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Did Prasugrel and Ticagrelor Offer the Same Benefits in Patients with Acute Coronary Syndromes after Percutaneous Coronary Interventions Compared to Clopidogrel?

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ABSTRACT

Background: the mainstay treatment for patients with acute coronary syndromes (ACS) that undergo revascularization with percutaneous coronary intervention (PCI) is dual antiplatelet therapy (DAPT). This usually involves combining aspirin with an additional $PY2_{12}$ receptor inhibitor, either clopidogrel, prasugrel or ticagrelor. Despite numerous researches comparing the effectiveness and safety of these three drugs, their relative merits with regards to each other remain to be further elucidated.

Objective: the aim of this research is to compare clopidogrel, prasugrel and ticagrelor in patients with ACS after undergoing PCI and subsequently shed more light on the debatable question of whether or not prasugrel and ticagrelor have the same benefits as clopidogrel.

Methods: a narrative literature review was conducted. Electronic databases, including PubMed, ClinicalKey, Wiley Online Library, Vilnius university library, European Heart Journal and the American Heart Association Journal, and Google Scholar tool, were searched for eligible publications. Searching strategy was focused on clopidogrel vs. prasugrel vs. ticagrelor in patients with ACS after PCI. Selected resulted publications had to be published in the last 5 years. Current society guidelines in the field of cardiology were also included.

Discussion: $P2Y_{12}$ inhibitors are important antiplatelet drugs that together with aspirin constitute the so-called DAPT. DAPT is the cornerstone treatment of patients with ACS after PCI, aimed at reducing ischemic events, such as stent thrombosis (ST). Their usage however, is associated with a certain bleeding risk. The main $P2Y_{12}$ inhibitors are clopidogrel, prasugrel and ticagrelor. Current guidelines recommend the more potent ticagrelor and prasugrel over clopidogrel, partly due to resistance of some patients to clopidogrel. Yet other groups of patients, like the elderly or East-Asian patients might not benefit from more potent drugs due to high bleeding risk. This risk-benefit trade-off is further complicated by the coronavirus disease 2019 (Covid-19) pandemic.

Conclusion: benefits are highly dependent on bleeding/ischemia balance for each individual patient. While prasugrel and ticagrelor are beneficial in patients with high ischemic risk, clopidogrel, especially when guided by genetics or platelet function assays, could still be advantageous in other subset of patients, like the elderly, patients with increased bleeding risk, such as patients who are taking anticoagulants, and East-Asian patients.

Keywords: acute coronary syndrome, percutaneous coronary intervention, dual antiplatelet therapy, efficacy and safety, outcomes, clopidogrel, prasugrel, ticagrelor, CYP2C19

ABBREVIATIONS AND ACRONYMS

ACS	acute coronary syndrome
PCI	percutaneous coronary intervention
DAPT	dual antiplatelet therapy
ESC	European society of cardiology
EACTS	European Association for Cardio-Thoracic Surgery
AHA	American Heart Association
ACC/AHA	American College of Cardiology/American Heart Association
RCT	randomized clinical trials
ECG	electrocardiogram
STEMI	ST-elevation myocardial infarction
NSTEMI	non-ST-elevation myocardial infarction
UA	unstable angina
MACE	major adverse cardiovascular events
NACE	net adverse clinical events
ST	stent thrombosis
MI	myocardial infarction
HTPR	high on treatment platelet reactivity
LPR	low platelet reactivity
CYP	cytochrome P450
WT	wild type
LoF	loss of function
GoF	gain of function
CHD	coronary heart disease
ARC-HBR	Academic Research Consortium for High Bleeding Risk
PFT	platelet function testing
ADP	adenosine diphosphate
AMI	acute myocardial infarction
TAT	triple antithrombotic therapy
DAT	dual antithrombotic therapy
OAC	oral anticoagulant
DM	diabetes mellitus

CKD	chronic kidney disease
IL-6	interleukin-6
PLATO	Platelet Inhibition and Patient Outcomes
TROPICAL	Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes
TRITON-TIMI 38	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction
ISAR REACT-5	Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5
POPular	Patient Outcomes After Primary PCI
TICAKOREA	Ticagrelor Versus Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Mmanagement
SARS-CoV- 2	severe acute respiratory syndrome corona virus 2
Covid-19	coronavirus disease 2019

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I. INTRODUCTION

Among patients who present with ACS, myocardial revascularization, and particularly PCI are the cornerstones of treatment. In addition to that, DAPT is the standard of care form of pharmacological treatment for patients undergoing PCI aimed at reducing atherothrombotic complications, including local thrombotic complications and systemic ischemic events (1,2). DAPT consists of the combination of aspirin and a platelet $P2Y_{12}$ receptor inhibitor; clopidogrel has classically been the most widely used $P2Y_{12}$ inhibitor for the past two decades. However, newer and more potent $P2Y_{12}$ inhibitors, such as prasugrel and ticagrelor, have been increasingly used in clinical practice (3). Furthermore, current guidelines, both from the European Society of Cardiology (ECS) and from the joint committee of the American College of Cardiology and the American Heart Association (ACC/AHA), favor ticagrelor or prasugrel over clopidogrel for patients with ACS undergoing PCI, due to the fact they showed in many randomized clinical trials (RCT) a reduction in thrombotic events as compared to clopidogrel. Nevertheless, the ostensible superiority of ticagrelor and prasugrel over clopidogrel come at the expanse of a higher bleeding risk. Therefore, these guidelines also mention that the choice of the DAPT regimen should be decided after the clinician weighs the benefits of reduced thrombotic events against the increased bleeding risks(4–7). Moreover, the evolution and development of new stent technologies in combination with high incidence of recurrence of ischemia after PCI and the better understating of prognostic implications that are associated with the risk of increased bleeding, have resulted in the development of different and refined antithrombotic treatment regimens as described in recent guidelines(1,5). Thus, even after 21 years of research, and despite the fact that DAPT is one of the most investigated treatments in the field of cardiovascular medicine, it remains to be elucidated regarding the optimal DAPT regimen, that is, the medication of choice. This uncertainty is partly derived due to limited and conflicting data from certain subsets of patients taking part in clinical trials, such as East-Asian patients and elderly patients with comorbidities and/or increased bleeding risk, in whom the balance between the advantages and disadvantages of DAPT possibly differ from patients that are included in more selective groups(5,8). On top of that, the recent coronavirus disease 2019 (COVID-19) pandemic introduced new challenges to the field of cardiovascular diseases. Therefore, following the uncertainty expressed above, this narrative literature review aims to explore the different treatment strategies and regimens offered to patients with ACS after undergoing PCI, while also considering COVID-19 pandemic related aspects, review the current guidelines, and the

existing evidence that are delineated in numerous medical and scientific articles all of which are concerned with the comparison of prasugrel, ticagrelor and clopidogrel, in order to derive the conclusion as to whether or not prasugrel and ticagrelor offer the same benefits in patients with ACS after PCI compared to clopidogrel.

II. METHODS

The goal of this narrative literature review was to explore current data regarding differences and similarities between clopidogrel and prasugrel and/or ticagrelor in patients with ACS after undergoing PCI. In order to achieve this goal, an extensive and thorough search for elegible citations was performed from electronic databases including PubMed, ClinicalKey, Wiley Online Library, Vilnius university library, European Heart Journal and the American Heart Association Journal, and also citations were acquired using Google Scholar tool. In order to ensure that this narrative literature review stayed up-to-date, a publication time range filter of 5 recent years was selected. The databases were queried in 2022 and 2023 and therefore selected studies and other citations represent a time span from 2017-2023, with the decisive majority of them not published earlier than 2018. Selected citations included RCTs and their sub-analyses, meta-analyses, observational studies, cohort studies, national registries, systemic reviews, literature reviews and review articles. It was imperative that all studies included patients with ACS and the comparison of the respective $P2Y_{12}$ inhibitors was performed after the patients underwent PCI. The main sources of literature concerning treatment recommendations in patients with ACS after undergoing PCI were also included and were aquired by reviewing the latest guidelines published by the ESC, European Association for Cardio-Thoracic Surgery (EACTS) and ACC/AHA.

The searching strategy included the following terms: “acute coronary syndrome/ACS”, “percutaneous coronary intervention/PCI”, “myocardial infarction/MI”, “dual antiplatelet therapy/DAPT”, “$P2Y_{12}$ inhibitors” (including “clopidogrel”, “prasugrel and ticagrelor”), “dual antiplatelet therapy /DAPT and CYP2C19 genetic polymorphism”, and “dual antiplatelet therapy /DAPT and stent thrombosis”. Searched terms were further used in combination with “mechanism of action” (including “pharmacokinetics” and “pharmacodynamics”) “comparison of effectiveness and safety” (“ticagrelor and/or prasugrel versus. clopidogrel”), “outcomes and clinical consequences”, “response to therapy” (including “residual platelet reactivity”) and “benefits”. Searched terms and strategy were subsequently combined with the term “Covid-19” in order to identify and include elements

related to the current Covid-19 pandemic. References in selected publications were then manually searched for potential eligibility in order to finalize the research.

III. DISCUSSION

1. Definition and pathophysiology of acute coronary syndromes

ACS is an umbrella term that can be divided into two patient categories based on electrocardiographic (ECG) features. The first group of patients are those presenting with symptoms consistent with myocardial ischemia and ST segment elevation on ECG. Most of these patients will go on and develop myocardial infarction (MI) which is then termed ST-segment elevation myocardial infarction (STEMI). The second group of patients are those presenting with symptoms consistent with myocardial ischemia but without persistent ST segment elevation on ECG; among these patients the majority will develop myocardial necrosis, reflected by a rise in the concentration of cardiac troponin in the blood, which is then termed non-ST- segment elevation myocardial infarction (NSTEMI), while the rest will have ongoing myocardial ischemia without myocardial necrosis, termed unstable angina (UA)(7). However, the increasing use of high-sensitivity cardiac troponin (hs-cTn) assay, lead to an increase in the number of patients diagnosed with NSTEMI and correspondingly a reduction in the number of patients diagnosed with UA(7). Furthermore, there is evidence that both sex differences in the pathophysiology of ACS and anatomical differences lead to different ischemic changes in the coronary arteries and different symptomatology. For example, women have smaller epicardial coronary arteries but at the same time higher myocardial flow, which makes the endothelial lining of the coronary arteries more susceptible to shear stress and can thus result in a coronary artery disease(9,10). ACS occur due to a rupture in the inner (intimal) lining of the coronary arteries, which exposes the underlying atheroma to the bloodstream. The platelets in the circulating blood are then activated, leading to their aggregation, release of vasoconstrictive substances, and the formation of blood clots. It is important to note, that while in women thrombus formation is thought to mainly occur due microvascular dysfunction and plaque erosion, in men it is thought that the principal mechanism is plaque rupture(11). The purpose of antiplatelet drugs is to disrupt these pathways and mitigate the negative consequences of platelet activation(12).

2. Antiplatelet therapy

2.1 $P2Y_{12}$ Inhibitors

$P2Y_{12}$ inhibitors are effective antiplatelet agents that act by blocking the adenosine purinergic receptors, namely $P2Y_{12}$ receptors, on the surface of platelets (13,14). A $P2Y_{12}$ receptor is a protein on the surface membrane of platelets that is coupled to G_i protein and plays a key role in the activation and aggregation of platelets, which can lead to thrombus formation. When cells and platelets are damaged it result in the release of adenosine diphosphate (ADP). ADP in turn binds to the P2Y12 receptors resulting in platelet activation and degranulation, thromboxane production which ultimately exposes activated glycoprotein IIb/IIIa (GPIIb/IIIa), and P-selectin. These sequential events drive further platelet aggregation and recruitment resulting in stabilization of thrombus formation. Therefore, by binding to $P2Y_{12}$ receptors, the various $P2Y_{12}$ inhibitors inhibit platelet activation and aggregation, thus reducing the risk of blood clots (15). Notably, the expression of $P2Y_{12}$ receptors on the surface of platelets may vary due to different reasons, including alterations in the $P2Y_{12}$ receptor gene, qualitative abnormalities of the $P2Y_{12}$ receptors on the surface of platelets, which can then lead to bleeding disorders and also chronic pathological conditions, such as type 2 diabetes mellitus (DM) and chronic kidney disease (CKD), both of each are linked with a higher activity of the $P2Y_{12}$ receptors(16).

2.2 Clopidogrel

Clopidogrel is an important, second generation thienopyridine $P2Y_{12}$ inhibitor that is widely used worldwide. As a prodrug it is metabolized and activated in the liver by cytochrome P450 enzymes which liberate active metabolites that irreversibly inhibit the $P2Y_{12}$ receptors on the surface of platelets. It is important to realize that after oral administration and intestinal absorption of clopidogrel, most of it is inactivated by esterases and only 15% of the dose is further metabolized by the various hepatic cytochrome P450 isoenzymes (17–19). In addition, clopidogrel shows an on average inhibitory effects on platelets, and due to genetic polymorphism of the cytochrome P450 enzymes, a highly variable and unpredictable effect (20). This elaborate metabolism of clopidogrel leads to delays in the onset of action of the drug up to 12 hours when administering 300 mg loading dose and from 2 to 6 hours after administering 600 mg loading dose(18). The primary factors that impact the reaction to clopidogrel consist of genetic elements, coexisting medical conditions, particularly DM and CKD, and additional pharmacological treatment such calcium-channel blockers, proton pump inhibitors, coumarin derivatives, and statins (21,22). Among patients who were treated with clopidogrel and had type 2 DM in their background, certain limitations have been documented, such as persistent insufficient response, that is, hypo-responsiveness to

clopidogrel even when titrated to high doses(23). Evidence of lower efficacy of clopidogrel in DM patient can be seen in a cohort study by Julia Spoendlin et al. that compared the effectiveness and safety of prasugrel and clopidogrel among patients with ACS and DM; prasugrel has been shown to have better cardiovascular outcomes than clopidogrel, but also had higher risk for short term bleeding(24). Consequently, around 33% of individuals taking clopidogrel may not respond to its anti-aggregatory effect, a phenomenon which is medically termed as high on-treatment platelet reactivity (HTPR) (16). HTPR is a condition where platelet $P2Y_{12}$ receptors remain active despite receiving clopidogrel treatment. One of the methods to test for this condition, is to introduce ADP agonist to a plasma sample, and subsequently platelet aggregation or intracellular markers of platelet activation are measured(25). Such phenomenon was demonstrated in a meta-analysis by Yu Wu et al. that found correlation between CKD and on-clopidogrel HTPR(26). Therefore, despite the fact that clopidogrel is a key player when it comes to DAPT, and that it has been shown to reduce major adverse cardiovascular events (MACE), these limiting factors have led to the need to develop more potent and powerful antiplatelet drugs(23).

2.2.1 Significance of genetic polymorphism of CYP2C19 gene in the metabolism of clopidogrel, platelet function testing / genotype-guided therapy

It is known, that although clopidogrel is effective in decreasing MACE, it has several limitations such as a slow onset of action, significant variability in response among individuals, and susceptibility to the effects of genetic polymorphisms(25,27). It has been found that genetic polymorphisms play an important role in the variability of clopidogrel response. As a result, numerous studies have consistently shown that patients who have received PCI treatment and have impaired platelet inhibition when using clopidogrel are at higher risk of recurrent ischemic events, particularly ST. These observations have led to consideration of personalized antiplatelet treatment plans that involve the use of stronger $P2Y_{12}$-inhibiting therapies in these patients (28,29). However, less than 20% of hypo-responsiveness to clopidogrel is attributed to genetic alterations(30). Therefore, in addition to genetic polymorphism, other modifiable and non-modifiable factors have been shown to affect the level of on treatment platelet reactivity. Figure 1 demonstrates these modifiable and non-modifiable factors and the interplay between low platelet reactivity and increased bleeding risk, and high platelet reactivity with increased ischemic risk. It also demonstrates that patients who exhibit low platelet reactivity (LPR), which accordingly have an increased risk to experience bleeding, can benefit from $P2Y_{12}$-directed de-escalation strategy, while

patients who exhibit HTPR, and which correspondingly are at increased risk for ischemic events, can benefit from $P2Y_{12}$- directed escalation strategy (31).

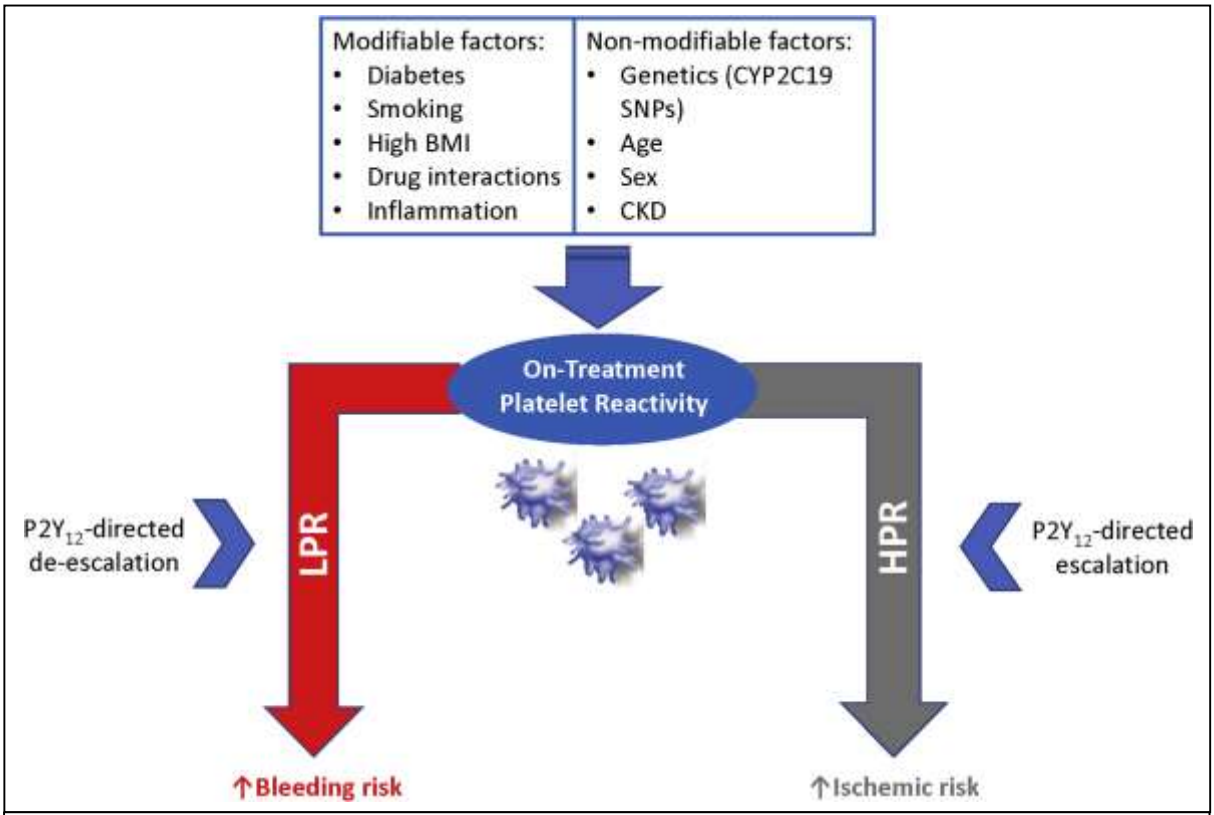

Figure 1. modifiable and nonmodifiable factors that affect the level of on-treatment platelet reactivity. BMI: body mass index. CKD: chronic kidney disease. SNP: single nucleotide polymorphism. LPR: low platelet reactivity. HPR: high platelet reactivity. CYP2C19: cytochrome P450 (31)

As already mentioned, clopidogrel is metabolized and bioactivated via a two-step cytochrome P450 (CYP) dependent process. CYP2C19 is the most detrimental isoform that plays a central role in the bioactivation of clopidogrel. There are three alleles, with CYP2C19-1 being the wild-type (WT) allele, which accounts for normal enzymatic function. Genetic variation and polymorphism lead to the presence of diverse alleles that exhibit varying levels of enzymatic function, ranging from complete loss of function (LoF) to increased activity and gain of function (GoF). The most frequent genetic variations are CYP2C19–2, –3, and –17, with CYP2C19–2 and –3 being the LoF alleles, while CYP2C19-17 exhibits enhanced enzymatic activity(15). Naujokaitis et al. in their retrospective study to assess allelic variations of three different CYP enzymes among Lithuanians, divided patients into five groups, based on allelic and phenotypic profile of their CYP2C19 enzyme. These groups

included normal metabolizers phenotype, corresponding to WT/WT genotype, intermediate metabolizers, corresponding to WT/LoF genotype and LoF/GoF genotype, rapid metabolizers, corresponding to WT/GoF genotype, ultrarapid metabolizers, corresponding to GoF/GoF genotype and poor metabolizers, corresponding to LoF/LoF genotype(32). Figure 2 demonstrates CYP2C19 genotype and the corresponding phenotype and clinical response to clopidogrel in a US representation(25). Moreover, the allelic polymorphism frequency varies substantially across geographic regions and ethnic groups(33). Figure 3 summarizes the population frequency estimates of CYP2C19 phenotypes by geographic region(25).

Metabolizer phenotype	Genotype	U.S. population	Response to clopidogrel
Ultra-rapid (UM)	2 increased function alleles (*17/*17)	1-5%	Normal or increased antiplatelet response to clopidogrel
Rapid (RM)	1 increased function and 1 normal function allele (*1/*17)	20-30%	Normal or increased antiplatelet response to clopidogrel
Normal (NM)	Absence of any tested increased function or LOF alleles (*1/*1)	35-50%	Normal antiplatelet response to clopidogrel
Intermediate (IM)	1 LOF allele (*1/*2, *1/3, *2/17, *3/*17)	20-30%	Reduced antiplatelet response to clopidogrel
Poor (PM)	2 LOF alleles (*2/*2, *2/3, *3/*3)	1-5%	Significantly reduced antiplatelet response to clopidogrel

Figure 2. CYP2C19 metabolic phenotype and the corresponding genotype and clinical. LoF: loss of function (25)

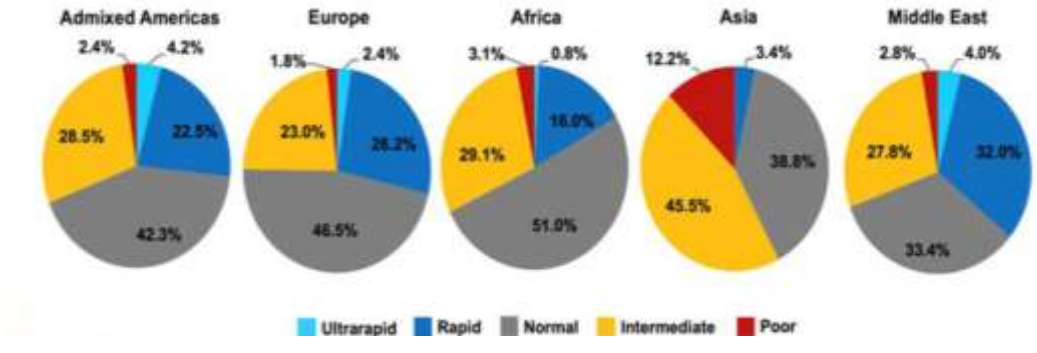

Figure 3. Frequency estimation of CYP2C19 phenotype across geographical regions (25)

Wenwen Qian et al. compared the treatment outcomes between patients with coronary heart disease (CHD) carrying a CYP2C19 LoF allele that were treated with clopidogrel and those

that were treated with ticagreolor. In their study they enrolled 170 patients with CHD that are being regularly treated with either orally administered clopidogrel 75mg/day or ticagrelor 180mg/day, with or without aspirin. In addition to collecting the patients' baseline data and the results of the patients' primary coronary angioplasty or coronary computed tomography angiography, they also detected the CYP2C19 genotype of each patient enrolled. Among 152 patients who completed the experimental observation, 80 patients were taking clopidogrel orally, and 72 patients took ticagrelor orally. In the clopidogrel group 1 patient was a rapid metabolizer (was excluded from the study), 37 patients were normal metabolizers, 28 patients were intermediate metabolizers, and 14 patients were poor metabolizers. They compared the prognosis between the three subgroups and demonstrated a statistically significant difference ($p=0.005$) between the normal and the intermediate metabolizer groups, and between the normal and the poor metabolizer groups, and no significant difference between the intermediate and poor metabolizer groups. The normal metabolizer group had a better prognosis in comparison to the intermediate and poor metabolizer groups. They concluded that CYP2C19 polymorphism was associated with a significantly increased incidence of poor prognosis after oral clopidogrel treatment, and on top of that, the risk was even doubled when compared to non-carriers. Finally it was shown that for patients with CHD that undergo PCI, the prognosis is better when taking ticagrelor, while for patients who did not undergo PCI, there was no significant clinical benefit in terms of prognosis when substituting clopidogrel with ticagrelor(34).

Further corresponding with these findings, Ha Young Yoon et al. carried out a systematic review and meta-analysis, where they compared the efficacy and safety of ticagrelor and prasugrel with those of clopidogrel in patients who are poor metabolizers. Their study analyzed twelve studies comprising 5,829 cardiovascular patients with CYP2C19 LoF alleles. They reached the conclusion that instead of using clopidogrel, alternative antiplatelet treatments can be used for LoF allele carriers, based on genotyping tests, which may result in better clinical outcomes. However, the choice of medication should be customized according to the patient's balance between the risk of ischemia and bleeding(35).

Min Zhang et al. conducted a prospective study that evaluated the effects of individualized antiplatelet therapy in patients that underwent PCI, based on CYP2C19 genotyping, and compared this treatment with the conventional antiplatelet therapy. 1,063 ACS patients were enrolled in this study and were randomly and equally divided into a conventional antiplatelet group and an individualized antiplatelet group. Patients in the individualized group were evaluated genetically for CYP2C19-2 and -3 LoF alleles and were then divided into normal

metabolizers (no LoF allele), intermediate metabolizers (carrying one LoF allele) and poor metabolizers (carrying two LoF alleles). All patients were treated with 100 mg aspirin per day. Patients in the conventional antiplatelet group were treated with 75 mg clopidogrel per day. Normal metabolizers were also given 75 mg clopidogrel per day, however, intermediate and poor metabolizers were prescribed 75 mg and 90 mg twice a day, respectively. Patients took these antiplatelet medications for 5 consecutive days, after which platelet function was assessed by means of thromboelastography and quantitated as maximum amplitude produced by adenosine diphosphate (MA_{ADP}) value. MA_{ADP} greater than 47 mm corresponded to residual HTPR, which indicated a high risk of thrombosis, while MA_{ADP} less than or equal to 37 indicated a high risk of bleeding. They found out that the individualized group had a significantly lower percentage of patients with MA_{ADP} greater than 47mm (29.6%) compared to the conventional group (38.1%). In contrast, the individualized group had a significantly higher percentage of patients with MA_{ADP} less than or equal to 31mm (31.0%) compared to the conventional group (21.3%). They concluded that customized antiplatelet therapy, which relies on the CYP2C19 genotype, can lower the occurrence of HTPR in patients with ACS following PCI compared to standard therapy. By taking a double dose of clopidogrel, patients who had a LoF allele in CYP2C19 could counteract the diminished effectiveness of clopidogrel that is linked to LoF alleles, without increasing the risk of bleeding(28). Nevertheless, even despite the evidence that suggests the merits of dedicated genotyping to direct the individualized antiplatelet regimen, due to lack of data from dedicated studies, the International Expert Consensus Group on Platelet Function does not recommend genotyping for patients with ACS who are LoF allele carriers, in order to escalate or de-escalate treatment(31).

On the other hand, Daniel M.F Classens et al. conducted the POPular (Patient Outcomes After Primary Percutaneous Coronary Intervention) Genetics trial. The POPular Genetics trial was a randomized and open-label trial, which was conducted across 10 European sites in the Netherlands, Belgium and Italy, and enrolled 2,488 patients with STEMI undergoing PCI with stent implantation. This trial compared conventional treatment with ticagrelor or prasugrel with a CYP2C19 genotype-guided therapy, where patients who were carriers of CYP2C19-2 or CYP2C19-3 LoF allele received ticagrelor or prasgrel, while non-carriers received the standard clopidogrel. Patients were treated and followed up for a duration of 12 months. Net adverse clinical events (NACE) were defined as death from any cause, MI, definite ST, stroke, or major bleeding as defined according to PLATO (Platelet Inhibition and Patient Outcomes) Criteria. The trial attempted to determine whether a CYP2C19 genotype-

guided therapy, in order to select the best $P2Y_{12}$ inhibitor, could reduce the bleeding risk without increasing thrombotic events. The trial results were based on two primary outcomes, with the first being combined outcome of NACEs, and the second was PLATO major bleeding or minor bleeding at 12 months, and secondary outcomes. In the genotype-guided group, that comprised of 1,242 patients, 60.6% of the patients were treated with clopidogrel, while 39.1% of the patients were treated with ticagrelor or prasugrel, and only 7% were treated with clopidogrel. After 12 months, death due to NACEs occurred among 63 patients (5.1%) in the genotype-guided group and in 73 patients (5.9%) in the standard-treatment group, that comprised 1,246 patients. In addition, the genotype-guided group met the prespecified criteria for non-inferiority regarding NACEs, however, it did not meet the criteria for superiority. Moreover, the PLATO major and minor bleeding was significantly less prevalent in the genotype-guided group when compared with the standard-treatment group. In the secondary outcomes they did not observe significant difference between the two groups regarding combined thrombotic events or other secondary thrombotic outcomes. Furthermore, there was shown to be no difference in the incidence of PLATO major bleeding between the two groups. The conclusion from the trial was that in case of patients with STEMI who also undergo PCI, the selection of the suitable $P2Y_{12}$ based on genetic testing for CYP2C19 LoF allele is non-inferior to standard treatment with prasugrel or ticagrelor at 12 months, in terms of thrombotic events, but resulted in lower incidence of bleeding(2). Daniel M.F Classens et al. further carried out a prespecified sub-analysis of thr POPular genetics trial. The sub-analysis evaluated 2,429 patients and consisted of two analyses. The first one evaluated the impact of CYP2C19-17 allele in patients treated with clopidogrel, and the second compared the effects of clopidogrel in patients who do not carry a LoF allele, with patients who are treated with ticagrelor and prasugrel, irrespective of their CYP2C19 genotype. The analysis concluded that the use of clopidogrel compared with ticagrelor or prasugrel, among patients after PCI who are not CYP2C19 LoF allele carriers, was associated with lower bleeding rates and without enhancing the incidence of thrombotic events. The analysis, however did not demonstrate any clinical effects attributed to having a CYP2C19-17 allele. It was also pointed out, that although other trials have failed so far to clarify whether the use of platelet function testing (PFT) in individualizing antiplatelet therapy is indeed beneficial compared to standard treatment, and therefore not routinely recommended, the results from the sub-analysis contribute to the increasing pool of evidence that CYP2C19 genotyping can direct the selection of tailored antiplatelet therapy and hence improved overall clinical outcomes(36). Although so far there is no conclusive evidence for the de-

escalation strategy of antiplatelet therapy after ACS, it is nevertheless common in clinical practice. In around 15-28% of cases among patients with ACS, a potent antiplatelet drug is switched to a less potent antiplatelet drug after discharge, partly due to adverse bleeding or non-bleeding events and even financial reasons. Inevitably, this de-escalation can possibly come at the risk of HTPR, which much like in case of CYP2C19 polymorphism and LoF allele, can lead to increased incidence or recurrent ischemic events, including ST and MI (37).

András Komócsi et al. conducted a research where they compared PFT- guided versus non-guided selection of $P2Y_{12}$ inhibitor for treatment of patients with acute myocardial infarction (AMI). Clinical characteristics and platelet function data were collected from the Hungarian Myocardial Infarction Registry, that contains data from fifteen interventional cardiology centers in Hungary. A total of 5,583 patients with AMI were registered of which, after exclusion process, a sample of 2,104 patients was left. The majority of patients in both groups were prescribed clopidogrel (96% in the unguided group versus 85% in the PFT-guided group). The risk of all-cause mortality at 1 year was then assessed and compared after propensity score matching between both groups. The results were that in the PFT-guided group, 19% of the patients had a HTPR when taking clopidogrel and 77% of them were switched to prasugrel. Accordingly, it was demonstrated that the group of patients with HTPR that were taking clopidogrel but switched to prasugrel, had a significantly lower mortality rate compared to the group of patients who continued being treated with clopidogrel. They reached the final conclusion that for patients with AMI, a PFT-guided treatment with high rate of switching to prasugrel was associated with a lower risk of mortality compared to no PFT-guided therapy. In addition, prasugrel also improved the survival of patients in the PFT-guided selection of $P2Y_{12}$ inhibitor group, who had HTPR with clopidogrel, compared to standard and high dose clopidogrel (38). In line of this evidence, which supports tailored $P2Y_{12}$ inhibitor regimen, either genotype-guided or PFT-guided, is the TROPICAL (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes) ACS trial, that aimed to assess the safety and efficacy of early de-escalation on antiplatelet regimen from prasugrel to clopidogrel which was guided by PFT. The TROPICAL ACS trial was a randomized, parallel group, open-label, assessor-blinded, multicenter trial in Europe that enrolled patients who had positive biomarkers for ACS with successful PCI and who also had a planned duration of DAPT with prasugrel for 12 months. Enrolled patients were randomly assigned to either a control group, where the patients received standard treatment with prasugrel for 12 months,

and to a PFT guided de-escalation group, where the patients received for the first week after hospital discharge prasugrel, for the second week clopidogrel, and from the third week onward patients either remained with clopidogrel or were switched to prasugrel when the PFT results correlated with HTPR and with insufficient platelet inhibition. The primary endpoint was assessed taking into account the net clinical benefit, including MI, cardiovascular death, cerebrovascular event or bleeding grade 2 or higher based on the BARC (Bleeding Academic Research Consortium) criteria, after 1 year of follow up. The trial reached the conclusion that a guided de-escalation of antiplatelet treatment was non-inferior to standard treatment with prasugrel regarding net clinical benefit. It also concluded, that due to high rate of adherence to treatment and being clinically attainable, a guided de-escalation could be considered as an alternative treatment strategy to the standard treatment with prasugrel(37). Moreover, in a pre-specified sub-study by Dániel Aradi et al. of the TROPICAL-ACS trial, it was concluded that patients with ACS could benefit from switching their therapy from clopidogrel back to prasugrel, in cases when the patients had HTPR on clopidogrel; the benefits stem from reduction in ischemic events to the level comparable with patients without HTPR. They also demonstrated that among patients with LPR, it was the LPR and not the type of treatment, that is prasugrel or clopidogrel, to be an independent and strong predictor of bleeding(20). A comprehensive network meta-analysis by Mattia Galli, showed that indeed, the best strategy of selecting $P2Y_{12}$ inhibitors for patients with ACS, which balances between safety and efficacy, that is between ischemic risk and bleeding risk, is PFT or genotype guided. However, it is not clear if it is the best strategy in order to reduce mortality(39).

2.3 Prasugrel and ticagrelor

Prasugrel is a third generation thienopyridine $P2Y_{12}$ inhibitor, which much like clopidogrel, is a prodrug that is metabolized in the liver by CYP enzymes, which generates active metabolites that irreversibly and selectively inhibit the $P2Y_{12}$ receptors on the surface of platelets. Despite the similarities between clopidogrel and prasugrel, prasugrel has been shown to exhibit a more predictable and less variable metabolism as a prodrug into an active metabolite. Furthermore, current research has shown that prasugrel has increased efficacy, and also a swifter onset of action due to a faster metabolic transformation into an active metabolite as compared to clopidogrel(14,18).

Ticagrelor is also a third generation $P2Y_{12}$ inhibitor however, unlike clopidogrel and prasugrel, it is a non-thienopyridine $P2Y_{12}$ inhibitor and belongs to the cyclopentyl-

triazolopyrimidines group(14). Moreover, ticagrelor, in a non-competitive manner, reversibly binds and inhibits $P2Y_{12}$ receptors, thus preventing ADP-induced signal transduction and subsequently leads to inhibition of platelet aggregation. In addition, ticagrelor is not a prodrug and hence does not require hepatic metabolism and activation to exert its pharmacological effect and therefore has a faster onset of action(17,18). Furthermore, ticagrelor has a relatively shorter half-life. Given these properties, ticagreor has been shown to manifest more stable and consistent effect on platelet reactivity in comparison to clopidogrel, and also a faster offset effect in comparison to clopidogrel and prasugrel(40,41). Figure 4 demonstrates the principal anti-aggregant agents used in clinical practice, namely clopidogrel, prasugrel and ticagrelor, and aspirin, and their respective mechanism of action and enzymatic bioactivation(14).

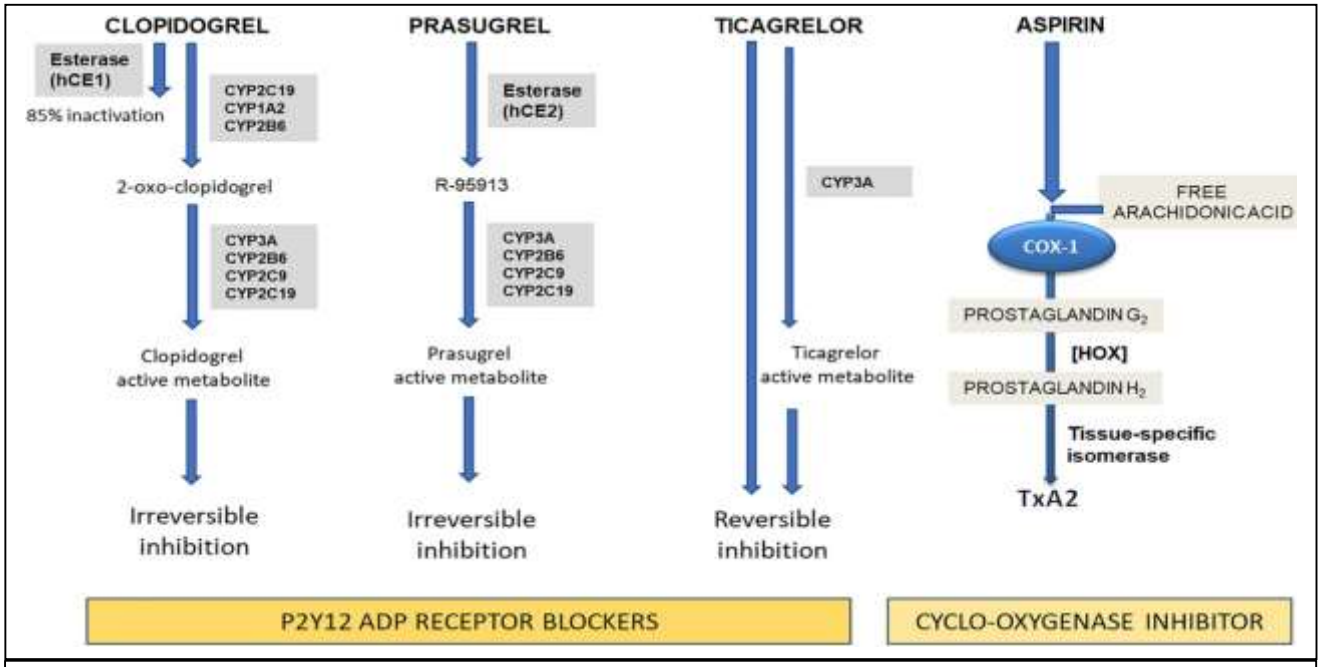

Figure 4. Antiplatelet drugs' mechanism of action and metabolism. CYP: cytochrome P450. hCE: human carboxylesterase. HOX: hydroperoxidases. ADP: adenosine diphosphate. COX: cyclooxygenase. TxA2: thromboxane A2. (14)

The advantageous characteristics of ticagrelor became clinically significant in the PLATO trial, which demonstrated how ticagrelor profoundly reduced the incidence of MACE among patients with ACS in comparison to clopidogrel, but at the expanse of increased risk of major bleeding in patients undergoing PCI (42). In the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) 5 trial it was shown that among patients with STE-ACS or NSTE-ACS, prasugrel was associated with a significantly lower incidence of death, MI or stroke in comparison to ticagrelor, and in

addition to that, the bleeding rate was not higher with prasugrel treated patients in comparison to ticagrelor treated patients. However, there was a higher rate of drug discontinuation in the ticagrelor group in comparison to the prasugrel group, and on top of that, there was a significant longer duration of treatment before treatment discontinuation in the prasugrel group. These factors might have contributed to the difference in the primary outcome and overestimation of prasugrel over ticagrelor(43).

Current guidelines suggest that ticagrelor and prasugrel, which are more powerful platelet inhibitors, are to be preferred over clopidogrel due to their superior ability to prevent thrombotic events(4–7). Nonetheless, this increased effectiveness is associated with a greater likelihood of causing bleeding(2,44). Moreover, both clopidogrel and prasugrel are associated with gastrointestinal bleeding through not fully clear mechanisms, such as inhibition of angiogenic factors that take part in the healing of gastric ulcers and stimulation of gut reflex(45).Therefore, despite the increased bleeding rate attributed to both prasugrel and ticagrelor, one study found that in comparison to clopidogrel, prasugrel and ticagrelor are associated with fewer gastrointestinal bleeding in ACS patients undergoing PCI(46). On the contrary, another study found prasugrel to have a higher risk of gastrointestinal bleeding in comparison to clopidogrel, with ticagrelor being the safer option out of all of them(45).

2.3.1 Pleiotropic effects of ticagrelor

Interestingly, in addition to its $P2Y_{12}$ inhibitory effects, ticagrelor possesses unique adenosine-mediated pleiotropic effects, which can partly explain its greater efficacy in comparison to clopidogrel. Administration of ticagrelor leads to the emergence of these effects via various mechanisms by way of increased concentration of adenosine in the interstitial space. The underlying mechanisms of increased adenosine concentration include inhibition of adenosine reuptake by cells through blockage of the human equilibrative nucleoside transporter 1 and 2, and also the increased release of adenosine triphosphate (ATP) which is in turn transformed into adenosine(47). Adenosine in turn, has a wide variety of effects, including a greater vasodilation of infarcted vessels and increased coronary blood flow velocity, cardioprotection against future ischemia-reperfusion injury (IRI), attenuation of inflammation, anti-atherosclerotic effect, and protection against adverse cardiac remodeling and at the same time improved myocardial remodeling. Furthermore, ticagrelor has been shown to increase the concentration of certain endothelial progenitor cells in the peripheral blood which contribute to endothelial regeneration in patients after ACS(16). Interestingly, a systemic review and meta-analysis, indeed demonstrated that ticagrelor had

cardioprotective properties, in terms of improving ventricular rhythm and cardiac function, but it was prasugrel in particular that also exhibited such properties(48).
While the adenosine-mediated effects of ticagrelor yield positive effects, these same mechanisms lead to the notable side effects of ticagrelor. These include bradycardia, through the stimulation of adenosine receptors on myocytes, and dyspnea, which stems from the action of adenosine on the adenosine receptors present on C fibers of the vagal nerve which in turn leads to bronchoconstriction(16,18). In addition to that, dyspnea was reported as side effect among patients using any third-generation oral $P2Y_{12}$ inhibitors. Based on this, Na Zhang et al. performed a meta-analysis of 25 RCTs, of which 21 studies assessed ticagrelor and 4 studies assessed prasugrel, and which comprised a total of 63,484 patients. They compared the risk of dyspnea among patients treated with prasugrel or ticagrelor with those treated with clopidogrel. They concluded that when using ticagrlor, the risk of dyspnea, which in this study showed to be mild to moderate, is higher than clopidogrel, and was not observed at all among patients treated with prasugrel(49). Finally, dyspnea due to ticagrelor usage could be an important explanation why in some studies there is no benefit of ticagrelor over clopidogrel in terms of MACEs reduction, as the adherence rate to ticagrelor in those study groups is lower in comparison to clopidogrel usage(50,51).

2.4 Dual antiplatelet therapy

For more than three decades, the recommended approach for preventing ischemic events following PCI, whether related to stenting or not, has been DAPT, which involves the use of both aspirin and a P2Y12-inhibitor. While this therapy has been effective in reducing ischemic events, there was also an increase in bleeding events associated with its use(40). Furthermore, the current guidelines recommend standard DAPT treatment for 6-12 months, after which patients should receive only aspirin therapy. Patients at high risk of bleeding may receive shorter DAPT treatment, while those at high risk of ischemia (such as ST or recurrent acute coronary syndrome) may receive DAPT treatment for more than a year, provided their bleeding risk is low, that is, no prior coagulopathy and no past events of bleeding while being on DAPT. While prasugrel and ticagrelor are more effective than clopidogrel in preventing thrombotic events, their increased antiplatelet effectiveness is offset by a higher risk of bleeding(5,14,52). Therefore, due to the fact that patients who are at higher ischemic risk for ACS, have reduced ischemic events while being on DAPT but, at the same time are predisposed to bleeding events, in recent years, in the attempt to balance the efficacy and safety of DAPT, some researchers even proposed to discontinue aspirin after a short-term

DAPT (1-3 months long) and rather to proceed using only P2Y12 inhibitor monotherapy in order to reduce bleeding events(40,53). Besides that, DAPT strategy should be individualized at the patients' level after PCI. This can be achieved after careful stratification of patients and the assessment of 3 main elements, namely bleeding risk, ischemic risk and responsiveness to an antiplatelet agent(1). Given the central role DAPT plays in the area of pharmacological treatment of patients with coronary artery diseases (CAD), targeted at preventing atherosclerotic complications, and the rapid evolution of this field, the ACC/AHA and ESC are continuously revising and updating their guidelines. While guidelines from either one of the association are essentially similar when it comes to recommendations on $P2Y_{12}$ selection and duration of DAPT, they still differ in some aspects. Nevertheless, both tend in the direction of a shift from a population-based treatment strategy towards a patient-centered treatment, taking into account individual variables such lifestyle, environmental effects and genetics, which one could call „precision medicine"(54). This individualized approach was demonstrated in one study that found no difference in the overall net adverse cardiac events in the long term between prasugrel and ticagrelor and clopidogrel-treated patients and in which it was concluded that DAPT regimen and duration should be adapted to each individual by considering the bleeding and ischemic risk factors(55).

2.5 Rationale for the use of antiplatelet therapy in patients undergoing PCI

As previously mentioned, the pathophysiological processes leading to ACS are complex and dynamic. The pathologic process is initiated with a disruption of a coronary atherosclerotic plaque by means of either rupture, fissure, or erosion in the intimal lining of the coronary arteries, which exposes the underlying atheroma to the bloodstream which is then followed by platelets activation and aggregation and as a result the formation of an occlusive or sub-occlusive thrombus, leading to a sudden, acute and symptomatic event. The ensuing clinical outcome is either myocardial ischemia or MI, depending on the extent of the occlusion(56). Implantation of a stent into the coronary artery, which is a common form of coronary intervention, further stimulates platelet activation. Therefore, patients undergoing PCI can benefit from more aggressive antiplatelet medication to reduce the risk of ST (12). Moreover, earlier research indicates that when a coronary artery is stented, it can trigger an immune or inflammatory response, which can lead to impaired responsiveness of the blood vessels in the affected area. While the exact reasons for this response are not yet understood, it is believed that the inflammation caused by the procedure can lead to dysfunction of the endothelium and cause negative vascular reactions, such as ST and in-stent restenosis. It is noteworthy that the

extent of endothelial dysfunction shortly after stent placement can predict the patient's long-term prognosis(57). Antiplatelet therapy is effective in reducing myocardial damage caused by periprocedural thrombotic events that involve damage to blood vessel walls, such as plaque ruptures, dissections, embolization or side branch occlusions. It also reduces the risk of ST, which occurs more frequently in the early phases after PCI(1,19). Figure 5 depicts the rational to use antiplatelet therapy during PCI(1).

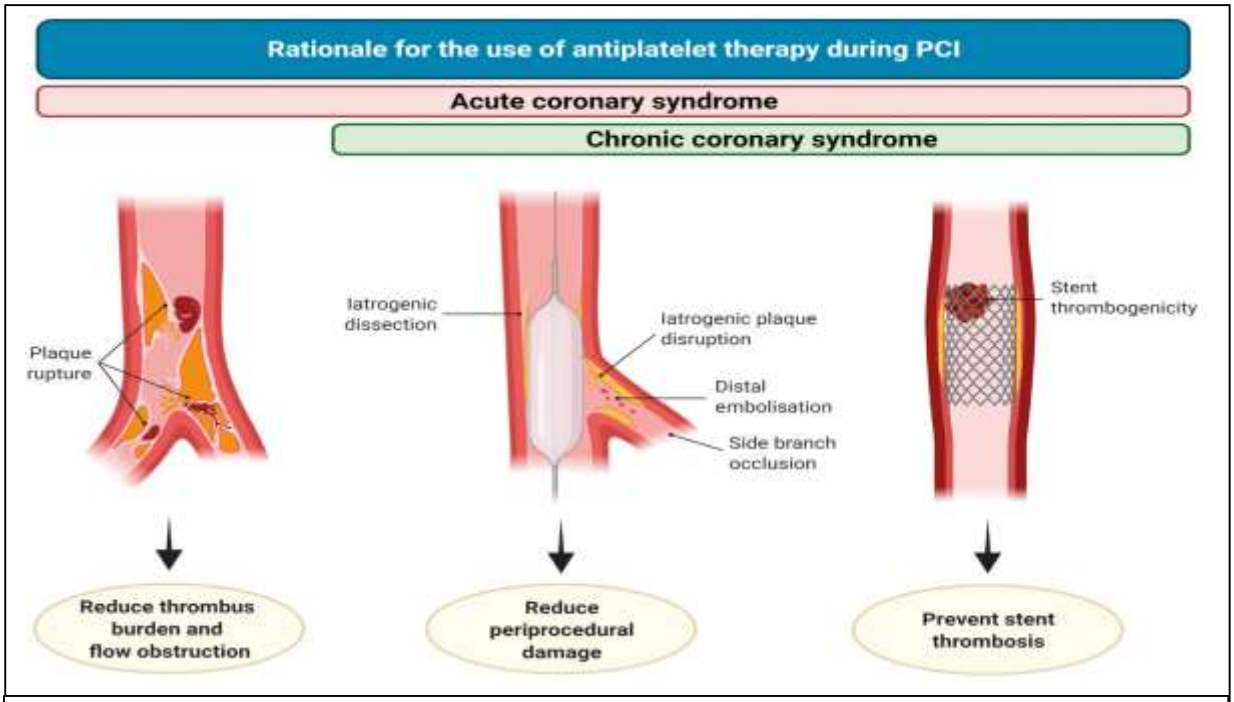

Figure 5. rational of using antiplatelet therapy among patients undergoing PCI (1)

2.5.1 Definition and pathophysiology of stent thrombosis

PCI with intracoronary stents is a commonly used method to prevent the reoccurrence of MI in patients with acute coronary syndrome ACS. However, it should be noted that ST is a serious complication that can occur after PCI and may even result in death(58). ST, although rare, is a fearsome and medically challenging complication that can occur after stent implantation. It is roughly associated with a mortality between 5-45%(59). ST is defined as a thrombotic occlusion of a coronary stent and it can be fatal with devastating clinical consequences and often times presents as a large MI(60,61). The underlying pathophysiology of ST is multifactorial and depends on patients‘ factors, including DM and malignancy as a concomitant illnesses, smoking status and genetic polymorphism, procedural and stent factors related to the stent and its placement, the coronary artery that is affected and the lesion type(62). Among the proposed pathophysiologic mechanisms responsible for ST are

neoatherosclerosis, stent malabsorption, impaired re-endothelialization, hypersensitivity reactions and stent dismantling(63). The elaboration of these mechanisms are beyond the scope of this narrative literature review. ST is usually classified according to the proposed definition of the Academic Research Consortium (ARC). According to this definition it can be designated as: an early ST, occurring within 30 days after stent implantation and further subdivided into acute ST (0-24 hours) and subacute ST (24 hours- 30 days); late ST, occurring between 1 month up to 1 year after stent implantation; and very late ST, occurring more than 1 year after stent implantation(64). However, new generation of drug eluting stents (DES) and DAPT have significantly reduced the occurrence of ST. DAPT is in fact a key element in preventing ST. Some studies have linked the premature discontinuation of clopidogrel and the occurrence of early ST, while the PARIS (Cessation of DAPT and Cardiac Events after PCI) registry found that almost three quarters of ischemic events, including ST, occurred while patients were still treated with DAPT(59,63). Katherine H. Chaue et al. in their analysis from ADAPT (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents)-DES, found out that the increased risk to experience ST, among patients who undergo PCI after MI, was associated with increased HTPR on clopidogrel(65). These finding contribute to the well-based notion that DAPT failure often occurs due to individual variable characteristics, such as the thoroughly discussed CYP2C19 polymorphism, and the need for more potent $P2Y_{12}$ inhibitors, such as prasugrel or ticagrelor, or alternatively PFT/genotype guided therapy(63,65). Indeed, a network meta-analysis of by Wenwen Chen et al. that included 14 studies, showed that both prasugrel and ticagrelor were more effective than clopidogrel in terms of lower rated of ST among patients presenting with ACS and undergoing PCI(66).

3. Dual antiplatelet therapy in patients with acute coronary syndromes

3.1 Dual antiplatelet therapy in patients with STEMI undergoing PCI

According to the 2017 ESC guidelines for the management of AMI in patients presenting with ST-segment elevation and the 2017 ESC focused update on DAPT in coronary artery disease, a maintenance DAPT regimen, consisting of aspirin maintenance dose of 75-100 mg once daily and ticagrelor or prasugrel, is recommended for patients after PCI for up to 12 months. Clopidogrel is recommended in case ticagrelor or prasugrel are not available or contraindicated. Moreover, it should be considered to discontinue the $P2Y_{12}$ inhibitor after 6 months in patients with high risk of bleeding, for example patients with PRECISE (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual

Antiplatelet Therapy) DAPT score that is 25 or more; alternatively, prolongation of DAPT beyond 12 months, preferably with ticagrelor, should be considered in patients who are at increased ischemic risk and have tolerated DAPT without bleeding complications (5,6). Much like in the European guidelines, according to the 2021 ACC/AHA/SCAI guideline for coronary artery revascularization and the 2016 ACC/AHA guideline focused update on DAPT in Patients with coronary artery disease, prasugrel or ticagrelor are preferred over clopidogrel(4,52). However, according to the AHA, for patients with a history of stroke or transient ischemic attack (TIA), prasugrel should not be administered, while for patients who are not at increased risk of bleeding and without prior history of TIA or stroke, it is recommended to consider prasugrel as the mainstay maintenance drug of choice (52). Finally, it is also recommended to consider PFT guided $P2Y_{12}$ de-escalation strategy, by switching from either prasugrel or ticagrelor to clopidogrel, in patients that are not suitable for a 12 months potent antiplatelet therapy(60). The reason why both guidelines favor ticagrelor or prasugrel over clopidogrel, is that multiple RCTs have demonstrated they provide a stronger and more consistent platelet inhibition than clopidogrel, albeit at the risk of increased bleeding incidence(1,14,39). One of the issues with these recommendations is, that the RCTs from which they were extrapolated, did not include certain populations such as elderly patients aged 75 years or older, and patients with prior bleeding or need for anticoagulants. For this reason, Mia Ravn Jacobsen et al. performed a single-center cohort study aimed to compare the effectiveness and safety of the three $P2Y_{12}$ inhibitors among all-comers with STEMI in order to achieve a wider perspective among all parts of the Danish population. 5,123 patients with STEMI were enrolled, of which 1,245 were treated with clopidogrel, 1,902 with prasugrel and 1,976 with ticagrelor, and more than 95% of the patients were also treated with aspirin. The elderly population accounted for 17% of the patients. The primary endpoint was established as a total of all-cause mortality, recurrent MI and ischemic stroke during a period of 7 days after discharge until the desired outcome, death or emigration up to 1 year. The study concluded that in real-life STEMI patients, both ticagrelor and prasugrel were superior to clopidogrel in reducing all-cause mortality without increase in bleedings that lead to hospitalization. It was also indicated, that no differences in terms of effectivity and safety were found between prasugrel and ticagrelor(67). In 2020, Alp Aytekin et al, after carried out a prespecified subgroup analysis of ISAR-REACT 5 trial, concluded that among patients with STEMI that undergo PCI, there were no significant differences between prasugerl and ticagrelor in terms of the incidence of MI, death or stroke after 1 year of follow-up. Nevertheless, ticagrelor was associated by a significant margin with increased risk

of recurrent MI. Stemming from these finding, their study raised the idea that, although both ticagrelor and prasugrel have similar efficacy in treatment of patients with STEMI undergoing PCI and also a similar bleeding risk, prasugrel should be considered in patients who also have a high risk to develop thrombotic complications(68). To the ever growing pool of evidence, that suggests the superiority of prasugrel and ticagrelor over clopidogrel, and also the superiority of prasugrel over ticagrelor, is a literature review by Alfredo E. Rodríguez et al., that examined multiple registries, RCTs and meta-analysis, whose purpose was to compare potential benefits of prasugrel and ticagrelor head-to-head with clopidogrel. They reached the conclusion that among patients with STEMI undergoing PCI, ticagrelor and prasugrel were both superior to clopidogrel, but in addition they observed that prasugrel was more effective than ticagrelor at 1 month and 1 year in reducing MACE, overall mortality and cardiovascular mortality(18). Arvindra Krishnamurthy et al. reached a similar conclusion in their study where prasugrel and ticagrelor were superior to clopidogrel, and prasugrel was associated with lower rates of adjusted mortality at 1 month in comparison to ticagrelor(69). As explained earlier, stent implantation is associated with an inflammatory response that leads to endothelial dysfunction and ultimately ST(57). Gao C.-Z. et al. conducted a study with the aim to compare the anti-inflammatory and endothelium protective effects exerted by clopidogrel and prasugrel and unveil how these effects influence the clinical prognosis, among patients with STEMI that undergo urgent PCI. 193 patients were enrolled, of which 97 assigned to the ticagrelor group and 96 assigned to the clopidogrel group. Inflammatory markers, including hypersensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6), as well as an endothelial function marker, namely endothelial cell-specific molecule 1 (ESM-1), were obtained at 24 hours, 4 days and 7 days after being treated with either one of the $P2Y_{12}$ inhibitors and patients were also followed for 30 days. Simultaneously they evaluated treatment outcomes as defined by ischemic end points such as cardiac death, AMI and stroke, and bleeding events. Results showed statistically significant decreased hs-CRP and IL-6 levels at 24 hours, 4 days and 7 days in the ticagrelor group compared with the clopidogrel group. Additionally, levels of ESM-1 were increased at 24 hours, 4 days and 7 days, but to a significantly lesser extent in the ticagrelor group in comparison to the clopidogrel group. These findings support the notion that ticagrelor has, in addition to its platelet inhibitory effect, pleiotropic effects, such as anti-inflammatory effects, making it superior to clopidogrel. The study also demonstrated that ticagrelol was superior to clopidogrel in terms of atherosclerotic plaque stabilization which was associated with decreased rate of ischemic events without increasing the risk of bleeding(70).

3.1.1 Dual antiplatelet therapy in patients with STEMI undergoing PCI after fibrinolysis

Although in patients presenting with STEMI, primary PCI is the preferred approach for revascularization and has widely replaced fibrinolysis, fibrinolysis is still being implemented among many patients around the world due to logistical barriers that limit their accessibility to PCI. (71). When primary PCI cannot be done in a timely fashion, that is when the door-to-balloon time (D2B) is 2 hours or more, guidelines recommend immediate fibrinolysis with subsequent transfer to a PCI-capable medical center where, in case of successful fibrinolysis, coronary angiography should be done within 2-24 hours after fibrinolytic drug administration, or in case of failed fibrinolysis, a rescue PCI should be carried out without any further delays(60). Moreover, during the COVID-19 pandemic it has been suggested to perform fibrinolysis instead of primary PCI as an alternative strategy among patients with suspected or active infection, even in the presence of PCI equipped centers in order to limit the spread to healthcare workers(72–74). Therefore, while under normal circumstances primary PCI is the strategy of choice for revascularization, COVID-19 can lead to delays in reperfusion and overloading of the healthcare system, and as a result fibrinolysis becomes a suitable alternative and non-inferior to primary PCI from which both the patients and the healthcare system can benefit(75).

Lastly, current guidelines recommend DAPT, with clopidogrel and aspirin, as an adjunctive lytic therapy to fibrinolysis. However, these guidelines do not specifically mention the choice of DAPT strategy in patients who initially underwent fibrinolysis and soon after underwent PCI. As such, these patients should be treated according to the guidelines that direct treatment strategy in patient with STEMI after undergoing PCI, as already discussed(6).

3.2 Dual antiplatelet therapy in patients with NSTEMI undergoing PCI

The guidelines for the post-interventional and maintenance antiplatelet treatment in patients with NSTEMI undergoing PCI are very similar to those dealing with STEMI patients as described above(4,5,7,52,60). However, in addition to these commonalities, some peculiarities can be described. According to the 2018 ESC/EACTS guidelines on myocardial revascularization, for patients with NSTEMI who are destined to undergo PCI and are $P2Y_{12}$ inhibitor naïve, prasugrel is recommended or otherwise ticagrelor is recommended irrespective of prior $P2Y_{12}$ inhibitor regimen and given that there are no contraindications(60). Although the ESC guideline recommend prasugrel in naïve patients destined to undergo PCI, there is no consensus about it. On this grounds, Farmakis IT et al.

carried out a network meta-analysis of nine studies, that attempted to assess the efficacy and safety of clopidogrel, prasugrel and ticagrelor among NSTE-ACS patients. Their results concurred with the current ESC guidelines and showed prasugrel to be more efficient than ticagrelor, in terms of reducing all cause-death, MI and definite ST, among patients with NSTE-ACS intended to undergo revascularization. Nonetheless, the authors also mentioned that there are existing discrepancies between different studies due to different testing methods, leading to inconsistencies in results and making it difficult to translate study outcomes into clinical practice(76). For example, in an RCT that investigated the effects of clopidogrel, prasugrel and ticagrelor on the function of platelets, inflammatory markers and endothelial function, among STEMI and NSTEMI patients who underwent PCI and were pretreated with prasugrel, it was revealed that therapy with prasugrel, in comparison to clopidogrel and ticagrelor, leads to better endothelial function, reduced inflammation and stronger platelet inhibition(57). On the other hand, in a meta-analysis of 14 studies that compared the degree of platelet reactivity between patients treated with prasugrel and patients treated with ticagrelor, a greater HTPR with prasugrel than with ticagrelor was shown(77). According to the 2016 ACC/AHA guideline focused update on duration of DPAT in patients with coronary artery disease, prasugrel treatment is contingent upon low risk for bleeding without prior history of stroke or TIA. Furthermore, patients who are at increased bleeding risk, such PRECISE-DAPT score of 25 or more or when the ARC-HBR (Academic Research Consortium for High Bleeding Risk) criteria are met, discontinuation of $P2Y_{12}$ inhibitors should be considered even after 3 months of therapy followed by aspirin monotherapy. For patients who are at a very high risk of bleeding, which is by definition a bleeding event in the last month or a planned surgery that cannot be postponed, a DAPT strategy combining aspirin and clopidogrel for a duration of only 1 month should be considered. Furthermore, PFT or genotype guided de-escalation therapy, or alternatively unguided de-escalation therapy based on clinical judgement should be considered in patients for whom DAPT with a potent $P2Y_{12}$ inhibitor is deemed to be inadequate(7).

In 2020, Marieke Gimbel et al. published their POPular AGE trial. The authors indicated that what sparked the need to conduct this trial is, that although TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction) and PLATO trials showed superiority of prasugrel and ticagrelor over clopidogrel respectively, in terms of reducing cardiovascular death, stroke and MI, TRITON-TIMI 38 did not show a clinical benefit of prasugrel in the subgroup of patients aged 75 years or older due to increased bleeding rates, and in the

PLATO trial, bleeding occurred more frequently in the older patients being treated with ticagrelor rather than with clopidogrel. This prompted the need to evaluate head-to-head clopidogrel, prasugrel and ticagrelor in terms of efficacy and safety among patients aged 70 years or older who had NSTE-ACS. The POPular-AGE trial was an open-label, multicenter RCT that enrolled 1,011 patients, of which 1,002 were analyzed, who were randomly treated with either clopidogrel, prasugrel or ticagrelor. 500 patients were assigned to the clopidogrel group and 502 patients were assigned to the ticagrelor group, of which 475 patients (95%) received ticagrelor and the rest received prasugrel. 891(89%) patients underwent coronary angiography and patients were followed up for 1 year. They concluded that in the subgroup of patients aged 70 years or older that present with NSTE-ACS, clopidogrel may be preferred over ticagrelol since it is associated with lower bleeding incidence and without increasing the incidence of all-cause death, MI and stroke. However, these results face some limitations. Included among these limitation is the fact that there a significantly higher premature discontinuation of treatment in the ticagrelor group (47%) in comparison with the clopidogrel group (22%), mainly due bleeding, dyspnea and treatment with oral anticoagulants, which might explain overestimation of clopidogrel over ticagrelor. Additionally, only 1% of patients were treated with prasugrel which hindered the evaluation of this drug in this trial(78)**.**

3.3 Dual antiplatelet therapy among patients with ACS that require oral anticoagulants

Among patients with ACS who have to undergo PCI and are also concurrently treated with oral anticoagulants (OAC), such as patients with atrial fibrillation, clopidogrel is the only recommended $PY2_{12}$ inhibitor(1). Approximately 5-10% of patients with atrial fibrillation have to undergo PCI (79). According to the 2020 ESC guidelines for the diagnosis and management of atrial fibrillation, patients with ACS who undergo PCI, should be treated with a triple antithrombotic therapy (TAT) which constitutes aspirin, a $P2Y_{12}$ inhibitor, which is preferably clopidogrel, and OCA, for 1 week and then continue a dual antithrombotic therapy (DAT) with clopidogrel and OAC for at least 12 months. In addition, TAT should be prolonged beyond 1 week but up to a maximal period of 1 month, in cases where the risk of ST outweighs the risk of bleeding(80). Recently the AUGUSTUS (a two-by-two factorial, randomized, controlled clinical trial) demonstrated that patients treated with an antithrombotic regimen consisting of apixaban and a P2Y12 inhibitor (more than 90% of the patients in the trial received clopidogrel) without aspirin had a lower risk of bleeding and hospitalization and a similar risk of ischemic events in comparison to regimens that included

a vitamin K antagonist, aspirin or both of them, further supporting the strategy of DAT regimen over TAT(81). On the other hand, according to both the 2017 ESC focused update on DAPT in coronary artery disease and the 2018 ESC/EACTS guidelines on myocardial revascularization, for patients with STEMI, TAT is recommended for at least 1 month and can be prolonged up to 6 months in patients with high ischemic risk(5,60). For patients with NSTE-ACS and concomitant atrial fibrillation, guidelines recommend TAT with non-vitamin K antagonist OAC (NOAC) for 1 week and up to 1 month, followed with DAT, preferably with clopidogrel as a $P2Y_{12}$ inhibitor for a period of 6-12 months(7). Regardless of the regimen and duration of therapy, only clopidogrel can be used as a $P2Y_{12}$ inhibitor in this subpopulation of patients since both ticagrelor and prasugrel could potentially lead to clinically relevant and worrisome bleeding events without beneficial reduction in MACE incidence, and hence are not recommended(5,82).

3.4 Dual antiplatelet therapy in East Asian populations

Most of the major guidelines, regarding antiplatelet therapy among patients with ACS that undergo PCI, are based on studies that included only a small percentage of East-Asian patients. For this reason, Western-based guidelines cannot be routinely applied to patients from the Asia-Pacific region(83,84). In addition, the prevalence of CYP2C19 LoF allele polymorphism is significantly higher among East-Asian patients than in Caucasian patients in Western countries(25,85,86). This difference in polymorphism prevalence between East Asian population and Caucasian population resulted in the “East Asian Paradox”, which refers to the observation that East Asian patients have a unique risk/benefit ratio profile with DAPT, that is a lower risk of experiencing an ischemic event while at the same time an increased bleeding risk despite a higher average on clopidogrel HTPR, in comparison to Western patients(8,87,88). Clinical manifestation of this phenomenon can be observed in some meta-analysis studies. One meta-analysis that compared ticagrelor and clopidogrel among East Asian patients with ACS found ticagrelor to be associated with a higher risk of bleeding compared to clopidogrel(89), while another meta-analysis study, that conducted a subgroup analysis in Caucasians and East Asians, found ticagrelor to be as effective as clopidogrel in terms of MACE but at the expanse of a higher bleeding risk, which can be explained by different therapeutic effects of ticagrelor in different ethnic groups such as East-Asians(90). Still in another study that compared ticagrelor and prasugrel in Chinese patients with UA, although ticagrelor was associated with a reduction in the incidence of PCI-induced myocardial injury, it also increased bleeding events in the hospital and at 12 months of

therapy in comparison to clopidogrel and was not beneficial in reducing MACEs in the hospital and at 12 months of therapy(91). On the other hand, in another study that compared $P2Y_{12}$ inhibitors among East Asian patients with ACS, it was concluded that both prasugrel and ticagrelor were associated with increased risk of bleeding, but ticagrelor also significantly reduced the rate of all cause death and also death due to stroke and cardiovascular reasons(92). The increased risk of bleeding associated with ticagrelor is greatly attributed to its stronger antiplatelet inhibitory and a lower HTPR in East Asian patients(93). In 2019, Duk-Woo Park et al. published the results of the TICAKOREA (Ticagrelor Versus Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Management) trial. This was a randomized, multicenter, open-label trial with 800 enrolled patients, that aimed to evaluate the safety and efficacy of a standard treatment with DAPT among Korean patients with STEMI or NSTEMI that are destined to undergo PCI, consisting of ticagrelor, in comparison with that consisting of clopidogrel. The study resulted with ticagrelor leading to clinically significant higher incidence of bleeding in comparison to clopidogrel and emphasized the need for further and larger RCTs to determine the appropriate antithrombotic treatment in East Asian patients(94). In another study that compared real-world bleeding events with ischemic events among Korean patients on DAPT, the authors deduced that DAPT with clopidogrel can be considered as first-line treatment regimen after PCI in Korean patients with high bleeding proclivity and reduced ischemic risk (the “East Asian Paradox”), because it was associated with lower incidence of bleeding, ischemic events and NACEs in their study. However, the authors also mentioned that it is possible that clopidogrel was overestimated due to higher adherence to DAPT with clopidogrel in comparison to DAPT with ticagrelor(95). Until further studies are performed, based on current evidence, the 2020 Asian Pacific Society of Cardiology Consensus Recommendations on the Use of P2Y12 Receptor Antagonists in the Asia-Pacific Region recommends ticagrelor or prasugrel over clopidogrel in patients with ACS undergoing PCI but with careful attention to the balance between ischemic and bleeding risks of each individual patient(83).

3.5 Dual antiplatelet therapy in the era of Covid-19 pandemic

In 2019, an outbreak of the severe acute respiratory syndrome corona virus 2 (SARS-CoV- 2) occurred in Wuhan, China, which further lead to the Covid-19 pandemic worldwide(96). Covid-19 infection is associated with a hypercoagulability state which puts patients at risk of thrombosis, including arterial, venous and microvascular thrombosis and therefore also

increases the risk of developing various cardiovascular disease, including myocardial ischemia and ACS(97–99). Moreover, studies showed that patients presenting with ACS and either ST-elevation acute coronary syndrome or non-ST-elevation acute coronary syndrome, that underwent PCI and were concomitantly diagnosed with Covid-19 infection, had significantly higher rates of in-hospital mortality (100–104). In addition to that, patients with cardiovascular risk factors or those who previously suffered from cardiovascular disease, have a poorer prognosis(105). The underlying pathophysiology leading to ACS in patients with Covid-19 is complex and can lead to type 1 MI, type 2 MI or MI with non-obstructive coronary arteries (MINOCA)(106). The mechanisms include, a pro-inflammatory state and a cytokine storm that destabilizes existing atherosclerotic plaques and can lead to microvascular thromboembolism, myocardial oxygen supply/demand due to hypoxemia resulting from Covid-19-related respiratory failure, coronary artery endothelium injury and inflammation which can lead to coronary vasospasm, and direct myocardial injury that is mediated through angiotensin-converting enzyme 2 (ACE2) receptors(96,105,107–109). Furthermore, it is important to distinguish between two groups of Covid-19 patients: those with an established or chronic cardiovascular disease in whom ACS is the result of atherothrombosis according to classical pathophysiological pathways, regardless of Covid-19 infection, and patients without a chronic cardiovascular disease background, in whom the Covid-19 is the primary cause for development of ACS(110). Moreover, the aforementioned hypercoagulability and pro-inflammatory states, not only affect the coronary arteries and manifest clinically as ACS, but also predispose patients with ACS that undergo PCI to experience higher rates of ST(106,111–113). In addition to that, some studies revealed that patients with ACS and Covid-19 infection have impaired coronary reperfusion results after primary PCI(98,114). According to a consensus statement from 2020 from the society for cardiovascular angiography and interventions (SCAI), the ACC, and the American college of emergency physicians (ACEP), primary PCI is superior to fibrinolysis and is the treatment of choice for STEMI patients with Covid-19 when it can be performed in a timely manner(96). Antiplatelet treatment after PCI remains the strategy to prevent ischemic events such as ST. However, patients with Covid-19 and ACS have an increased risk of both thrombosis and bleeding, making the decision on the best combination and duration of DAPT more difficult(106). Some evidence suggests a shorter duration of DAPT post-PCI with a continued potent $P2Y_{12}$ inhibitor, preferably with ticagrelor, after 1-3 months of DAPT, in order to counterbalance the increased bleeding risk(115,116). In Covid-19 patients, platelet activation leads to release of coagulation and inflammatory molecules which promote platelet-leukocyte

aggregates that in turn lead to thrombosis. Therefore, $P2Y_{12}$ inhibitors have an additional beneficial effect in these patient, because in addition to their platelet inhibitory effects, they exert anti-inflammatory effects(117). In particular, ticagrelor, has unique properties as it does not only inhibit $P2Y_{12}$ receptors, but it also inhibits the equilibrative nucleoside transporter 1 (ENT1), a receptor responsible for cellular ADP uptake, thus conferring an even stronger anti-inflammatory effect(47,115,118). Despite this, in an RCT by Reza Arefizadeh et al. the researchers aimed to compare the possible beneficial effects of ticagrelor over clopidogrel, in Covid-19 patients presenting with ACS who underwent urgent PCI. However, ticagrelor did not confer better outcomes in comparison to clopidogrel in terms of all-cause mortality, MI and ST after a follow up period of 30 days. Nevertheless, patients treated with ticagrelor had higher oxygen saturation levels than patients treated with clopidogrel, which could be a clue to ticagrelor's possible advantage in improving pulmonary function in these patients(119).

IV. CONCLUSION

This narrative literature review evaluated current guidelines as well as ongoing research concerned with comparing the effectiveness and safety of three $P2Y_{12}$ inhibitors, namely clopidogrel, prasugrel and ticagrelor, among patients with ST-segment elevation acute coronary syndromes and non-ST segment elevation acute coronary syndromes who underwent percutaneous coronary interventions. The main challenge in this group of patients is post-procedural ischemic events, both systemic and local. In particular stent thrombosis presents the greatest challenge. One component of the underlying pathophysiological mechanism of both acute coronary syndrome and stent thrombosis is platelet activation and aggregation and consequently formation of a thrombus. Hence, $P2Y_{12}$ inhibitors combined with aspirin, as part of dual antiplatelet therapy, play a central role in disrupting these mechanisms. However, by inhibiting platelets, these medications introduce the risk of bleeding. Stemming from this, the standard of care for these patients necessitated the meticulous evaluation of bleeding risks against ischemic risks. This delicate bleeding-ischemic balance was further challenged in patients with concomitant coronavirus disease 2019 infection. While clopidogrel has lower bleeding risk, it has been associated with resistance to treatment and thus with higher ischemic events in comparison to more potent $P2Y_{12}$ inhibitors, prasugrel and ticagrelor, which confer more protection against ischemic events yet at the expanse of higher bleeding risk. Current guidelines recommend ticagrelor or prasugrel over clopidogrel for most patients but the developing trend is towards more

individualized decision based on risk/benefit ratio. All $P2Y_{12}$ inhibitors have the same purpose, but their relative merits vary form one patient to another. Ticagrelor has unique effects due pleiotropic properties, prasugrel emerges as a possible drug of choice from recent studies, and clopidogrel‘s effectiveness varies depending on genetic profile and other factors. Therefore, prasugrel and ticagrelor do not offer the same benefits as clopidogrel. While ticagrelor and prasugrel are better options in patients with higher ischemic risk, clopidogrel seems to be beneficial, especially platelet function testing or genetically guided, in patients with high bleeding risk, including patients taking anticoagulants, and also specific populations like the elderly and East-Asian patients.

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