Review Article | Open Access

Antiplatelet Agents in Diabetic Patients: Clinical Advances and Remaining Questions

Pierre Sabouret[1*], Magali Taiel-Sartral[2], Jean-Philippe Kevorkian[3] and Bruno Vergès[4]

[1]Institute of Cardiology, INSERM UMRS937, Pitié-Salpêtrière Hospital (AP-HP), University Paris, France

[2]Cardiovascular Intensive Care Unit, Lilly France-24 boulevard Vital Bouhot CS, Neuilly-sur-Seine, France

[3]Department of Diabetology, Lariboisière Hospital, 2 rue Ambroise Paré, Paris, France

[4]Endocrinology, Diabetes and Metabolic Diseases Service, 14 rue Gaffarel, BP, Dijon, France

*Corresponding author: Pierre Sabouret, Cardiology Department, Heart Institute, Pitié-Salpêtrière University Hospital, 47-83 bld de l'Hôpital, 75013 Paris, France, Tel: +33181793507; E-mail: pierre.sabouret@psl.aphp.fr

Abstract

Patients with diabetes mellitus (DM) are at significantly greater risk for major cardiovascular events (MACE) than non-DM patients. Primary and secondary prevention of cardiovascular disease (CVD) involves a multifactorial approach that aims to treat the cluster of risk factors associated with this condition including blood disorders and clinical features, such as hyperglycaemia, dyslipidemia, hypercoagulation, obesity and hypertension.

Platelet activation and aggregability play a key role in the genesis of arterial thrombus secondary to plaque rupture. For patients in secondary prevention, inhibition of platelet function is crucial to significantly decrease the rate of MACE. Inhibiting plaque rupture would therefore prevent platelet aggregation.

For patients with DM presenting with an acute coronary syndrome (ACS), a dual antiplatelet therapy with antagonism of COX1 and P2Y12 is central to their treatment, especially in the setting of percutaneous coronary intervention (PCI) and stenting. Large randomized trials have demonstrated that platelet inhibition with the P2Y12 antagonist clopidogrel, is associated with a better short and long-term prognosis after an acute coronary syndrome. Despite the clinical benefits of clopidogrel in patients with ACS, it has limitations in urgent and early PCI due to its slow onset of action, large interindividual variability and drug-drug interactions resulting in inconsistent drug response with reduced efficacy, especially in patients with diabetes. Therefore, newer drugs with a rapid onset of action, and a more potent and predictable effect have been developed. Prasugrel and ticagrelor have demonstrated net clinical benefit over clopidogrel in two major randomized trials, including a large number of diabetic patients, in patients presenting with non-ST elevation ACS (NSTE-ACS) and ST-elevation ACS (STE-ACS) revascularized by PCI. The aim of this review is to provide an overview of aspirin, P2Y12 receptor antagonists, and Glycoprotein (GP) IIb-IIIa inhibitors in the management of diabetic patients, with a focus on perspectives in optimal and appropriate agent selection and timing of treatment in both primary and secondary prevention.

Keywords: Platelet reactivity; P2Y12 receptor antagonist; Diabetes

Abbreviations

AA: Arachidonic Acid; ACS: Acute Coronary Syndrome; ADA: American Diabetes Association; ADP: Adenosine Diphosphate; ASA: Aspirin; ATC: Antithrombotic Trialists' Collaboration; BARC: Bleeding Academic Research Consortium; BID: Twice a Day; CAD: Coronary Artery Disease; CAPRIE: Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events study; CI: Confidence Interval; COX-1 inhibitors: Cyclooxygenase-1 inhibitors; CVD: Cardiovascular Disease; DAPT: Dual Antiplatelet Therapy; DES: Drug Eluting Stent; DM: Diabetes Mellitus; DSMB: Data Safety and Monitoring Board; GP IIb-IIIa inhibitors: Glycoprotein IIb-IIIa inhibitors; GUSTO: Global Strategies for Opening Occluded Coronary Arteries; HPI: High on-treatment Platelet Inhibition; HPR: High on-treatment Platelet Reactivity; IGT: Impaired Glucose Tolerance; INSERM: Institut National de la Santé et de la Recherche Médicale; IV: Intra Venous; LD: Loading Dose; LTA: Light Transmission Aggregometry; MACE: Major Cardiovascular Events; MD: Maintenance Dose; MI: Myocardial Infarction; NNH: Number Needed to Harm; NNT: Number Needed to Treat; NSTEMI: Non ST-Elevation Myocardial Infarction; OD: Once a Day; PCI: Percutaneous Coronary Intervention; PFT: Platelet Function Test; PPP: Platelet-Poor Plasma; PPI: Proton Pump Inhibitor; PRI: Platelet Reactivity Index; PRP: Platelet-Rich Plasma; PRU: P2Y12 Reaction Units; Iso-TRAP: Iso-Thrombin Receptor Activating Peptide; PGE1: Prostaglandin E1; STEMI: ST-Elevation Myocardial Infarction; TIMI: Thrombolysis In Myocardial Infarction; UA: Unstable Angina; VN-P2Y12; Verify Now P2Y12; VASP: Vasodilator-Stimulated Phosphoprotein; VKA: Warfarin

Introduction

Diabetes is associated with an increased risk of major cardiovascular events compared with non-diabetic status. The frequent presence of multiple cardiovascular risk factors and abnormal platelet function in diabetic patients contribute to this increased risk. Platelets play a pivotal role in atherothrombotic events [1-5]. Therefore, the therapeutic targets, which regulate one or more

pathways in platelet activation and aggregation, play a key part in decreasing major thrombotic events in diabetes.

This article reviews pharmacological and clinical data available for antiplatelet therapy in diabetes, the limitations of aspirin and second generation thienopyridine, the advances provided by the new $P2Y_{12}$ antagonists, and the perspectives to improve prognosis in this field.

Three different classes of platelet inhibiting drugs are available:

- COX-1 inhibitors, represented by aspirin

-ADP-P2Y12 antagonists: clopidogrel, prasugrel, ticagrelor, cangrelor

- GP IIb-IIIa inhibitors: abciximab, tirofiban, eptifibatide

Aspirin inhibits irreversibly the genesis of thromboxane A2 by selective acetylation of the COX-1 enzyme [4,5]. The irreversible effect of inhibition is due to the fact that platelets are enucleated, and, thus, unable to resynthesize the COX-1.

Ticlopidine is a first-generation thienopyridine, which irreversibly blocks the platelet ADP $P2Y_{12}$ receptor. Its proven clinical efficacy in combination with aspirin in patients undergoing coronary stenting, related to a more enhanced inhibition of platelet function, compared with aspirin in monotherapy or in combination with warfarin (VKA), has led to the development of this class [6]. However, its poor safety profile prompted the emergence of clopidogrel, a second-generation of thienopyridine.

Despite the clinical benefits of clopidogrel in combination therapy with aspirin in patients with an acute coronary syndrome, it has several limitations including a slow onset of action with suboptimal platelet inhibition during urgent and early PCI, a large interindividual variability due to the metabolism of this prodrug, and numerous pharmacologic interactions [7,8]. Thus, new $P2Y_{12}$ receptor antagonists have been developed, with a faster onset, and more potent and more predictable effect on platelet inhibition.

The current ESC and ACCF/AHA guidelines for UA/NSTEMI and STEMI state, that DAPT should be given as soon as possible after a diagnosis is made [9-13].

Aspirin

Aspirin in primary prevention

The role of chronic administration of aspirin in primary prevention of arterial vascular events remains a matter of debate, especially in diabetes. The Food and Drug Administration has not approved aspirin for use in primary prevention while the American Diabetic Association (ADA) and the American Heart Association (AHA) recommended low doses of aspirin (75-162 mg/day) in primary prevention in diabetics at high cardiovascular risk (i.e. those >40 years of age or with additional risk factors: family history of CV disease, arterial hypertension, cigarette smoking, dyslipidemia, or albuminuria) [14]. However, because of the lack of clear clinical benefit evidence, antiplatelet therapy with aspirin in adults at a low CVD risk is not recommended by the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on CVD Prevention in Clinical Practice [15]. A clear benefit of aspirin (versus placebo) in primary prevention of major cardiovascular events or mortality in diabetes was unconfirmed in a major meta-analysis [16]. Therefore, the decision to give aspirin in primary prevention must be taken on an individual patient basis, with an evaluation of balance

between ischemic and bleeding risk, which remains delicate. To help the decision of practitioners, two clinical trials are currently underway, which will provide insights into the usefulness of aspirin in primary prevention in diabetes: A Study of Cardiovascular Events in Diabetes (ASCEND; aspirin 75 mg versus omega-3 fatty acids 1 g) (NCT00135226), and Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D; simvastatin 20-40 mg versus aspirin 100 mg, or simvastatin alone) (ISRCTN48110081).

Aspirin in secondary prevention

In secondary prevention, the American Diabetes Association (ADA) recommends low-dose aspirin (75-162 mg/d) in diabetic patients based on two large meta-analyses by the Antithrombotic Trialists' Collaboration (ATC) [16]. In the secondary prevention trials, aspirin allocation yielded a greater absolute reduction in serious vascular events (6.7% vs. 8.2% per year, p<0.0001), with a non-significant increase in haemorrhagic stroke but reductions of about a fifth in total stroke (2.08% vs. 2.54% per year, p=0.002) and in coronary events (4.3% vs. 5.3% per year, p<0.0001). The proportional reductions in the aggregate of all serious vascular events seemed similar for men and women. No heterogeneity between subgroups is mentioned by the authors. In the secondary prevention trials, aspirin seemed to reduce vascular mortality (RR 0.91 (0.82–1.00), p=0.06) and had no significant effect on other mortality (RR 0.85 (0.66–1.08), p=0.2), yielding a 10% reduction in total mortality (RR 0.90 (0.82–0.99), p=0.02).

Aspirin non-responsiveness: fact or fiction?

Certain patients do not benefit from the antithrombotic effects of aspirin. The phenomenon of so-called aspirin non-responsiveness includes the failure of aspirin to target, namely the Cox-1 enzyme and also other factors such as drugs interaction, absorption alteration, patients adherence... Potential mechanisms of high on-aspirin platelet reactivity in diabetes include elevated platelet turnover that results in an immature platelet fraction able to synthesize the uninhibited therapeutic target of aspirin, cyclooxygenase-1 (COX-1); residual thromboxane production by both COX-1-dependent and COX-1-independent pathways; up-regulation of aspirin-insensitive pathways of platelet function, such as adenosine diphosphate signaling; and increased underlying atherosclerotic disease burden that results in elevated underlying platelet hyper-reactivity [4,5]. High on-aspirin platelet reactivity in diabetes may be related to glycemic control. Potential approaches to treatment include controlling modifiable risk factors to achieve effective glycemic control, guided increases in aspirin dose or frequency of administration, or the use of additional antiplatelet therapies. While evidence suggests that altering antiplatelet therapy, particularly by increasing frequency of aspirin administration, can overcome incomplete inhibition of thromboxane synthesis, no clinical studies to date have assessed the effectiveness of these in preventing breakthrough atherothrombosis [17,18]. While some clinicians currently alter therapy on the basis of theoretical potential benefit of these strategies, aspirin resistance in the laboratory is not a reliable indicator of aspirin non-responsiveness and is not supported by clinical evidence of a benefit yet, and clear clinical guidelines for the management of aspirin resistance are lacking.

Furthermore, a recent study has highlighted that pharmacological resistance to aspirin is rare; this study failed to identify a single case of true drug resistance. Pseudo-resistance, reflecting delayed and reduced

drug absorption, complicates enteric coated but not immediate release aspirin administration [19]. However there is a time dependent aspirin efficacy [17,18].

Can we override aspirin resistance in diabetic patients?

The biological efficacy of the same daily dose of aspirin given either once (OD) (150 mg in the morning) or twice a day (BID) (75 mg in the morning and 75 mg in the evening) in a population of diabetic patients with previous coronary artery disease demonstrated that biological resistance (maximum aggregation intensity ≥ 20%) was doubled in OD versus BID (42% vs. 17%; P<0.001). Of the 39 patients with biological resistance on OD, 24 (62%) overcame resistance on BID [18]. In this population of diabetic patients with coronary artery disease and a high risk of time-dependent aspirin resistance, aspirin given BID can significantly decrease the rate of biological loss of efficacy at trough level and may be a valid therapeutic strategy, but must be confirmed by a randomized study with clinical "hard" endpoints (MI, stroke, cardiovascular mortality).

Clopidogrel

Clopidogrel is a second-generation thienopyridine derivative that binds specifically and irreversibly to the platelet P2Y12purinergic receptor, inhibiting ADP-mediated platelet activation and aggregation [20,21]. It is a prodrug that is metabolized to its active form in the liver. In particular, approximately 85% of a clopidogrel dose is hydrolyzed by esterases into an inactive metabolite, whereas the remaining dose is converted into the active metabolite in a process which requires 2 sequential CYP-dependent steps. The non-responsiveness to clopidogrel has been extensively explained by several factors, such as active metabolite exposure, drugs interaction, genetic factors, absorption interactions, patients' clinical profile and adherence. In diabetic patients, the esterases' activity is increased, resulting in a higher proportion of inactive metabolite [5]. The reactive thiol group of the active metabolite of clopidogrel forms a disulfide bridge between one or more cysteine residues of the $P2Y_{12}$ receptor. This interaction is irreversible, accounting for the observation that platelets are inhibited, even if no active metabolite is detectable in plasma. Genetic polymorphisms of the CYP2C9, CYP2C19, 17 and ABCB1 can limit conversion into the active metabolite resulting in a lower response of clopidogrel. The limited exposure to the active metabolite cannot be overcome by higher dosages due to saturable absorption and metabolism of clopidogrel. Clopidogrel has until recently been the standard of care in dual antiplatelet therapy (DAPT).

Clopidogrel in primary prevention

There is no conclusive data for the use of thienopyridines in the setting of primary prevention. The only available data are from the subgroup of patients with multiple risk factors in the CHARISMA study, for whom dual antiplatelet therapy provided no benefit, with a trend of harmful effect. Consistent with the results in the total population (n=6556), no benefit of combined therapy was observed in the diabetic patients (type 1 or 2 diabetes with drug therapy n=2655) who represented 80% of the multiple risk factors population [22].

Clopidogrel in secondary prevention monotherapy

Thienopyridines may represent an alternative in cases of aspirin intolerance. The subgroup of diabetic patients (20% of the study population) has been analyzed retrospectively in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study

[23]. Clopidogrel was significantly more effective than aspirin in reducing the risk of ischemic events in diabetic patients with a history of atherothrombosis, and the absolute risk reduction was 2.1% compared to ASA (p=0.042) [15]. Therefore, the ADA guidelines currently recommend the use of clopidogrel only in very high-risk diabetic patients, or as an alternative strategy in aspirin-intolerant patients [9].

Clopidogrel in secondary prevention with dual antiplatelet therapy

The CHARISMA Trial included 15,603 patients with clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg per day) plus low-dose aspirin (75 to 162 mg per day) or placebo plus low-dose aspirin, and followed them for a median of 28 months [22]. There was no significant reduction in the primary efficacy end point (a composite of myocardial infarction, stroke, or death from cardiovascular causes): 6.8% with clopidogrel plus aspirin vs. 7.3% with placebo plus aspirin (relative risk, 0.93; 95 percent confidence interval, 0.83 to 1.05; P=0.22). A principal secondary efficacy end point, including hospitalizations for ischemic events, was 16.7% vs. 17.9% (relative risk, 0.92; 95 percent confidence interval, 0.86 to 0.995; P=0.04). Bleeding risk was 1.7% vs. 1.3% (relative risk, 1.25; 95 percent confidence interval, 0.97 to 1.61 percent; P=0.09). Among patients with multiple risk factors, there was no significant reduction in primary endpoint (6.6% with clopidogrel and 5.5% with placebo; 95 percent confidence interval, 0.91 to 1.59; P=0.20) and the rate of death from cardiovascular causes was higher with clopidogrel combined with aspirin (3.9% vs. 2.2% P=0.01). In the subgroup with clinically evident atherothrombosis, the rate was 6.9% with clopidogrel and 7.9% with placebo (relative risk, 0.88; 95 percent confidence interval, 0.77 to 0.998; P=0.046). There was a trend of benefit with clopidogrel treatment in patients with symptomatic atherosclerosis and no clinical benefit or harm in patients with multiple risk factors, mainly represented by diabetic patients (42% of the overall population of the CHARISMA study) [24].

Clopidogrel in secondary coronary prevention

The CURE trial is the key landmark analysis that exemplified clopidogrel efficacy. In this study of 12,562 patients presenting with NSTE-ACS within 24 hours of symptom onset, clopidogrel 300 mg then 75mg and aspirin was compared with aspirin alone. Clopidogrel resulted in a 20% relative risk reduction of the prevalence of the primary composite outcome of cardiovascular death, non-fatal MI and stroke compared with aspirin monotherapy. The diabetic population (n=2840) represented 22.6% of the overall population (n=12562). The CURE data also showed the consistency of the benefit of clopidogrel in various subgroups, including the diabetic subgroup (Primary endpoint: 16.7% with aspirin alone vs. 14.2% with dual antiplatelet therapy; RR=0.84 (0.70;1.02)) [25]. Regarding the PCI CURE substudy (CURE patients undergoing PCI n=2658), the results of the diabetic population (n=504) were less significant than in the overall population (primary endpoint: 12,9% for dual antiplatelet therapy vs. 16,5% for aspirin alone; RR: 0,077 (0.48;1.22)) with no heterogeneity. This clinical benefit was also demonstrated in patients presenting with STEMI and treated with thrombolysis in the CLARITY TIMI 28 trial whereby there was a similar reduction in the clinical endpoint of CV death, MI and recurrent ischemia [26]. The results of the diabetic subgroup (n=575) were not reported. Regarding the PCI CLARITY subgroup (n=1863), the diabetic patients (n=282) showed a favorable trend (primary endpoint: 6% for dual antiplatelet therapy vs. 10.1% for

aspirin alone OR: 0,61 (0.24;1.53)), which was not significant probably due to the lack of power.

A higher loading dose of clopidogrel was assessed in ACS patients in the CURRENT-OASIS 7 trial with 600 mg administered on day 1,150 mg day 2-7 and 75 mg thereafter [27]. There was overall no benefit of this strategy with respect to rate of the primary outcome of cardiovascular death, MI or stroke after 30 days (HR 0.94 (CI) 0.83-1.06, p=0.3). There was, however, a significant increase in the rate of bleeding in the high double dose group (2.5%) versus those with the low dose (2.0%, HR 1.24, 95% CI 1.05-1.46; P=0.01). In a subgroup analysis of 17,263 patients who underwent PCI, high dose appeared to have benefit in moderate to high risk patients, decreasing the primary composite end-point of myocardial infarction (MI), stroke or cardiovascular death at 30 days (3.9% vs. 4.5%; HR 0.86, 95% CI 0.74-0.99; P=0.039), and also reducing the rate of occurrence of stent thrombosis (ST) (0.7% vs. 1.3%, respectively; HR 0.54, 95% CI 0.39-0.74; P=0.0001). The diabetic population represented about 23% (n=5880) of the overall population (n=25086) and the results were consistent with the rest of the population (primary endpoint: 5.2% for double clopidogrel dose vs. 6.1% for standard clopidogrel dose). Furthermore, the COMMIT trial, which included 45,852 patients with acute myocardial infarction, demonstrated that 75mg (without a loading dose) within 24 hours of presentation produced a 9% proportional reduction in death, reinfarction, or stroke [28].

Clopidogrel in combination with aspirin for stroke prevention

Currently, there is no evidence to suggest that a combination of aspirin and clopidogrel, even in high-risk patients, such as those with diabetes, has any therapeutic advantage in the secondary prevention of cardio-vascular events after ischemic stroke/TIA. The MATCH trial considered patients with stroke or TIA and one other risk factor. Individuals already taking clopidogrel were randomized to receive either aspirin or placebo, in addition to clopidogrel. The trial failed to show a reduction in its composite cardiovascular end point (which included stroke) but did demonstrate increased rates of bleeding when using a combination of the two drugs [29]. Further, the CHARISMA study, which compared over 15000 people with cardiovascular disease in primary or secondary prevention, did not show any benefit of clopidogrel and aspirin combined, when compared with aspirin alone, in their chosen end point, a composite of myocardial infarction, stroke, or cardiovascular death [22].

CHANCE showed that in 5170 Chinese patients with TIA/ischemic stroke, treated within 24 hours after the onset of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the first 90 days and does not increase the risk of haemorrhage [30]. The potential explanation of the benefit of DAPT in the CHANCE study is probably the short course of the combination aspirin plus clopidogrel treatment, in contrast with the long duration of DAPT in the MATCH study.

Newer antiplatelet agents

To overcome the sub optimal pharmacodynamic and pharmacokinetic profile of clopidogrel, new $P2Y_{12}$ inhibitors were developed that are more predictable, more potent and have a faster onset of action, characteristics that make them particularly attractive for PCI. Prasugrel and ticagrelor are two agents that are now approved for the treatment of NSTE-ACS and STEMI predominantly treated with PCI based on evidence that has demonstrated a reduction in

mortality and recurrent cardiovascular events when compared with clopidogrel [31-34].

Prasugrel

Prasugrel is a third generation thienopyridine that has a similar mechanism of action to clopidogrel in that its active form binds covalently to the $P2Y_{12}$ receptor, via a disulfide bond causing irreversible blockade for ADP binding. It has however much more rapid, potent and consistent inhibitory effects on platelet aggregation than clopidogrel due to more efficient in vivo generation of its active metabolite [35]. The esterase-mediated step for prasugrel occurs mainly in the intestine, as does the CYP-mediated oxidative step leading to the active metabolite formation [36]. The polymorphisms in CYP2C9, CYP2C19, 17 and ABCB1 that have an effect on clopidogrel, do not significantly alter prasugrel clinical efficacy, pharmacokinetics or pharmacodynamics [37,38]. The peak concentration of the active metabolite of prasugrel is achieved rapidly at 30 minutes and a maximum of 60-70% inhibition is usually achieved within 2-4 hours [38].

The ACAPULCO trial specifically evaluated the pharmacodynamic effects of a 10 mg maintenance dose prasugrel in 56 patients with UA/NSTEMI, compared with high maintenance dose clopidogrel (150 mg daily) after high loading dose (900 mg). Greater platelet inhibition with prasugrel 10 mg daily was observed over 14 days compared with clopidogrel 150 mg daily [39].

The superior antiplatelet effect of prasugrel was demonstrated in the phase II PRINCIPLE-TIMI (prasugrel in Comparison to clopidogrel for Inhibition of Platelet Activation and Aggregation-TIMI) 44 trial (overall population: n=201) which compared a 60 mg prasugrel dose with a 600 mg loading dose of clopidogrel. Among patients planned for PCI, loading with 60 mg prasugrel resulted in greater platelet inhibition than a 600 mg clopidogrel loading dose. Daily maintenance therapy with prasugrel 10 mg resulted in a greater antiplatelet effect than 150 mg daily clopidogrel. As often in this type of population, the diabetic subgroup represented around 30% of the overall cohort [40].

The pharmacodynamic benefit of prasugrel in diabetic patients with CAD (n=35) was assessed in the OPTIMUS-3 study, in which prasugrel was compared with high-dose clopidogrel. Compared with clopidogrel 600 mg LD, a prasugrel 60 mg LD demonstrated significantly higher levels of IPA as measured by VN-P2Y12 as early as 1 hour following the LD and this effect was maintained over the subsequent 24 hours (greater platelet inhibition with prasugrel at 4 hours post-LD than clopidogrel: least squares mean, 89.3% vs. 27.7%, p<0.0001). Prasugrel 10 mg MD maintained a higher IPA than clopidogrel 150 mg MD after 1 week of therapy (61.8% vs. 44.2%, p<0.0001) [41].

The superior pharmacodynamic and pharmacokinetic profile of prasugrel has been translated into clinical benefit when compared with clopidogrel. The TRITON TIMI-38 trial evaluated 13,608 patients with moderate to high-risk ACS including 10,074 patients with unstable angina (UA) or non-ST segment elevation myocardial infarction and 3,534 patients with STEMI33. Patients were randomized to receive prasugrel 60-mg loading dose, followed by 10mg/day, or clopidogrel 300 mg, followed by 75 mg/day. Patients continued therapy for 6-15 months after enrollment. Prasugrel was associated with a significant 18% relative risk reduction of the primary endpoint (CV death, non-fatal MI or nonfatal stroke) compared with clopidogrel (p<0.001), and a number needed to treat (NNT) of 46. In the total population,

prasugrel's ischemic benefit was partly counterbalanced by a 0.6% absolute risk increase of TIMI major non-CABG related bleeding with a number needed to harm of 167. Regarding the bleeding risk, the study showed that three specific subgroups were at high risk for bleeding: patients ≥75 years old, <60 kg, with previous TIA or stroke. When the rates of certain efficacy and bleeding end points (death from any cause, nonfatal myocardial infarction, nonfatal stroke, and TIMI major hemorrhage) were included in a prespecified analysis of net clinical benefit, the findings favored prasugrel (13.9% of patients in the clopidogrel group vs. 12.2% in the prasugrel group; hazard ratio, 0.87; 95% CI, 0.79 to 0.95; P=0.004).

For the pre-specified analysis of the diabetic subgroup of the TRITON study, Prasugrel significantly reduced the incidence of the primary endpoint compared with clopidogrel among nondiabetics (9.2 and 10.6%, respectively; HR 0.86; P=0.02) and DM patients (12.2 and 17.0%, respectively; HR 0.70; P<0.001, P interaction=0.09) [42]. DM subjects taking insulin also had greater benefit with reduced the incidence of the primary endpoint when treated with prasugrel compared to clopidogrel (DM patients with insulin: 14.3 and 22.2%, respectively; HR 0.63; P=0.009; DM patients without insulin: 11.5 and 15.3%, respectively; HR 0.74; P=0.009). Nondiabetics taking prasugrel were more likely than those receiving clopidogrel to develop major hemorrhage (2.4% vs. 1.6%, HR 1.43; P=0.02). Rates of major hemorrhage with clopidogrel and prasugrel were similar in DM patients (2.6 and 2.5%, respectively; HR 1.06, P=0.81, Pinteraction=0.29) [42]. Therefore, prasugrel produced a greater (14.6%) net clinical benefit (composite of all-cause mortality, nonfatal MI, nonfatal stroke or nonfatal TIMI major bleeding not related to CABG) than clopidogrel in DM patients (19.2%, HR 0.74; P=0.001) and this was greater than in those without DM (11.5 and 12.3%, respectively; HR 0.92; P=0.16, Pinteraction=0.05), as stated in the ESC Guidelines regarding diabetic ACS PCI patients [10].

Prasugrel was approved by the FDA (US) in July 2009 and by the EMEA (Europe) in February 2009. In the field of NSTE-ACS patients, pretreated with aspirin and a P2Y12 antagonist is a class I recommendation and common practice. However, no trial has ever randomized patients presenting with NSTE-ACS, invasively managed, to pre-treatment with clopidogrel, prasugrel or ticagrelor versus no pre-treatment. Therefore the debate about the usefulness of preloading has remained opened until the ACCOAST trial. This study was designed to randomize 4100 patients to an early administration of prasugrel vs. an administration in the catheterization laboratory. In November 2012, Daiichi Sankyo and Eli Lilly and Company discontinued enrollment in the ACCOAST trial at 4033 patients, following a recommendation by an independent Data and Safety Monitoring Board (DSMB), which found that pre-treatment in NSTEMI patients resulted in no reduction of cardiovascular events, but was associated with an increased risk of early TIMI major (including life-threatening) bleeding, without difference in mortality. However, the power of the trial was not affected, since at the time the trial was stopped, 398 patients had had a primary efficacy end-point event, and this event driven study was due to stop when 400 patients had an end-point event. Among patients with NSTE myocardial infarction, no heterogeneity was found in diabetic patients (20% of the study population). These results, consistent among patients undergoing PCI, support the administration of prasugrel when the coronary anatomy is known and after PCI is selected as the treatment strategy [43]. Whether the use of a fast acting and potent platelet inhibitor may play an upstream role in STEMI patients is investigated in the on-going ATLANTIC study.

For medically-treated patients with unstable angina or myocardial infarction without ST-segment elevation, the results of the TRILOGY study, including almost 40% of diabetic patients, showed that prasugrel did not significantly reduce the frequency of major cardiovascular events, as compared with clopidogrel [44].

Ticagrelor

Tigagrelor is the first of a new class of antiplatelet family called cyclopentyl-trazolo-pyrimidines (CPTP) and is also the first oral, reversible selective P2Y12 receptor antagonist. Like the thienopyridines, ticagrelor binds the platelet P2Y12 receptor to inhibit ADP's prothrombotic effects. However, unlike the thienopyridines this effect is non-competitive and reversible. Ticagrelor appears to act through an allosteric modulation site and exhibits a conformational change in the receptor by binding independently of ADP. It therefore does not prevent ADP binding but seems to have an effect on ADP-receptor induced signaling and platelet aggregation [45,46]. It is a direct acting compound and does not require metabolic activation thus obviating any influence of the CYP450 pathway on the antiplatelet response. It is, however, also metabolized into an active metabolite (approximately 30-40%) by CYP3A4 [32]. The plasma half-life of ticagrelor may be prolonged by co-administration of cytochrome P450 (CYP)3A4 inhibitors, such as diltizem, since hepatic metabolism via CYP3A is the principal mode of excretion of ticagrelor [47]. Ticagrelor demonstrates linear pharmacokinetics, and exposure to ticagrelor active metabolite (AR-C124910XX) is approximately dose proportional up to 1260 mg, with a median Tmax of approximately 2.5 hours [31]. It achieves greater antiplatelet effect than clopidogrel and also has a relatively short half-life and an offset of action more rapid than clopidogrel [48]. However, this pharmacodynamic profile also could put patients at risk of acute events like stent thrombosis especially after DES implantation if they are not strictly compliant with therapy.

Ticagrelor has shown clinical benefit in head to head phase II and III studies with clopidogrel in ACS showing decreased incidence of adverse cardiac events with a higher rate of non-CABG related bleeding [34,49].

The PLATO study is the largest randomized study to compare ticagrelor with clopidogrel. In total 18,624 patients with ACS were included and randomized to either ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) or clopidogrel (300-600 mg loading dose, 75 mg daily thereafter). All patients took aspirin and treatment began within 24 hours of symptom onset.

The design of PLATO differs from TRITON-TIMI 38 in several ways. Firstly, the proportion of patients with NSTE-ACS was 59.5 and 59.3% in the ticagrelor and clopidogrel arms respectively compared with 74% in the TRITON trial. Secondly, in TRITON 99% of the patients were treated with PCI, while this was only 64% in PLATO. Thirdly, the PLATO protocol allowed clopidogrel treatment before randomization, while TRITON patients were naive patients (no use of any thienopyridine within 5 days before enrolment). The median duration of the follow up in PLATO was 9 months vs. 14.5 in TRITON.

At 12 month follow-up there was a lower rate of the primary composite endpoint of cardiovascular mortality, MI or stroke in patients receiving ticagrelor (9.8% vs. 11.7%; P<0.001), which translates to a NNT of 53. This ischemic benefit was balanced by an increased bleeding for major non-CABG related bleeding with the PLATO definition (4.5 vs. 3.8%, respectively; p=0.03) and with the

TIMI definition (an absolute 0.6% increased bleeding risk: 2.8 vs. 2.2%; p=0.025, with a NNH of 167). No increase of overall bleeding (PLATO definition) was observed.

The analysis of the diabetic subgroup showed the following results for the primary endpoint: 14.1% with ticagrelor vs. 16.2% with clopidogrel, HR 0.88 (0.76-1.03) (in non- diabetics 8.4% vs. 10.2% (HR 0.83 (0.73-0.93)). P-value for interaction was not significant (Pinteraction=0.49) [50]. Thus, this benefit was consistent with the overall trial results but did not reach nominal statistical significant. No diabetes status-by-treatment interaction was found.

Apart from the increased bleeding risk, ticagrelor has the propensity to elevate uric acid and creatinine concentrations, increase ventricular pauses and cause dyspnea, side-effects which represent potential barriers to optimal compliance. Ticagrelor received regulatory approval in Europe in December 2010 and in the US in July 2011.

Cangrelor

Cangrelor (AR-C69931MX) belongs to a family of ATP analogs that are relatively resistant to the breakdown of endonucleotidases. It does not require metabolic activation and acts as a reversible, competitive antagonist on the $P2Y_{12}$ receptor. Administered parentally rather than orally, it has a short half-life of <5 minutes with a rapid onset of effect, inhibiting platelets to a high degree, and a quick offset of effect with resolution of normal platelet function within an hour of cessation of treatment [51,52]. While the pivotal trials to date have shown a satisfactory rate of major bleeding side effects, the highly potent cangrelor has not impacted significantly the occurrence of adverse cardiac events. The phase III CHAMPION-PCI and CHAMPION-PLATFORM trials compared cangrelor with clopidogrel 600 mg in ACS patients scheduled for PCI and were discontinued prematurely due to insufficient evidence of the clinical effectiveness of cangrelor, including that in diabetic patients [53]. The lack of overall demonstrable clinical benefit of cangrelor may be related to the definition of myocardial infarction used that made it difficult to adjudicate early ischemic events. This hypothesis is supported by a pooled analysis of the two trials using the universal definition of MI that showed cangrelor to be associated with a significant reduction in early ischemic events when compared with clopidogrel in patients with non-ST elevation ACS undergoing PCI [54,55].

The definition of MI was carefully chosen in a subsequent trial to assess cangrelor, the CHAMPION PHOENIX study [56,57]. This was a randomized double-blind, double-dummy trial that compared cangrelor with clopidogrel standard of care in 11,145 patients who had not previously received a $P2Y_{12}$ antagonist and who required PCI, including patients with stable angina and with acute coronary syndromes (with or without ST-segment elevation), the diabetic patients representing 28% of the study population. The primary efficacy end point (death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 hours after randomization) was lower in the cangrelor group versus the clopidogrel group (4.7% versus 5.9%; OR 0.78, p=0.005), driven by the reduction of the rate of acute periprocedural MI and by a reduced rate of stent thrombosis (0.8% versus 1.4% p=0.01). The benefit from cangrelor was consistent across several prespecified subgroups, with no significant interaction, including the diabetic subgroup (pinteraction=0.26). The rate of the primary safety end point was 0.16% versus 0.11% in the cangrelor and clopidogrel groups, respectively (p=0.44). Future studies are needed, however, to determine the optimal way to transition patients from cangrelor to prasugrel or ticagrelor, in patients with ACS and PCI, who represented only 43% of patients recruited in the CHAMPION-PHOENIX.

Due to its rapid on/off effect cangrelor has also the potential as a bridging agent in patients requiring surgery by adequately preventing ischemic events while allowing rapid restoration of platelet function on therapy discontinuation in the event of bleeding. The BRIDGE study evaluated this strategy for patients taking thienopyridine antiplatelet agents such as clopidogrel who are scheduled for surgery. Study drug was discontinued one to six hours before CABG surgery. Patients randomized to cangrelor had lower levels of platelet reactivity throughout the treatment period compared with placebo. There was no significant difference in major bleeding prior to CABG surgery. With the use of a surrogate endpoint, platelet reactivity as the primary endpoint, the findings of this trial must be interpreted with caution. However, it does demonstrate the potential role of cangrelor in this not uncommon setting.

Anti-GP IIb-IIIa

Numerous trials have shown clinical benefits for the GPIIb/IIIa antagonists (abciximab, eptifibatide and agrastat). These agents significantly reduce mortality after PCI, including that in diabetic patients. Thus, there is support for the use of GPIIb/IIIa receptor antagonists in high risk ACS patients [10,11]. These potent intravenous antiplatelet agents can restore a TIMI III flow in emergency cases of no-reflow procedure during PCI. For NSTEMI PCI patients, their use is mainly based on angiographic results (e.g. presence of thrombus and extent of disease), with a level of recommendation Ib [10].

For STEMI primary PCI patients, their use is recommended both in bail-out (massive thrombus, no-reflow) and planned in-lab situations, with a level of evidence of IIbA for abciximab, IIbB for eptifibatide and IIbB for agrastat. Furthermore, upstream use might be considered in high risk patients (IIbB recommendation) [11]. Having said that, the reduction of MACE with anti GPIIbIIIa might be linked to various factors, such as the ischemic level of risk of the included ACS population, the time of initiation of anti GPIIbIIIa, the P2Y12 inhibitors used (clopidogrel, prasugrel or ticagrelor) for the dual antiplatelet therapy with aspirin or the choice of anti-thrombotic drugs (UFH or LMWH or bivalirudin). Furthermore, the delay of action observed even with the new P2Y12 antagonists may be longer than expected especially in STEMI population, and recent studies have shown that optimal inhibition of platelet aggregation is reached between 2 to 6 hours after the LD administration and rarely before one hour [58,59]. Thus, GPIIb/IIIa antagonists may be useful in the early phase of ACS. However, their place will probably be challenged by Cangrelor in IV administration, because its antiplatelet effect stops quickly after cessation of the infusion.

Clinical implications of novel agents in diabetic patients

The above mentioned trials have clearly changed experts' recommendations with ESC guidelines recommending the use of either prasugrel or ticagrelor over clopidogrel for both STE-ACS and NSTE-ACS [10,11]. Prasugrel was approved by the FDA (US) in July 2009 and by the EMA (Europe) in February 2009. Ticagrelor received regulatory approval in Europe in December 2010 and in the US in July 2011.

Although there has been no trial with outcome endpoint, but exclusively pharmacodynamics studies comparing prasugrel with

ticagrelor, additional analysis of the pivotal trials may help identify preferential targets for these agents [59].

Is there still a place for clopidogrel in diabetic patients with ACS ?

With the advent of newer P2Y12 antagonists, the question as to the future role if any for clopidogrel in the acute and long-term treatment of ACS in diabetes must be addressed. Indeed, the newer agents are now recommended as first line for moderate to high-risk presenting patients. However, there are several clinical situations where clopidogrel may be preferable to these agents in the non-diabetic population. Firstly, for low risk, biomarker negative patients, clopidogrel remains the preferable agent. Secondly, for patients with high bleeding risk or for STEMI patients treated with lytics, or on concomitant oral anticoagulant therapy, the current guidelines advocate short duration of triple therapy and that the P2Y12 agent is clopidogrel [10,12]. Thirdly, generic clopidogrel is considerably cheaper and so may temper the enthusiasm for these newer agents in real-life practice. However, in a cost analysis comparing clopidogrel with prasugrel, prasugrel remained an economically dominant strategy: if a hypothetic generic cost for clopidogrel of $1 per day is used, the incremental net cost with prasugrel is $996 per patient, yielding an incremental cost-effectiveness ratio of $9727 per life-year gained [60]. Furthermore, putting in perspective the clinical outcome of diabetic patients, switching from prasugrel to clopidogrel will expose some patients to a higher risk of ischemic events, by reducing the level of platelet inhibition, and is probably not a wise strategy for this group [61]. Furthermore, based on clinical and health-economic evidence from the PLATO study, the treatment with ticagrelor was associated with increased health-care costs of 362 and a QALY gain of 0.13 compared with generic clopidogrel, yielding a cost per QALY gained with ticagrelor of €2753. Thefore, treating ACS patients with ticagrelor for 12 months is associated with a cost per QALY below generally accepted thresholds for cost-effectiveness [62].

Personalized treatment

The concept for personalized treatment based on platelet reactivity assessment with bedside monitoring assay and genotyping with rapid genetic testing platforms has been the subject of much debate recently. High-on treatment platelet reactivity (HPR) is well established as an independent predictor of increased cardiovascular events [63]. The factors related to variability of response to clopidogrel can broadly be divided into four categories: environmental, cellular, clinical and genetic [64]. Environmental factors include diet, age, smoking, and drug-drug interactions. Cellular mechanisms such as the accelerated platelet turnover and up regulation of the ADP platelet receptor pathway may also be important. There are multiple clinical factors such as diabetes, body mass index, renal impairment, drug-drug interactions and compliance, which also play a significant role in clopidogrel response.

Genetic variability in drug absorption and metabolism is a key factor responsible for the inefficient generation of the active drug metabolite. The two-step hepatic cytochrome P450 (CYP)-dependent oxidative metabolism of the prodrug appears to be of particular importance. Pharmacogenomic analyses have identified loss-of-function variant alleles of CYP 2C19 and specifically the 2C19*2 allele, to be the predominant genetic mediators of the antiplatelet effect of clopidogrel [65]. Carriers were shown to have lower active metabolite levels of clopidogrel, higher platelet reactivity and associated poorer outcomes.

Several trials have assessed whether adjustment of P2Y12 antagonist therapy in patients with poor metabolic response to clopidogrel or HPR improves clinical outcome. The TRIGGER PCI trial was to evaluate this but was discontinued due to low event rate [66]. In addition, two key randomized trials, GRAVITAS and ARCTIC have shown no benefit of the platelet monitoring, however have some methodology limitations [67,68]. The trend observed in reducing bleeding events by monitoring platelet activity must be confirmed by the ANTARTIC study that will evaluate the impact of platelet monitoring in terms of safety (bleeding events).

The aim of personalized treatment is to determine the best treatment option for each patient, based on several factors, such as clinical features, biological parameters, and genetic polymorphism, in order to optimize the net individual clinical benefit. This approach has already shown promising results in specific situations, such as patients with history of stent thrombosis [69].

Conclusion

Recent findings do not support the systematic use of aspirin in primary prevention of cardiovascular events in diabetics. However, while we await the results of two ongoing primary prevention trials (ASCEND and ACCEPT-D), patients with type 2 DM at high risk of cardiovascular events can be considered for low-doses of aspirin (75-162 mg/day) in primary prevention. Decisions should be taken on an individual patient basis. The global management of diabetic patients, especially the optimal control of hyperglycemia and also of the other risk factors (arterial hypertension, dyslipidemia, and smoking cessation) is necessary to decrease platelet reactivity and to enhance the efficacy of antiplatelet treatments.

Despite classic dual antiplatelet therapy with aspirin and clopidogrel in secondary coronary prevention, recurrent cardiovascular events in diabetic patients remain high, which casts doubt over the use of clopidogrel in these patients and thus the need for more potent and probably individualized antiplatelet regimens. More specific antiplatelet strategies have been integrated in recent European and American guidelines, and should be applied for diabetic patients in clinical practice.

References

1. López E, Berna-Erro A, Hernández-Cruz JM, Salido GM, Redondo PC, et al. (2013) Immunophilins are involved in the altered platelet aggregation observed in patients with type 2 diabetes mellitus. Curr Med Chem 20: 1912-1921.

2. Dalamaga M, Karmaniolas K, Lekka A, Antonakos G, Thrasyvoulides A, et al. (2010) Platelet markers correlate with glycemic indices in diabetic, but not diabetic-myelodysplastic patients with normal platelet count. Dis Markers 29: 55-61.

3. Bochenek M, Zalewski J, Sadowski J, Undas A (2013) Type 2 diabetes as a modifier of fibrin clot properties in patients with coronary artery disease. J Thromb Thrombolysis 35: 264-270.

4. Drouet L, Bal dit Sollier C, Henry P (2010) The basis of platelets: platelets and atherothrombosis: an understanding of the lack of efficacy of aspirin in peripheral arterial disease (PAD) and diabetic patients. Drugs 70 Suppl 1: 9-14.

5. L Drouet, C Bal di Sollier, P Henry. Les antiagrégants plaquettaires dans le diabète. http//www. Cardiologie.pratique.com/journal/article/therapeutique-les-antiagrégants-plaquettaires-dans-le-diabète

6. Barragan P, Sainsous J, Silvestri M, Bouvier JL, Comet B, et al. (1994) Ticlopidine and subcutaneous heparin as an alternative regimen following coronary stenting. Cathet Cardiovasc Diagn 32: 133-138.

7. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, et al. (2005) Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 366: 1607-1621.

8. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, et al. (2001) Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 345: 494-502.

9. Patrick T. O'Gara, Frederick G. Kushner, Deborah D. Ascheim, Donald E. Casey Jr, Mina K. Chung, et al. (2013) 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: Executive Summary - A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 127: 529-555.

10. Hamm CW, Bassand J-P, Agewall S, Bax J, Boersma E, et al. (2011) ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation. Eur heart J 32: 2999-3054.

11. Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, et al. (2012) ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). Eur heart J 33: 2569-2619.

12. Wright RS, Anderson JL, Adams CD, Bridges CR, Casey DE, et al. (2011) 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/ Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): a report of the American College of Cardiology Foundation/American Heart Association. Circulation 123: 2022-2060.

13. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, et al. (2013) 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. Circulation 127: e362-425.

14. Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, et al. (2007) American Heart Association; American Diabetes Association. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 30: 162-172.

15. Lars Ryde´n, Peter J. Grant, Stefan D. Anker, Christian Berne, Francesco Cosentino, et al. (2013) ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Authors/Task Force Members: European Heart Journal 34: 3035-3087.

16. Antithrombotic Trialists' (ATT) Collaboration1, Baigent C, Blackwell L, Collins R, Emberson J, et al. (2009) Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 373: 1849-1860.

17. Henry P, Vermillet A, Boval B, Guyetand C, Petroni T, et al. (2011) 24-hour time-dependent aspirin efficacy in patients with stable coronary artery disease. Thromb Haemost 105: 336-344.

18. Dillinger JG, Drissa A, Sideris G, Bal dit Sollier C, Voicu S, et al. (2012) Biological efficacy of twice daily aspirin in type 2 diabetic patients with coronary artery disease. Am Heart J 164: 600-606.

19. Grosser T, Fries S, Lawson JA, Kapoor SC, Grant GR, et al. (2013) Drug resistance and pseudoresistance: an unintended consequence of enteric coating aspirin. Circulation 127: 377-385.

20. Savi P, Pereillo JM, Uzabiaga MF, Combalbert J, Picard C, et al. (2000) Identification and biological activity of the active metabolite of clopidogrel. Thromb Haemost 84: 891-896.

21. Herbert JM, Savi P (2003) P2Y12, a new platelet ADP receptor, target of clopidogrel. Semin Vasc Med 3: 113-122.

22. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, et al. (2006) Clopidogrel plus aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 354: 1706-1717.

23. Bhatt DL, Marso SP, Hirsch AT, Ringleb PA, Hacke W, et al. (2002) Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. Am J Cardiol 90: 625-628.

24. Dasgupta A, Steinhubl SR, Bhatt DL, Berger PB, Shao M, et al. (2009) Clinical outcomes of patients with diabetic nephropathy randomized to clopidogrel plus aspirin versus aspirin alone (a post hoc analysis of the clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance [CHARISMA] trial). Am J Cardiol 103: 1359-1363.

25. Mehta SR, Yusuf S (2000) Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Study Investigators. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme; rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. Eur Heart J 21: 2033-2041.

26. MS Sabatine, CP Cannon, CM Gibson, JL Lopez-Sendon, G Montalescot, et al. (2005) Effect of Clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics. The PCI-CLARITY study. JAMA 294: 1224-1232.

27. The CURRENT–OASIS 7 Investigators (2010) Committee members of the Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Event -Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT–OASIS 7) trial. Dose Comparisons of Clopidogrel and Aspirin in Acute Coronary Syndromes. N Engl J Med 363: 930-942.

28. COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Early intravenous then oral metoprolol in 45852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005; 366: 1622–32.

29. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ; MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet. 364: 331-337.

30. Wang Y1, Wang Y, Zhao X, Liu L, Wang D, et al. (2013) Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 369: 11-19.

31. Prasugrel SPC - http://www.ema.europa.eu.

32. Ticagrelor SPC – Date of first authorization : 3rd December 2010

33. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, et al. (2007) Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 357: 2001-2015.

34. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, et al. (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 361: 1045-1057.

35. Brandt JT, Payne CD, Wiviott SD, Weerakkody G, Farid NA, et al. (2007) A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. Am Heart J 153: 66.

36. Norgard NB, Abu-Fadel M (2009) Comparison of prasugrel and clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Vasc Health Risk Manag 5: 873-882.

37. Mega JL, Close SL, Wiviott SD, Shen L, Walker JR, et al. (2010) Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. Lancet 376: 1312-1319.

38. Jean-Philippe Collet, Jean-Sébastien Hulot, Anna Pena, Eric Villard, Jean-Baptiste Esteve, et al. (2008) Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study.

39. Gilles Montalescot, Georgios Sideris, Remy Cohen, Catherine Meuleman, Claire Bal dit Sollier, et al. (2010) Prasugrel compared with high-dose clopidogrel in acute coronary Syndrome - The randomized, double-blind ACAPULCO* study. Thrombosis and Haemostasis 103.

40. Stephen D. Wiviott, Dietmar Trenk, Andrew L. Frelinger, Michelle O'Donoghue Franz-Josef Neumann, et al. (2007) Prasugrel Compared

With High Loading- and Maintenance-Dose Clopidogrel in Patients With Planned Percutaneous Coronary Intervention. The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation Thrombolysis in Myocardial Infarction 44 Trial Circulation.

41. Angiolillo DJ, Badimon JJ, Saucedo JF, Frelinger AL, Michelson AD, et al. (2011) A pharmacodynamic comparison of prasugrel vs. high-dose clopidogrel in patients with type 2 diabetes mellitus and coronary artery disease: results of the Optimizing anti-Platelet Therapy In diabetes MellitUS (OPTIMUS)-3 Trial. Eur Heart J 32: 838-846.

42. Stephen D. Wiviott, Eugene Braunwald, Dominick J. Angiolillo, Simha Meisel, Anthony J. Dalby, et al. (2008) Greater Clinical Benefit of More Intensive Oral Antiplatelet Therapy With Prasugrel in Patients With Diabetes Mellitus in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis in Myocardial Infarction . Circulation.

43. Gilles Montalescot , Leonardo Bolognese, Dariusz Dudek, Patrick Goldstein, Christian Hamm, et al. (2013) Pretreatment with Prasugrel in Non–ST Segment Elevation Acute Coronary Syndromes N Engl J Med.

44. Matthew T. Roe, Paul W. Armstrong, Keith A.A. Fox, Harvey D. White, Dorairaj Prabhakaran, et al. (2012) Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization N Engl J Med.

45. Wallentin L (2009) P2Y(12) inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. Eur Heart J 30: 1964-1977.

46. van Giezen JJ, Berntsson P, Zachrisson H, Björkman JA (2009) Comparison of ticagrelor and thienopyridine P2Y(12) binding characteristics and antithrombotic and bleeding effects in rat and dog models of thrombosis/hemostasis. Thromb Res 124: 565-571.

47. Storey RF (2011) Pharmacology and clinical trials of reversibly-binding P2Y12 inhibitors. Thromb Haemost 105 Suppl 1: S75-81.

48. Storey RF, Angiolillo DJ, Patil SB, Desai B, Ecob R, et al. (2010) Inhibitory Effects of Ticagrelor Compared With Clopidogrel on Platelet Function in Patients With Acute Coronary Syndromes The PLATO (PLATelet inhibition and patient Outcomes) PLATELET Substudy. J Am Coll Cardiol 56: 1456-1462.

49. Gurbel PA, Bliden KP, Butler K, Antonino MJ, Wei C, et al. (2010) Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies: the RESPOND study. Circulation 121: 1188-1199.

50. James S, Angiolillo DJ, Cornel JH, Erlinge D, Husted S, et al. (2010) Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J 31: 3006-3016.

51. Bhatt DL, Lincoff AM, Gibson CM, Stone GW, McNulty S, et al. (2009) Intravenous platelet blockade with cangrelor during PCI. N Engl J Med 361: 2330-2341.

52. Huang J, Driscoll EM, Gonzales ML, Park AM, Lucchesi BR (2000) Prevention of arterial thrombosis by intravenously administered platelet P2T receptor antagonist AR-C69931MX in a canine model. J Pharmacol Exp Ther 295: 492-499.

53. Harrington RA, Stone GW, McNulty S, White HD, Lincoff AM, et al. (2009) Platelet inhibition with cangrelor in patients undergoing PCI. N Engl J Med 361: 2318-2329.

54. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction (2007) Universal definition of myocardial infarction. J Am Coll Cardiol 50: 2173-2195.

55. White HD, Chew DP, Dauerman HL, Mahaffey KW, Gibson CM, et al. (2012) Reduced immediate ischemic events with cangrelor in PCI: a pooled analysis of the CHAMPION trials using the universal definition of myocardial infarction. American heart journal 163: 182-190.

56. Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, et al. (2013) Effect of platelet inhibition with cangrelor during PCI on ischemic events. N Engl J Med 368: 1303-1313.

57. Leonardi S, Mahaffey KW, White HD, Gibson CM, Stone GW, et al. (2012) Rationale and design of the Cangrelor versus standard therapy to acHieve optimal Management of Platelet InhibitiON PHOENIX trial. Am Heart J 163: 768-776.

58. Marco Valgimigli, Matteo Tebaldi, Gianluca Campo, Stefania Gambetti, Laura Bristot, Monia Monti, et al.(2012) Prasugrel Versus Tirofiban Bolus With or Without Short Post-Bolus Infusion With or Without Concomitant Prasugrel Administration in Patients With Myocardial Infarction Undergoing Coronary Stenting. The FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) Trial. J Am Coll Cardiol Intv 5: 268-277.

59. Dimitrios Alexopoulos, Ioanna Xanthopoulou, Vassilios Gkizas, George Kassimis, Konstantinos C. Theodoropoulos, et al. (2012) Randomized Assessment of Ticagrelor Versus Prasugrel Antiplatelet Effects in Patients with ST-Segment–Elevation Myocardial Infarction. Circ Cardiovasc Interv 5: 797-804.

60. Mahoney EM, Wang K, Arnold SV, Proskorovsky I, Wiviott S, et al. (2012) Cost-effectiveness of prasugrel versus clopidogrel in patients with acute coronary syndromes and planned percutaneous coronary intervention: results from the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with Prasugrel-Thrombolysis in Myocardial Infarction TRITON-TIMI 38. Circulation. 121: 71-79.

61. Kerneis M, Silvain J, Abtan J, Cayla G, O'Connor SA, et al. (2013) Switching acute coronary syndrome patients from prasugrel to clopidogrel. JACC Cardiovasc Interv 6: 158-165.

62. Elisabet Nikolic, Magnus Janzon, Ole Hauch, Lars Wallentin, and Martin Henriksson, Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study for the PLATO Health Economic Substudy Group European Heart Journal.

63. Bonello L, Tantry US, Marcucci R, Blindt R, Angiolillo DJ, et al. (2010) Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol 56: 919-933.

64. O'Connor SA, Hulot JS, Silvain J, Cayla G, Montalescot G, et al. (2012) Pharmacogenetics of clopidogrel. Curr Pharm Des 18: 5309-5327.

65. Shuldiner AR, O'Connell JR, Bliden KP, Gandhi A, Ryan K, et al. (2009) Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA 302: 849-857.

66. Trenk D, Stone GW, Gawaz M, Kastrati A, Angiolillo DJ, et al. (2012) A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI (Testing Platelet Reactivity. Journal of the American College of Cardiology 59: 2159-2164.

67. Price MJ, Berger PB, Teirstein PS, Tanguay J-F, Angiolillo DJ, et al. (2011) Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA: the journal of the American Medical Association 305: 1097-1105.

68. Collet JP, Cuisset T, Rangé G, Cayla G, Elhadad S, et al. (2012) Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med 367: 2100-2109.

69. Cayla G, Hulot JS, O'Connor SA, Pathak A, Scott SA, et al. (2011) Clinical, angiographic, and genetic factors associated with early coronary stent thrombosis. JAMA 306: 1765-1774.