Efficacy and Safety of Platelet Inhibitors

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Abstract - Ischemic heart disease is the second leading cause of death in the world. The proportion of deaths resulting from this condition has decreased in the last two decades, mainly as a result of improved primary and secondary prevention of cardiovascular events, as well as the development of patient awareness and medical and pharmacological management. The purpose of the present review is to analyze pathophysiological events leading to platelet involvement in cardiovascular thrombosis, as well as the role of pharmacogenetics in modulating the risk of cardiovascular disorders. The present work was performed using a PubMed search with combinations of key words relevant to the subject in both English and French. In addition to the pharmacokinetic and pharmacodynamic characteristics of platelet inhibitors, this work reviews the efficacy and adverse events observed during the clinical trials with these drugs. This review further summarizes possible therapeutic drug monitoring strategies for antiplatelet drugs. The novelty of this work is the description of the lymphocyte toxicity assay as a specific method of diagnosing and predicting possible idiosyncratic adverse events attributable to antiplatelet medication.

INTRODUCTION

In 2006, the Public Health Agency of Canada published a report indicating that cardiovascular (CV) diseases were the leading cause of death in Canada. The number of deaths from CV diseases represented 30% of all reported deaths. Of these, 23% (16109 individuals) were due to myocardial infarction (MI). In 2009, this number increased to 21000 (1).

MI, with or without ST segment elevation, is part of acute coronary syndrome (ACS). ACS describes a clinical heart condition characterized by the formation of blood clots, resulting from the erosion and rupture of an atheromatous coronary plaque (2). ACS represents a burden for the society and to the healthcare system. In Canada, it is estimated that almost 2% of the general population will be hospitalized with MI, with treatment costs expected to surpass $1.6 billion (3). The same trend is observed in the US, where ACS costs exceed $150 billion annually. Moreover, almost 20% of MI patients are re-hospitalized within 1 year (4). In France, ischemic heart diseases caused 38806 deaths in 2006, which represented 27% of all CV deaths. Ischemic heart disease is recognized as the second leading cause of death for men and women. However, the incidence of mortality as result of this condition has decreased between 1990 and 2006 due to improvement of primary and secondary prevention of CV events and the development of patient management (5).

The pathophysiological process of CV diseases is linked to plaque formation, fibrogenesis and inflammation. Inflammation is the first step involved in the formation of an atheromatous plaque. Inflammation activates the endothelium and permits the recruitment of monocytes and lymphocytes, which are further responsible for the production of pro-inflammatory cytokines (6). Matrix proteases degrade the fibrous layer of the endothelium. Ultimately, inflammation induces apoptosis of plaque cells, leading to the formation of a lipid core inside the plaque. Erosion is brought about by a combination of weakening of the fibrous layer of the endothelium and stimuli applied onto the plaque (7). When an atherosclerotic plaque ruptures, blood cells come into contact with thrombogenic elements from the lipid center, inducing activation of platelets, blood clotting and the formation of thrombi (7, 8).

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Abbreviations
ACS, acute coronary syndrome
ADP, adenosine diphosphate
CABG, coronary-artery bypass surgery
COX-1, cyclooxygenase-1
CV, cardiovascular
CYP, cytochrome p450
HIV, human immunodeficiency virus
HPLC, high-performance liquid chromatography
GP, glycoprotein
IgE, immunoglobulin E
HSR, hypersensitivity syndrome reactions
LC, liquid chromatography
LSC, liquid scintillation counting
MI, myocardial infarction
MS, mass spectrometry
NSTEMI, non-ST segment elevation myocardial infarction
PCI, percutaneous coronary intervention
STEMI, ST segment elevation myocardial infarction
TDM, therapeutic drug monitoring
TXA_2, thromboxane A2
UA, unstable angina
VASP, vasodilator-stimulated phosphoprotein

The accumulation and migration of thrombi can lead to partial or total obstruction of coronary arteries, resulting in a lack of oxygen to the heart. This leads to a spectrum of heart conditions ranging from chest pain (unstable angina (UA)) to MI and heart damage (7).

Platelets play a critical role in the pathophysiology of CV diseases through their interaction with the injured endothelium (9). They are involved in the build-up of atherosclerotic plaque, while their activation is partially stimulated by systemic inflammatory reaction syndrome (10). Platelets are also associated with an inflammatory process that leads to the secretion of pro-inflammatory agents such as chemokines, eicosanoids, thromboxane A2 (TXA_2), leukotrienes and platelet activation factor (11). Inflammation leads to coagulation through an extrinsic pathway involving thrombin generation. This process is initiated by tissue factor, a transmembrane protein released by damaged endothelial tissue or synthesized by macrophages. A higher abundance of tissue factor is associated with mononuclear cells present in the atherosclerotic plaque, probably due to the pro-inflammatory environment to which these cells are exposed, particularly interleukin (IL)-6 (8). In blood, tissue factor combines with factor VIIa, forming a complex that is able to catalyze the conversion of factor X to factor Xa. Factor Xa, together with factor Va, factor II (prothrombin) and Ca^{2+}, further forms a prothrombinase complex that leads to the generation of thrombin (factor IIa). Thrombin in turn strengthens coagulation by converting fibrinogen into fibrin (factor Ia), thereby allowing fibrin polymerization (8, 12). Fibrin stimulates the activity of neutrophils, platelets and endothelial cells. Platelets are essential for the pathogenesis of inflammation-mediated thrombosis, as is the case with ACS (8). Platelet adhesion and activation can be further achieved through contact with subendothelial collagen present on the tunica intima, the innermost layer of a blood vessel that can become exposed upon the rupture of an atherosclerotic plaque. Other molecules can also activate platelets, including platelet-activating factor, a pro-inflammatory mediator, as well as thrombin itself (8).

Hemostasis is a normal physiological function whose deregulation can lead to obstruction of blood vessels with thrombi, giving rise to MI or UA (13). This process is composed of 3 phases, namely initiation, activation/aggregation and stabilization. Hemostasis is initiated by exposed collagen from the subendothelial matrix leading to adherence of platelets by binding to the $\alpha_2\beta_1$ (glycoprotein (GP) Ia/IIa) and $\alpha_{IIb}\beta_3$ (GP IIb/IIIa) membrane integrins, and GP receptors present on platelet membrane. Vasoconstriction further improves adherence (13, 14). Platelet rolling, the initial contact between platelets and the exposed endothelium, is mediated by selectins present on the surfaces of both platelets and endothelial cells. For example, P-selectin is rapidly translocated to the plasma membrane following inflammatory stimuli. Platelet accumulation on the surface of the activated endothelium is mediated by the $\alpha_{IIb}\beta_3$ integrin (15). Platelet adhesion is further mediated by the $\alpha_V\beta_3$ integrin (vitronectin receptor) and the GP Ib/IX/V (von Willebrand factor) receptor. The vitronectin receptor can be activated by IL-1β or thrombin, while the von Willebrand factor is produced by the injured tissue (13-15). The von Willebrand factor fixes GP Ib-IX, a platelet membrane receptor, and this binding induces a conformational change that captures and activates platelets, leading to thrombus formation (14, 16). The GP VI receptor associates with the Fc receptor γ subunit and activates phospholipase $C_{\gamma 2}$. Phospholipase C phosphorylation and activation can be further mediated by integrins. Phospholipase C activation can hydrolyze phosphatidylinositol-4,5-bisphosphate membrane protein into the secondary messengers inositol-3-phosphate and diacylglycerol. Inositol-3-phosphate leads to

mobilization of intracellular Ca^{2+}, which provokes platelets contractions through cytoskeletal reorganization and filopodia extension. Ca^{2+} and adenosine diphosphate (ADP) are essential to initiate platelet coagulation (16).

Fibrinogen binds the GP IIb/IIIa platelet membrane receptor, creating a bridge between two platelets. Thrombin transforms fibrinogen into fibrin, which is an insoluble protein that activates platelets and strengthens coagulation through the formation of a platelet-fibrin thrombus (8). Moreover, thrombin triggers an amplification of platelet aggregation by activating tissue factor V, which in turn activates tissue factor XIII, stabilizing the clots through the formation of an insoluble fiber. During normal physiological conditions, building of clots is balanced by their destruction following reconstruction of the endothelial layer, a process known as fibrinolysis (12).

Because thrombotic events are involved in the pathogenesis of atherosclerosis and artery diseases, most therapies for ACS modulate platelet function and coagulation. Platelet inhibitors in combination with aspirin are recommended for the prevention of CV events.

METHODS

The present work was performed following a PubMed search with combinations of key words using one of "antiplatelet drug", "platelet inhibitor", "clopidogrel", "ticlopidine", "prasugrel" and "ticagrelor", and one of "efficacy", "adverse drug reaction", "hypersensitivity reaction", "metabolism", "pharmacokinetics", "pharmacodynamics", "pharmacogenomics", "therapeutic drug monitoring" and "clinical trials". A considerable portion of the safety and efficacy data was compiled from the various clinical trials involving clopidogrel, while the main conclusions presented are those of the respective study investigators. Additional material used to support the main findings was retrieved from the Google Scholar database. Furthermore, reports from various health agencies in Canada and France were consulted, as well as the product monographs of the drugs studied. Reviewed material includes work published in both English and French.

RESULTS AND DISCUSSION

I) Review of Platelet Inhibitors

a. Pharmacology

Platelet inhibitors are molecules aimed at reducing atherothrombotic events. These agents are often used in combination with aspirin in order to induce sufficient vasodilation to avoid the formation of blood clots. Cyclooxygenase (COX)-1 normally produces TXA_2, a platelet aggregation agent. Aspirin is an irreversible COX-1 inhibitor that leads to inhibition of TXA_2 formation, such that platelets are permanently inhibited until new platelets are synthetized. A 75 mg dose is sufficient to obtain adequate inactivation of COX-1. Aspirin also reduces the incidence of both MI and CV death when administered during the acute phase of ACS (7). Platelet inhibitors currently in use include the thienopyridine family (ticlopidine, clopidogrel and prasugrel) and the newer cyclopentyl triazolopyrimidine, ticagrelor. The oldest of the thienopyridines, ticlopidine (Ticlid®), was commercialized in 1991 by Sanofi. The second and the most widely-used thienopyridine is clopidogrel (Plavix®), marketed by Sanofi and Bristol Myers Squibb in 1997. The latest thienopyridine is prasugrel (Effient®), put on the market in 2009 by Eli Lilly and Company. In 2011, Astra Zeneca developed a new antiplatelet agent, the cyclopentyl triazolopyrimidine ticagrelor (Brilinta®) (17, 18).
Thienopyridines have similar structures and similar mechanisms of action. As prodrugs, these molecules require hepatic biotransformation by cytochrome p450 (CYP) 2C19, 3A4, 3A5, 2C9, 2B6 or esterases in order to induce antiplatelet effects (17). The active metabolite (with a thiol moiety) binds irreversibly to the G-coupled receptor $P2Y_{12}$, forming a disulfide bond with one of the receptor's cysteine residues. $P2Y_{12}$ is a purinergic receptor belonging to the seven transmembrane class of receptors, found on platelet cell membranes. A second purinergic receptor, $P2Y_1$, initiates the platelet response to ADP, while $P2Y_{12}$ promotes this response. $P2Y_{12}$ thus plays an important role in the activation of platelets and their aggregation. The interaction between ADP and $P2Y_{12}$ results in adenylate cyclase inhibition, leading to platelet aggregation (19). Initially, the interaction between ADP and $P2Y_{12}$ causes a change in the platelet's shape from a disc to a sphere with pseudopodia. This change involves Ca^{2+} influx, intracellular Ca^{2+} mobilization and actin polymerization. Platelet aggregation is further mediated by the change in conformation of GP IIb/IIIa complexes on the platelet's surface, which become fibrinogen receptors upon activation. Fibrinogen links platelets by creating a bridge between two GP IIb/IIIa platelet receptors (19). ADP comes from the general circulation after the transformation of ATP as result of cellular or tissue damage. ADP can be further produced by CD39, an integral

membrane protein on the endothelial cells. Collagen and thrombin also cause platelet shape changes and promote platelets to secrete the contents of their granules, including ADP and thus amplifying the mechanism. The binding of collagen and thrombin to their receptors further leads to the production of the pro-aggregation agent TXA_2 (19). Blockage of the $P2Y_{12}$ receptor leads to inactivation of platelets, with blockage of GP IIb/IIIa, which in turn inhibits the rest of the aggregation stunt to ultimately prevent clot formation (20). In contrast to thienopyridines, the structure of ticagrelor is very similar to adenosine. As such, it does not bind the ADP site, but rather it reversibly binds another site on the $P2Y_{12}$ receptor. Ticagrelor is therefore a non-competitive inhibitor. The conformational change of this receptor is blocked and activation and aggregation of platelets cannot occur (21). Ticagrelor is already an active drug, but *in vitro* evidence suggests that it can also be further converted to an active metabolite by CYP3A4/5 (22-24).

b. Indications and Dosages

Long-term platelet inhibitors administered orally are indicated for the prevention of atherothrombotic events in patients suffering from MI, ischemic stroke, established peripheral arterial disease and ACS (patients undergoing stent placement following percutaneous coronary intervention (PCI), ST segment elevation MI (STEMI) or non-ST segment elevation MI (NSTEMI)). Platelet inhibitors were indeed shown to reduce the occurrence of new CV events after certain surgeries (25). These drugs are useful to limit the prothrombogenic effect of reperfusion treatment (thrombolysis and primary angioplasty) in ACS with ST segment elevation. In ACS without ST segment elevation, they prevent vascular occlusion and therefore MI (7). The Canadian Cardiology Society and Health Canada recommends aspirin (75-162mg daily) in combination with clopidogrel (75mg daily) as the gold standard treatment in patients who underwent a CV event (26). The synergy between aspirin and platelet inhibitors provides a greater antiplatelet effect, and subsequently a more significant reduction in the risk of atherothrombotic disease.

Aspirin is recommended for acute MI and acute ischemic stroke, as well as for prophylaxis in MI and CV disease. Clopidogrel is the standard treatment used for the prevention of atherothrombotic events. This drug is indicated in adults who have recently experienced MI (treatment to be initiated between 7-35 days post event), ischemic stroke (treatment to be initiated between 7 days-6 months post event) or peripheral arterial disease (27).

Other thienopyridines or ticagrelor are used as second-line in long-term treatment following ACS in cases of adverse drug reactions (ADR) or low responsiveness to clopidogrel. Ticlopidine is recommended to reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a complete thrombotic stroke (28). The newer generation thienopyridine prasugrel, co-administered with aspirin, is indicated for the prevention of atherothrombotic events in patients with ACS (UA/NSTEMI or STEMI) undergoing primary or delayed PCI (29). Ticagrelor, co-administered with aspirin, is also indicated for the prevention of atherothrombotic events in adults with ACS (UA/NSTEMI or STEMI), including patients managed medically, or with PCI or coronary-artery bypass surgery (CABG) (30). Dosing indications for platelet inhibitors prescribed as dual-therapy in combination with aspirin are presented in Table 1 (21, 31).

In 2011, the Canadian Cardiovascular Society published guidelines about the use of antiplatelet therapy in the outpatient setting (26). Indefinite therapy with low dose aspirin (75-162 mg/day) is recommended in all patients with acute or chronic ischemic heart disease. Indefinite therapy with clopidogrel (75 mg/day) is recommended in all patients with acute or chronic ischemic heart disease who are intolerant or allergic to aspirin. Clopidogrel plus aspirin treatment is recommended in STEMI patients (up to 1 year in patients with no excessive risk of major bleeding, otherwise up to 14 days) and in non-ST segment elevation ACS patients (up to 1 year in patients with no excessive risk of major bleeding, otherwise up to 1 month). Continuing daily therapy beyond 1 year is recommended in all ACS patients who are managed medically with a low risk of bleeding (26). Furthermore, in the absence of contraindications to aspirin therapy, clopidogrel plus aspirin treatment is also recommended post-PCI in patients with bare metal stent implantation (up to 1 year in patients with no excessive risk of major bleeding, otherwise up to 1 month), as well as drug-eluting stent implantation (1 year). Patients with recent bleeding or at increased risk of bleeding may benefit from a short course of clopidogrel plus aspirin (≥2 weeks) post-PCI, while patients with an increased risk of stent thrombosis and a tolerable risk of bleeding are encouraged to continue dual-therapy beyond 1 year (26).

While not recommended in patient with an increased risk of bleeding, patients likely to undergo CABG within 7 days, patients with a history of stroke or transient ischemic attack, and patients >75 years or age and <60 kg in weight, prasugrel plus aspirin may prove beneficial in ACS patients with stent implantation who are at increased risk of stent thrombosis (1 year) (26).

Table 1. Dosing indications for platelet inhibitors

	Dosing Frequency	Maintenance Dose	Loading Dose	Aspirin Dose/day
Ticlopidine	Twice daily	250 mg	500 mg	75-162 mg
Clopidogrel	Daily	75 mg	300 mg	75-162 mg
Prasugrel	Daily	10 mg	60 mg	75-162 mg
Ticagrelor	Twice daily	90 mg	180 mg	≤100 mg

c. Pharmacokinetics and Metabolism

All thienopyridines are prodrugs and require hepatic biotransformation. They each have their own metabolism pathway. Hepatic metabolism of ticlopidine by CYP2C19 and 2B6 results in the production of four metabolites, of which only UR-4501, the oxidation product of 2-oxo-ticlopidine, is active. The parent molecule is 98% bound to plasma proteins (32).

The first step in clopidogrel hepatic metabolism involves the formation of an intermediate metabolite, 2-oxo-clopidogrel, via CYP2C19, 3A4, 2B6 and 1A2. Subsequently, this compound is transformed to an active thiol metabolite which forms a disulfide bridge by irreversibly binding to a cysteine residue on the platelet ADP receptor, causing inhibition of platelet aggregation (17, 24, 27, 33-35). Only 15% of the prodrug is metabolized to the active metabolite, while bioactivation by human carboxylesterase 1 leads directly to an inactive carboxylic acid metabolite (85% of circulating metabolites) (36). Clopidogrel metabolites were shown *in vitro* to have the 2-{1-[1-(2-chlorophenyl)-2-methoxy-2-oxoethyl]-4-sulfanyl-3-piperidinylidene}acetic acid primary structure, with the active metabolite showing S configuration at carbon 7 and Z configuration at the carbon 3-16 double bond (34). Due to its extensive metabolism via hepatic enzymes, clopidogrel presents complex pharmacokinetic and pharmacodynamic properties.

The third generation thienopyridine prasugrel requires only one step to be biotransformed to its active metabolite, known as R-138727, via a thiolactone intermediate compound which is rapidly formed in the intestine through the action of human carboxylesterase 2. More than 50% of the administered dose is absorbed and around 90% of the parent drug is transformed into the active metabolite (24). CYP3A4/5 and 2B6 are the main CYPs involved in the metabolism of prasugrel, with a minor contribution from CYP2C19 and 2C9 (24). Interestingly, intestinal metabolism plays an important role in the formation of the active metabolite, with a major proportion of active metabolite being formed by CYP3A4 via first-pass intestinal metabolism (17). Prasugrel has a faster antiplatelet effect than ticlopidine and clopidogrel. Genetic variability has a less pronounced effect on its pharmacodynamics. Prasugrel also provides better protection against MI or stent thrombosis, yet it carries a more pronounced risk of hemorrhagic events. Genetic polymorphisms have a lesser impact on these parameters as well, making this third generation thienopyridine an important alternative to clopidogrel (31).

While ticagrelor is already an active drug, CYP3A4 and 3A5 were shown *in vitro* to lead to the creation of an active metabolite that is nearly 3 times as potent as the parent compound (21, 24). Since ticagrelor is a substrate of CYP3A4 and P-glycoprotein, drug-drug interactions can occur. For instance, if ticagrelor is co-administered with the CYP3A4 inhibitor ketoconazole, exposure to ticagrelor would be increased 7-fold, while maximum plasma concentration (C_{max}) and area under the curve (AUC) for its active metabolite were reduced by 89% and 56% respectively (35). Ticagrelor has rapid onset and offset of action. Indeed, the antiplatelet effect is observed as soon as 30 min post-administration (200 mg) and full clearance of ticagrelor and its active metabolite, with functional recovery of platelet aggregation returning to normal, was observed 48h post-administration (20, 22, 24). Table 2 displays the pharmacokinetic profiles of ticlopidine and ticagrelor, as well as those of the active metabolites of clopidogrel, prasugrel and ticagrelor (22, 37-41).

II) Clinical Trials with Platelet Inhibitors

Clinical trials assessing the efficacy and safety of platelet inhibitors are introduced in Table 3 (42-84).

Table 2. Pharmacokinetic profiles of active metabolites of platelet inhibitors

Parameters	Ticlopidine (250 mg)	Clopidogrel active metabolite (300 mg)	Prasugrel active metabolite (60 mg LD/10 mg MD)	Ticagrelor (200 mg)	Ticagrelor active metabolite (200 mg)
Cmax (ng/mL)	573	35.9	453/56	923	264
Tmax (h)	1.9	1.0	0.5	1.5	3.0
AUC (ng/h/mL)	$AUC_{(0-\infty)}$ 1808	$AUC_{(0-\infty)}$ 43.8	$AUC_{(0-t)}$ 460/54	$AUC_{(0-t)}$ 6591	$AUC_{(0-t)}$ 2477
T1/2 (h)	6.9	0.52	7.4	8.4	3.0

a. Characteristics of Patients Requiring Antiplatelet Therapy

The Euro Heart Survey describes characteristics of patients requiring antiplatelet therapy (85). Electrocardiogram results showed ST segment elevation in almost 47.0% of 6385 ACS patients included in this study. The mean age in this population was 64.7. The most common diagnosis was typical angina (80.8%). Some common characteristics of this population include a history of past/current smoking, diabetes mellitus, hypertension and hyperlipidemia. A considerable amount of ACS patients were found to have had previous MI, PCI, CABG, stroke, transient ischemic attack or renal failure (85). Similar values were observed in the CURE study (43). In this study, female gender was 38.5%, with a mean age for the sample of 64.2. Common co-medication included aspirin, warfarin, heparin, GP IIb/IIIa inhibitors, proton pump inhibitors (PPI), Ca^{2+} channel blockers (CCB), β-blockers, statins, angiotensin-converting enzyme inhibitors, lipid-lowering agents and intravenous nitrate (43, 85). The ACTIVE study describes a slightly older population (mean age 70.2), with an even wider array of co-medication (86).

III) Efficacy of Platelet Inhibitors

The main findings of the clinical trials assessing the efficacy of platelet inhibitors are described in detail in Table 4.

Efficacy of platelet inhibitors is typically assessed in terms of the primary study end-points defined in each clinical trial. These often include CV death, recurrent MI, recurrent ischemia or stroke, as well as the occurrence of stent thrombosis. CAPRIE was the earliest trial to test the antiplatelet drug clopidogrel, proving its superiority over aspirin. Subsequent trials further showed the efficacy of dual-therapy with clopidogrel and aspirin to be superior to either clopidogrel or aspirin alone. The combination of platelet inhibitors and aspirin was thus accepted as the standard of care. Yusuf et al. report a reduction of 20% in the incidence of MI, death and stroke with clopidogrel (75mg/day) plus aspirin over aspirin alone (43). This combination prevented about 50 major vascular events per 1000 patients treated (51). Dual-therapy with platelet inhibitors and aspirin was shown to be superior to aspirin and placebo for the long-term prevention of ischemic complications after a coronary angioplasty, while the risk of bleeding is also increased (7, 43, 46). Clopidogrel and aspirin, dual-therapy decreases mortality and morbidity rates (46, 54). The use of lower doses of aspirin (e.g. 75 mg/day) is generally recognized as being comparable to that of higher doses, with the added benefit of a reduced hemorrhagic risk (87).

a. Comparative Antiplatelet Effects

The CURE (43) and COMMIT (51) studies in particular showed the superiority of clopidogrel and aspirin dual-therapy over aspirin mono-therapy in terms of a reduced risk of the combination of the primary study end points of CV death, MI and stroke, as well as a decreased risk of each of these end points separately. These data are presented in Table 4.

Clopidogrel was subsequently shown to be superior to ticlopidine, while both prasugrel and ticagrelor were superior to clopidogrel (Table 4). Ticagrelor inhibits platelet aggregation in a dose-dependent manner (70, 71). All of ticagrelor, prasugrel and clopidogrel 600 mg were superior to clopidogrel 300 mg with respect to reducing the rates of major CV events (88). Ticagrelor was associated with superior antiplatelet effects during both the first hours of treatement as well as during maintenance therapy (78). Furthermore, non-responsiveness to clopidogrel can be overcome by ticagrelor (74). Effects of ticagrelor were similar between clopidogrel responders and clopidogrel non-responders (74). Clinical superiority of prasugrel over clopidogrel was more pronounced in patients with diabetes mellitus (66), while the superiority of ticagrelor over clopidogrel was more pronounced in patients with chronic kidney disease compared to patients with normal renal function (77).

b. Inhibition of Platelet Aggregation

One method used to compare the efficacy of antiplatelet agents is the inhibition of platelet aggregation (IPA). IPA is calculated as the

percentage of decrease in the maximal platelet aggregation (MPA) from baseline according to the formula $[1-(MPA_t/MPA_0)]x100\%$ (89).

Using patients with coronary arterial diseases, Nawarskas and Snowden calculated a maximum IPA with 20 µmol/L ADP (agonist) after loading dose (LD) of 30-50% for clopidogrel, 75-80% for prasugrel and 80-90% for ticagrelor (21). The time to maximum IPA was 4-8h for clopidogrel, 2-4h for prasugrel and 2-4h for ticagrelor (21). In healthy volunteers (18-65 years of age) who weren't taking aspirin, the maximum IPA with 20 µmol/L ADP after LD was 35±24.5% for clopidogrel and 78.8±9.2% for prasugrel. The time to maximum IPA was 4h for clopidogrel and 1h for prasugrel (89). Prasugrel was found to have a superior IPA profile to clopidogrel at therapeutic doses, with lower inter-patient variability in terms of platelet inhibition, as well as fewer patients considered poor responders or hyporesponders (63). Prasugrel generally achieved a faster and higher IPA than clopidogrel (17, 89, 90). Similarly, IPA was greater and maximum IPA was achieved faster in ticagrelor patients compared to clopidogrel patients (72). Ticagrelor further induced IPA in patients with poor response to clopidogrel, as well as inducing further IPA in patients who responded to clopidogrel (71). Ticagrelor was associate with a lower prevalence of high on-treatment platelet reactivity compared to clopidogrel ($p<0.0001$) in the combined data from the ONSET/OFFSET and RESPOND clinical trials, which can help explain the lower incidence of CV adverse events observed in ticagrelor patients compared to clopidogrel patients (91).

c. Interindividual Response Variability

The effectiveness of antiplatelet drugs to reduce ischemic events after ACS is modulated by interindividual response variability to the antiplatelet agents themselves, non-compliance, progression of atherosclerosis and a modest IPA response. As a relatively high incidence of non-responsiveness and ADRs is encountered, proper optimization of treatment is becoming a priority for physicians. Drug discontinuation can be responsible for a recurrence of CV events and adverse outcomes. This is applicable for all platelet inhibitors but particularly for ticagrelor due to its rapid onset and offset of antiplatelet action. The IPA for ticagrelor is lower than that seen for clopidogrel 48h after taking the drug. For instance, the IPA with ticagrelor after 72h is only 20%, similar to the IPA for clopidogrel 5-7 days post-dose (21, 72, 92).

Generally, lack of adherence can lead to resistance to platelet inhibitors, decreasing their activity and increasing the risk of ADRs. Two ways to define clopidogrel resistance on platelet function testing have been proposed (93). The first of these recognizes a poor response to clopidogrel treatment and is assessed by a change in ADP-induced platelet reactivity compared to baseline, while the second is high on-treatment platelet reactivity (93). Gurbel et al. define drug resistance as an absolute difference between baseline aggregation and post-treatment aggregation of ≤10% with 5 µmol/L ADP (agonist) (94). Around 30% of patients treated with clopidogrel do not achieve sufficient platelet inhibition (95). High on-treatment platelet reactivity describes suboptimal IPA achieved after administration of clopidogrel LD. It is associated with the occurrence of thrombotic events following PCI, and can often be attributed to interindividual variability (96). Clopidogrel resistance is mediated by a combination of pharmacokinetic, pharmacodynamic and pharmacogenetic factors. Different elements can influence patient response to clopidogrel, including environmental, medical or genetic factors, all of which depend on adherence to therapy, age, body mass index and presence of diabetes mellitus, as well as drug and dietary inhibition of hepatic metabolism (97). For instance, diabetic and obese individuals are more likely to be poor clopidogrel responders and to develop sensitivity to ADP (93).

d. Pharmacogenetics

Patient variability first comes into play during intestinal absorption, which may be modified by the P-glycoprotein ABCB1. A C3435T single nucleotide polymorphism in the gene encoding for this efflux transporter may significantly reduce clopidogrel absorption, at either 300 or 600 mg LD. Not surprisingly, homozygous carriers of this polymorphism were found to suffer from increased rates of CV adverse events (98). A greater focus is placed upon the genes responsible for the metabolism of platelet inhibitors, as loss-of-function (LOF) mutations in these genes are important determinants of drug reactive metabolite availability, drug resistance and the incidence of CV adverse events (93). Around 30% of clopidogrel patients have poor responsiveness to this treatment (94, 95). Clopidogrel poor responsiveness is due to its complex pharmacokinetic and pharmacodynamic profile, with a considerable implication of CYP2C19 (95).

CYP2C19 is the main drug-metabolizing enzyme responsible for the formation of ticlopidine and clopidogrel active metabolites. CYP2C19 polymorphisms lead to decreased functional activity and affect the pharmacokinetic profiles, as well as the pharmacodynamic responses to these thienopyridines (99). CYP2C19*2 and *3 alleles are associated with reduced prodrug metabolism, resulting in decreased levels of the active metabolite and a consequent lack of $P2Y_{12}$ inhibition. Conversely, CYP2C19*17 is associated with increased metabolism (100). Genetic variations were found to lead to a lack of response to treatment in a recent study (101). A poor metabolizer genotype is defined by two LOF alleles. This genotype occurs in 2-14% of the population, and it is highly dependent on ethnicity (102, 103). Intermediate metabolizers have only one LOF allele. This genotype is more common in the population (30-60%), and its incidence also varies based on one's ethnic background (102, 103). The frequency of the *2 LOF allele is higher in Asians (30%), African Americans (18%) and Caucasians (13%). The less common *3 LOF allele is also more wide-spread in Asians (10%). The incidence of the *17 gain-of-function (GOF) allele is higher in Caucasians and Ethiopians (18%), and low in Asians (4%) (104). Consequently, the distribution of poor metabolizers (i.e. *2/*2 or *3/*3 homozygotes, as well as *2/*3 compound heterozygotes) is more predominant in Asian populations (10-25%), and to some extent in Caucasians (3%) and Africans (4%) (104). Gurbel et al. observed that 31% of clopidogrel patients experienced insufficient platelet inhibition after five days of treatment and 15% after 30 days (94). A recent meta-analysis revealed that both LOF, as well as GOF mutations, have the potential to influence the pharmacological response to clopidogrel. Heterogeneity across studies makes it hard to draw a definitive conclusion (105), although inter-individual variability is a clinical issue that needs to be addressed (106).

CYP2C9 also decreases the activity of clopidogrel with respect to platelet inhibition. Both CYP2C19 and CYP2C9 play a role in clopidogrel resistance (104, 107, 108). Diminished clopidogrel effect (109) and higher rates of CV adverse events (98) were observed in individuals with two CYP2C19 LOF alleles. On the other hand, GOF mutations are associated with a decreased incidence of CV adverse events but an increased risk of bleeding (105). Based on limited consensus with respect to the influence of one's CYP2C19 genetic status, genotyping is not currently recommended prior to commencing antiplatelet treatment (110). Although switching to another platelet inhibitor is one solution to bypass pharmacogenetic barriers, the same observation is valid for all antiplatelet agents whose metabolism is mainly dependent on CYP2C19 activity. Nonetheless, it was demonstrated that prasugrel metabolism is affected by gene variability to a lesser degree, owing to its one step metabolism and the relatively minor implication of CYP2C19 (99, 101).

Although to a lesser extent, thienopyridines are substrates of CYP3A4 and CYP3A5, and can thus be involved in drug-drug interactions with inhibitors (e.g. ketoconazole) or inducers (e.g. rifampicine) of these enzymes (24). The non-expressor CYP3A5*3 allele was associated with increased rates of atherothrombotic events, as well as a higher risk of drug-drug interactions with other CYP3A4 substrates as more of the drug is shunt through this pathway (111). An increase in the clopidogrel LD (900 mg) at the beginning of the treatment can improve its efficacy, yet this was valid only in heterozygous carriers of the LOF allele (103, 112, 113).

The liver esterase paraoxonase-1 is also implicated, with the Q192R polymorphism associated with more efficient clopidogrel bioactivation and increased clinical activity. Alternatively, a QQ192 homozygous genotype is associated with a high level of stent thrombosis, as this enzyme is a key factor associated with antiplatelet activity following clopidogrel administration (114).

CYP polymorphisms are less of an issue with regards to ticagrelor metabolism as the parent drug is already active and CYP2C19 is not involved in its biotransformation.

IV) Adverse Drug Reactions

Any substances able to produce a therapeutic effect can also provoke unwanted ADRs. The World Health Organization defines an ADR as "*a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function*". It is alternatively defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" (115). There are two main types of ADRs. Type A ADRs give rise to predictable reactions. They are dose-, time- and frequency-dependent and host-independent. On

the other hand, type B ADRs are unpredictable reactions independent of the dose, time and frequency of treatment. Type B ADRs are host-dependent (115, 116).

Clopidogrel is associated with ADRs due to its complex pharmacogenetic and pharmacokinetic profiles. The vast majority of ADRs associated with antiplatelet drugs are well-characterized in the clinical trials that assessed the efficacy and toxicity of these agents. The incidence of ADRs varies with respect to the medication regimen being investigated, as well as the characteristics of the population being assessed. The main findings of the clinical trials assessing the safety of platelet inhibitors are described in detail in Table 5. The main ADR associated with platelet inhibitors is bleeding, while close to 1% of patients exposed to clopidogrel develop severe allergic, hematologic and hepatologic ADRs (117). Other severe ADRs identified in relations to clopidogrel include diarrhea, upper gastrointestinal (GI) discomfort, intracranial hemorrhage and GI hemorrhage (42, 118). GI tract bleeding (incidence 2-3%) is a particularly problematic ADR associated with platelet inhibitors (119-121).

While a relatively wide array of ADRs was identified in the CAPRIE trial, the first study to assess the antiplatelet effect and the safety of clopidogrel in patients with atherosclerotic vascular disease, the incidence of severe ADRs was rare and comparable between patients randomized to receive either clopidogrel or aspirin (42). Risk factors for clopidogrel-associated toxicity include documented coronary disease, documented cerebrovascular disease, or documented symptomatic peripheral arterial disease (53). As the safety and efficacy of this new thienopyridine derivative was shown, future studies have focused on the safety and efficacy of clopidogrel in combination with aspirin, compared to placebo and aspirin. Clopidogrel was associated with an increased risk of bleeding in the CURE trial (43-45). With the exception of the CURE trial, similar rates of bleeding between clopidogrel and placebo were observed in most studies comparing these two regimens. Furthermore, a higher risk of bleeding was observed for the combination of clopidogrel and aspirin, compared to placebo and aspirin (54). A recent study shows that the risk of bleeding observed with clopidogrel is dose-dependent (56, 57), while a smaller study failed to confirm this association (55). Nonetheless, clopidogrel and aspirin remains the standard treatment in ACS patients.

Ticlopidine is associated with a risk of life-threatening blood dyscrasias, including thrombocytopenic purpura, neutropenia/agranulocytosis and aplastic anemia (28, 122). Other ticlopidine ADRs include GI intolerance, skin rash and severe hematologic side effects. Neutropenia and thrombocytopenic purpura was also observed. Thus, monitoring blood counts is recommended every two weeks for the first three months after initiating ticlopidine treatment (117). Previously, based on the findings of Müller et al. (58) as well as those from CLASSICS (59) and TOPPS (60), clopidogrel was shown to have a more favorable safety profile than ticlopidine, with an equal or better therapeutic potential (60). Ticlopidine is thus not used as first-line treatment due to its relatively poor safety profile. However, ticlopidine can be an important second-line drug in patients who discontinue clopidogrel treatment due to poor responsiveness, poor metabolism or hypersensitivity syndrome reactions (HSR). In this case, this is a commonly used approach to reduce risk of thrombosis after a stent implantation (123). Ticlopidine should also be reserved for patients who are intolerant or allergic to aspirin or those who have failed aspirin therapy, and as adjunctive therapy with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation (28).

The safety of clopidogrel was further compared to that of the third generation thienopyridine derivative, prasugrel. While bleeding events were found to be relatively infrequent (65), findings of the TRITON-TIMI 38 clinical trial point to an increased risk of bleeding in prasugrel patients, compared to clopidogrel patients (63, 64, 66). It is interesting to note that these differences were found in the larger populations only, while being absent in subpopulations undergoing PCI (61, 68). Serious bleeding was associated with female sex, use of GP IIb/IIIa inhibitors, duration of intervention, age >75 years old, body weight <60 kg, and admission diagnosis of STEMI, femoral access for angiography, creatinine clearance, hypercholesterolemia and arterial hypertension (124, 125). However, the principal finding of the TRITON-TIMI 38 clinical trial was that prasugrel is preferred to clopidogrel due its superior benefit in reducing ischemic events (63, 126) and reduced mortality ($p=0.025$) (69). Prasugrel is contraindicated in patients with a history of stroke or ischemic attacks (97, 127).

The PLATO study was an international, randomized, double-blind clinical trial comparing

the safety and efficacy of clopidogrel and ticagrelor in a large cohort of ST segment elevation ACS patients with scheduled primary PCI, as well as non-ST segment elevation ACS patients (128). Bleeding was observed in ticagrelor patients, yet most reports show similar rates between ticagrelor and clopidogrel. Furthermore, there were similar rates of major bleeding, fatal bleeding or non-coronary bypass-related major bleedings in patients with chronic kidney disease and patients with normal renal function in the PLATO cohort (77). Dyspnea, defined as shortness of breath either during exercise or at rest, is recognized as the major non-hematological ADR of ticagrelor (21). The incidence of dyspnea was found to be higher in ticagrelor patients, compared to either clopidogrel or placebo (20, 72, 73, 75). There is a dose-response relationship between ticagrelor treatment and dyspnea (21, 70, 73). In the PLATO trial, the incidence of dyspnea was almost 2-fold higher in ticagrelor patients compared to clopidogrel patients (75). Dyspnea often occurs during the first week of ticagrelor treatment, with most cases lasting less than 24 h, and some lasting up to a week (70, 73, 75). Most cases of dyspnea recorded in the ONSET/OFFSET and the PLATO trials were characterized as mild or moderate (21). Dyspnea was not associated with changes in cardiac or pulmonary function in the ONSET/OFFSET trial (73). Another ADR associated with ticagrelor was asymptomatic ventricular pauses (70, 83).

Clopidogrel may also induce hematotoxicity, characterized by anemia, thrombocytopenia, neutropenia and/or agranulocytosis. Recently, bone marrow toxicity was described in an *in vitro* model of human umbilical cord blood. Both parent drug and metabolites were toxic towards myeloid progenitor cell (129).

An interesting alternative to dual-treatment is triple therapy with aspirin, clopidogrel and cilostazol. This phosphodiesterase III inhibitor antiplatelet drug has been shown to be effective, particularly in patients suffering from diabetes mellitus, who have been shown to be generally poorer responders to clopidogrel than patients not suffering from this co-morbidity. Cilostazol was shown to be safe, as it carries no increased risk of bleeding, thus providing a treatment alternative for patients at risk of bleeding or those who cannot receive alternative antiplatelet agents (130).

V) Hypersensitivity Syndrome Reactions

HSRs are examples of type B ADRs. Cases of HSR associated with antiplatelet medication are rarely reported in clinical trials. However, several case reports describe clopidogrel cutaneous HSR. A "true" HSR is defined by the triad of fever, rash and internal organ involvement (131). Around 6% of clopidogrel patients develop HSR (132). Cutaneous reactions are the most common type of allergic reactions associated with clopidogrel exposure (42), while rash is the most common manifestation of cutaneous HSR associated with antiplatelet agents, occurring in approximately 4% of ticlopidine patients and 5% of clopidogrel patients (117, 123, 133). Allergic ADRs are commonly referred to as HSRs, but HSRs concern both allergic and autoimmune mechanisms. Based on the definition proposed by Gell and Coombs in 1963, HSRs are undesirable reactions of the normal immune system, and include allergies and autoimmunity. These damaging, uncomfortable, or occasionally fatal reactions require a pre-sensitized (immune) state of the host (134). Clopidogrel HSR case reports often concern people requiring chronic daily use of clopidogrel. Allergic dug HSRs are classified as type I allergic reactions (135).

The exact incidence of clopidogrel HSR is not known, but it has been observed in 1-6% of the population (132). The incidence of clopidogrel HSR was 1.6% in a large sample of 3877 PCI patients. This was even higher in older patients (≥60 years), but that may be so because the elderly are the target population for this drug (118). The initial phase of the reaction was identified after a mean period of 5 days, with 3 main cutaneous presentations. Of the 62 probable/definite clopidogrel HSR cases observed, 49 (79.0%) were characterized as generalized, pruritic, exanthematous rash, affecting predominantly the trunk, with or without involvement of the upper and lower extremities, a further 10 (16.1%) patients developed rash localized in a focal or symmetrical manner, while the remaining 3 (4.8%) cases involved symptoms and signs of angioedema, with swelling of the tongue and lips, or generalized urticaria (118). Time to onset varied with clinical severity, such that the more severe cases of generalized, pruritic, exanthematous rash were observed after a longer mean period of time. Time to onset and severity of reaction were not dependent on the clopidogrel LD used (118). A relatively low incidence of cutaneous clopidogrel HSR (0.7% of 2701 patients undergoing PCI) was noted in another study. The onset of skin HSR was observed after a mean period of 4.5 days following clopidogrel initiation (136).

Clinical and histological data, as well as results of skin testing, suggest that clopidogrel

HSRs can be of two types, the first of which is a delayed, lymphocyte-mediated immune reaction with cutaneous symptoms, while the other is an immediate HSR with angioedema and urticaria (118). The mechanism of clopidogrel HSR was describe by Nakamizo et al., who report a case of generalized exanthematous pustulosis and fever developed secondary to clopidogrel exposure (137). Laboratory investigation revealed leukocytosis (12.9×10^9/L), with elevated eosinophils (0.13×10^9/L) and neutrophils (10.9×10^9/L), as well as C-reactive protein (66 mg/L) levels. Histologically, neutrophil infiltration, edema and spongiosis were observed, as well as eosinophils in the deeper layers. Based on these findings, T cell involvement is suspected, with $CD4^+$ T helper response (Th) 17, IL-17, IL-8 and neutrophils observed. A drug lymphocyte stimulation test was positive for clopidogrel, with increased IL-17A and IL-17F levels showing a Th17 response. IL-17 induces IL-8 production, which in turn attracts neutrophils (137). Use of β-blockers has been identified as a risk factor for developing clopidogrel cutaneous HSR (138).

a. Cutaneous Hypersensitivity Syndrome Reactions

Several cases of cutaneous clopidogrel HSR have been reported in the literature, the most common feature of which was rash, including maculopapular pruritic rash (133, 139), erythematous papular rash (140), generalized pruritus (141-145), diffuse rash (146) and urticarial rash (147-150). Symptoms occurred 1 day-3 weeks after initiating treatment with clopidogrel (140, 143, 146, 149, 151, 152). Other symptoms can include fever, hives, severe itching, swelling, angioedema, neutropenia, thrombocytopenia, lymphopenia, aseptic leukocyturia, tachycardia, rigors, abdominal pain, nausea, vomiting, as well as elevated aminotransferase, amylase and γ-glutamyltranspeptidase levels (141, 142, 144, 145, 147, 148, 150, 151). Worsening of cutaneous symptoms is observed after rechallenge with the same drug (151).

Although prasugrel represents a good alternative to clopidogrel, allergic reactions have been recently observed. Cutaneous features include generalized pruritic maculopapular eruption (153), pruritic maculopapular exanthematous rash (154) and extensive pruritic maculopapular rash (155). Symptoms occurred between 2 days-1 week of initiating prasugrel treatment (153-155).

b. Cross-reactivity

Antiplatelet treatment is required in patients with ACS in order to prevent stent thrombosis. While treatment interruption is contraindicated, substituting one platelet inhibitor for another is one of the treatment alternatives available for patients who develop HSR. However, clopidogrel has the potential for allergic cross-reaction with ticlopidine and prasugrel (117, 118, 132, 156) due to a similar molecular structure. Cheema et al. observed a high level of cross-reactivity in a sample of 42 immediate-onset clopidogrel HSR patients (23.8% with ticlopidine, 16.7% with prasugrel and 7.1% with both) (118).

Cross-reactivity between ticlopidine and clopidogrel is most common, as these two platelet inhibitors have been on the market the longest. Lokhandwala et al. observed a relatively high incidence of cross-reactivity among patients who switched to ticlopidine following clopidogrel HSR (14 of 52 (26.9%) patients) (123). In instances of cross-reactivity, the type of ADR developed while receiving ticlopidine was similar to the initial ADR that prompted clopidogrel discontinuation (123). Switching to ticlopidine led to reoccurrence of rash in two patients who have interrupted clopidogrel treatment due to this ADR. Ticlopidine was interrupted as well, while one patient redeveloped the rash after reinitiating clopidogrel treatment (133). It is also interesting to note that no matter which thienopyridine is taken first, cross-reactivity with other thienopyridines can occur.

An additional downside of switching clopidogrel with ticlopidine is the more extensive toxicity profile associated with the latter. For example, the use of ticlopidine is not recommended in patients who develop severe hematological ADRs while on clopidogrel, or in patients with baseline hematological abnormalities (117). Ticlopidine was well-tolerated in the short term, yet it was not recommended in a 77 year-old woman with a history of clopidogrel rash and pre-existing neutropenia (151). Another case report of cross-reactivity describes a 58 year-old man who was switched to ticlopidine following the development of clopidogrel rash, yet developed severe diarrhea while taking the first generation thienopyridine (146). There are also reports in which ticlopidine was safely substituted in place of clopidogrel. Ticlopidine was administered safely in place of clopidogrel in two patients with clopidogrel cutaneous HSR (148, 149). Tolerance to ticlopidine was observed in an 81 year-old male patient with clopidogrel generalized pruritus, erythema and desquamation (143).

Guidelines for managing patients with UA/NSTEMI or STEMI from the American College of Cardiology Foundation/American Heart Association recommend prasugrel as an alternative to clopidogrel (157). Knowledge about cross-reactivity between clopidogrel and prasugrel is more limited, due to exclusion from prasugrel clinical trials of patients with a history of drug allergy to ticlopidine and/or clopidogrel (117). It is still relatively soon to observe allergic reactions and cross-reactivity with this third generation thienopyridine, even though some cases of prasugrel HSR are reported in the literature. For example, Raccah et al. describe a case of prasugrel rash in a patient with a history of clopidogrel itching cutaneous rash (155). On the other hand, clopidogrel was well-tolerated and efficient in a patient with prasugrel-induced drug-HSR and a history of clopidogrel treatment. Interestingly, this patient has previously shown poor response to clopidogrel (156). Prasugrel was well-tolerated in two patients with an allergic reaction to clopidogrel (145, 152). Both prasugrel and ticlopidine were well-tolerated in a patient with a history of clopidogrel Stevens-Johnson syndrome (158). However, cases of Stevens-Johnson syndrome are rarely reported in relation to clopidogrel (159), whereas toxic epidermal necrosis was not associated with clopidogrel use (160).

As thienopyridines have been shown to provoke similar types of ADRs, clopidogrel could be switched with a different class of platelet inhibitors, such as ticagrelor. However, this cyclopentyl triazolopyrimidine antiplatelet agent is relatively new, and even though cases of ticagrelor HSR have not yet been reported, the possibility of cross-reactivity with the older thienopyridines cannot be ruled out.

c. Desensitization Protocols

Premature discontinuation of antiplatelet treatment following stent implantation is recognized as the main risk factor for developing thrombotic events, particularly stent thrombosis (4, 117, 155, 161). For instance, Iakovou et al. showed that 29% of patients who discontinued their treatment prematurely after drug eluting stent implantation develop stent thrombosis (162). This is particularly problematic in the days immediately following stent implantation, which coincides with the time frame in which most drug-associated HSR cases occur (151). Higher rates of rehospitalization, coronary stent thrombosis and mortality have been associated with clopidogrel non-adherence and discontinuation (4). Moreover, this treatment often concerns elderly patients (≥65 years-old). Elderly patients may experience changes in their capacity to metabolize drugs (renal, hepatic, physiological and/or pathological dysfunction). In addition, due to polymedication, the frequency of ADRs is higher in this population than it is in younger individuals (121, 163). Around 40% of patients ≥65 years of age usually take more than five drugs. Therefore it is difficult to monitor their treatment, and polymedication is recognized as a risk factor for developing ADRs (164). Furthermore, the potential for cross-reactivity among chemically-related thienopyridines described in the previous section highlights the need for an alternative avenue to deal with clopidogrel HSR. To avoid such consequences, some physicians may decide to practice desensitization on patients with clopidogrel cutaneous HSR (excluding Stevens-Johnson syndrome/toxic epidermal necrolysis). Desensitization is recommended in patients with cutaneous HSR symptoms to clopidogrel, in which no treatment alternative is available. Different protocols are being tested.

Desensitization is possible since allergic clopidogrel cutaneous HSRs are immunoglobulin E (IgE)-mediated (135, 139, 153). Camara and Almeda describe a protocol inspired from antibiotic desensitization, using escalating doses of clopidogrel (0.005-75 mg) administered at 30 min intervals (135). This desensitization protocol was used successfully in 3 patients with clopidogrel cutaneous HSR and ticlopidine intolerance (135). Walker et al. describe a similar desensitization protocol using escalating doses of clopidogrel, administered at 15 min intervals, with doses between 0.02-45 mg (165). The full dose of 75 mg is administered the following day. Patients are monitored for HSR symptoms. Ticlopidine is not considered a viable alternative due its relatively poor safety profile and high degree of cross-reactivity to clopidogrel (165). Clopidogrel desensitization over a 7h period using doses from 0.005 mg to the full 75 mg tablet was successful in a cohort of 24 patients with clopidogrel HSR. The allergic reaction persisted in 4 patients during the desensitization period. However, desensitization was successful in all 24 patients, with 2 patients requiring repeat desensitization (166). Doses between 0.005-75 mg were administered over a 7h interval in two other patients with clopidogrel cutaneous HSR (139, 144).

Doses between 0.0005-75 mg were administered over an 8h interval in a patient with clopidogrel rash and ticlopidine intolerance (146). Fajt and Petrov (138) describe a similar

desensitization protocol, in which the patient is allowed to go home between sessions, over a 2-3 days period. The protocol involves increasing doses of clopidogrel being administered in solution (138). Another patient was successfully desensitized to both aspirin and clopidogrel, using escalating doses, after developing similar cutaneous HSR to both drugs (150).

Because prasugrel allergy is also IgE-mediated, prasugrel desensitization was performed in a patient with generalized pruritic maculopapular eruption, using escalating doses ranging from 0-60 mg administered at 30 min intervals over a period of 7h. The patient was subsequently able to tolerate prasugrel (153).

d. Suppressive Therapy with Corticosteroids and Antihistamines

Short-course corticosteroids and antihistamines can be used to create physiological tolerance in patients with clopidogrel HSR, thereby preventing drug discontinuation in this population (132). A wash out period is often necessary in patients undergoing clopidogrel desensitization, yet it is undesirable. Cheema et al. observed a resolution rate of 95.2% after a mean period of 5 days since initiating prednisone treatment (30 mg/day for 5 days, followed by doses decreasing every 3 days for 15 days) in a cohort of 62 cutaneous clopidogrel HSR patients. Diphenhydramine (25-50 mg 3-4 times/day) was used in patients with pruritus (118).

Use of antihistamines and steroids is recommended only in cutaneous clopidogrel HSR in patients treated with dual aspirin plus clopidogrel therapy (136). Prednisone (30 mg/day for 5 days) and chlorpheniramine (4 mg 3 times/day for 7 days) is the standard treatment used. Resolution is noted after an average of 3.2 days, usually with ≥90.0% resolution and continuation of clopidogrel treatment (136). Campbell et al. used corticosteroids and antihistamines in 25 patients with clopidogrel HSR developed after PCI. Suppressive therapy allowed symptoms resolution without treatment discontinuation in 22 (88.0%) patients (132). The importance of these studies is that short-course corticosteroids and antihistamines allow the management of clopidogrel HSR without treatment interruption, providing protection against CV adverse events (118, 132, 136, 155, 161).

Steroids and antihistamines led to improvement of clopidogrel cutaneous HSR (142, 147, 148), as well as prasugrel rash symptoms (155). Intravenous solumedrol and antihistamines were administered in a patient with clopidogrel maculopapular urticarial rash in which previous treatment with prednisone and antihistamines did not achieve relief from HSR symptoms (149). Intravenous methylprednisolone and antihistamines were also successfully used in a patient with clopidogrel erythematous papular rash who was initially unresponsive to antihistamines (140). Symptoms persisted for over 2 weeks despite corticosteroids and antihistamine treatment in a patient with erythematous and pruriginous symptoms (143). In a separate report, additional antihistamines were successful in treating pruritus in a patient who previously underwent partially successful clopidogrel desensitization with escalating doses of the drug (166).

e. Alternatives: The Lymphocyte Toxicity Assay

The lymphocyte toxicity assay (LTA) is an in vitro test that can be used to diagnose and predict drug HSR (167). This laboratory tool is based on the principle that human lymphocytes in vitro mimic functional cells in vivo. Therefore, lymphocytes from patients with a suspected HSR can be used as surrogate target cells for safe in vitro re-challenge. The LTA can be used to test toxicity of individual drugs, as well as additive effects of other pharmaceutical agents that might be prescribed together with or in place of the incriminated drug, thus uncovering potential drug-drug interactions or cross-reactivity. These cells are suitable as they possess the patient's genotype and express phenotypic variability in drug detoxification enzymes (116, 131, 167-170). Reactive metabolites of the drug believed to have caused the HSR can lead to mitochondrial damage and cellular apoptosis in susceptible patients. This assay measures drug toxicity in terms of cell viability, based on the reduction of the yellow MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diophenyl tetrazolium bromide] to a purple MTT formazan product by the mitochondria-specific succinate dehydrogenase, an indicator of mitochondrial function (167). Our laboratory has been performing LTAs for over 20 years, validating this technique for numerous anticonvulsants including carbamazepine, phenytoin, zonisamide and phenobarbital, as well as non-steroidal anti-inflammatory drugs and sulfonamide antibiotics (116, 131, 167, 169-171). Moreover, our laboratory is in the process of performing LTA on clopidogrel patients, with the hope of safely diagnosing clopidogrel HSR, as well as checking for potential prasugrel or ticagrelor cross-reactivity (Neuman MG, unpublished data). Once a drug is identified as the culprit agents using the

diagnostic potential of the LTA, a safe alternative can be found using the assay's predictive power.

f. Drug Induced Liver or Renal Hypersensitivity

Although the most common clopidogrel HSRs comprise of cutaneous manifestations, some studies report HSR-associated hepatic toxicity and renal toxicity. Elevated hepatic enzyme levels (usually aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) and high fever have been reported in relation to clopidogrel use. Chills and white blood cell increases have been observed. Abnormal liver function is observed in approximately 3% of patients receiving clopidogrel (42, 172). In most of these cases, improvement in liver transaminase levels and return to liver function baseline is observed upon clopidogrel discontinuation. The onset of symptoms is often reported within the first week of treatment (mean time 5 days) (118). Goyal et al. report the case of an elderly patient who developed hepatocellular injury and cholestatic jaundice 3 weeks after starting clopidogrel treatment (173). The patient experienced AST (179 U/L), ALT (234 U/L), alkaline phosphatase (1011 U/L) and total bilirubin (7.3 mg/dl) elevations, as well as anemia and basal metabolic panel disruptions, but no hepatosplenomegaly (173). *In vitro* tests suggest T cells involvement in cholestatic hepatitis. Transient eosinophilia observed in two ticlopidine patients supports this hypothesis (174).

Tholl et al. report the case of a 46-year-old with MI who developed membranous nephropathy (stage II) without glomerular or tubule-interstitial scarring after 2 months of treatment with clopidogrel (175). His initial treatment included ticlopidine in combination with aspirin. All medication was stopped after GI complaints were reported, and clopidogrel was introduced after 16 months. Clopidogrel provoked non-selective proteinuria (11.5 g/day) with decreased creatine clearance (106 mL/min/1.73m²) and increased IgE (140 U/mL) and serum protein (45 g/day, containing 20 g/L albumin) (175).

A case of drug-induced HSR with fever (38.1°C) with elevated leukocytes 7.23×10^9/L (eosinophils 2.4%) and abnormal liver enzyme levels is describes after prasugrel (60 mg LD/10 mg MD) exposure in a patient with a history of clopidogrel treatment (156). The patient's fever persisted by day 23, while liver enzyme levels remained elevated. By this time, the leukocyte count returned within normal limits, yet the patient developed eosinophilia (eosinophils 9.7% at day 19). Symptoms improved following replacement of prasugrel with clopidogrel (156).

g. Hypersensitivity Syndrome Reaction and Viruses

Drug HSR has been been associated with transient immunosuppression, leading to reactivation of latent or opportunist viruses. Ghosh and Bandyopadhyay describe a human immunodeficiency virus (HIV)-negative 49 year-old woman presenting with hemorrhagic herpes zoster virus lesions during treatment with clopidogrel, and believe that clopidogrel caused thrombocytopenia, which in turn was responsible for the hemorrhagic herpes zoster virus lesions (176).

VI) Drug Interactions

Platelet inhibitors take part in drug-drug interactions as results of enzyme induction or inhibition, particularly as the target population of this type of medication is generally polymedicated (163). The main classes of drugs involved in drug-drug interactions with platelet inhibitors are PPIs, statins, CCBs and antibiotics. Interactions with HIV antiretroviral drugs are briefly touched upon.

a. Proton Pump Inhibitors

Long-term dual-therapy with aspirin and platelet inhibitors has the potential to cause GI bleeding. For this reason, PPIs and H2 antagonists are commonly administered in patients treated with platelet inhibitors. In particular, PPIs offer long-lasting inhibition of gastric acid production (31, 177). These drugs are generally recognized as CYP2C19 inhibitors, an enzyme involved in clopidogrel metabolism (178, 179). PPIs and clopidogrel will thus compete for the same drug-metabolizing enzyme, such that PPIs may alter the metabolism of the thienopyridine and the bioavailability of its active metabolite, leading to a higher risk of developing CV adverse events (179). The main PPI involved in drug-drug interactions with clopidogrel is the CYP2C19 inhibitor omeprazole, while an interaction with esomeprazole was also noted. Clopidogrel patients are advised to avoid these agents (31, 124). Several studies have assessed the consequences of combining PPIs with clopidogrel, often with contrasting results.

The combination of clopidogrel and either omeprazole or esomeprazole was associated with a significantly higher risk of developing new CV adverse events in a case-control study, compared to clopidogrel alone (179). Similarly, a recent meta-analysis showed the potential for increased

rates of CV adverse events and MI in patients taking concomitant clopidogrel and PPIs, with an increase in mortality. However, a high degree of heterogeneity was noted in the reviewed data (180). Use of PPIs following acute MI was associated with reinfarction in a large population-based nested case-control study. However, this was observed only for PPIs with CYP2C19 inhibitory potential, while the use of pantoprazole, a PPI that is not a substrate of CYP2C19, had no significant effect (181). In the PRINCIPLE-TIMI 44 trial, concomitant use of high-dose clopidogrel and PPIs was associated with a lower mean IPA compared to no PPI use in a relatively small sample. No interaction was found between PPIs and prasugrel (182). Furthermore, the interaction between PPIs and clopidogrel or prasugrel was deemed not significant in terms CV death, non-fatal myocardial infarction, or non-fatal stroke in the TRITON-TIMI 38, suggesting that concomitant treatment with PPIs and thienopyridines is acceptable in patients requiring it (182).

Omeprazole and esomeprazole decrease the efficacy and safety of clopidogrel (179). A metabolic interaction between clopidogrel and the strong CYP2C19 inhibitor omeprazole was shown in a sample of healthy individuals, with the PPI (80 mg) decreasing the $AUC_{0\text{-}24h}$ of clopidogrel's active metabolite by 40% when administered concomitantly, by 47% when administered 12h apart, by 41% when a double clopidogrel dose (600 mg LD/150 mg MD) was used and by 14% when pantoprazole was used instead of omeprazole. The maximal platelet aggregation induced by 5 μmol/L ADP was significantly increased (183). Omeprazole further decreases the IPA of clopidogrel by 21% when clopidogrel was administered at MD (27) and increases the rate of clopidogrel non-responsiveness (184). Lanzoprazole decreased the C_{max} of prasugrel's active metabolite by 29%. AUC and T_{max} of the active compound were not altered (29). Pantoprazole was shown to interfere with clopidogrel metabolism to a lesser degree, and it could thus be used as a safer alternative (10, 35). Pantoprazole had no effects on the pharmacokinetic profiles of clopidogrel and its active metabolite (183).

In contrast, the rate of major CV adverse events was found to be comparable between patients not exposed to PPIs and patients exposed to either omeprazole, esomeprazole, lansoprazole, pantoprazole or rabeprazole in 4 separate cohorts of clopidogrel patients compared to clopidogel use alone (185, 186). Similarly, use of PPIs was not associated with serious CV diseases in another large cohort study. Interestingly, only a small fraction of this population was co-exposed to the CYP2C19 inhibitor omeprazole, while the majority of patients took pantoprazole (187).

The clinical relevance of these findings remains debatable. Evidence of an interaction is based mostly on *in vitro* tests, while clinical studies frequently report contrasting outcomes, often based on the interaction between clopidogrel and PPIs as a whole (188). Nonetheless, some studies show that only specific PPIs interact with thienopyridines. Furthermore, PPIs themselves were found to have either harmful, neutral or protective effects in terms of CV adverse events, independent of clopidogrel use, which may further confound results (185, 189). High dose H2 antagonists are an alternative to PPIs that can be used to avoid drug-drug interactions with other CYP2C19 substrates (178).

b. Statins

Statins are a class of anti-cholesterol agents commonly used to reduce morbidity and mortality after coronary stent implantation, owing to their anti-inflammatory, anti-oxidative and anti-thrombotic properties (190, 191). CYP3A4 plays a major role in the metabolism and elimination of the lipophilic atorvastatin and simvastatin. As an inhibitor of CYP3A4, atorvastatin can inhibit clopidogrel metabolism in a dose-dependent manner, leading to insufficient platelet inhibition and an increased risk of CV adverse events (184). A similar interaction is not observed with hydrophilic statins, as they are not significant CYP3A4 substrates (10, 184). Thus, prescribing clopidogrel in combination with atorvastatin is contraindicated (10).

However, the possible interaction between clopidogrel and statins is controversial. Atorvastatin reduced the IPA of clopidogrel with 300 mg LD but not with 600 mg LD, while the effect of CYP3A4 polymorphism is unknown (184). Several *ex vivo* studies suggest that the use of statins, in particularly atorvastatin (192-194), simvastatin (194, 195) and fluvastatin (195), decreases the effect of clopidogrel, particularly during the loading phase. At the same time, other studies did not find interactions between clopidogrel and atorvastatin (195, 196), pravastatin (195, 196), rosuvastatin (195), simvastatin (196) or fluvastatin (196). Furthermore, atorvastatin does not interfere with the pharmacokinetics of prasugrel (35). On the other hand, ticagrelor increases the C_{max} of simvastatin by 81% and its AUC by 56% (30).

Nonetheless, hydrophilic statins present a safer alternative.

c. Ca^{+2} Channel Blockers

CCBs are often used to treat hypertension. Co-administration of these CYP3A4 substrates together with platelet inhibitors creates the potential for drug-drug interactions, decreasing responsiveness to the latter class (184). Once again, this is a controversial topic, as evidence is often contradictory. Co-administration of the moderate CYP3A4 inhibitor diltiazem increases the C_{max} of ticagrelor by 69% and its AUC by 2.7-fold, while decreasing the C_{max} of the active metabolite by 38% with no changes in its AUC (30). An *ex vivo* study on platelet function showed that CCBs can interfere with clopidogrel metabolism, leading to reduced levels of the active metabolite and impaired platelet inhibition (197). Decreased response to clopidogrel following co-administration of CCBs is also reported elsewhere (198, 199). On the other hand, no evidence was found that CCBs decrease the efficacy of clopidogrel one year after PCI in the CREDO trial (197). Based on these findings, Schmidt et al. suggest that co-administration of clopidogrel and CCBs is safe in patients undergoing PCI (200).

d. Antibiotics

Co-administration of the strong CYP3A4 inhibitor ketoconazole, a synthetic antifungal drug, is associated with a 2.4-fold increase in ticagrelor C_{max} and a 7.3-fold increase in AUC, while the C_{max} for the active metabolite was decreased by 89% and the AUC by 56% (30). Srinivasan and Smith describe the case of a male patient who developed suspected clopidogrel resistance following co-administration of the platelet inhibitor, aspirin and antimycobacterial treatment including rifampicin (CYP3A4 inducer), ethambutol and clarithromycin (CYP3A4 inhibitors) (201). The patient developed stent thrombosis within five days of treatment initiation, and it was hypothesized that these drug-drug interactions can reduce clopidogrel efficacy and induce resistance (201). There was also less exposure to the clopidogrel active metabolite and a subsequent reduction in IPA when ketoconazole was co-administered with clopidogrel (99).

e. Human Immunodeficiency Virus Antiretroviral Drugs

CV diseases are of concern for HIV-infected patients, as they represent more than 10% of deaths in this population (202). A possible drug-drug interaction was uncovered *in vitro* between prasugrel and ritonavir, a potent CYP3A4 and 2B6 inhibitor. However, more work is needed to evaluate long-term clinical risks (203).

VII) Poor Responsiveness: Evidence and Perspectives

In order to assess clopidogrel resistance, reliable assays that provide sufficient predictive value are needed. Platelet function testing and genetic testing can be used to identify individuals at risk of developing CV adverse events and to facilitate treatment changes. The mechanism of clopidogrel resistance involves modifications in the pharmacokinetics and pharmacodynamics of this drug. Therefore, it is important to monitor these data.

a. Personalized Medicine

The goals of personalized medicine are to maximize the therapeutic effects of a drug, while minimizing its toxicity (204). Personalized medicine is defined as the practice of tailoring therapeutic intervention to a patient's disease, demographic characteristics, genetics, environment, lifestyle and health status (205). There are many tools that allow physicians to uncover those factors that distinguish one individual for another, among which pharmacogenomics testing is of paramount importance. Dosing based on one's pharmacokinetic profile, as well as therapeutic drug monitoring (TDM), are other examples (204).

b. Therapeutic Drug Monitoring

The two main clinical reasons for which pharmacological response**s** to platelet inhibitors should be measured are that an insufficient inhibition of platelet function may result in atherothrombotic complications such as thromboembolic events, while excessive IPA may lead to bleeding complications. For these reasons, the appropriate identification of resistant or poor responders to platelet inhibitors remains challenging in the clinical practice. TDM may help facilitate these challenges. It requires knowledge about the patient's pharmacokinetic and pharmacodynamic profiles in order to assess the factors that mediate drug exposure (204). Specifically, *a priori* TDM is designed to prescribe the most adequate starting dose based on knowledge about the patient's pharmacokinetic and pharmacodynamic profiles, while *a posteriori* TDM assesses the adequacy of drug dosing based on measurements of drug concentration ranges in

blood or plasma (204). This section will provide a brief overview of the analytical tools that are used to measure plasma levels of platelet inhibitors and their metabolites. These measurements are used mainly for pharmacodynamic and pharmaco-kinetic determination. Pharmacodynamic measurements involve the examination of residual platelet function following drug administration. While thienopyridines require metabolic activation to exert their antiplatelet effect, both ticagrelor and its active metabolite possess pharmacological properties. Therefore, measuring both ticagrelor parent compound and active metabolite will have different implications for drug interactions.

Drug resistance, including resistance to antiplatelet drugs, defines a state in which the drug is unable to reach its pharmacological target (206). For this reason, laboratory methods used to evaluate the effects of antiplatelet drugs should be designed to measure the direct pharmacodynamic effect of a drug, rather than its consequences for global platelet function (206, 207). Based on pathophysiological, pharmacological and practical considerations, it seems logical to assess pharmacological inhibition of platelet function in terms of ADP agonist-induced platelet aggregation. As a result, responses induced by TXA_2 or arachidonic acid (light transmission aggregometry, whole-blood aggregometry) should be measured to assess the effects of aspirin, while vasodilator stimulated phosphoprotein (VASP) using flow cytometry or ADP-induced responses using light transmission aggregometry, whole-blood aggregometry, and possibly flow cytometry, should be measured for the detection of clopidogrel actions. However, it should be noted that while serum TXA_2 levels <2 ng/ml reflect aspirin-induced inhibition of COX-1 activity with high sensitivity, VASP exhibits a wide variability upon treatment with clopidogrel or prasugrel.

Most of these methods use a liquid chromatography/tandem mass spectrometry (LC/MS/MS) positive electrospray ionization method for the assay of clopidogrel in human plasma. Nirogi et al. separated the analytes using an isocratic mobile phase on a reversed-phase column and analyzed their products by MS with a linear dynamic range of 5-6000 pg/mL (208). Shin and Yoo described an LC/MS/MS assay validated to be linear over a concentration range of 10-10000 pg/mL (209). Clopidogrel was extracted by single liquid-liquid extraction with pentane, followed by chromatographic separations on a C_{18} column (209). Subsequently, Takahashi et al. also measured clopidogrel and its active metabolite in human plasma by LC/MS/MS, using the alkylating reagent 2-bromo-3'-methoxyacetophenone to stabilize the thiol group-containing active metabolite (38). An analog of the derivatized clopidogrel active metabolite was used as the internal standard. The calibration curve ranged between 0.5-250 ng/mL (38).

Farid et al. developed LC/MS/MS assays to quantify the active and three inactive metabolites of prasugrel (210). The analytes were detected and quantified with a triple quadrupole MS using positive electrospray ionization. The concentration range was 1-500 ng/mL for the inactive metabolites and 0.5-250 ng/mL for the active metabolite. Derivatization of the active metabolite in blood with 2-bromo-3'-methoxyacetophenone immediately after collection was essential to ensure the stability of the metabolite during sample processing and storage (210). Sillén et al. reported the pharmacokinetic analysis of ticagrelor employing LC/MS/MS (211). Teng and Butler reported the disposition and metabolism of ticagrelor in six healthy volunteers, using a single oral dose of ^{14}C radiolabeled ticagrelor (200 mg ticagrelor as a 10 g suspension, 222.7 kBq/g) (212). Blood samples, for the purpose of measuring total radioactivity in whole blood and plasma of ticagrelor and in plasma for its active metabolite AR-C124910XX, were collected pre-dose and at various time points up to 36h post-dose. Total ^{14}C radioactivity was determined by liquid scintillation counting in whole blood and plasma, with 25 dmp above background set as the limit of detection. In addition, ticagrelor and its metabolite concentrations in urine and plasma were analyzed using LC/MS/MS, with assay lower limits of quantification of 5.0 ng/mL for ticagrelor and 2.5 ng/mL for AR-C124910XX in plasma (212).

Light transmission aggregometry is the principal assay designed to assess clopidogrel resistance, which measured platelet aggregation in response to 20 μmol/L ADP stimulation. Residual platelet aggregation in excess of 50% of the baseline level is considered to predict clopidogrel resistance. The main limitation of this assay is that it provides no indication of the clinical tendency of the patient to develop thrombosis (93). In contrast, the point-of-care platelet function test offers more valuable information. This assay measures agglutination of fibrinogen-coated beads mixed with whole blood in response to ADP stimulation (213). The VASP platelet reactivity index, an assay designed to measure $P2Y_{12}$ activity, measures by flow calorimetry the activity of the VASP protein, which becomes phosphorylated in the presence of $P2Y_{12}$

stimulation. This assay has been successfully used to personalize the clopidogrel dose for improved clinical outcome (214). A modified Thrombelastograph assay provides continuous assessment of platelet function (215). However, these tests are not routinely recommended in patients undergoing PCI due to a relative lack of evidence. Such tests should be considered only if a patient is known to be at high risk of clopidogrel ADRs or resistance (93). Anderson et al. argue that a better way to follow the absorption and the metabolism of clopidogrel is to measure the C_{max} of the drug or its active metabolite (97).

CONCLUSION

Platelet inhibitors are common treatments for ACS patients. Thienopyridine drugs are widely used, particularly clopidogrel. However, the complex pharmacogenetic and pharmacokinetic profiles of clopidogrel lead to interindividual variability, which can increase the incidence of ADRs, including HSR. To overcome those issues, switching to alternative medicine or desensitization protocols can be considered. Even though not routinely used, genetic tests and platelet function assays can be particularly beneficial for high-risk patients or for those who have already developed an ADRs, as they can help predict tolerability and response to treatment. Newer drugs like prasugrel and ticagrelor present fewer problems, owing to their simpler mechanisms of activation and action. Both of these drugs have demonstrated better efficacy than clopidogrel, and even though they have a slightly less favorable safety profile, they are overall associated with better outcomes in ACS patients. New antiplatelet agents, such as the $P2Y_{12}$ inhibitors cangrelor and elinogrel, are tested (216), the latter of which was discontinued due to an unfavorable safety profile.

Preventable ADRs carry a substantial risk of morbidity and even mortality to the patient, while placing a high financial burden on the health system (217). Therefore, ACS patients receiving concomitant treatment with platelet inhibitors and other medication should be closely monitored for ADRs, drug-drug interactions and loss of drug efficacy. It thus becomes essential that the right drugs are administered to the right patients in order to avoid complications. Laboratory assays and *in vitro* tools provide useful methods to monitor medication efficacy and toxicity. While clinical trials provide valuable information about common ADRs, it remains vitally important that rare ADRs and drug-drug interactions are reported and make their way into pharmacovigilance databases, where they become available for health care providers and patients alike. TDM can help identify the patients who would benefit most from alternative treatments and personalized medicine.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare and have contributed equally in this research.

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Table 3. Clinical trials with platelet inhibitors

Clinical Trial (Ref. #)	Population Characteristics	Medication Compared	Medication Doses	Risk Factors and Medical History
CAPRIE (42)	19185 patients with atherosclerotic CV disease manifested as either recent ischemic stroke, recent MI or symptomatic peripheral arterial disease Mean age 62.5	Clopidogrel vs. aspirin	Clopidogrel (75 mg/day) Aspirin (325 mg/day)	History of ischemic stroke Transient ischemic attack/reversible ischemic neurological deficit Diabetes mellitus Hypertension Hypercholesterolemia Angina MI Congestive heart failure Cardiomegaly Atrial fibrillation Intermittent claudication Past or current smoking
CURE (43, 44)	6259 patients receiving clopidogrel plus aspirin 6303 patients receiving placebo plus aspirin Mean age 62.2	Clopidogrel plus aspirin vs. placebo plus aspirin	Clopidogrel (300 mg LD, 75 mg MD) plus aspirin (75-325 mg) Placebo plus aspirin (75-325 mg)	History of MI History of CABG/ percutaneous transluminal coronary angioplasty Stroke Heart failure Hypertension Diabetes Past or current smoking Aspirin Heparin Angiotensin-converting enzyme inhibitors β-blockers Calcium channel blockers Lipid-lowering agents Intravenous nitrate
PCI-CURE (45)	1313 patients with non-ST segment elevation ACS undergoing PCI receiving clopidogrel plus aspirin 1345 patients receiving placebo plus aspirin Mead age 61.5	Clopidogrel plus aspirin vs. placebo plus aspirin	Clopidogrel (300 mg LD, 75 mg MD) plus aspirin (75-325 mg) Placebo plus aspirin (75-325 mg)	Diabetes Previous MI Previous PCI Previous CABG Smoking

Table 3. Continued…..

CREDO (45)	2116 patients undergoing elective PCI Mean age 61.6	Clopidogrel plus aspirin vs. placebo plus aspirin	Clopidogrel (300 mg LD, 75 mg MD) plus aspirin (75 mg) Placebo plus aspirin (75 mg)	History of MI Stroke Peripheral vascular disease Diabetes Hypertension Hyperlipidemia Family history of CV disease Past or current smoker Aspirin β-blockers Statins Angiotensin-converting enzyme inhibitors Calcium channel blockers
CARESS (47)	107 patients with asymptomatic microembolic signals (indicator of future stroke and transient ischemic attack) at baseline Mean age 64.5	Clopidogrel plus aspirin vs. placebo plus aspirin	Clopidogrel (300 mg LD, 75 mg MD) plus aspirin (75 mg) Placebo plus aspirin (75 mg)	History of stroke Hypertension Diabetes Hypercholesterolemia Prior MI Prior coronary bypass Prior coronary stenting/angioplasty Peripheral artery disease Statin therapy Drugs acting on the renin-angiotensin system β-blocking agents Calcium channel blockers Peroxisome proliferator-activated receptor-γ agonists
CLARITY-TIMI 28 (48)	3491 patients with STEMI Mean age 57.5	Clopidogrel plus aspirin vs. placebo plus aspirin	Clopidogrel (300 mg LD, 75 mg MD) plus aspirin (75-162 mg) Placebo plus aspirin (75-162 mg)	Hypertension Fibrinolytic agents Aspirin Heparin (dispensed according to body weight) Prior lipid-lowering agents
PCI-CLARITY (49)	1863 patients undergoing PCI after mandated angiography Mean age 57.3	Clopidogrel plus aspirin vs. placebo plus aspirin	Clopidogrel (300 mg LD, 75 mg MD) plus aspirin (75-162 mg) Placebo plus aspirin (75-162 mg)	Hypertension Hyperlipidemia Current smoker Diabetes mellitus Prior MI Prior PCI Fibrinolytic agents and heparin

Table 3. Continued…..

ECG CLARITY-TIMI 28 (50)	2431 patients with STEMI with available electrocardiogram Mean age 57.5	Clopidogrel plus aspirin vs. placebo plus aspirin	Clopidogrel (300 mg LD, 75 mg MD) plus aspirin (75-162 mg) Placebo plus aspirin (75-162 mg)	Hypertension Diabetes Prior aspirin Prior lipid-lowering agents
COMMIT (51)	45852 patients with acute MI Mean age 61.3	Clopidogrel plus aspirin vs. placebo plus aspirin	Clopidogrel (75 mg) plus aspirin (162 mg) Placebo plus aspirin (162 mg)	Prior MI Hypertension Aspirin Fibrinolytic agents β-blocking agents Anticoagulants Antiarrhythmic agents Angiotensin-converting enzyme inhibitors Nitrate Diuretics Calcium channel blockers
CHARISMA (52, 53)	15603 patients with CV disease or multiple CV risk factors Mean age 64.0	Clopidogrel plus aspirin vs. placebo plus aspirin	Clopidogrel (75 mg) plus aspirin (75-162 mg) Placebo plus aspirin (75-162 mg)	Past or current smoking Hypertension Hypercholesterolemia Congestive heart failure Prior MI Atrial fibrillation Prior stroke Prior transient ischemic attack Diabetes Peripheral arterial disease Prior PCI Prior CABG
MATCH (54)	7599 patients with recent ischemic stroke or transient ischemic attack and at least one additional CV risk factor Mean age 66.3	Clopidogrel plus aspirin vs. clopidogrel plus placebo	Clopidogrel (75 mg) plus aspirin (75-162 mg) Clopidogrel (75 mg) plus placebo	Previous ischemic stroke Previous transient ischemic attack Previous MI Angina pectoris Symptomatic peripheral arterial disease Hypertension Diabetes mellitus Hypercholesterolemia Past or current smoker

Table 3. Continued…..

GRAVITAS (55)	2214 patients with high on-treatment platelet reactivity after PCI Mean age 63.7	Clopidogrel high-dose plus aspirin vs. clopidogrel standard-dose plus aspirin	High-dose clopidogrel (600 mg LD, 150 mg MD) plus aspirin (75-162 mg) Standard-dose clopidogrel (75 mg) plus aspirin (75-162 mg)	Diabetes mellitus Hypertension Hyperlipidemia Previous MI Previous PCI Previous CABG Renal insufficiency Past or current smoker Aspirin β-blocking agents Angiotensin-converting enzyme inhibitors Calcium channel blockers Statins Proton pump inhibitors
CURRENT OASIS 7 (56, 57)	25086 patients with ACS	Clopidogrel high-dose vs. clopidogrel standard-dose, plus aspirin high-dose or standard-dose	High-dose clopidogrel (600 mg LD, 150 mg MD) or standard-dose clopidogrel (300 mg LD, 75 mg MD) High-dose aspirin (300-325 mg) or standard-dose aspirin (75-100 mg)	Current tobacco use Hypertension Dyslipidemia Diabetes mellitus Previous MI Previous PCI Previous CABG
Müller et al. (58)	700 patients with successful coronary stenting Mean age 64.5	Clopidogrel plus aspirin vs. ticlopidine plus aspirin	Clopidogrel (75 mg) plus aspirin (100 mg) Ticlopidine (500 mg) plus aspirin (100 mg)	Diabetes mellitus Previous CABG Previous MI Acute MI Unstable angina Three vessel disease Glycoprotein IIb/IIIa receptor antagonist
CLASSICS (59)	1020 patients with successful coronary stenting Mean age 60	Clopidogrel plus aspirin vs. ticlopidine plus aspirin	Clopidogrel (300 mg LD, 75 mg MD) plus aspirin (325 mg/day) Ticlopidine (250 mg twice/day) plus aspirin (325 mg/day)	Previous MI Treatment for diabetes Hypertension Treatment for hypercholesterolemia Past or current smoker
TOPPS (60)	1016 patients with successful coronary stenting	Clopidogrel plus aspirin vs. ticlopidine plus aspirin	Clopidogrel (300 mg LD, 75 mg MD) plus aspirin Ticlopidine (500 mg LD, 250 mg twice/day MD) plus aspirin	Not specified

Table 3. Continued…..

JUMBO-TIMI 26 (61)	904 patients undergoing elective or urgent PCI Mean age 60	Clopidogrel plus aspirin vs. prasugrel plus aspirin	Low dose prasugrel (40 mg LD, 7.5 mg MD) plus aspirin (325 mg) Intermediate dose prasugrel (60 mg LD, 10 mg MD) plus aspirin (325 mg) High dose prasugrel (60 mg LD, 15 mg MD) plus aspirin (325 mg) Clopidogrel (300 mg LD, 75 mg MD) plus aspirin (325 mg)	Smoking Diabetes mellitus Prior aspirin
SWAP (62)	100 patients with ACS Mean age 57.1	Clopidogrel plus aspirin vs. prasugrel plus aspirin	Clopidogrel (75 mg MD) plus aspirin (81-325 mg) Prasugrel (10 mg MD) plus aspirin (81-325 mg)	Not specified
TRITON-TIMI 38 (63-69)	13608 patients with moderate-to-high risk of ACS with scheduled PCI Mean age 61	Clopidogrel plus aspirin vs. prasugrel plus aspirin	Prasugrel (60 mg LD, 10 mg MD) plus aspirin (75-162 mg) Clopidogrel (300 mg LD, 75 mg MD) plus aspirin (75-162 mg)	Hypertension Hypercholesterolemia Diabetes mellitus Tobacco use Previous MI Previous CABG Heparin Bivalirudin
DISPERSE-2 (70, 71)	990 patients with non-ST segment elevation ACS Mean age 63	Clopidogrel plus aspirin vs. ticagrelor plus aspirin	Ticagrelor (180 mg) plus aspirin (75-100 mg) Ticagrelor (90 mg twice/day) plus aspirin (75-100 mg) Clopidogrel (300 mg LD, 75 mg MD) plus aspirin (75-100 mg)	Diabetes mellitus Prior MI Prior PCI Prior CABG
ONSET/OFFSET (72, 73)	123 patients with stable aspirin-treated coronary artery disease Mean age 64	Clopidogrel plus aspirin vs. ticagrelor plus aspirin vs. placebo plus aspirin	Ticagrelor (180 mg LD 90 mg twice/day MD) plus aspirin (75-100 mg) Clopidogrel (600 mg LD, 75 mg MD) plus aspirin (75-100 mg) Placebo plus aspirin (75-100 mg)	Hypertension Hyperlipidemia Diabetes mellitus Prior MI Prior CABG Prior PCI Statins Angiotensin-converting enzyme inhibitors β-blockers Diuretics Organic nitrates Proton pump inhibitors Calcium channel blockers

Table 3. Continued…..				
RESPOND (74)	98 patients with stable aspirin-treated coronary artery disease Mean age 65	Clopidogrel plus aspirin vs. ticagrelor plus aspirin vs. placebo plus aspirin	Ticagrelor (180 mg LD, 90 mg twice/day MD) plus aspirin (75-100 mg) Clopidogrel (600 mg LD, 75 mg MD) plus aspirin (75-100 mg)	Same as ONSET/OFFSET
PLATO (75-84)	18624 patients with ACS, with or without ST-segment elevation Mean age 62	Clopidogrel plus aspirin vs. ticagrelor plus aspirin	Ticagrelor (180 mg LD, 90 mg twice/day MD) plus aspirin (75-100 mg) Clopidogrel (300-600 mg LD, 75 mg MD) plus aspirin (75-100 mg)	Habitual smoker Hypertension Dyslipidemia Diabetes mellitus

Abbreviations: ACS - acute coronary syndrome; CABG - coronary-artery bypass grafting; CV - cardiovascular; LD - loading dose; MD - maintenance dose; MI - myocardial infarction; PCI - percutaneous coronary intervention; STEMI - ST segment elevation myocardial infarction

Table 4. Efficacy of platelet inhibitors in clinical trials

Clinical Trial (Ref. #)	Population Demographics	Efficacy of Treatments
CAPRIE (42)	19185 patients with atherosclerotic CV disease	Clopidogrel decreased rates of ischemic stroke, MI or CV death (5.32%) more than aspirin (5.83%) (p=0.043)
CURE (43, 44)	12562 patients	Clopidogrel decreased combined rate of CV death, non-fatal MI or stroke (9.3%) more than placebo (11.4%) (RR 0.80, 95% CI 0.72-0.90, p<0.001) Clopidogrel decreased rates of CV death (5.1% vs. 5.5%), non-fatal MI (5.2% vs. 6.6%) or stroke (1.2% vs. 1.4%) more than placebo
PCI-CURE (45)	2658 patients with non-ST segment elevation ACS undergoing PCI	Clopidogrel decreased rates of CV death, non-fatal MI or stroke (4.5%) more than placebo (6.4%) (RR 0.70, 95% CI 0.50-0.97, p=0.03)
CREDO (46)	2116 patients undergoing elective PCI	Clopidogrel did not reduce combined risk of death, MI or urgent target vessel revascularization more than placebo Clopidogrel associated with reduced risk of ischemic adverse events
CARESS (47)	107 patients with asymptomatic microembolic signals at baseline	Clopidogrel decreased incidence of patients positive for microembolic signals (43.8%) more than placebo (72.7%) at day 7 (risk reduction 39.8%, 95% CI 13.8-58.0%, p=0.0046) No difference in the rate of microembolic signals per hour between regimens
CLARITY-TIMI 28 (48)	3491 patients with STEMI	Clopidogrel decreased rates of infarct-related occluded artery, death or recurrent MI more than placebo (p<0.001) Clopidogrel decreased rates of CV death, recurrent MI or recurrent ischemia leading to the need for urgent revascularization more than placebo (p=0.03)
PCI-CLARITY (49)	1863 patients undergoing PCI	Clopidogrel decreased rates of CV death, MI or stroke more than placebo (OR 0.59, 95% CI 0.43-0.81, p=0.001)
ECG CLARITY-TIMI 28 (50)	2431 patients with STEMI	Clopidogrel decreased rates of CV death or MI in patients with partial (p=0.003) or complete (p=0.056) ST-segment resolution at 90 min more than placebo

Table 4. Continued…..

COMMIT (51)	45852 patients with acute MI	Clopidogrel decreased combined rate of CV death, MI or stroke (9.2%) more than placebo (10.1%) (p=0.002) Clopidogrel decreased rates of CV death (7.5% vs. 8.1%) or MI (1.2% vs. 1.4%) more than placebo, with the same rate of stroke (0.6%)
CHARISMA (52)	15603 patients with CV disease or risk factors	Clopidogrel efficient in patients with symptomatic atherothrombosis and potentially harmful in patients with CV risk factors
CHARISMA (53)	9478 patients with documented prior MI, ischemic stroke or symptomatic PAD peripheral arterial disease	Clopidogrel decreased rate of CI death, MI or stroke (7.3%) more than placebo (8.8%) (HR 0.83, 95% CI 0.72-0.96, p=0.01) Clopidogrel decreased rate of hospitalizations for ischemia (11.4%) more than placebo (13.2%) (HR 0.86, 95% CI 0.76-0.96, p=0.008)
MATCH (54)	7599 patients with recent ischemic stroke or transient ischemic attack and risk factors	Non-significant difference in reducing major CV events between aspirin and placebo
GRAVITAS (55)	2214 patients with high on-treatment platelet reactivity after PCI	No difference in incidence of CV death, non-fatal MI or stent thrombosis between clopidogrel high-dose and clopidogrel standard-dose Superior antiplatelet effect in high-dose regimen
CURRENT OASIS 7 (56)	25086 patients with ACS	Clopidogrel high-dose decreased rates of stent thrombosis more than clopidogrel standard-dose (HR 0.68, 95% CI 0.55-0.85, p=0.001) Aspirin dose had no significant effect Clopidogrel dose had no effect on incidence of CV death, MI or stroke
CURRENT OASIS 7 (57)	17263 patients with ACS undergoing PCI	Clopidogrel high-dose decreased rates of stent thrombosis more than clopidogrel standard-dose (HR 0.54, 95% CI 0.39-0.74, p=0.0001)
Müller et al. (58)	700 patients with successful coronary stenting	Rates of primary cardiac events (CV death, urgent target vessel revascularization, angiographically-evident thrombotic stent occlusions or non-fatal MI) comparable between ticlopidine and clopidogrel
CLASSICS (59)	1020 patients with successful coronary stenting	Rates of major cardiac events comparable between ticlopidine and clopidogrel
TOPPS (60)	1016 patients with successful coronary stenting	Frequency of stent thrombosis and CV death comparable between ticlopidine and clopidogrel
JUMBO-TIMI 26 (61)	904 patients undergoing elective or urgent PCI	Slightly lower incidence of 30-day major cardiac adverse events including MI, recurrent ischemia and clinical target vessel thrombosis in prasugrel patients compared to clopidogrel patients
SWAP (62)	100 patients with ACS	Switching from clopidogrel maintenance dose to prasugrel associated with enhanced antiplatelet activity
TRITON-TIMI 38 (63)	13608 patients with moderate-to-high risk of ACS with scheduled PCI	Prasugrel decreased rates of CV death, non-fatal MI or non-fatal stroke more than clopidogrel (HR 0.81, 95% CI 0.73-0.90, p<0.001) Prasugrel decreased rates of MI (p<0.001), urgent target-vessel revascularization infarction (p<0.001) and stent thrombosis (p<0.001) more than clopidogrel
TRITON-TIMI 38 (64)	13457 patients with ACS undergoing PCI	Prasugrel superior to clopidogrel in preventing ischemic events Net clinical benefit superior with prasugrel compared to clopidogrel

Table 4. Continued…..

TRITON-TIMI 38 (65)	13608 patients with ACS with initial non-fatal CV events, MI or stroke	Prasugrel decreased rates of CV events, MI or stroke more than clopidogrel (HR 0.65, 95% CI 0.46-0.92, p=0.016)
TRITON-TIMI 38 (66)	13608 patients with ACS	Prasugrel reduced the risk of CV events, MI or stroke more than clopidogrel in patients with (HR 0.70, p<0.001) and without diabetes mellitus (HR 0.86, p=0.02), and in patients with diabetes mellitus receiving (HR 0.63, p=0.009) or not receiving insulin (HR 0.74, p=0.009)
TRITON-TIMI 38 (67)	12844 patients with moderate-to-high risk of ACS with coronary stent	Prasugrel reduced the risk of CV death, non-fatal MI or non-fatal stroke more than clopidogrel in stented cohort (HR 0.81, p=0·0001) Prasugrel associated with fewer ischemic outcomes, including stent thrombosis, compared to clopidogrel
TRITON-TIMI 38 (68)	3534 patients with PCI for STEMI	Prasugrel reduced the risk of CV death, non-fatal MI or non-fatal stroke more than clopidogrel (HR 0.79, 95% CI 0.65-0.97, p=0.0221) Prasugrel reduced the risk of CV death, non-fatal MI or urgent target vessel revascularisation more than clopidogrel at day 30 (HR 0.75, 95% CI 0.59-0.96, p=0.0205) and at month 15 (HR 0.79, 95% CI 0.65-0.97, p=0.0250)
TRITON-TIMI 38 (69)	346 patients with ACS undergoing CABG	Prasugrel reduced mortality more than clopidogrel (p=0.025)
DISPERSE-2 (70, 71)	990 patients with non-ST-segment elevation ACS	Ticagrelor superior platelet inhibitor to clopidogrel
ONSET/OFFSET (72)	123 patients with stable aspirin-treated coronary artery disease	Ticagrelor associated with faster and more efficient rate of platelet inhibition compared to clopidogrel (p<0.0001)
PLATO (75)	18624 patients with ACS	Ticagrelor decreased combined rates of CV death, MI and stroke more than clopidogrel (HR 0.84, 95% CI 0.77-0.92, p<0.001) Ticagrelor decreased MI alone (5.8% vs 6.9%, p=0.005) and CV death alone (4.0% vs. 5.1%, p=0.001) more than clopidogrel
PLATO (76)	13408 patients with ACS planned for invasive strategy	Ticagrelor decreased combined rates of CV death, MI and stroke more than clopidogrel (HR 0.84, 95% CI 0.75-0.94, p=0·0025) Ticagrelor decreased MI (HR 0.80, 95% CI 0.69–0.92, p=0.0023) and CV death (HR 0.82, 95% CI 0.68–0.98, p=0.0250) more than clopidogrel
PLATO (79)	7544 patients with ACS with ST-segment elevation or left bundle-branch block	Ticagrelor decreased combined rates of CV death, MI and stroke (10.8%) more than clopidogrel (9.4%) (HR 0.87, 95% CI 0.75-1.01, p<0.07)
PLATO (82)	5216 patients with ACS intended for non-invasive management	Ticagrelor decreased combined rates of CV death, MI and stroke (12.0%) more than clopidogrel (14.3%) (HR 0.85, 95% CI 0.73-1.00, p=0.04) Overall death rate lower in ticagrelor patients (6.1%) compared to clopidogrel patients (8.2%) (HR 0.75, 95% CI 0.61-0.93, p=0.01)

Abbreviations: ACS - acute coronary syndrome; CABG - coronary-artery bypass grafting; CI - confidence interval; CV - cardiovascular; HR - hazard ratio; MI - myocardial infarction; PCI - percutaneous coronary intervention; STEMI - ST segment elevation myocardial infarction; RR - risk ratio

Table 5. Adverse drug reactions of platelet inhibitors in clinical trials

Clinical Trial (Ref. #)	Population Demographics	Adverse Drug Reactions
CAPRIE (42)	19185 patients with atherosclerotic CV disease	Rash, diarrhea, indigestion, nausea, vomiting, bleeding disorders, intracranial hemorrhage, gastrointestinal hemorrhage, abnormal liver function Incidence of rash higher in clopidogrel compared to aspirin ($p<0.05$)
CURE (43, 44)	12562 patients	Incidence of bleeding (RR 1.69, $p<0.001$), especially major bleeding (RR 1.38, $p=0.001$), higher in clopidogrel (3.7%) compared to placebo (2.7%)
PCI-CURE (45)	2658 patients with non-ST segment elevation ACS undergoing PCI	Incidence of major bleeding comparable between clopidogrel and placebo Risk of minor bleeding following PCI higher in clopidogrel (3.5%) compared to placebo (2.1%) (RR 1.68, 95% CI 1.06–2.68, $p=0.03$)
CREDO (46)	2116 patients undergoing elective PCI	Incidence of bleeding comparable between clopidogrel and placebo
CARESS (47)	107 patients with asymptomatic microembolic signals at baseline	Incidence of bleeding or recurrent vascular events comparable between clopidogrel and placebo
CLARITY-TIMI 28 (48)	3491 patients with STEMI	Incidence of major bleeding and intracranial hemorrhage comparable between clopidogrel and placebo
PCI-CLARITY (49)	1863 patients undergoing PCI	Incidence of major or minor bleeding comparable between clopidogrel and placebo
COMMIT (51)	45852 patients with acute MI	Incidence of bleeding comparable between clopidogrel and placebo
CHARISMA (53)	9478 patients with documented prior MI, ischemic stroke or symptomatic PAD peripheral arterial disease	Incidence of severe bleeding comparable between clopidogrel and placebo Incidence of moderate bleeding higher in clopidogrel (2.0%) compared to placebo (1.3%) (HR 1.60, 95% CI 1.16-2.20, $p=0.001$)
MATCH (54)	7599 patients with recent ischemic stroke or transient ischemic attack and risk factors	Incidence of major (HR 1.36, 95% CI 0.86-1.86, $p<0.0001$), minor (HR 2.16, 95% CI 0.64-1.88, $p<0.0001$) and life-threatening bleeding (HR 1.26, 95% CI 1.51-2.81, $p<0.0001$) higher in clopidogrel plus aspirin compared to clopidogrel plus placebo
GRAVITAS (55)	2214 patients with high on-treatment platelet reactivity after PCI	Incidence of bleeding comparable between clopidogrel high-dose and clopidogrel standard-dose
CURRENT-OASIS 7 (56)	25086 patients with ACS	Incidence of major bleeding higher in clopidogrel double-dose compared to clopidogrel standard-dose (HR 1.24, 95% CI 1.05-1.46, $p=0.01$)
CURRENT-OASIS 7 (57)	17263 25086 patients with ACS undergoing PCI	Incidence of major bleeding higher in clopidogrel double-dose compared to clopidogrel standard-dose (HR 1.41, 95% CI 1.09-1.83, $p=0.009$)
Müller et al. (58)	700 patients with successful coronary stenting	Incidence of non-cardiac events (non-cardiac death, hemorrhagic complications, vascular complications, stroke, leukopenia or thrombocytopenia, intolerance) higher in ticlopidine (9.6%) compared to clopidogrel (4.5%) ($p=0.01$)
CLASSICS (59)	1020 patients with successful coronary stenting	Major peripheral or bleeding complications, skin disorders, allergy, gastrointestinal disorders Incidence of major peripheral or bleeding complications, neutropenia, thrombocytopenia or early discontinuation of study drug as the result of non-cardiac ADRs higher in ticlopidine (9.1%) compared to clopidogrel (4.6%) ($p=0.005$)
TOPPS (60)	1016 patients with successful coronary stenting	Incidence of side effects higher in ticlopidine (3.64%) compared to clopidogrel (1.62%)
JUMBO-TIMI 26 (61)	904 patients undergoing elective or urgent PCI	Incidence of hemorrhagic complications comparable between prasugrel and clopidogrel

Table 5. Continued…..

TRITON-TIMI 38 (63)	13608 patients with moderate-to-high risk ACS with scheduled PCI	Incidence of major (HR 1.32, 95% CI 1.03-1.68, p=0.03), life-threatening (p=0.01) and fatal bleeding (p=0.002) higher in prasugrel compared to clopidogrel Incidence of non-fatal bleeding comparable between prasugrel and clopidogrel
TRITON-TIMI 38 (64)	13457 patients with ACS undergoing PCI	Incidence of major non-CABG bleeding similar between prasugrel and clopidogrel during the first 3 days and higher in prasugrel compared to clopidogrel after day 3
TRITON-TIMI 38 (65)	13608 patients with ACS with initial non-fatal CV events, MI infarction or stroke	Major bleeding infrequent
TRITON-TIMI 38 (66)	13608 patients with ACS	Incidence of major bleeding higher in prasugrel compared to clopidogrel in patients without diabetes mellitus (HR 1.43, p=0.02) and similar between regimens in patients with diabetes mellitus
TRITON-TIMI 38 (68)	3534 patients with ACS presenting with STEMI	Incidence of major bleeding after CABG higher in prasugrel compared to clopidogrel (p=0.003) Incidence of major bleeding unrelated to CABG, life-threatening bleeding, or major or minor bleeding comparable between prasugrel and clopidogrel
DISPERSE-2 (70)	990 patients with non-ST segment elevation ACS	Chest pain, headache, nausea, insomnia, diarrhea, hypotension, dizziness, syncope, rash Incidence of major or minor bleeding comparable between ticagrelor and clopidogrel Incidence of asymptomatic ventricular pauses >2.5 sec higher in ticagrelor 90 mg twice/day and ticagrelor 180 mg/day compared to clopidogrel (p=0.01) Incidence of dyspnea higher in ticagrelor 180 mg/day compared to clopidogrel (p<0.0002)
ONSET/OFFSET (72)	123 patients with stable aspirin-treated coronary artery disease	Incidence of dyspnea judged by physician to be related to studied drug higher in ticagrelor (24.1%) compared to clopidogrel (4.0%) (p<0.01)
ONSET/OFFSET (73)	123 patients with stable aspirin-treated coronary artery disease	Incidence of dyspnea higher in ticagrelor (38.6%) compared to clopidogrel (9.3%)
RESPOND (74)	98 patients with stable aspirin-treated coronary artery disease	Incidence of dyspnea higher in ticagrelor compared to clopidogrel
PLATO (75)	18624 patients with ACS	Incidence of bleeding, major bleeding or life-threatening bleeding comparable between ticagrelor and clopidogrel Incidence of procedure-unrelated bleeding higher with ticagrelor compared to clopidogrel Incidence of major bleeding not related to CABG higher in ticagrelor (4.5%) compared to clopidogrel (3.8%) (p=0.03) Incidence of drug discontinuation due to ADRs higher in ticagrelor (7.4%) compared to clopidogrel (6.0%) (p<0.01) Incidence of dyspnea higher in ticagrelor (13.8%) compared to clopidogrel (7.8%) (HR 1.84, 95% CI 1.68–2.02, p<0.001) Incidence of dyspnea requiring treatment discontinuation higher in ticagrelor (0.9%) compared to clopidogrel (0.1%) (HR 6.12, 95% CI 3.41–11.01, p<0.001) Incidence of ventricular pauses ≥3 sec higher in ticagrelor (5.8%) compared to clopidogrel (3.6%) (p<0.01)
PLATO (76)	13408 patients with ACS planned for invasive strategy	Incidence of major bleeding or life-threatening bleeding comparable between ticagrelor and clopidogrel

Table 5. Continued…..

PLATO (77)	15202 patients with ACS	Incidence of dyspnea higher in ticagrelor (14.4%) compared to clopidogrel (8.3%) (HR 1.84, 95% CI 1.66–2.04, p=0.04)
PLATO (79)	7544 patients with ACS with ST segment elevation or left bundle-branch block	Incidence of dyspnea higher in ticagrelor (12.6%) compared to clopidogrel (8.4%) (p<0.0001)
PLATO (80)	18624 patients with ACS	Incidence of major or severe bleeding comparable between ticagrelor and clopidogrel Incidence of bleeding not related to CABG higher in ticagrelor (4.5%) compared to clopidogrel (3.8%) (p=0.02) Incidence of procedure-unrelated major bleeding higher in ticagrelor (3.1%) compared to clopidogrel (2.3%) (p=0.05)
PLATO (81)	1261 patients with ACS undergoing CABG	Incidence of major or severe bleeding comparable between ticagrelor and clopidogrel
PLATO (82)	5216 patients with ACS intended for non-invasive management	Incidence of major or non-CABG-related major bleeding higher in ticagrelor compared to clopidogrel patients (n.s.)
PLATO (83)	2908 patients with ACS undergoing prospective continuous electrocardiographic assessment	Incidence of ventricular pauses ≥3 sec higher in ticagrelor (5.8%) compared to clopidogrel (3.6%) (RR 1.61, p=0.006) during first week of treatment Incidence of ventricular pauses ≥3 sec at 1 month (most asymptomatic) comparable between ticagrelor and clopidogrel
PLATO (84)	18421 patients with ACS	Incidence of dyspnea higher in ticagrelor (14.5%) compared to clopidogrel (8.7%) Incidence of dyspnea judged by physician to be related to studied drug higher in ticagrelor (15.0%) compared to clopidogrel patients (6.9%) (p<0.0001)

Abbreviations: ACS - acute coronary syndrome; CABG - coronary-artery bypass grafting; CV - cardiovascular; HR - hazard ratio; MI - myocardial infarction; n.s. - not significant; PCI - percutaneous coronary intervention; STEMI - ST segment elevation myocardial infarction; RR - risk ratio