 2023). Cardiac magnetic resonance (CMR) is considered the gold standard technique for detecting and quantifying MVO. In addition, CMR can detect intramyocardial hemorrhage and providing accurate estimates of infarct size (Niccoli et al., 2019). MVO can be also detected at coronary angiography (defined as TIMI [Thrombolysis In Myocardial Infarction] flow grade <3 or 3 with a myocardial blush grade 0 to 1), or as an incomplete (<70%) ST-segment elevation resolution on ECG after pPCI (Niccoli et al., 2019; Ndrepepa & Kastrati, 2023). MVO may be assessed using invasive coronary physiology indices, including coronary flow velocity patterns, coronary flow reserve, index of microvascular resistance (IMR), hyperemic microvascular resistance, resistive reserve ratio, instantaneous hyperemic diastolic flow velocity-pressure slope and coronary zero flow pressure (Konijnenberg, et al., 2020). IMR is the most frequently used of these indices in current clinical practice. An elevated IMR (>40 U) may help identify high-risk patients undergoing pPCI who are likely to benefit from a more proactive therapeutic approach targeting MVO (Niccoli et al., 2019).

It has been established that morbidity and mortality following STEMI are closely linked to myocardial infarct size. Notably, recent clinical findings suggest that MVO may be a more predictive factor for clinical outcomes after pPCI than the actual infarct size. As a result, both infarct size and MVO emerge as two interrelated therapeutic targets for patients with STEMI (Niccoli et al., 2019).

Randomized clinical trials to reduce ischemia-reperfusion injury

In recent decades, various pharmacological approaches have been studied to assess their potential cardioprotective effects.

Adenosine

Through its robust vasorelaxant effect and potential anti-inflammatory and platelet inhibition properties, adenosine may improve myocardial microcirculation and offer protection against reperfusion injury (Murphy & Steenbergen, 2008; Heusch, 2020). In a prospective, double-blind, placebo-controlled clinical study, high-dose adenosine administered selectively to the ischemic myocardium prior to reperfusion failed to improve CMR-derived myocardial salvage index or MVO in patients with STEMI (Desmet et al., 2011). The REOPEN-AMI (Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction) trial demonstrated that intracoronary administration of high-dose adenosine improved ST-segment resolution, a surrogate for MVO, whereas angiographic correlates of MVO or MACE (a composite of cardiac death, myocardial infarction, target lesion revascularization, and heart failure hospitalization) did not show improvement at 1 month (Niccoli et al., 2013). In the REFLO-STEMI (REperfusion Facilitated by LOcal adjunctive therapy in STEMI) trial, high-dose intracoronary adenosine during pPCI did not reduce infarct size or MVO measured by CMR. Moreover, per-protocol analysis demonstrated that patients who had two doses of adenosine (immediately following thrombectomy and again following stenting) had significantly increased infarct size and MACE in the mid-term (Nazir et al., 2016). Overall, these data suggest that intracoronary adenosine should not be used as a routine treatment during pPCI to prevent reperfusion injury.

Nitric oxide donors

Preclinical studies indicate that nitric oxide donors may mitigate myocardial reperfusion injury (Murphy & Steenbergen, 2008; Heusch, 2020). The NIAMI (Nitrates in Acute Myocardial Infarction) trial found that in patients with STEMI receiving intravenous infusion of sodium nitrite or placebo, infarct size assessed by CMR was comparable at both 6-8 days and 6 months (Siddiqi et al., 2014). In the REOPEN-AMI trial, intracoronary administration of sodium nitroprusside had no significant effect on ST-segment resolution, angiographic MVO or MACE compared with placebo treatment (Niccoli et al., 2013). The REFLO-STEMI study failed to demonstrate a beneficial effect of intracoronary sodium nitroprusside administration on CMR-assessed infarct size or MVO in patients with STEMI (Nazir et al., 2016). Based on these data, there appears to be no clinical benefit of nitrite or nitroprusside for myocardial salvage and MVO during pPCI.

Beta-blockers

In preclinical models, the administration of the beta-blocker metoprolol before reperfusion during an ongoing MI effectively restricted the infarct size and reduced MVO (Niccoli et al., 2019). CMR revealed that intravenous infusion of metoprolol prior to reperfusion reduced myocardial infarct size 1 week after anterior STEMI in the METOCARD-CNIC (Effect of METOprolol in CARDioproteCtioN during an acute myocardial InfarCtion) trial (Ibanez et al., 2013). However, the larger EARLY-BAMI (Early-Beta blocker Administration before reperfusion pPCI in patients with ST-elevation Myocardial Infarction) trial failed to demonstrate the infarct-limiting effect of metoprolol (Roolvink et al., 2016). Variations in the timing of metoprolol administration may explain the differences observed between studies. According to current guidelines, intravenous beta-blockers (preferably metoprolol) should be considered at the time of presentation in patients with a working diagnosis of STEMI undergoing pPCI in the absence of signs of acute heart failure, with a systolic blood pressure >120 mmHg and no other contraindications (recommendation class IIa, level of evidence A) (Byrne et al., 2023).

Antiplatelet therapy

Of the platelet $P2Y_{12}$ receptor inhibitors, prasugrel and ticagrelor produce more rapid, consistent, and stronger inhibition of platelet aggregation than clopidogrel. Large randomized trials, TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38) and PLATO (Platelet Inhibition and Patient Outcomes), showed that the third-generation $P2Y_{12}$ receptor inhibitors are superior to clopidogrel in reducing ischemic events in patients undergoing PCI for the entire spectrum of ACS (Wiviott et al., 2007; Wallentin et al., 2009). The results in the STEMI cohorts of these trials were consistent with the overall results with respect to reduction in ischemic risk by prasugrel or ticagrelor compared with clopidogrel (Montalescot et al., 2009; Steg et al., 2010). The ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery) trial showed that prehospital (i.e. in-ambulance) administration of ticagrelor shortly before pPCI in patients with ongoing STEMI did not improve pre-PCI coronary reperfusion of the target vessel (Montalescot et al., 2014). In the REDUCE-MVI (Reducing Micro Vascular Dysfunction in Acute Myocardial Infarction by Ticagrelor) trial, the impact

on coronary microvascular dysfunction and myocardial injury was comparable between ticagrelor and prasugrel maintenance therapy following pPCI in STEMI. At 1-month follow-up, the infarct-related artery IMR and CMR-derived infarct size did not differ between the 2 groups (van Leeuwen et al., 2019). Of importance, subgroup analyses of the ISAR REACT-5 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5) study revealed that in STEMI patients undergoing pPCI prasugrel resulted in a reduction in ischemic risk without a trade-off in terms of bleeding risk in comparison to ticagrelor (Aytekin et al., 2020). In STEMI patients treated with pPCI, oral $P2Y_{12}$ platelet inhibitors do not provide maximal platelet inhibition at the time of reperfusion (Montalescot et al., 2014). The PITRI (Platelet Inhibition to Target Reperfusion Injury) trial may clarify whether intravenous cangrelor administration prior to reperfusion in STEMI patients would reduce acute infarct size and MVO, as assessed by CMR (Bulluck et al., 2019).

Glycoprotein IIb/IIIa inhibitors have been proposed to improve microvascular perfusion by decreasing the incidence of thrombotic events such as distal embolization. The On-TIME-2 (Ongoing Tirofiban in Myocardial Infarction Evaluation 2) study showed that prehospital initiation of bolus tirofiban resulted in improved ST-segment resolution before and one hour after pPCI, while angiographic correlates of MVO were unaffected (Van't Hof et al., 2008). 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 (Akpek et al., 2015). The INFUSE-AMI (Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction) 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 (Stone et al., 2012). Medium- and large-scale clinical trials have investigated the safety and efficacy of intracoronary versus standard intravenous bolus application of glycoprotein IIb/IIIa inhibitors in patients with STEMI undergoing pPCI. In the CICERO (Comparison of Intracoronary Versus Intravenous Abciximab Administration During Emergency Reperfusion of ST-Segment Elevation Myocardial Infarction) trial, intracoronary administration of abciximab improved the angiographic correlate of MVO (i.e. achievement of myocardial blush grade 2/3) without affecting ST-segment resolution and reduced enzymatic infarct size, while the incidence of MACE at 30 days was comparable between groups (Gu et al., 2010). The AIDA STEMI (Abciximab Intracoronary vs.

intravenous Drug Application in STEMI) trial showed that intracoronary bolus administration of abciximab was not associated with an advantage over standard intravenous bolus administration in terms of the combined primary endpoint of death, reinfarction or heart failure within 90 days. Moreover, the secondary endpoints including early ST-segment resolution, epicardial perfusion (I.e. TIMI flow grade), and enzymatic infarct size did not differ between groups (Thiele et al., 2012). The CMR substudy of the AIDA STEMI trial completed within 1 week failed to detect any difference between the two regimens in terms of final infarct size, MVO, intramyocardial hemorrhage or left ventricular function (Eitel et al., 2013). 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 (recommendation class IIa, level of evidence C) (Byrne et al., 2023).

Conclusions

While reperfusion is essential to rescue ischemic myocardium from imminent infarction, it also causes additional irreversible damage, leading to an augmented infarct size and microvascular dysfunction. Consequently, infarct size and MVO appear as two interrelated therapeutic targets for cardioprotection. Nevertheless, the implementation of effective cardioprotective strategies in clinical practice remains an unmet medical need.

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Submission of the doctoral dissertation and declaration of the originality of the dissertation

The undersigned,
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to the
PR-7, S-53 , Cardiac adaptation in physiological and pathological conditions
of the Doctoral School of Health Sciences, Faculty of Health Sciences, University of Pécs.

Names of the supervisor(s): András Komócsi and István Szokodi

At the same time, I declare that
- I have not submitted my doctoral dissertation to any other Doctoral School (neither in this country nor abroad),
- my application for degree earning has not been rejected in the past two years,
- in the past two years I have not had unsuccessful doctoral procedures,
- my doctoral degree has not been withdrawn in the past five years,
- my dissertation is independent work, I have not presented others' intellectual work as mine, the references are definite and full, on preparation of the dissertation I have not used false or falsified data.

Furthermore, I declare that I contribute to the request of DOI identification of my doctoral dissertation.

Dated: 24/05/2024

signed by Candidate

Supervisor

Co-supervisor