Clinical impact of high platelet reactivity and platelet function test based antiplatelet treatment strategy in patients after percutaneous coronary intervention

Ph. D. thesis

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Content

Abbreviations

ACS = acute coronary syndrome

ACE-I = angiotensin-converting enzyme inhibitor

ADP = adenosine diphosphate

AMI= acute myocardial infarction

ARB = angiotensin receptor blocker

ARC= Academic Research Consortium

ASA= acetylsalicylic acid

AUC = area under the curve

BARC= Bleeding Academic Research Consortium

BMS= bare metal stent

CABG = coronary artery bypass grafting

CAD= coronary artery disease

cAMP= cyclic adenosine monophosphate

CI = confidence interval

COX= cyclooxygenase

CPTP= cyclopentyl-triazolopyrimidine

CV= cardiovascular

Cx = circumflex artery

CYP= cytochrome P

DAPT= dual antiplatelet therapy

DEB = drug-eluting balloon

DES= drug-eluting stent

eGFR = estimated glomerular filtration rate

GPI = glycoprotein IIb/IIIa inhibitor

HPR = high platelet reactivity

HR = hazard ratio

ISR= in-stent restenosis

LAD = left anterior descending

LD = loading dose

MACE= major adverse cardiac events

MDRD = modification of diet in renal disease

MI = myocardial infarction

N/A = not available

NPR= normal platelet reactivity

NSTEMI = non–ST-segment elevation myocardial infarction

OAC = oral anticoagulation

OCT= optical coherence tomography

PCI = percutaneous coronary intervention

PFT= platelet function testing

PPI = proton pump inhibitor

pts = patients

RCA = right coronary artery

RR= relative risk

SD= standard deviation

ST= Stent thrombosis

STEMI = ST-segment elevation myocardial infarction

TIA = transient ischemic attack

TVR= target vessel revascularisation

VASP= vasodilator stimulated phosphoprotein

Introduction

The long-term success of myocardial revascularisation requires the optimisation of pharmacological and interventional treatment protocols which consider both the thrombotic and bleeding complications. However, the treatment based on the current therapeutic recommendations still fails to fully eliminate these adverse events after percutaneous coronary intervention (PCI). The short – and long-term results of PCI are multifactorial and depend on the clinical setting (chronic coronary syndrome or acute coronary syndrome), the complexity of the coronary disease, the operator experience, the patient status and comorbidities. The most important ischemic complications after PCI include recurrent ischemia due to the thrombosis of the previously stented segment or the overproliferation of the intimal layer of the treated vessel which leads to thickened neointima and reduced vessel lumen.

Ischemic outcomes after PCI

Stent thrombosis

Stent thrombosis (ST) is the most important short-term complication after PCI, which caused by mostly the total occlusion of the previously stented segment and usually manifests in acute myocardial infarction (AMI) and associated significantly with mortality (1) (2). It is a multifactorial adverse event associated with both procedural (stent under-expansion, lack of stent strut apposition, malposition, edge dissection) and clinical (AMI, diabetes, impaired renal function, heart failure) abnormalities, as well as platelet and coagulation factors (not eligible use of antiplatelet therapy, high platelet reactivity) (3). Based on the Academic Research Consortium (ARC) definition, ST is categorised as definite, probable, or possible (4). Alternatively, ST can be classified based on timing of occurrence and categorized as early (≤ 30 days), which is further divided into acute (within the first 24 h) and subacute (days 2–30), late (between 31 days and 1 year), and very late (beyond 1 year). Definite ST occurs in 0.5-1.9 % after 12 month and lowest in patients treated with new-generation drug-eluting stent (DES) followed by early-generation DES and bare metal stent (BMS).

Several large-sale randomized trials showed the superiority of dual antiplatelet therapy (DAPT) with the administration of aspirin plus thienopyridine to reduce both stent thrombosis and bleeding complications compared to aspirin monotherapy or aspirin plus oral anticoagulation, which was the initial standard treatment after PCI (5) (6) (7) (8). A recent randomised trial has also shown that, DAPT is more effective compared to aspirin monotherapy to reduce the incidence of very late stent thrombosis (9). The newer P2Y12 inhibitors prasugrel and ticagrelor showed a significant reduction of early and late stent thrombosis compared to clopidogrel in patients with ACS, however, there were significant increases in the rate of major bleeding complications with both novel P2Y12 inhibitors (2) (10).

In-stent restenosis

The most prevalent adverse event within 9-12 months after PCI is target lesion revascularization owing to in-stent restenosis (ISR) (11). Despite ST, in-stent restenosis (ISR) is a chronic process which caused by the overproliferation of the endothelial and smooth muscle cells and leads to neointimal hyperplasia in the stented segment that reduces progressively the target vessel lumen (12) (13). Similarly to ST, ISR is also caused by multiple risk factors, such as procedural (e.g. angiographic complexity), clinical (e.g. diabetes) and hemorheological abnormalities (slow flow, poor outflow), which can play a significant role in the development of ISR (14) (15). Platelet activation and insufficient antiplatelet therapy may play also a significant role in the development of ISR as activated platelets might trigger the proliferation of the neointimal layer by releasing growth factors and recruiting leucocytes (12).

In most of the cases ISR manifests as a stable coronary artery disease (CAD) with recurrent stable angina. However it can also present as myocardial infarction (MI) (16) (17) (18) and angiographically, patients with MI tend to have an aggressive pattern of restenosis and total occlusion of the target lesion. One of the most likely explanation of MI in ISR include late stent or device thrombosis, which can be caused by incomplete neointimal coverage, early termination of antiplatelet therapy and/or increased neointimal thrombogenic tissue factors such as tissue factor and collagen (16).

The prevalence of target vessel revascularisation (TVR) due to ISR is 9 - 15% with BMS and <5% with new-generation DES (19). DES successfully decreased the incidence if ISR compared to BMS due to the anti-proliferative and/or cytostatic drugs that are released from the stent to the intimal layer and prevent the neointimal overproliferation and the development of ISR. On the other hand, these antiproliferative effect leads to prolonged endothelization of the stented segment which can lead to stent thrombosis, therefore sufficient antiplatelet therapy has a substantial role in the treatment strategy.

The recent European guidelines consider drug-eluting balloon (DEB) and DES to be equal possible alternatives for treatment of ISR since several randomized studies demonstrated the safety, efficacy and non-inferiority of DEB compared to DES for the treatment of ISR (20) (21) (22) (23) (24) (25) (26) (27).

Antiplatelet therapy

COX-1 inhibitor: Aspirin

The anti-inflammatory and analgesic effects of willow bark have already been recorded in the Egyptian pharmacopoeia known as the Ebers papyrus scroll. The bactericidal, anti-inflammatory effect of the preparation has been used in ancient Greece. However, during use, most of the problems were caused by the gastric irritant effect. The synthesis and acetylation of salicylic acid to reduce its irritant effect took place in 1897. The drug thus prepared became available in 1903 as acetylsalicylic acid (ASA) aspirin. Aspirin is the most commonly used analgesic and antiplatelet agent. Inhibition of platelet aggregation based on irreversible COX-1 (cyclooxygenase) inhibition is one of the most effective treatments in modern cardiology, and its efficacy and benefits are supported by a large number of studies in almost the entire spectrum of coronary heart disease.

ADP-receptor antagonists

The molecular target of the ADP (adenosine diphosphate) receptor antagonists is the P2Y12 receptor, which is a surface bound protein found on blood platelets and one of the key initiator of platelet activation (28). The P2Y12 receptor is a G-protein binded receptor and is activated by adenosine diphosphate. ADP binds to the P2Y12 receptor that leads to inhibition of adenyl cyclase and which leads to the decrease of the intracellular levels of cAMP (cyclic adenosine monophosphate). The cAMP reduction reduces phosphorylation of vasodilator stimulated phosphoprotein (VASP) that leads to the activation of the glycoprotein IIb/IIIa receptors (29). Activation of the glycoprotein IIb/IIIa receptors increases thromboxane production and therefore platelet aggregation (30). These drugs antagonize the P2Y12 platelet receptors and this leads to a decrease platelet aggregation which inhibits thrombus formation.

The group of thienopyridines includes ticlopidine, clopidogrel and prasugrel, these are prodrugs and need to be converted to an active metabolite which cause irreversible inhibition of P2Y12 receptor. Thienopyridines are metabolized in the liver and the intestinal tract to active metabolites (31). Ticagrelor belongs to the non-thienopyridine family and is a reversible P2Y12 receptor antagonist. Ticagrelor is not a prodrug, it does

not require a metabolic activation and act directly on the P2Y12 receptor which leads to a faster onset and offset of action.

Ticlopidine

Ticlopidine was the first generation thienopyridine which was withdrawn from clinical use following high incidence of hematopoietic side effects such as thrombotic thrombocytopenic purpura, aplastic anaemia and neutropenia. Next to the potential severe side effects the main disadvantages included the slow onset of action (approx. 24 h), gastrointestinal symptoms, rash and twice daily intake. The clinical use of the drug was quickly replaced by clopidogrel, since the latter had quicker onset of action and a better safety profile mainly in terms of allergy, skin and gastrointestinal side effects and neutropenia (32) (33).

Clopidogrel

Clopidogrel, a second generation thienopyridine, started in preclinical trials in 1987 and reached global market in 1998. Clopidogrel is a prodrug and metabolized by two pathways. After gastrointestinal absorption almost 75 % of clopidogrel is hydrolysed to an inactive metabolite by blood esterases and rapidly cleared via glucuronidation followed by renal excretion. The other pathway is the hepatic metabolic activation through the cytochrome P450 (CYP450) enzyme system which is a two-step process. First clopidogrel is metabolised via oxidation into 2-oxo-clopidogrel and hydrolysed to the thiol derivate which is the active metabolite that binds irreversibly to the P2Y12 receptor (34). These processes are mainly catalysed by the CYP2C19. The CYP1A2, CYP3A4, CYP3A5 isoenzymes are also considered to be involved in clopidogrel metabolism however, with a lesser extent (35).

Although clopidogrel had better activity/toxicity ratio than ticlopidine, in significant proportion of the patients the efficacy of the bioactivation of clopidogrel is decreased. The major factor in the decreased activation is CYP2C19 polymorphism, which occurs in approximately 30% of the Caucasian population. This led to loss of function of the CYP2C19 isoenzyme which led to poor metabolization of clopidogrel into its active form (36). In addition, drugs that are CYP2C19 inhibitors may interact with the metabolism

of clopidogrel and lead to decreased activity. All proton pump inhibitors except for rabeprazole and pantoprazole are metabolized by the hepatic CYP450 enzyme and might cause drug interactions and impaired active metabolite generation (37).

The clinically approved dosage of clopidogrel is a 600-mg loading dose and a 75-mg a day maintenance dose per os and with this administration clopidogrel has a measurable effect at 2 hours and a peak effect at 6 hours.

It has been shown in several randomised studies, clopidogrel is an effective antiplatelet agent through the significant reduction of the ischemic events in patients with coronary heart disease with a superiority compared to aspirin (38), followed by trials to demonstrate the clinical benefit of dual antiplatelet therapy with clopidogrel on top of aspirin (39)(40)(41).

For many years dual treatment with aspirin and clopidogrel was routine practice and served as the main antiplatelet agents for the prevention of thrombotic events in patients with ischemic heart disease but the inconsistent and unpredictable efficacy and the inefficient bioavailability of clopidogrel limited its use in patients with high on treatment platelet reactivity and supported the need of new more potent P2Y12 blockers with more consistent degree of ADP-receptor inhibition.

New generations

The new generational P2Y12 receptor inhibitors aimed to address these issues with improvement in outcome for patients with ischemic heart disease. These ADP- receptor antagonists achieve a faster, more consistent and stronger inhibition of platelets by more efficiently antagonizing the P2Y12 receptor compared to clopidogrel. Although the new P2Y12 blockers are associated with a significant decrease of the ischemic events, this more potent platelet inhibition comes at the cost of a higher bleeding risk (42)(43). The European guidelines favour ticagrelor and prasugrel over clopidogrel in patients with acute coronary syndrome (ACS) on top of aspirin for 12 months (44) however, in an era with a wide spread of generic clopidogrel, in addition with the high treatment costs of novel P2Y12 inhibitors together with the higher risk of bleeding suggest the need of a tailored individual antiplatelet therapy to achieve the maximum efficacy with the lowest harm to the patients. In patients with stable CAD clopidogrel on top of aspirin for 6 months is recommended (44).

Prasugrel

Prasugrel is a third generation thienopyridine which achieves a faster, more potent, and consistent degree of P2Y12 inhibition compared to clopidogrel. The main difference between prasugrel and clopidogrel is that prasugrel is metabolized more efficiently than clopidogrel. Prasugrel is also a pro-drug but its metabolism starts in the intestines where it is metabolized by esterase into a thiolactone, which is then converted to the active metabolite in a single CYP-dependent step. That means prasugrel and its metabolite are not inactivated by plasma esterases and all absorbed molecules are converted into active metabolite. Prasugrel is not metabolized by CYP2C19 like clopidogrel and genetic CYP variants do not have a significant influence on the active metabolites of prasugrel. In addition, drug interactions do not affect the metabolization and efficacy of prasugrel (45)(46).

The clinically approved dose of prasugrel is a 60-mg loading dose and a 10-mg a day maintenance dose. The degree of the platelet inhibition at 30 minutes after loading dose is equal with the peak effect of 600 mg clopidogrel and the peak effect of prasugrel at approximately 2 hours achieves 2-3 times stronger platelet inhibition than clopidogrel.

Ticagrelor

Ticagrelor is a non-thienopyridine which belongs to a novel chemical class, cyclopentyl-triazolopyrimidine (CPTP) (44). Ticagrelor came to the market in 2010 in Europe, and 2011 in USA.

Ticagrelor was the first direct oral reversible inhibitor of the P2Y12 receptor. Ticagrelor is not a prodrug and is active after oral administration without the need for any metabolic activation. It is rapidly absorbed and undergoes enzymatic degradation to at least one active metabolite which is almost as potent as its parent compound and together with the original molecule is responsible to the receptor inhibition (46). Ticagrelor has improved pharmacokinetic and pharmacodynamic profiles compared to currently available drugs with a plasma half-life approx. 12 hours. Similarly to prasugrel, ticagrelor is not metabolized by CYP enzymes and CYP2C19 genotypes that are known to influence the effect of clopidogrel do not influence the effect of ticagrelor (35).

Ticagrelor is a much more potent inhibitor of platelet aggregation than clopidogrel and compared to clopidogrel, ticagrelor showed a significant risk reduction in the composite ischemic outcomes however, with a significant increase in the rate of major bleeding complications and an increase of dyspnoea episodes in patients (42) (47).
The approved clinical dosage of ticagrelor is a 180-mg loading dose and a 90-mg twice daily maintenance dose.

High platelet reactivity on clopidogrel treatment

A wide interindividual variability of the concentrations of the active metabolite has been shown in previous studies after administration of the recommended loading- and maintenance dose of clopidogrel (48) (49) (50). One of the crucial enzymes in clopidogrel metabolism is CYP2C19 which is involved in both steps of the biotransformation. A polymorphism of the enzyme CYP2C19 leads to decreased enzymatic activity and reduced development of the active metabolite of clopidogrel. The insufficient generation of the active metabolite is largely responsible for the interindividual differences in posttreatment platelet reactivity (51). As the active metabolite formation is influenced by genetic, clinical, and pharmacologic factors, the development of high platelet reactivity (HPR) is a multifactorial process (52).
Numerous studies have showed that patients defined with HPR on clopidogrel treatment were at higher risk for recurrent ischemic events (53). It was demonstrated in a metaanalysis including 20 trials and almost 9200 patients, HPR associated with 3-fold higher risk for nonfatal MI, 3.4-fold increase in cardiovascular (CV) death and 4-fold higher rate for ST and it is a strong independent predictor of recurrent ischemic events and mortality after coronary stent implantation (52). The prevalence of HPR showed large heterogeneity in the included trials with a mean prevalence of 32.3% (53). The results of since then published large-scale randomised trials also support these findings (54).

Aims

The main aims of our studies were the following:

A. to determine the clinical and pharmacodynamic impact of optimizing P2Y12 inhibition based on platelet function testing in patients with acute coronary syndrome after percutaneous coronary intervention.

B. to evaluate the impact of high platelet reactivity together with conventional risk factors and procedural characteristics on clinical outcomes in patients with ISR undergoing PCI with DEB.

Methods

Study design

As part of our studies we built two single centre prospective registries in the Heart Institute, University of Pécs. We aimed to recruit real-life, high risk, all-comer population of patients with ACS (PECS-HPR registry) and also patients with stable CAD including ISR (PECS-DEB registry).

Patient population

Starting on September 1, 2011, consecutive high-risk patients with ACS who were pre-treated with clopidogrel and undergoing successful PCI with stent implantation and there was no contraindication to treatment with a P2Y12 inhibitor for 1 year were enrolled in a prospective registry (PECS-HPR registry). Clopidogrel pre-treatment was defined as either a loading dose of 600 mg before or during the PCI or long-term treatment for more than 5 days with 75 mg/day. Exclusion criteria included an indication for chronic oral anticoagulation and age older than 80 years, lack of pre-treatment with clopidogrel, or administration of other $P2Y_{12}$inhibitors before or during PCI. Importantly, ticagrelor was not available in Hungary during enrolment in the registry.

Starting on October 1, 2009, patients treated with DEB for ISR were enrolled in a single centre prospective registry (PECS-DEB registry). In our all-comer registry there were no exclusion criteria.

All included patients have been properly instructed and have given written informed consent to comply with the offered antiplatelet therapy and to be available for follow-up and telephone visit for 1 year after PCI.

Percutaneous coronary intervention

The selection of technique and revascularization strategy was at the discretion of the operators, including the choice of vascular access, type and number of stent or DEB and

need for pre- or post-dilatation or bailout stenting. All patients received 60 to 80 IU/kg of unfractionated heparin for PCI. Tirofiban was given at the discretion of the operator as a 25-mg/kg bolus followed by an optional 6- to 12-h infusion in patients with ACS.

Platelet function testing and choice of P2Y12 inhibitor treatment

Antecubital venous blood samples were collected using a sterile 21-gauge needle into hirudin coated vacuum tubes (Becton and Dickinson, Munich, Germany) without stasis. Platelet function testing was performed with the Multiplate analyser (Roche Diagnostics GmbH, Rotkreuz, Switzerland/Mannheim, Germany) 6 to 36 hours after PCI. If tirofiban was administered, assessment of platelet function was postponed until 24 h after cessation of treatment. HPR was defined according to the consensus cut-off, which was an adenosine diphosphate (ADP)-test value greater than 46 U. (55)

In ACS-patients without HPR standard dose (75 mg/day) of generic clopidogrel was continued after PCI (no HPR group). ACS-patients with HPR were either switched to prasugrel (HPR + prasugrel group) with a loading dose of 60 mg followed by a maintenance dose of 10 mg/day or treated with adjusted, high dose clopidogrel (HPR + clopidogrel group) as previously described and proposed by Bonello et al. (56) Patients were treated with additional loading doses of 600 mg of clopidogrel up to 4 times on the basis of controlled Multiplate testing each day to normalize platelet reactivity below the pre-defined cut-off of HPR. According to the achieved level of platelet reactivity, a maintenance dose of 75 mg/day (no HPR) or 150 mg/day (HPR) was selected.
Patients were not randomly allocated to the prasugrel or high-dose clopidogrel groups; the choice of treatment was at the discretion of the 7 expert operators. Some operators favoured a switch to prasugrel, whereas others supported the use of high-dose clopidogrel.
All patients received a loading dose of 300 mg aspirin followed by a maintenance dose of 100 mg/day.

In ISR-patients antiplatelet treatment was given according to the actual European guidelines of myocardial revascularization and treatment of stable angina.(3) All

patients received 100 mg of aspirin, and clopidogrel was the choice from oral P2Y12-inhibitors. A small group of patients with prior acute myocardial infarction within a year were treated with prasugrel that was continued regardless of the platelet function testing. Patients on clopidogrel continued treatment with an optional loading dose at the time of PCI decided by the operator. Patients without chronic P2Y12-inhibitors were treated with a 300/600 mg loading dose of clopidogrel, followed by a maintenance dose of 75 mg/day. Results of platelet function testing did not lead to treatment corrections regarding P2Y12-inhibitor treatment in ISR-patients.

Dual antiplatelet therapy was proposed to maintain during 12 months after the PCI.

Registered data

Data were collected prospectively from dedicated hospital records, follow-up visits and a national vital record database. Follow-up data were obtained at clinical presentations and at a telephone visit scheduled at 12 months after the index PCI. Detailed procedural parameters of the intervention as well as risk factors, demographic data, medication information and laboratory parameters were also registered.

Clinical endpoints and follow-up

The clinical follow-up was 1 year after the index PCI in both studies.

The primary composite efficacy endpoint of the PECS-HPR registry was all-cause mortality, stent thrombosis, nonfatal myocardial infarction, or stroke at 1 year. The primary safety endpoint was the occurrence of major bleeding events.

The primary endpoint of the PECS-DEB registry was the occurrence of major adverse cardiac events (MACE) defined as the composite of cardiovascular mortality, any revascularization, myocardial infarction or stroke/transient ischemic attack (TIA).

Secondary endpoints included the individual elements of the composite endpoint and rates of target vessel revascularization were also compared in both registries.

Stent thrombosis was defined as definite or probable according to the Academic Research Consortium criteria.(4) Myocardial infarction was defined according to the universal definition, including type 1, 4a, and 4b in the PECS-HPR registry.(58) Type 4 periprocedural MI was not considered as an endpoint in the PECS-DEB registry. Any revascularization included percutaneous or surgical interventions of the coronary arteries after the DEB PCI. Stroke and TIA was defined according to American Heart Association/American Stroke Association definition. (59) (60) Major bleeding was defined according to the Bleeding Academic Research Consortium (BARC) criteria, including type 3 and 5 in the analysis.(61)

Statistical analysis

Continuous variables with normal distribution are presented as mean ± standard deviation (SD), whereas non-normally distributed variables are presented as median and interquartile range. Categorical variables are expressed as frequencies and percentages. Differences between groups were assessed with the Fisher's exact test or chi-square test, as appropriate for categorical variables. Unpaired t tests were used for comparisons of normally distributed continuous variables, whereas non-normally distributed variables were compared using the Mann-Whitney U test.

Patients with HPR were compared with the no HPR group in Cox regression models. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for occurrence of clinical endpoints at follow-up. Cox regression and Kaplan-Meier analysis was performed to assess the impact of demographic, clinical and procedural characteristics on the study's endpoint. Variables were assessed in univariate as well as in multivariate Cox proportional model analyses. In the latter, covariates with a threshold of $p < 0.10$ (PECS-DEB registry)/ $p < 0.05$ (PECS-HPR registry) in the univariate Cox analyses were entered into an initial multivariate model than removed stepwise based on the probability of the likelihood-ratio statistic to determine independent predictors of the clinical endpoint. Improvement over the baseline model was checked with Omnibus tests of model coefficients. Survival differences between the groups and the cumulative incidence of the clinical endpoint were calculated according to the Kaplan-Meier method.

Statistical analysis was performed using SPSS Statistics V22 (IBM Corporation, Armonk, NY, USA) and Graph Pad Prism software 5 (GraphPad Software, Inc., La Jolla, CA, USA). Values of $p<0.05$ were considered statistically significant and values of $p<0.1$ were considered as a trend.

Special statistical methods applied in our studies

In the PECS-HPR registry prior data were only available for the impact of treatment with high-dose clopidogrel in HPR, so the sample size was calculated to show a clinically relevant difference in primary endpoints between the HPR + clopidogrel and the no HPR groups. On the basis of the results of a prior registry (62), we estimated a 2-fold risk (relative risk [RR]: 2.00) in the primary endpoint between groups with an estimated 1-year absolute risk of 12% for the no HPR group (63) (64). Assuming a 30% rate of HPR and an equal distribution of patients with HPR treated with high-dose clopidogrel or prasugrel, 605 patients were required to detect a difference between the HPR + clopidogrel and no HPR groups with 80% power at a 2-sided alpha level of 0.05. Together with the prasugrel group, 700 patients were needed. Allowing for dropouts, we planned to enrol 750 patients in the PECS-HPR registry.

Specificity and sensitivity of platelet function test cut-off points in predicting the occurrence of the primary endpoint were determined by ROC curve analysis in the PECS-DEB registry.

Results

A. Optimizing $P2Y_{12}$ receptor inhibition in patients with acute coronary syndrome on the basis of platelet function testing: impact of prasugrel and high-dose clopidogrel

Patient characteristics

Between September 1, 2011 and August 31, 2012, 1519 patients with ACS were admitted to our centre for urgent coronary angiography. After coronary angiography, 976 patients underwent successful PCI with stent implantation. From these patients based on the inclusion criteria, 741 patients (65 % male) were enrolled in the PECS-HPR registry with a mean age of 62 (Fig. 1, Table 1A). Baseline clinical, procedural, laboratory, and treatment characteristics are shown in Table 1.A and according to the treatment groups in Table 1.B. Based on the cardiovascular risk factors, the patient population composed a very high-risk, all-comer, consecutive cohort of patients with ACS. 85% of the patients had an acute myocardial infarction, 48% had an ST-segment elevation myocardial infarction, and 4.5% had cardiogenic shock (Table 1A). Patients with HPR were significantly younger and had a higher incidence of diabetes and ST-segment elevation myocardial infarction as well as a longer total stent length witch reflects a more complex coronary disease. In addition, platelet count, leukocyte count, and high-sensitivity C-reactive protein levels were significantly higher in patients with HPR compared with those without HPR (Table 1A). In contrast, patients with HPR who were treated with prasugrel or high-dose clopidogrel had comparable baseline characteristics except for greater use of statins and beta-blockers in the prasugrel group (Table 1B).

Table 1.A Baseline characteristics of the patient population

Baseline characteristics	Overall (n=741)	HPR+ adjustment (n=219)	no HPR (n=522)	P (HPR vs. no HPR)
Clinical characteristics				
Age, years	62.3 (10.9)	60.8 (10.7)	62.9 (10.9)	<0.05
Male	483 (65.2)	136 (62.1)	347 (66.5)	0.27
Type 2 diabetes mellitus	193 (26.0)	68 (31.1)	125 (23.9)	0.05
Type 2 diabetes mellitus (insulin-treated)	64 (8.6)	25 (11.4)	39 (7.5)	0.09
Hypertension	530 (71.5)	158 (72.1)	372 (71.3)	0.86
Known dyslipidaemia	174 (23.5)	46 (21.0)	128 (24.5)	0.34
Smoking	146 (19.7)	41 (18.7)	105 (20.1)	0.69
Prior PCI	84 (11.3)	32 (14.6)	52 (10.0)	0.08
Prior CABG	64 (8.6)	15 (6.8)	49 (9.4)	0.32
Prior MI	115 (15.5)	39 (17.8)	76 (14.6)	0.27
Admission characteristics				
Troponin positive	626 (84.5)	192 (87.7)	434 (83.1)	0.15
STEMI	358 (48.3)	124 (56.6)	234 (44.8)	<0.01
NSTEMI	268 (36.2)	68 (31.1)	200 (38.3)	0.07
Unstable angina	115 (15.5)	27 (12.3)	88 (16.9)	0.15
Cardiogenic shock	33 (4.5)	14 (6.4)	19 (3.6)	0.12
Loading dose of 600 mg of clopidogrel	706 (95.3%)	212 (96.8%)	494 (94.6%)	0.26
Use of clopidogrel ≥5 days before PCI	35 (4.7%)	7 (3.2%)	28 (5.4%)	
PCI procedure				
Bare-metal stent	549 (74.1)	160 (73.1)	389 (74.5)	0.71
Total stent length, mm	31 (21.5-50)	33 (23-59)	30 (18.8-48)	0.01

Stent count/patient	2 (1-2)	2 (1-3)	2 (1-2)	0.06
Laboratory findings 1 day after PCI				
Hemoglobin, g/dl	13.5±1.7	13.6±1.8	13.5±1.7	0.45
Leukocyte count, g/l	10.7 (8.6-14)	11.6 (9.2-15.0)	10.5 (8.2-13.3)	0.0001
Platelet count, g/l	253 (215-302)	271.5 (232-324)	245 (208-290)	<0.0001
Creatinine, µmol/l	76 (64-92)	74 (63-92)	78 (65-93)	0.19
eGFR, MDRD	87.2±31.2	88.5±31.6	86.7±31.1	0.47
C-reactive protein, mg/l	4.7 (1.7-20.9)	6.3 (2.6-31.2)	3.8 (1.5-16.2)	0.0004
Discharge medication				
Aspirin	736 (99.3)	217 (99.1)	519 (99.4)	0.64
ACE-I/ARB	573 (77.3)	168 (76.7)	405 (77.6)	0.85
Beta-blocker	571 (77.1)	169 (77.1)	402 (77.0)	1.00
Proton pump inhibitor	703 (94.9)	202 (92.2)	501 (96.0)	<0.05
Statin	662 (89.3)	197 (90.0)	465 (89.1)	0.79

Table 1.B Baseline characteristics of the patient population

Baseline characteristics	HPR (n = 219)			No HPR (n = 522)	p †
	Prasugrel (n = 91)	High-Dose Clopidogrel (n = 128)	p *		
Clinical characteristics					
Age, years	59.3 ± 9.5	61.8 ± 11.5	0.09	62.9 ± 10.9	<0.05
Male	52 (57.1)	84 (65.6)	0.21	347 (66.5)	0.27
Type 2 diabetes mellitus	33 (36.3)	35 (27.3)	0.18	125 (23.9)	0.05
Type 2 diabetes mellitus (insulin-treated)	12 (13.2)	13 (10.2)	0.53	39 (7.5)	0.09
Hypertension	64 (70.3)	94 (73.4)	0.65	372 (71.3)	0.86
Known dyslipidaemia	21 (23.1)	25 (19.5)	0.61	128 (24.5)	0.34
Smoking	16 (17.6)	25 (19.5)	0.86	105 (20.1)	0.69
Prior PCI	12 (13.2)	20 (15.6)	0.70	52 (10.0)	0.08
Prior CABG	4 (4.4)	11 (8.6)	0.28	49 (9.4)	0.32

Prior MI	14 (15.4)	25 (19.5)	0.48	76 (14.6)	0.27
Admission characteristics					
Troponin positive	81 (89.0)	111 (86.7)	0.68	434 (83.1)	0.15
STEMI	55 (60.4)	69 (53.9)	0.41	234 (44.8)	<0.01
NSTEMI	26 (28.6)	42 (32.8)	0.55	200 (38.3)	0.07
Unstable angina	10 (11.0)	17 (13.3)	0.68	88 (16.9)	0.15
Cardiogenic shock	4 (4.4)	10 (7.8)	0.41	19 (3.6)	0.12
Loading dose of 600 mg of clopidogrel	88 (96.7)	124 (96.9)	1.00	494 (94.6)	0.26
Use of clopidogrel ≥5 days before PCI	3 (3.2)	4 (3.1)		28 (5.4)	
PCI procedure					
Bare-metal stent	60 (65.9)	100 (78.1)	0.06	389 (74.5)	0.71
Total stent length, mm	32 (24–56)	36 (23–60)	0.86	30 (18.8–48)	0.01
Stent count/patient	2 (1–2)	2 (1–3)	0.52	2 (1–2)	0.06
Laboratory findings 1 day after PCI					
Haemoglobin, g/dl	13.6 ± 1.6	13.5 ± 1.9	0.91	13.5 ± 1.7	0.45
Leukocyte count, g/l	11.4 (9.0–14.7)	12.2 (9.3–15.3)	0.25	10.5 (8.2–13.3)	0.0001
Platelet count, g/l	270 (232–331)	272 (232–318.5)	0.81	245 (208–290)	<0.0001
Creatinine, µmol/l	71.5 (63–82.8)	76 (63–96)	0.29	78 (65–93)	0.19
eGFR, MDRD	90.3 ± 26.3	87.1 ± 35.0	0.48	86.7 ± 31.1	0.47
C-reactive protein, mg/l	6.2 (2.6–25.2)	6.4 (2.0–36.3)	0.77	3.8 (1.5–16.2)	0.0004
Discharge medication					
Aspirin	90 (98.9)	127 (99.2)	1.00	519 (99.4)	0.64
ACE-I/ARB	70 (76.9)	98 (76.6)	1.00	405 (77.6)	0.85
Beta-blocker	77 (84.6)	92 (71.9)	0.03	402 (77.0)	1.00
Proton pump inhibitor	83 (91.2)	119 (93.0)	0.62	501 (96.0)	<0.05
Statin	87 (95.6)	110 (85.9)	0.02	465 (89.1)	0.79

Values are mean ± SD, n (%), or median (interquartile range). *Comparisons between patients with HPR treated with prasugrel and patients treated with high-dose clopidogrel. † Comparisons between patients with and without HPR.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; HPR = high platelet reactivity; MDRD = modification of diet in renal disease; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Platelet function results

Based on the Multiplate results after PCI and clopidogrel pre-treatment, 219 patients (29.5%) had HPR (Figs. 1 and 2A). The 522 patients (70.5%) with normal platelet reactivity continued treatment with 75 mg/day of generic clopidogrel for 1 year. In the HPR patient-group, 128 patients (58%) were treated with adjusted high-dose clopidogrel and 91 patients (42%) were switched to treatment with prasugrel (Fig. 1). In the high-dose clopidogrel group, 100%, 24%, and 7% of patients required a second, third, and fourth loading dose of 600 mg of clopidogrel, respectively. At discharge, 20% of the patients were being treated with 150 mg/day of clopidogrel and 76% were being treated with 75 mg/day. Four percent of the patients died before the maintenance dose could be established.

After PCI and clopidogrel pre-treatment, there was no difference in the level of platelet reactivity between the patients in the latter HPR + clopidogrel- and prasugrel group (Fig. 2B). Although both prasugrel and repeated loading doses of 600 mg of clopidogrel reduced platelet reactivity from baseline ($p < 0.0001$ for both), a single loading dose of 60 mg of prasugrel followed by a maintenance dose of 10 mg/day provided significantly more potent platelet inhibition than the repeated boluses of 600 mg of clopidogrel at discharge ($p < 0.0001$) (Fig. 2B). Although platelet reactivity significantly increased with the 10-mg/day dose of prasugrel during the maintenance phase ($p < 0.0001$), 86% of the prasugrel-treated patients still remained below the cut point for HPR. In contrast, the standard dose and the doubled maintenance dose of clopidogrel were ineffective to maintain the level of platelet reactivity achieved with repeated loading doses of clopidogrel, resulting in rebound platelet reactivity during the maintenance phase ($p < 0.0001$) and 51% of patients returned to HPR (Fig. 2). There was no difference between the effect of 75 mg/day and 150 mg/day of clopidogrel in patients with HPR ($p = 0.42$).

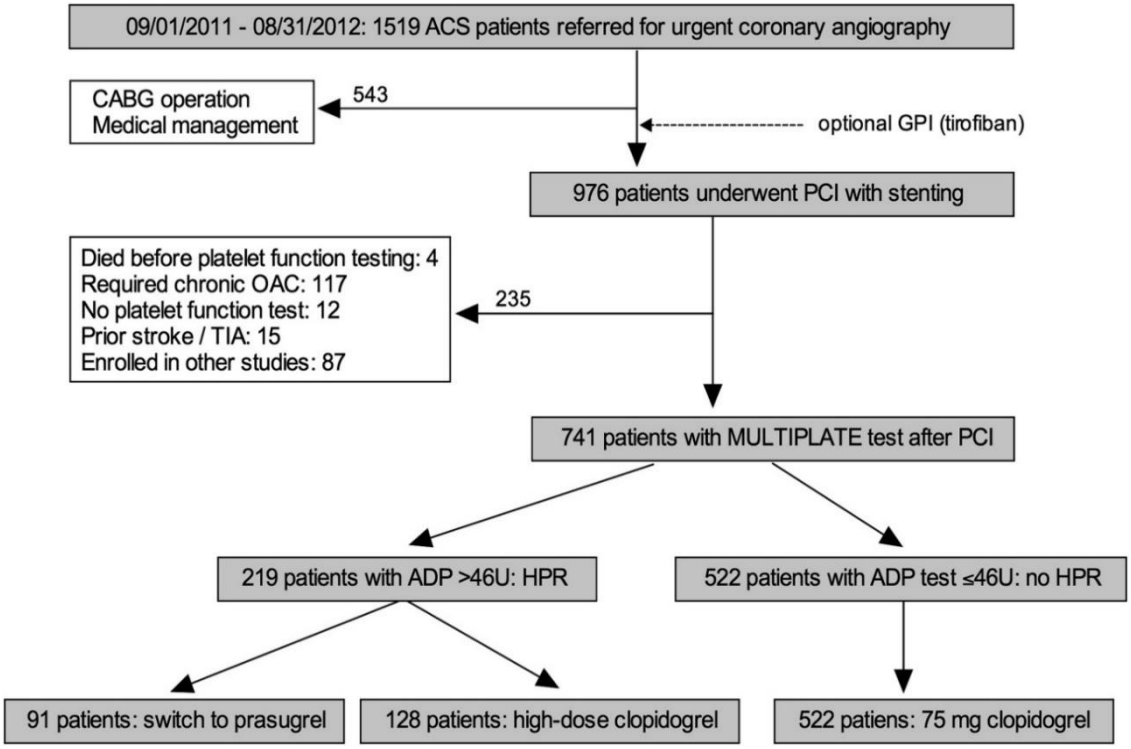

Figure 1. Flowchart of patient enrolment in the PECS-HPR registry

ACS = acute coronary syndrome(s); ADP = adenosine diphosphate; CABG = coronary artery bypass grafting; GPI = glycoprotein IIb/IIIa inhibitor; HPR = high platelet reactivity; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

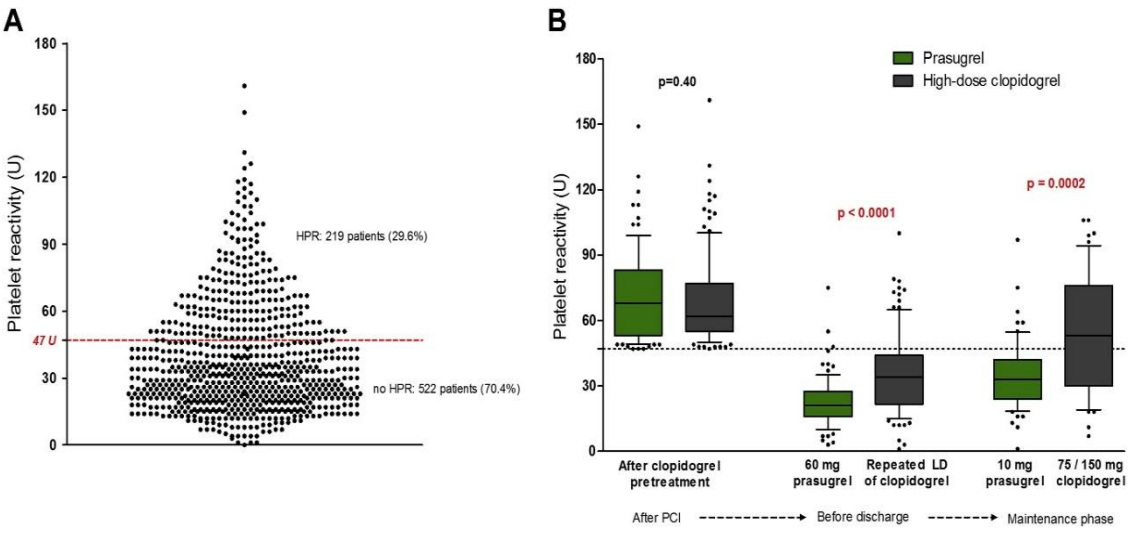

Figure 2. Platelet function results before and after P2Y12 inhibitor treatment adjustments in patients with ACS after PCI

A: A scatter plot of platelet reactivity with the Multiplate device in all 741 patients after pre-treatment with clopidogrel, before treatment modification was initiated. **B:** Changes in platelet reactivity among 219 patients with HPR who either switched to treatment with prasugrel or were treated with adjusted high-dose clopidogrel. LD = loading dose; other abbreviations as in Figure 1.

Clinical outcomes

During 1-year follow-up, all-cause mortality was 8.1%. The rate of definite/probable stent thrombosis was 2.8%, and 5.3% of patients had major bleeding. There was a significant increase in all-cause mortality or stent thrombosis in the pooled HPR group compared to the patients without HPR (Fig. 3A). The risk of the primary composite endpoint increased 1.7-fold in the HPR group compared with the no HPR group despite treatment adjustments (HR: 1.67; 95% CI: 1.11 to 2.51; p = 0.015), whereas there was no difference in major bleeding complications between the groups (Fig. 3B).

Compared the high-dose clopidogrel group with the no HPR patient group, a significantly higher risk of thrombotic events was observed (Figs. 4A to 4C, Table 2). The risk of all-cause death, nonfatal myocardial infarction, stent thrombosis, or stroke was more than 2-fold higher in the high-dose clopidogrel group than in the no HPR group (HR: 2.27; 95% CI: 1.45 to 3.55; p < 0.0001). Notably, BARC type 3 or 5 major bleeding was also significantly increased (Fig. 4D, Table 2). In contrast, patients with HPR who were switched to treatment with prasugrel had rates of thrombotic complications that were similar to those in the no HPR group without any difference in all-cause death, myocardial infarction, stent thrombosis, or stroke (HR: 0.90; 95% CI: 0.44 to 1.81; p = 0.76) (Figs. 4A to 4C, Table 2). There was no excess of major bleeding after switching patients to treatment with prasugrel compared with patients without HPR (Fig. 4D). After adjusting for age, diabetes, cardiogenic shock, drug-eluting stent(s), angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, beta-blocker use, statin use, and creatinine level, there was still a 2.5-fold increased risk of the primary composite endpoint in the high-dose clopidogrel group versus the prasugrel group (HR: 2.53; 95% CI: 1.08 to 5.93; p < 0.03).

Because of the clinical differences between patients with and without HPR, univariate and multivariate models were generated to identify independent predictors of the composite primary endpoint. Using univariate models, 20 baseline variables were identified that were significantly associated with all-cause death, myocardial infarction, stent thrombosis, or stroke (Table 3). According to the multivariate model, HPR with high-dose clopidogrel remained a significant, independent predictor of the primary endpoint (HR: 1.90; 95% CI: 1.17 to 3.08; p = 0.01), whereas patients with HPR who were switched to treatment with prasugrel had no increase in thrombotic events (Table 3).

When the impact of outcome events was tested on subsequent mortality, both stent thrombosis and major bleeding proved to be a strong and independent predictor of 1-year mortality. Interestingly, patients with stent thrombosis had a 6-fold higher risk of major bleeding (RR: 6.23; 95% CI: 2.93 to 13.25; p < 0.00001), and patients with a major bleeding event had a 7-fold risk of stent thrombosis (RR: 7.20; 95% CI: 2.96 to 17.54; p < 0.00001).

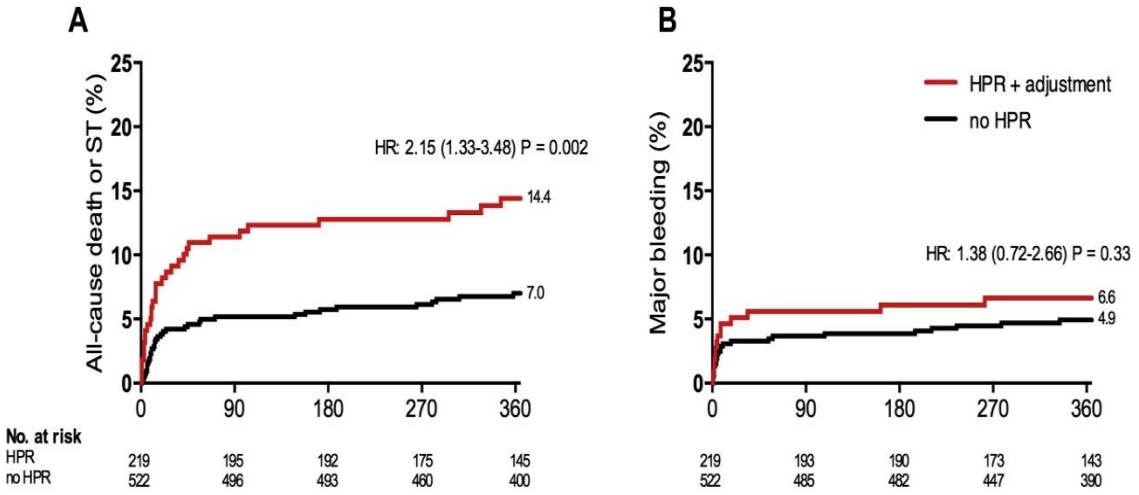

Figure 3. Thrombotic and bleeding complications in patients with and without HPR

A: All-cause death or ST. **B:** Major bleeding. Of note, all patients with HPR are grouped together in these comparisons regardless of whether they were treated with prasugrel or high-dose clopidogrel. HR = hazard ratio; ST = stent thrombosis; other abbreviations as in Figure 1.

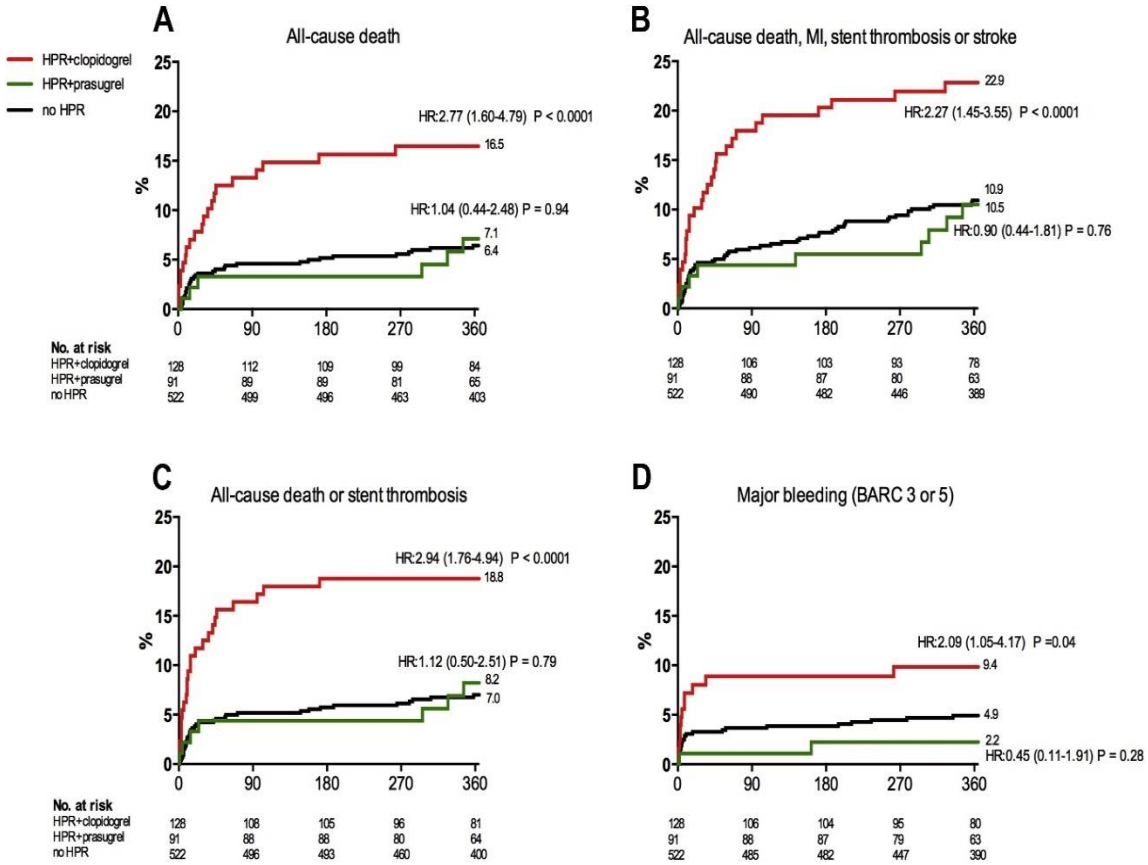

Figure 4. Impact of prasugrel and high-dose clopidogrel on thrombotic and bleeding events in patients with HPR

A: All-cause death. **B:** All-cause death, MI, ST, or stroke. **C:** All-cause death or ST. **D:** Major bleeding (BARC 3 or 5). Event rates at 1 year are shown for each group as Kaplan-Meier estimates. HRs with 95% CIs were calculated in Cox proportional hazards models with the no HPR group as a reference. BARC = Bleeding Academic Research Consortium; MI = myocardial infarction; other abbreviations as in Figures 1 and 3.

Table 2. Clinical outcomes at 12 months stratified according to the $P2Y_{12}$ inhibitor used in HPR

Clinical endpoints	No HPR (Reference) (n = 522)	HPR + Prasugrel (n = 91)	HR (95% CI)*, p	HPR + High-Dose Clopidogrel (n = 128)	HR (95% CI)*, p
Efficacy					
All-cause death	33 (6.32)	6 (6.59)	1.04 (0.44–2.48), 0.94	21 (16.41)	2.77 (1.60–4.79), <0.0001
Definite or probable stent thrombosis	10 (1.92)	3 (3.30)	1.72 (0.47–6.25), 0.41	8 (6.25)	3.48 (1.37–8.83), 0.009
MI	27 (5.17)	3 (3.30)	0.63 (0.19–2.07), 0.44	12 (9.38)	2.02 (1.02–3.99), 0.04
Stroke	3 (0.57)	0 (0.00)	N/A	1 (0.78)	1.52 (0.16–14.57), 0.72
TVR	95 (18.2)	20 (21.98)	1.02 (0.62–1.70), 0.93	22 (17.19)	1.22 (0.76–1.96), 0.40
All-cause death or stent thrombosis	36 (6.90)	7 (7.69)	1.12 (0.50–2.51), 0.79	24 (18.75)	2.94 (1.76–4.94), <0.0001
Death, MI, stent thrombosis, or stroke	57 (10.92)	9 (9.89)	0.90 (0.44–1.81), 0.76	29 (22.66)	2.27 (1.45–3.55), <0.0001
Safety					
Major bleeding (BARC 3 or 5)	25 (4.79)	2 (2.20)	0.45 (0.11–1.91), 0.28	12 (9.38)	2.09 (1.05–4.17), 0.04

Values are n (%). ∗Cox regression analyses using the no HPR group as a reference.

BARC = Bleeding Academic Research Consortium; CI = confidence interval; HR = hazard ratio; N/A = not available; TVR = target vessel revascularization; other abbreviations as in Table 1.

Table 3. Clinical, procedural, and pharmacological predictors of all-cause death, MI, stent thrombosis and stroke at 1 year

Predictors	Univariate Cox Proportional Hazard Model		Multivariate Cox Proportional Hazard Model	
	HR (95% CI)	p	HR (95% CI)	p
Cardiogenic shock	15.87 (9.95–25.32)	<0.0001	9.49 (5.42–16.62)	<0.0001
Acute renal failure (stage 4/5)	7.45 (4.28–12.96)	<0.0001		
High-dose clopidogrel, if HPR	2.27 (1.45–3.55)	<0.0001	1.90 (1.17–3.08)	0.01
Prasugrel, if HPR*	0.90 (0.44–1.81)	0.76*		
Leukocyte count (per 10-G/l increase)	2.39 (1.70–3.35)	<0.0001		
Type 2 diabetes mellitus (insulin-treated)	2.31 (1.35–3.95)	0.002		
Prior MI	1.92 (1.21–3.06)	0.006	2.47 (1.46–4.19)	0.001
STEMI	1.79 (1.18–2.70)	0.006		
Age (per 10-year increase)	1.69 (1.38–2.06)	<0.0001	1.56 (1.25–1.94)	<0.0001
Type 2 diabetes mellitus	1.57 (1.03–2.39)	0.04		
No. of stents used (per 1 increase)	1.44 (1.22–1.70)	<0.0001		
Stent length (per 10-mm increase)	1.16 (1.08–1.25)	<0.0001	1.13 (1.03–1.24)	0.01
C-reactive protein (per 10-mg/l increase)	1.08 (1.05–1.11)	<0.0001		
Creatinine (per 10-µol/l increase)	1.04 (1.03–1.06)	<0.0001		
Unstable angina	0.22 (0.08–0.60)	0.003		
Drug-eluting stent (vs. bare-metal stent)	0.35 (0.19–0.66)	0.001	0.38 (0.16–0.89)	0.03
ACE-I/ARB	0.39 (0.26–0.59)	<0.0001	0.45 (0.27–0.72)	0.001
Statin	0.60 (0.33–0.96)	0.03		
Beta-blocker	0.62 (0.41–0.96)	0.03		

eGFR (per 10-ml/min/1.73 m^2increase)	0.82 (0.77–0.88)	<0.0001		
Haemoglobin (per 10-g/l increase)	0.86 (0.76–0.97)	0.01		

∗Nonsignificant variable included for demonstration. Abbreviations as in Tables 1 and 2.

B. Clinical outcomes in patients treated for coronary in-stent restenosis with drug-eluting balloons: impact of high platelet reactivity

Clinical characteristics

Between October 1, 2009 and March 31, 2015, 194 patients (60.6% male) were enrolled in the PECS-DEB registry with a median age of 60 (range: 31–86) years. All of the recruited cases were treated during an elective DEB intervention due to stable angina and ISR. No patients were lost to follow up. Baseline clinical, procedural, laboratory and treatment characteristics are shown in Table 4.

Based on their cardiovascular risk factors, study patients composed a low-to-moderate risk cohort with 89% hypertension, 49% dyslipidaemia and 25% diabetes. Sixty-nine percent of the patients had previous MI and 19% of them had previous coronary artery bypass grafting (CABG). The vast majority of the patients were treated with clopidogrel (90%) while 9% received prasugrel and 1% of the patients received ticlopidine therapy. Regarding procedural data, 26% of the ISR cases were found in a previously implanted DES. Eighty-seven percent of the cases underwent predilatation prior to the use of DEBs. Overall, 152 (78%) patients had ADP-test available after DEB PCI. The reasons for omission of the ADP test were logistic reasons, transfer or discharge of the patient without blood sampling in 14% or unavailable lab on the day after the PCI in 8%. Patients with and without ADP-test available had comparable baseline characteristics except for greater use of allopurinol in those who did not present ADP-test. The median value of the ADP-test after DEB PCI was 28 U.

From the 152 subjects tested, 32 (21%) had HPR according to Multiplate assay. There was a significant difference in the frequency of DES and BMS use by the prior PCI between HPR and no HPR groups; with significantly more DES ISR in the HPR group. In addition, the choice of DEB differed among the groups with or without HPR; however, these parameters did not have an effect on the composite clinical endpoint.

Table 4. Baseline characteristics of the patient population

Baseline characteristics	Entire patient population (n=194)	HPR (n=32)	no HPR (n=120)	p¶
Clinical characteristics				
Age, years	59.7 (31.4-85.7)	57.7 (37.9-72.2)	59.6 (31.4-85.7)	0.15
Male	118 (60.6)	23 (71.9)	67 (55.8)	0.11
Smoking	47 (24.1)	10 (31.3)	25 (20.8)	0.24
Hypertension	173 (88.7)	27 (84.4)	112 (93.3)	0.14
Diabetes mellitus	48 (24.6)	11 (34.4)	29 (24.2)	0.26
Statin treatment (dyslipidaemia)	95 (48.7)	15 (46.9)	60 (50.0)	0.84
Prior MI	135 (69.2)	23 (71.9)	85 (70.8)	1.00
Prior CABG	36 (18.5)	3 (9.4)	26 (21.7)	0.14
High platelet reactivity	32 (16.4)			
Prior PCI procedure				
Indication				0.93
STEMI	63 (32.5)	11 (34.4)	36 (30.0)	
NSTEMI	17 (8.8)	3 (9.4)	9 (7.5)	
Unstable angina	26 (13.4)	5 (15.7)	19 (15.8)	
Stable angina	82 (42.3)	12 (37.5)	51 (42.5)	
Target vessel				0.14
LAD	76 (39.2)	10 (31.3)	51 (42.5)	
RCA	86 (44.3)	20 (62.5)	50 (41.7)	
CX	24 (12.4)	2 (6.3)	12 (10.0)	
Graft	8 (4.1)	0 (0.0)	7 (5.8)	
Total stent length, mm	30 (8-138)	31 (13-101)	30 (8-138)	0.88
Stent count/patient	2 (1-7)	2 (1-5)	2 (1-7)	0.64
Drug eluting stent	51 (26.2)	4 (12.5)	37(30.8)	0.04
DEB procedure				
Type of DEB				0.04
SeQuent Please	58 (29.9)	4 (12.5)	43 (35.8)	

Invatec In-Pact.	70 (36.1)	16 (50.0)	45 (37.5)	
Protege	39 (20.1)	10 (31.3)	22 (18.3)	
Pantera Lux	24 (12.4)	1 (3.1)	9 (7.5)	
Total DEB length, mm	25.5 (12-90)	23 (12-60)	20 (12-60)	0.78
Total DEB length ≥ 22.5, mm	103 (52.8)	16 (50.0)	59 (49.2)	1.00
Largest DEB diameter, mm	3 (2.5-5)	3.5 (2.5-4)	3 (2.5-5)	0.19
DEB count/patient	1 (1-4)	1 (1-2)	1 (1-2)	0.71
Predilatation	169 (86.7)	28 (87.5)	107 (89.2)	0.75
ADP-test, U	28 (2-91)			
ADP-test ≥ 52.5, U	23 (11.8)			
ADP-test ≥ 63.5, U	15 (7.7)			
Type 4 MI troponin	13 (6.7)	4 (12.5)	6 (5.0)	0.21
Complication	31 (15.9)	6 (18.8)	22 (18.3)	1.00
Laboratory findings on the day or 1 day after PCI				
Red blood cell distribution width	15.2 ± 1.9	14.3 (13.6-18.2)	15.1 (12.5-17.1)	0.77
Leukocyte count, g/l	7.9 (4.5-13.7)	8.5 ± 3.0	8.5 ± 1.9	0.98
Platelet count, g/l	251 ± 60	286.8 ± 83.5	248.7 ± 57.2	0.33
Mean platelet volume	8.7 ± 1.1	8.3 ± 1.2	8.8 ± 1.1	0.33
C-reactive protein, mg/l	2.2 (0.6-23.6)	12.1 ± 11.0	2.2 ± 1.6	0.26
Discharge medication				
Clopidogrel	175 (90.2)	25 (78.1)	111(92.5)	0.04
Prasugrel	17 (8.8)†	7 (21.9)	8 (6.7)	0.02
ACE-I	139 (71.3)	23 (71.9)	84 (70.0)	1.00
ARB	39 (20.0)	9 (28.1)	23 (19.2)	0.32
Beta-blocker	155 (79.5)	25 (78.1)	96 (80.0)	0.81
Calcium channel blocker	65 (33.3)	11 (34.4)	40 (33.3)	1.00
Allopurinol	17 (8.7)	0 (0)	9 (7.5)	0.21
PPI	158 (81.0)	28 (87.5)	95 (79.2)	0.45
Antacid	37 (18.9)	5 (15.6)	25 (20.8)	0.62

Values are mean ± SD, n (%), or median (interquartile range). ¶ Comparison between HPR vs. no HPR patients. †2 (1%) patients received ticlopidine therapy.

HPR = high platelet reactivity; MI = myocardial infarction; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; LAD = left anterior descending; RCA = right coronary artery; Cx = circumflex artery; DEB = drug eluting balloon; ADP = adenosine diphosphate; ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; PPI = proton pump inhibitor

Clinical outcomes

Thirteen (6.7%) patients had elevated troponin level after the procedure defined according to the universal definition of MI type 4 after the DEB PCI,(58) and other complications occurred in 31 cases (coronary dissection and perforation, no flow) during the DEB PCI (Table 4). Twenty-seven patients reached the composite endpoint during the follow-up period. One patient died due to cardiovascular cause, 12 patients suffered MI during follow-up. Twenty-six patients had a revascularization event, out of that 17 were target vessel revascularisation (TVR). There were no documented cases of stroke (Table 5).

The rate of the composite clinical endpoint, revascularization and MI were significantly higher in the HPR group compared to patients without HPR ([MACE: HR: 2.5; CI: 1.0–5.9; p = 0.03]; [Revascularisation: HR: 2.5; CI: 1.0–5.9; p = 0.03]; [MI: HR: 3.9; CI: 1.3–12.2; p = 0.01]). Compared with no HPR patients, HPR group showed a non-significant trend for higher rate of TVR (HR: 2.8; CI: 0.9–8.8; p = 0.06) (Table 5).

Table 5. Clinical outcomes in the patient population and stratified according to the platelet reactivity

Clinical endpoints	Patient population (n=194)	no HPR (n=120)	HPR (n=32)	HR (95 % CI)	p
Composite endpoint	27 (13.9)	13 (10.8)	8 (25.0)	2.5 (1.0-5.9)	0.03
Any revascularization	26 (13.3)	13 (10.8)	8 (25.0)	2.5 (1.0-5.9)	0.03
TVR	17 (8.7)	7(5.8)	5 (15.6)	2.8 (0.9-8.8)	0.06
MI	12 (6.2)	6 (5.0)	6 (18.8)	3.9 (1.3-12.2)	0.01
CV death	1 (0.5)	0 (0.0)	0 (0.0)	N/A	N/A
TIA/stroke	0 (0.0)	0 (0.0)	0 (0.0)	N/A	N/A

Values are n (%).

HPR = high platelet reactivity; HR = hazard ratio; CI = confidence interval; TVR = target vessel revascularization; MI = myocardial infarction; CV = cardiovascular; TIA = transient ischaemic attack; N/A = not available

Predictors of ischemic events

According to the Cox regression analyses HPR (HR: 2.45; CI: 1.01–5.92; p = 0.03) (Fig 5A), and prasugrel therapy (HR: 2.74; CI: 1.04–7.26; p = 0.03) were significant predictors of the primary endpoint and only patients with recent myocardial infarction received prasugrel at the time of the DEB procedure.

ROC curve analysis identified two potential cut-off values 52.5 U (33% sensitivity, 12% specificity) and 63.5 U (28% sensitivity, 7% specificity) of the platelet function test. Using these and the consensus defined 46 U (38% sensitivity, 12% specificity), Kaplan-Meier analyses demonstrated similarly significant higher risk of composite endpoint ([46 U (HPR): HR: 2.42; CI: 1.01–5.92; p = 0.03]; [52.5 U: HR: 3.09; CI: 1.24–7.67; p = 0.01]; [63.5 U: HR: 4.25; CI: 1.64–10.96; p = 0.001]) with higher risk but smaller at risk population with the higher cut-off values (Fig 5A-C; Fig 6). Based on the Kaplan Meier curve morphology and separation, the consensus cut-off value predicts the risk of later (>60 days) events, whereas, the higher cut-off values are rather predictors for the earlier cardiovascular events (Fig 5A-C). Furthermore, we found a tendency of poorer

outcomes associated with the total length of the DEB (HR 1.02; CI: 0.99–1.05; p = 0.06) which reflects a more complex coronary disease.

In order to clarify the role of platelet function testing related to other covariates of the primary endpoint multivariate models were generated to identify independent predictors. According to the multivariate analysis, HPR and the efficacy of ADP receptor antagonist treatment as assessed by the platelet function test remained significant, independent predictor of the primary endpoint ([HPR: HR: 2.88; CI: 1.02–8.14; p = 0.04]; [ADP test, U: HR: 1.03; CI: 1.00–1.05; p = 0.04]) (Table 6). In the multivariate analysis, history of statin treatment and the total length of the DEB were significant, independent predictor of the composite endpoint ([statin: HR: 0.28; CI: 0.09–0.84; p = 0.02]; [total DEB length: HR: 1.04; CI: 1.00–1.08; p = 0.03]) (Table 6).

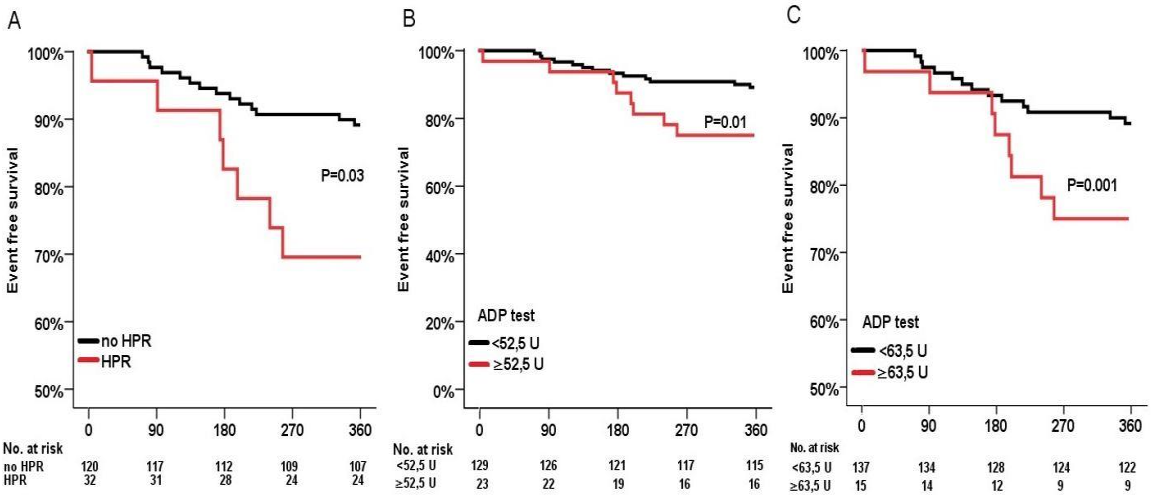

Figure 5. Event free survival of the patients based on the platelet reactivity during the follow up period

A: Event free survival of the patients with and without HPR based on the consensus cut-off value. **B, C:** Event free survival of the patients based on the ROC curve analysis identified two potential cut-off values. Event rates at one year are shown for each group as Kaplan-Meier estimates.

HPR = high platelet reactivity; ADP = adenosine diphosphate

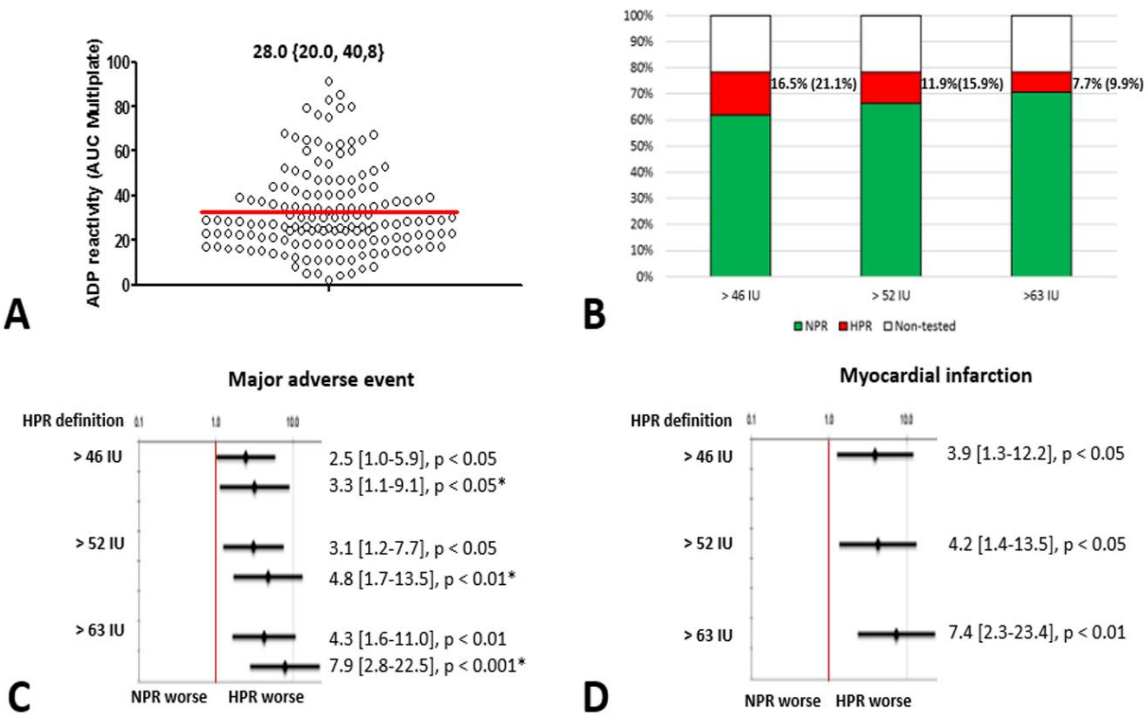

Figure 6. Results of the platelet function test, frequency of high platelet reactivity and its relation to clinical endpoints

A: A scatter plot of platelet reactivity with the Multiplate device in all patients. Values are presented as median {25% percentile, 75% percentile}, ADP reactivity presents as U. **B:** Percent of the platelet function tested cases with percent of HPR and no HPR patients in the total cohort based on the platelet reactivity values. **C:** Impact of platelet reactivity on MACE. **D:** Impact of platelet reactivity on MI. Values are presented as HR [95% CI]. *: asterix marks hazard ratios from multivariate Cox regression analyses.

ADP = adenosine diphosphate; AUC = area under the curve; HPR = high platelet reactivity; NPR= normal platelet reactivity; MACE = major adverse cardiovascular event; MI = myocardial infarction; HR = hazard ratio; CI = confidence interval

Table 6. Clinical and procedural predictors of the composite endpoint at one year

Predictors	Univariate Cox Proportional Hazard Model		Multivariate Cox Proportional Hazard Model	
	HR (95% CI)	p	HR (95% CI)	p
Age	0.98 (0.95-1.02)	0.56		
Male gender	1.28 (0.57-2.86)	0.53		
Smoking	1.07 (0.44-2.61)	0.87		
Hypertension	2.08 (0.28-15.40)	0.46		
Diabetes mellitus	0.90 (0.36-2.26)	0.83		
Statin treatment	0.49 (0.20-1.17)	0.10	0.28 (0.09-0.84)	0.02
Prior MI	2.20 (0.75-6.41)	0.13		
Prior CABG	1.03 (0.39-2.76)	0.94		
Indication of prior PCI				
STEMI	1.52 (0.69-3.35)	0.29		
NSTEMI	0.41 (0.05-3.04)	0.36		
Unstable angina	0.84 (0.25-2.82)	0.78		
Stable angina	0.88 (0.39-1.97)	0.77		
Target vessel				
LAD	0.62 (0.27-1.43)	0.26		
RCA	1.67 (0.78-3.57)	0.18		
CX	1.20 (0.41-3.47)	0.73		
Graft	0.04 (0.00-160.28)	0.26		
Drug eluting stent restenosis	0.76 (0.30-1.88)	0.55		
Type of DEB				
SeQuent Please	0.63 (0.25-1.58)	0.32		
Invatec In-Pact	1.39 (0.65-2.97)	0.39		
Protege	1.42 (0.60-3.37)	0.41		
Pantera Lux	0.54 (0.12-2.28)	0.39		
Total DEB length	1.02 (0.99-1.05)	**0.06**	1.04 (1.00-1.08)	0.03
Largest DEB diameter	1.01 (0.44-2.32)	0.97		
DEB count/patient	1.52 (0.75-3.05)	0.24		

Predilatation	1.24 (0.37-4.12)	0.72		
ADP-test	1.02 (0.99-1.04)	**0.06**	1.03 (1.00-1.05)	0.04
Prasugrel treatment	2.74 (1.04-7.26)	0.03		

HR = hazard ratio; CI = confidence interval; MI = myocardial infarction; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; LAD = left anterior descending; RCA = right coronary artery; Cx =circumflexus; DEB = drug eluting balloon; ADP = adenosine diphosphate;

Novel findings

Based on the results of the cited studies, our major novel findings can be summarized as follows:

- Switching ACS patients with HPR after PCI to treatment with prasugrel resulted in a more potent $P2Y_{12}$ inhibition than repeating high-dose boluses of clopidogrel on the basis of platelet function testing. A reduced rate of HPR can be maintained with 10 mg/day of prasugrel during long-term treatment, but a clear rebound in platelet reactivity occurred with maintenance doses of clopidogrel.
- Patients with ACS who had HPR and were treated with high-dose clopidogrel had an elevated risk of thrombotic events after PCI, whereas those who were switched to treatment with prasugrel had event rates that were comparable to those of patients without HPR. In addition, patients treated with high-dose clopidogrel had a higher risk of major bleeding complications.
- In a multivariate model, use of high-dose clopidogrel in ACS patients with HPR was an independent predictor of all-cause mortality, myocardial infarction, stent thrombosis, or stroke at 1 year, whereas switching to treatment with prasugrel was not associated with thrombotic events.
- HPR may be a predictor of adverse ischemic events in chronic angina patients treated with DEB due to ISR. HPR is significantly associated with a higher risk for recurrent ischemic events, mostly due to a higher risk for MI and revascularization.
- In addition to HPR, total DEB length and statin treatment were shown to significantly interfere with clinical outcomes in ISR patients.

Discussion

In patients with ACS undergoing PCI and stent implantation dual antiplatelet therapy (DAPT) with $P2Y_{12}$ inhibitor on top of aspirin for 1 year is recommended. European guidelines favour ticagrelor and prasugrel over clopidogrel whereas American guidelines consider these options to be possible alternatives (65)(66)(67)(68)(11).

Both prasugrel and ticagrelor provide faster, more potent, more predictable and consistent $P2Y_{12}$ receptor inhibition than clopidogrel (65)(66)(67)(68)(11). The European recommendation mainly based on two large-scale randomized studies, which showed a significant reduced rate of ischemic outcomes such as cardiovascular death, myocardial infarction, or stroke in patients with ACS who were treated with novel $P2Y_{12}$ inhibitors as compared with clopidogrel (69) (63). Although both prasugrel and ticagrelor showed a significant reduction in ischemic endpoints, there were significant increases in the rate of major bleeding complications with both novel $P2Y_{12}$ inhibitors (69) (63).

A wide interindividual variability of the concentrations of the active metabolite has been shown in previous studies after administration of the recommended loading- and maintenance dose of clopidogrel (70) (71) (72). Although HPR in patients on clopidogrel has been demonstrated to be a strong and independent predictor of recurrent ischemic events and mortality in patients after coronary stent implantation (73) (74), the optimal treatment strategy in this case not fully explored yet. In an era with a wide-spread use of generic clopidogrel, in addition with the high treatment costs of novel $P2Y_{12}$inhibitors together with the higher risk of bleeding limit their use in current routine practice.

A possible solution to these limitations might be to use prasugrel or ticagrelor selectively, with the restriction of their use in patients with HPR on clopidogrel, while continuing the treatment with generic clopidogrel in patients with good treatment response. Theoretically, platelet function assays could be useful to measure the level of platelet reactivity after clopidogrel and guide the choice of the optimal $P2Y_{12}$ inhibitor to reduce costs and bleeding complications; however, all, at the time point of our PECS-HPR registry, available large-scale, randomized studies failed to show clinical improvements when treatment modifications were implemented on the basis of platelet function testing (75) (76) (77). Two large-scale randomized studies

demonstrated that the use of platelet function testing to treat patients with high-dose clopidogrel who are at low-to-moderate risk for mortality and have HPR does not improve outcomes (75) (76). However, these studies used high-dose clopidogrel to overcome HPR and included patients with stable CAD or NSTEMI with low risk for recurrent thrombotic events. A lack of clinical effectiveness of high-dose clopidogrel in patients with HPR was further supported by the RECLOSE-2 ACS (REsponsiveness to CLOpidogrel and Stent-related Events in Acute Coronary Syndromes) registry (62). In this registry with ACS patients Parodi et al. showed that HPR status significantly associated with the rate of recurrent ischemic events irrespectively of the treatment modifications (62). These studies lead to establishing the concept that HPR may be a marker of higher risk but not a modifiable risk factor (75) (62) (78). The only large-scale randomized study to show a benefit for high-dose clopidogrel is the CURRENT (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events) trial. The study suggested a slight advantage in patients with ACS undergoing PCI with high-dose clopidogrel, which was associated with a significant reduction in the secondary outcome of stent thrombosis but there was no significant difference in the rate of the primary ischemic endpoints (79). However, because the trial compared a loading dose of 300 and 600 mg of clopidogrel with and without use of a double maintenance dose for 1 week, where the patients with ACS were randomly assigned to the different treatment regimen without evidence of platelet reactivity, the results are not comparable to our PECS-HPR registry and to prior platelet function studies and prevent any meaningful conclusion on dose escalations of clopidogrel in patients receiving the recommended loading dose of 600 mg. In the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) trial prasugrel was compared with low-dose clopidogrel in stable CAD low-risk patients with HPR but the study was stopped prematurely because of the low rate of ischemic events and the study failed to demonstrate the clinical impact of this treatment strategy (77).

However, no data were available on the clinical impact of prasugrel or ticagrelor in patients with ACS with HPR and there was a lack of evidence on the potential clinical benefits of switching patients with ACS who have HPR to treatment with prasugrel. Based on that our aim was to evaluate the clinical and pharmacodynamic impact of

using prasugrel or high-dose clopidogrel on the basis of platelet function testing in a consecutive, all-comer, single-centre registry of patients with ACS after PCI.

In PECS-HPR registry we recruited a real-life patient population of all-comer, consecutive, high-risk patients with ACS, similar to the populations enrolled in the RECLOSE-2 ACS registry but not like the cohorts of prior large-scale randomized platelet function studies (75) (76) (77). Compared with an all-cause mortality of 2% in ARCTIC (Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting) (76), <1% in GRAVITAS (Gauging Responsiveness with A VerifyNow assay–Impact on Thrombosis And Safety) (75), and 0% in TRIGGER PCI (77), we found an 8.1% all-cause mortality rate in our high-risk cohort. These differences can help explain how almost twice as many primary endpoint events occurred in a study that was one-third the size of the entire GRAVITAS study (95 vs. 50). Our results are also in line with the RECLOSE-2 ACS registry (62), which showed a more than 2-fold higher risk of all-cause death, myocardial infarction, stent thrombosis, or stroke in patients with HPR despite high-dose clopidogrel treatment.

On the basis of the discussed evidence, high-dose clopidogrel seems to have an insufficient clinical effect to overcome the higher risk of events in patients with ACS who have HPR (75) (76) (62). Based on our results, treatment with prasugrel in patients with ACS who have HPR is significantly more effective than adjusted high-dose clopidogrel both after loading doses and during the maintenance phase. Treatment with prasugrel reduced thrombotic events to a level similar to that of patients without HPR, whereas treatment with high-dose clopidogrel resulted in a higher risk of thrombotic complications. Therefore, our PECS-HPR registry suggests that switching patients to treatment with prasugrel might decrease the risk of thrombotic events to a level similar to that of patients without HPR (Fig. 4). Platelet function results supported these findings at the pharmacodynamic level, confirming superior platelet inhibition by prasugrel (Fig. 2).

In the ADAPT-DES (Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents) study (80), a prior large-scale platelet function registry, it has been showed that HPR after PCI was an independent positive predictor of both stent thrombosis and

myocardial infarction and it was inversely associated with major bleeding, but was not associated with mortality. In addition, both stent thrombosis and major bleeding were independent predictors of mortality, that associations were also replicated in our cohort. On the basis of this bidirectional association, they speculated that it will be impossible to reduce mortality in patients with HPR using more potent $P2Y_{12}$ inhibitor strategies, because for every stent thrombosis prevented, 4 extra major bleeds will be caused (80).

Our results suggest that the impact of more potent $P2Y_{12}$inhibitor strategies on major bleeding and stent thrombosis is more complex; the less potent clopidogrel reloading approach caused not only more stent thrombosis but also more major bleedings (Fig. 4). The lower rate of bleeding with prasugrel might be somewhat surprising in light of the results of TRITON (5); however, we administered prasugrel selectively to patients with HPR instead of a general population as analysed in the cited trial. Although the observed differences in bleeding might be due to chance because of the low number of events or might be attributed to a less sensitive bleeding scale used during follow-up (BARC 3/5 instead of BARC ≥2), a recent Scandinavian registry also found a lower rate of visible bleeding with prasugrel (81). These results should not confute the higher risk of bleeding with prasugrel in a general ACS population but suggest that selected patients (such as those with HPR on clopidogrel) might tolerate more potent $P2Y_{12}$ inhibition without an excess risk of bleeding.

The recent European guideline on dual antiplatelet therapy from 2017 does not recommend platelet function testing in the routine practice, among already discussed studies included patients with stable CAD (75) (76) (77), based on the results of the ANTARCTIC (Assessment of a Normal Versus Tailored Dose of Prasugrel After Stenting in Patients Aged > 75 Years to Reduce the Composite of Bleeding, Stent Thrombosis and Ischemic Complications) study (82), the only previous randomized trial which used platelet function testing to tailor DAPT in patients with ACS aged 75 years or older (Fig. 7). Figure 7 from the recent European guideline shows the most important milestone trials in the topic of the DAPT in patients with CAD until end of 2016.

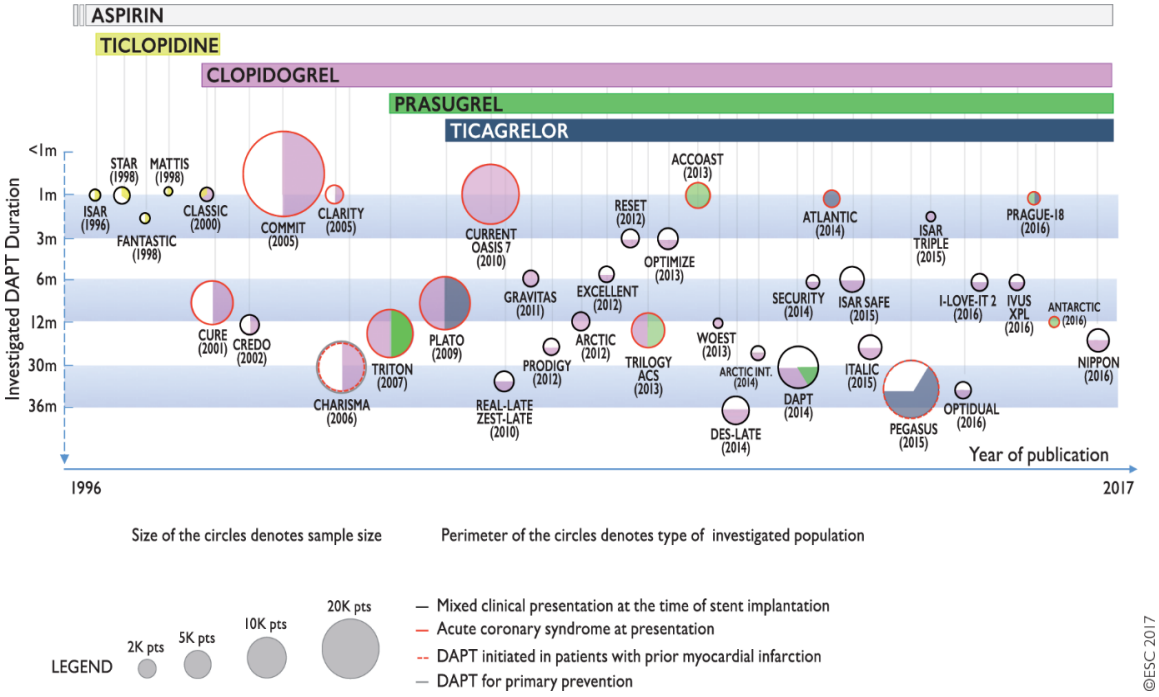

Figure 7: History of dual antiplatelet therapy (DAPT) in patients with coronary artery disease. (Figure 1 from the recent European guideline)

The size of the circles denotes sample size. The colours of perimeters identify the type of included patient populations within each study. The colours within each circle identify the antiplatelet agent(s) investigated. Head-to-head studies comparing similar durations of two different antiplatelet strategies are shown with a vertical line, whereas those investigating different treatment durations are shown with a horizontal line. Studies investigating different treatment strategies or regimens and not treatment durations or type are represented with a single colour indicating the $P2Y_{12}$ inhibitor, which was tested on top of aspirin. pts = patients. (11)

In the ANTARCTIC study patients were randomly assigned to receive 5 mg prasugrel daily with or without treatment modification based on platelet function testing 14 days after discharge and at day 28. In patients with high platelet reactivity prasugrel dose was increased to 10 mg, in case of low platelet reactivity prasugrel was replaced with 75 mg clopidogrel and in patients with normal platelet reactivity no treatment modification was done with the possibility of dose or drug adjustment at 28 days based on platelet function testing (PFT), however this therapeutic strategy had no improvement on the rate of the ischemic and bleeding outcomes (82). Although the study is a multi-centre randomized study, the size of the patient population, the

exclusion of patients aged under 75 year which might reduce the generalizability of the result (82) and the use of 5 mg prasugrel compared with standard 75 mg dose clopidogrel of which the superiority has never been confirmed in previous studies in respect to clinical outcomes (83), are limitations related to the study design.

In a recent multi centre large-scale randomized trial has been showed the platelet function test guided de-escalation of the $P2Y_{12}$inhibitor treatment was non-inferior to standard treatment with prasugrel in terms of net clinical benefit in an all-comer cohort with ACS patients (83). In The TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes) trial ACS patients were randomly assigned into the control group and received standard prasugrel treatment for a year after discharge, or got into the guided de-escalation group, where the patients received 7-day prasugrel follow by 7-day standard dose of clopidogrel after discharge. At day 14 after discharge platelet function test was performed and based on the platelet reactivity in the monitoring group the patients continued the standard dose clopidogrel (patients with normal platelet reactivity) or received prasugrel for further 11.5 months (patients with HPR). The principles of this study is that, on treatment with the potent antiplatelet drugs the rate of ischemic complications are the highest in the early phase after PCI in patients with ACS when the greatest benefits are seen, while the rate of haemorrhagic events arise during the chronic treatment (84) (85) (83). Based on the results PFT-tailored de-escalation is safe, because the rate of the ischemic endpoints was not higher than in the control group. Although a slightly higher rate of the bleeding outcomes has been observed in the control group, the difference was not statistically significant. Sibbing et al identified the PFT-guided DAPT de-escalation is an alternative treatment strategy in patients with ACS, who are unable to maintain the potent $P2Y_{12}$inhibitor treatment for a socioeconomic- or medical reason, such as recurrent bleeding events or high bleeding risk (83).

The ambivalent results of the cited randomised trials support the need of further clinical trials in terms of the optimal platelet inhibitor therapy in patients with acute coronary syndrome.

In patients with stable CAD undergoing PCI and stent implantation dual antiplatelet therapy with clopidogrel on top of aspirin for 6 months is recommended based on large

scale randomised trials (11), however there is a lack of dedicated clinical trials investigating the optimal length and intensity of DAPT in patients treated with DEB for ISR. Although in the large scale randomised clinical trials investigating DEB efficacy and safety in patients with ISR has been recommended between 3-12 months DAPT duration (86) (87) (26), there are no evidences in this topic. Clopidogrel non-responsiveness and HPR is a strong independent predictor of recurrent ischemic events and mortality after coronary stent implantation (73) and may play a relevant prognostic role in patients after DEB PCI however, the relevance of HPR in the setting of ISR and DEB dilation is unknown. Earlier optical coherence tomography (OCT) examination discovered uncovered or malapposed stent struts immediately after the DEB procedure and in all images dissections were seen throughout the DEB-dilated segment which were not visible with angiography and remained untreated (88). Therefore, although DEB PCI was shown to be an effective treatment for ISR (20) (21) (22) (23) (24) (25) (26) (27), it may result in a large prothrombotic surface with delayed healing consequent to the paclitaxel treatment. This represents a potential risk and may necessitate effective antiplatelet therapy to prevent adverse events. In line with the intraluminal imaging findings, we found a significant association between platelet reactivity and adverse outcomes and patients with HPR had a 2.5-fold higher risk for ischemic events. The higher risk was mainly driven by MI and revascularization, while ST and mortality were rare. This is in line with earlier randomized trials and a multicentre registry showing a low rate of early thrombosis of the DEB treated stented segment (89) (90) (27). In our study, there was only one diagnosed ST (0.5%) after 4 days of the procedure, in a patient with HPR. In patients with HPR most of the repeated revascularisations were triggered by events of acute MI (75% of revascularisation and 80% of TVR), whereas, in patients without HPR 46% of revascularisations and 57% of TVR were performed because of an acute MI. In-stent restenosis can frequently present as MI (16) (17) (18) and angiographically, patients with MI tend to have an aggressive pattern of restenosis and total occlusion of the target lesion. One of the most likely explanation of MI in ISR include late stent or device thrombosis, which can be caused by incomplete neointimal coverage, early termination of antiplatelet therapy and/or increased neointimal thrombogenic tissue factors such as tissue factor and collagen (16). The average time between the DEB procedure and the appearance of adverse events was 6 months (mean

181 days) in our study. When assessed with OCT at 6 months >94%, therefore almost complete neointimal coverage was found after stent implantation postdilated with DEB (91). Based on these findings, incomplete neointimal coverage may play a less important role in the mechanisms of late ischemic events also but supports the relevant role and importance of ineffective antiplatelet therapy and residual platelet reactivity in the mechanisms of late ST and occurrence of repeated MI.

As a consequence of paucity of relevant data corrective treatment in terms of intensification of antiplatelet therapy based on platelet function studies is not established. As already mentioned, previous large scale, randomized trials showed the prognostic role of HPR in patients underwent coronary stent implantation but failed to demonstrate the clinical improvements when treatment modifications were implemented on the basis of platelet function testing in patients with elective PCI (75) (76) (77). Using different primary end-point definition, we found a 14% event rate in our real-life cohort and a significantly greater rate of the composite end-point in patients with HPR compared to patients without HPR (25% vs 11%) after PCI with DEB while there were no significant differences in clinical, laboratory and treatment parameters between the HPR and no HPR group. Patients treated with prasugrel because of an acute coronary event within one year had worse outcome in our study. As this difference persisted in multivariate analyses taking antiplatelet efficacy in account we hypothesize that this worse prognosis is rather explainable with the recent ACS than with the antiplatelet therapy itself. Furthermore, due to the low numbers and lack of randomized comparisons and protocolled treatment modification our data do not allow drawing conclusion regarding the efficacy of corrective treatment.

Our analyses of the predictive value of different level residual platelet reactivity identified two potential alternative cut-off values. Using these and the consensus defined 46 U, Kaplan-Meier analyses demonstrated similarly significant higher risk of composite endpoint with higher risk but smaller at risk population with the higher cut-off values (Fig. 5A-C; Fig. 2). Different time-distribution of end-points and separation patterns of the Kaplan Meier were observed using these values. Using the lowest consensus cut-off value, we observed a late (>60 days) occurring difference of event frequencies, whereas the higher cut-off values appeared to be better predictors for the earlier events. These findings may draw the attention to the fact that the proposed cut-

off values for platelet function tests are mainly based on stent implanted ACS populations while in different clinical scenarios the predictive value and the optimal cut-offs may differ.

Several randomized studies demonstrated the safety and efficacy of DEB for the treatment of ISR (20) (21) (22) (23) (24) (25) (26) (27) and the recent European guideline consider DEB and DES to be equal possible alternatives for treatment of ISR. Previous registries and studies investigated the correlation between patient and procedural characteristics and clinical outcome with heterogeneous results. Our cohort comprised a routine all-comer population with low-to-moderate risk clinical and procedural features. The incidence of the composite endpoint was 14% during the 1-year follow-up period, higher than in randomized trials (4-9%) (92) (22) (23) (25), but similar to a multicentre prospective registry (89), none the less these studies included patients with ACS also. Regarding to procedural characteristics, DEB length was found to be an important predictor of adverse outcomes: the longer the DEB, the higher the risk of ischemic events. Although the length of DEB should be selected to fully cover the restenotic segment, operators should find the shortest appropriate size, without large mismatch. Therefore, the length of the DEB reflects the length of the stented coronary segment which reflects a more complex coronary disease.

According to the multivariate analysis, beside platelet reactivity, history of statin treatment and the total length of the DEB were significant, independent predictors of the cardiovascular events. The other clinical and procedural characteristics had no important influence on the outcomes. This finding is in contrast with the earlier published registry from Calé et al. In their analysis of 156 patients the predictors of poorer outcome were previous MI and CABG, acute coronary syndrome at presentation, and PCI in the LAD, while DEB length and dyslipidaemia were not predictive of one-year outcome (89). In our study, only elective DEB treated ISR patients were recruited which cohort is dissimilar to the populations of Calé et al. with acute coronary syndrome and small vessel disease included which may explain the differences in the verified determinants of worse results.

Based on the current recommendations, patients undergoing PCI with DEB should receive 6 month standard clopidogrel treatment however there is a lack of evidence which based on large-scale trials or registries. Our results support the importance of

HPR on clopidogrel as an independent risk factor of ischemic events in patients with ISR undergoing DEB PCI and further studies are needed to investigate the safety and efficacy of treatment modification regarding P2Y12-inhibitor therapy and the optimal duration of treatment in DEB patients with HPR.

Study limitations

A. First and most importantly, the prasugrel and clopidogrel groups were not randomized in the PECS-HPR registry. Although this might decrease the validity of our comparisons, registries are important for collecting real-life data on unselected patients. Although it was left to the discretion of the operator whether to choose prasugrel or high-dose clopidogrel, the 2 groups ended up with a very balanced distribution (42% vs. 58%) and most baseline variables were well matched between the 2 groups (Table 1B). Second, it is unknown how these findings are transferable to ticagrelor because the drug was not available during the enrolment period in Hungary. Third, we only collected data on BARC type 3/5 major bleeding events, and the difference in major and minor bleeding complications remains unknown. Finally, our results cannot be extrapolated to elderly patients (older than 80 years of age) who might require dose reduction with prasugrel but were generally excluded from our PECS-HPR registry.
B. The most important limitations of the PECS-DEB registry are the single-centre design and consequent small sample size and the lack of blinding. It was left to the discretion of the operator to perform platelet function testing and not all of the patients were tested. Furthermore, although our inclusion criteria allowed the inclusion of ISR patients also presenting with acute coronary syndrome all of the cases entered the PECS-DEB registry were treated during an elective intervention. This allows only to draw conclusions regarding patients with elective DEB treatment.

Conclusion

Our aims were to determine the clinical and pharmacodynamic impact of optimizing P2Y12 inhibition on the basis of platelet function testing in patients with ACS after PCI and to evaluate the impact of HPR together with conventional risk factors and procedural characteristics on clinical outcomes in patients with ISR undergoing PCI with DEB.

We showed that switching ACS patients with HPR after PCI from clopidogrel to treatment with prasugrel is superior in terms of ischemic and bleeding complications than treatment with high-dose clopidogrel. This treatment strategy had a significantly better efficacy to maintain the platelet reactivity under the cut-off value then high dose clopidogrel. The ambivalent results of the large-scale randomised trials in this topic support the need of further clinical trials in terms of the optimal platelet inhibitor therapy in patients with acute coronary syndrome.

We showed that, in our all-comer patient cohort with stable angina HPR is an independent risk factor of adverse ischemic events after DEB PCI due to ISR. In addition to HPR, total DEB length and statin treatment were shown to significantly interfere with clinical outcomes in ISR patients. Based on the current recommendations, patients undergoing PCI with DEB should receive 6 month standard clopidogrel treatment however there is a lack of evidence which based on large-scale trials or registries. Our results support the importance of HPR on clopidogrel as an independent risk factor of ischemic events in patients with ISR undergoing DEB PCI and further studies are needed to investigate the safety and efficacy of treatment modification regarding P2Y12-inhibitor therapy and the optimal duration of treatment in DEB patients with HPR.

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Publication list

Topic-related international articles

1. **Tornyos A**, Aradi D, Horváth IG, Kónyi A, Magyari B, Pintér T, Vorobcsuk A, Tornyos D, Komócsi A. Clinical outcomes in patients treated for coronary in-stent restenosis with drug-eluting balloons: Impact of high platelet reactivity. PLoS One. 2017 Dec 7; 12(12):e0188493.
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2. Aradi D, **Tornyos A**, Pintér T, Vorobcsuk A, Kónyi A, Faluközy J, Veress G, Magyari B, Horváth IG, Komócsi A. Optimizing P2Y12 receptor inhibition in patients with acute coronary syndrome on the basis of platelet function testing: impact of prasugrel and high-dose clopidogrel. J Am Coll Cardiol. 2014 Mar 25; 63(11):1061-70.
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Non-topic-related international articles

1. **Tornyos A**, Kehl D, D'Ascenzo F, Komócsi A. Risk of Myocardial Infarction in Patients with Long-Term Non-Vitamin K Antagonist Oral Anticoagulant Treatment. Prog Cardiovasc Dis. 2016 Mar-Apr; 58(5):483-94. *IF: 8.177*
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PLOS ONE

RESEARCH ARTICLE

Clinical outcomes in patients treated for coronary in-stent restenosis with drug-eluting balloons: Impact of high platelet reactivity

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Abstract

Background

The impact of high platelet reactivity (HPR) on clinical outcomes after elective percutaneous coronary interventions (PCI) with drug-eluting balloons (DEB) due to in-stent restenosis (ISR) is unknown.

Objective

We sought to evaluate the prognostic importance of HPR together with conventional risk factors in patients treated with DEB.

Methods

Patients treated with DEB due to ISR were enrolled in a single-centre, prospective registry between October 2009 and March 2015. Only patients with recent myocardial infarction (MI) received prasugrel, others were treated with clopidogrel. HPR was defined as an ADP-test >46U with the Multiplate assay and no adjustments were done based on results. The primary endpoint of the study was a composite of cardiovascular mortality, MI, any revascularization or stroke during one-year follow-up.

Results

194 stable angina patients were recruited of whom 90% were treated with clopidogrel. Clinical characteristics and procedural data were available for all patients; while platelet function testing was performed in 152 subjects of whom 32 (21%) had HPR. Patients with HPR had a higher risk for the primary endpoint (HR: 2.45; CI: 1.01–5.92; p = 0.03). The difference was primarily driven by a higher risk for revascularization and MI. According to the multivariate analysis, HPR remained a significant, independent predictor of the primary endpoint (HR: 2.88; CI: 1.02–8.14; p = 0.04), while total DEB length and statin treatment were other independent correlates of the primary outcome.

Conclusion

HPR was found to be an independent predictor of repeat revascularization and MI among elective patients with ISR undergoing PCI with DEB.

Introduction

Coronary in-stent restenosis (ISR) is a common complication with bare metal stents and is still a limitation of concern with current-generation drug-eluting stents.[1] In the last few years, drug-eluting balloon (DEB) dilatation has emerged as a therapeutic alternative to drug eluting stent (DES) implantation for percutaneous treatment of ISR. DEB may offer a benefit to treat ISR without repeat implantation of a metal layer into the restenotic mass, that itself, with the polymer on its surface is a key driver of the adverse process. [2] Several randomized studies have demonstrated the safety and efficacy of this technology. [3] [4] Moreover, a meta-analysis including more than 1400 patients demonstrated that DEB was clinically non-inferior to DES in the treatment of ISR in different clinical scenarios. [2]

After DEB percutaneous coronary intervention (PCI), patients receive double antiplatelet therapy (DAPT) for a certain timeframe but the optimal intensity and duration is not clearly defined. High residual platelet reactivity (HPR) in patients on clopidogrel has been demonstrated to be a strong and independent predictor of recurrent ischemic events and mortality in patients after coronary stent implantation. [5]

However, the relevance of HPR in the setting of ISR and DEB dilation is unknown. A prior study with optical coherence tomography (OCT) demonstrated uncovered or malapposed stent struts and intimal dissections in DEB-dilated segments [6] that may provide a prothrombotic surface after balloon dilation. As healing may be delayed consequent to paclitaxel treatment, this may have potential implications regarding the efficacy of antiplatelet therapy. The objective of our study was to evaluate the impact of HPR together with patient-related and procedural characteristics on clinical outcomes in patients with ISR treated with DEB.

Methods

Population

Starting on October 1, 2009, patients treated with DEB for ISR were enrolled in a single centre prospective registry in the Heart Institute, University of Pécs. There were no exclusion criteria; this was an all-comer registry. The registry adhered to the tenets of the most recent revision of the Declaration of Helsinki. The institutional ethical board (Regional Research Ethics Committee, University of Pécs, Clinical Centre) reviewed the protocol and approved this study under the protocol number 3551/2009. All included subjects have been properly instructed and have given written informed consent.

Registered data

Data were collected prospectively from dedicated hospital records. Follow-up data were obtained at clinical presentations and at a telephone visit scheduled at 12 months after the index DEB PCI. Detailed procedural parameters of the intervention as well as risk factors, demographic data, medication information and laboratory parameters were also registered (Table 1).

Table 1. Baseline characteristics of the patient population.

Baseline characteristics	Entire patient population (n = 194)	HPR (n = 32)	no HPR (n = 120)	p¶
Clinical characteristics				
• Age	59.7 (31.4–85.7)	57.7 (37.9–72.2)	59.6 (31.4–85.7)	0.15
• Male	118 (60.6)	23 (71.9)	67 (55.8)	0.11
• Smoking	47 (24.1)	10 (31.3)	25 (20.8)	0.24
• Hypertension	173 (88.7)	27 (84.4)	112 (93.3)	0.14
• Diabetes mellitus	48 (24.6)	11 (34.4)	29 (24.2)	0.26
• Statin treatment (dyslipidaemia)	95 (48.7)	15 (46.9)	60 (50.0)	0.84
• Prior MI	135 (69.2)	23 (71.9)	85 (70.8)	1.00
• Prior CABG	36 (18.5)	3 (9.4)	26 (21.7)	0.14
• High platelet reactivity	32 (16.4)			
Prior PCI procedure				
• Indication				0.93
• STEMI	63 (32.5)	11 (34.4)	36 (30.0)	
• NSTEMI	17 (8.8)	3 (9.4)	9 (7.5)	
• Unstable angina	26 (13.4)	5 (15.7)	19 (15.8)	
• Stable angina	82 (42.3)	12 (37.5)	51 (42.5)	
• Target vessel				0.14
• LAD	76 (39.2)	10 (31.3)	51 (42.5)	
• RCA	86 (44.3)	20 (62.5)	50 (41.7)	
• CX	24 (12.4)	2 (6.3)	12 (10.0)	
• Graft	8 (4.1)	0 (0.0)	7 (5.8)	
• Total stent length, mm	30 (8–138)	31 (13–101)	30 (8–138)	0.88
• Stent count/patient	2 (1–7)	2 (1–5)	2 (1–7)	0.64
• Drug eluting stent	51 (26.2)	4 (12.5)	37(30.8)	0.04
DEB procedure				
• Type of DEB				0.04
• SeQuent Please	58 (29.9)	4 (12.5)	43 (35.8)	
• Invatec In-Pact.	70 (36.1)	16 (50.0)	45 (37.5)	
• Protege	39 (20.1)	10 (31.3)	22 (18.3)	
• Pantera Lux	24 (12.4)	1 (3.1)	9 (7.5)	
• Total DEB length, mm	25.5 (12–90)	23 (12–60)	20 (12–60)	0.78
• Total DEB length $\geq$ 22.5, mm	103 (52.8)	16 (50.0)	59 (49.2)	1.00
• Largest DEB diameter, mm	3 (2.5–5)	3.5 (2.5–4)	3 (2.5–5)	0.19
• DEB count/patient	1 (1–4)	1 (1–2)	1 (1–2)	0.71
• Predilatation	169 (86.7)	28 (87.5)	107 (89.2)	0.75
• ADP-test, U	28 (2–91)			
• ADP-test $\geq$ 52.5, U	23 (11.8)			
• ADP-test $\geq$ 63.5, U	15 (7.7)			
• Type 4 MI troponin	13 (6.7)	4 (12.5)	6 (5.0)	0.21
• Complication	31 (15.9)	6 (18.8)	22 (18.3)	1.00
Laboratory findings				
• Red blood cell distribution width	15.2 ± 1.9	14.3 (13.6–18.2)	15.1 (12.5–17.1)	0.77
• Leukocyte count, g/l	7.9 (4.5–13.7)	8.5 ± 3.0	8.5 ± 1.9	0.98
• Platelet count, g/l	251 ± 60	286.8 ± 83.5	248.7 ± 57.2	0.33
• Mean platelet volume	8.7 ± 1.1	8.3 ± 1.2	8.8 ± 1.1	0.33
• C-reactive protein, mg/l	2.2 (0.6–23.6)	12.1 ± 11.0	2.2 ± 1.6	0.26
Discharge medication				

(*Continued*)

Table 1. (*Continued*)

Baseline characteristics	Entire patient population (n = 194)	HPR (n = 32)	no HPR (n = 120)	p¶
• Clopidogrel	175 (90.2)	25 (78.1)	111(92.5)	0.04
• Prasugrel	17 (8.8)†	7 (21.9)	8 (6.7)	0.02
• ACE-I	139 (71.3)	23 (71.9)	84 (70.0)	1.00
• ARB	39 (20.0)	9 (28.1)	23 (19.2)	0.32
• Beta-blocker	155 (79.5)	25 (78.1)	96 (80.0)	0.81
• Calcium channel blocker	65 (33.3)	11 (34.4)	40 (33.3)	1.00
• Allopurinol	17 (8.7)	0 (0)	9 (7.5)	0.21
• PPI	158 (81.0)	28 (87.5)	95 (79.2)	0.45
• Antacid	37 (18.9)	5 (15.6)	25 (20.8)	0.62

Values are mean ± SD, n (%), or median (interquartile range).

¶ Comparison between HPR vs. no HPR patients.

† 2 (1%) patients received ticlopidine therapy.

HPR = high platelet reactivity; MI = myocardial infarction; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; LAD = left anterior descending; RCA = right coronary artery; Cx = circumflex artery; DEB = drug eluting balloon; ADP = adenosine diphosphate; ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; PPI = proton pump inhibitor

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Percutaneous coronary intervention and antiplatelet therapy

The selection of technique and revascularization strategy was at the discretion of the operators, including the choice of vascular access, type and number of DEB and need for pre- or post-dilatation or bailout stenting. Antiplatelet treatment was given according to the actual European guidelines of myocardial revascularization and treatment of stable angina.[7] All patients received 100 mg of aspirin, and clopidogrel was the choice from oral P2Y12-inhibitors. Only a small group of patients with prior acute myocardial infarction (AMI) within a year were treated with prasugrel that was continued regardless of the platelet function testing. Patients on clopidogrel continued treatment with an optional loading dose at the time of PCI decided by the operator. Patients without chronic P2Y12-inhibitors were treated with a 300/600 mg loading dose of clopidogrel, followed by a maintenance dose of 75 mg/day. Dual antiplatelet therapy was proposed to maintain during 12 months after DEB PCI.

Platelet function testing

Antecubital venous blood samples were collected using a sterile 21-gauge needle into hirudin coated vacuum tubes (Becton and Dickinson, Munich, Germany) without stasis. Platelet function testing was performed with the Multiplate analyser (Roche Diagnostics, Rotkreuz, Switzerland), at least 6 hours after PCI. HPR was defined according to the consensus cut-off, which was an adenosine diphosphate (ADP)-test value greater than 46 U. [8] Importantly, results of platelet function testing did not lead to treatment corrections regarding P2Y12-inhibitor treatment.

Endpoints and follow-up

Patients were followed for one year after DEB intervention. The primary endpoint of the study was the occurrence of major adverse cardiac events (MACE) defined as the composite of cardiovascular (CV) mortality, any revascularization, myocardial infarction (MI) or stroke/

transient ischemic attack (TIA). Secondary endpoints included the individual elements of the composite endpoint.

Any revascularization included percutaneous or surgical interventions of the coronary arteries after the DEB PCI. MI was defined according to the universal definition.[9] Type 4 periprocedural MI was not considered as an endpoint. Stroke and TIA was defined according to American Heart Association/American Stroke Association definition.[10] [11]

Statistical analysis

Continuous variables with normal distribution are presented as mean ± standard deviation (SD), whereas non-normally distributed variables are presented as median and interquartile range. Categorical variables are expressed as frequencies and percentages. Differences between groups were assessed with the Fisher's exact test or chi-square test, as appropriate for categorical variables. Unpaired t tests were used for comparisons of normally distributed continuous variables, whereas non-normally distributed variables were compared using the Mann-Whitney U test. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for occurrence of clinical endpoints at follow-up. Cox regression and Kaplan-Meier analysis was performed to assess the impact of demographic, clinical and procedural characteristics on the study's endpoint. Variables were assessed in univariate as well as in multivariate Cox proportional model analyses. In the latter, covariates with a threshold of $p < 0.10$ in the univariate Cox analyses were entered into an initial multivariate model than removed stepwise based on the probability of the likelihood-ratio statistic to determine independent predictors of the clinical endpoint. Improvement over the baseline model was checked with Omnibus tests of model coefficients.

Survival differences between the groups and the cumulative incidence of the clinical endpoint were calculated according to the Kaplan-Meier method. Specificity and sensitivity of platelet function test cut-off points in predicting the occurrence of the primary endpoint were determined by ROC curve analysis. Values of $p<0.05$ were considered statistically significant and values of $p<0.1$ were considered as a trend.

Statistical analysis was performed using SPSS Statistics V22 (IBM Corporation, Armonk, NY, USA) and Graph Pad Prism software 5 (GraphPad Software, Inc., La Jolla, CA, USA).

Results

Clinical characteristics

Between October 1, 2009 and March 31, 2015, 194 patients (60.6% male) were enrolled in the registry with a median age of 60 (range: 31–86) years. All of the recruited cases were treated during an elective DEB intervention due to stable angina. No patients were lost to follow up. The mean follow-up time was one year. Baseline clinical, procedural, laboratory and treatment characteristics are shown in Table 1.

Based on their cardiovascular risk factors, study patients composed a low-to-moderate risk cohort with 89% hypertension, 49% dyslipidaemia and 25% diabetes. Sixty-nine percent of the patients had previous MI and 19% of them had previous coronary artery bypass grafting (CABG). The vast majority of the patients were treated with clopidogrel (90%) while 9% received prasugrel and 1% of the patients received ticlopidine therapy.

Regarding procedural data, 26% of the ISR cases were found in a previously implanted DES. Eighty-seven percent of the cases underwent predilatation prior to the use of DEBs.

Overall, 152 (78%) patients had ADP-test available after DEB PCI. The reasons for omission of the ADP test were logistic reasons, transfer or discharge of the patient without blood sampling in 14% or unavailable lab on the day after the PCI in 8%. Patients with and without

ADP-test available had comparable baseline characteristics except for greater use of allopurinol in those who did not present ADP-test. The median value of the ADP-test after DEB PCI was 28 U.

From the 152 subjects tested, 32 (21%) had HPR according to Multiplate assay. There was a significant difference in the frequency of DES and bare metal stent (BMS) -use by the prior PCI between HPR and no HPR groups; with significantly more DES ISR in the HPR group. In addition, the choice of DEB differed among the groups with or without HPR; however, these parameters did not have an effect on the composite clinical endpoint.

Clinical outcomes

Thirteen (6.7%) patients had elevated troponin level after the procedure defined according to the universal definition of MI type 4 after the DEB PCI,[9] and other complications occurred in 31 cases (coronary dissection and perforation, no flow) during the DEB PCI (Table 1). Twenty-seven patients reached the composite endpoint during the follow-up period. One patient died due to cardiovascular cause, 12 patients suffered MI during follow-up. Twenty-six patients had a revascularization event, out of that 17 were target vessel revascularisation (TVR). There were no documented cases of stroke (Table 2).

The rate of the composite clinical endpoint, revascularization and MI were significantly higher in the HPR group compared to patients without HPR ([MACE: HR: 2.5; CI: 1.0–5.9; p = 0.03]; [Revascularisation: HR: 2.5; CI: 1.0–5.9; p = 0.03]; [MI: HR: 3.9; CI: 1.3–12.2; p = 0.01]). Compared with no HPR patients, HPR group showed a non-significant trend for higher rate of TVR (HR: 2.8; CI: 0.9–8.8; p = 0.06) (Table 2).

Predictors of ischemic events

According to the Cox regression analyses HPR (HR: 2.45; CI: 1.01–5.92; p = 0.03) (Fig 1A), and prasugrel therapy (HR: 2.74; CI: 1.04–7.26; p = 0.03) were significant predictors of the primary endpoint and only patients with recent myocardial infarction received prasugrel at the time of the DEB procedure.

ROC curve analysis identified two potential cut-off values 52.5 U (33% sensitivity, 12% specificity) and 63.5 U (28% sensitivity, 7% specificity) of the platelet function test. Using these and the consensus defined 46 U (38% sensitivity, 12% specificity), Kaplan-Meier analyses demonstrated similarly significant higher risk of composite endpoint ([46 U (HPR): HR: 2.42; CI: 1.01–5.92; p = 0.03]; [52.5 U: HR: 3.09; CI: 1.24–7.67; p = 0.01]; [63.5 U: HR: 4.25; CI: 1.64–10.96; p = 0.001]) with higher risk but smaller at risk population with the higher cut-off values (Fig 1A, 1B and 1C; Fig 2). Based on the Kaplan Meier curve morphology and separation, the

Table 2. Clinical outcomes in the patient population and stratified according to the platelet reactivity.

Clinical endpoints	Patient population (n = 194)	no HPR (n = 120)	HPR (n = 32)	HR (95% CI)	p
Composite endpoint	27 (13.9)	13 (10.8)	8 (25.0)	2.5 (1.0–5.9)	0.03
Any revascularization	26 (13.3)	13 (10.8)	8 (25.0)	2.5 (1.0–5.9)	0.03
TVR	17 (8.7)	7(5.8)	5 (15.6)	2.8 (0.9–8.8)	0.06
MI	12 (6.2)	6 (5.0)	6 (18.8)	3.9 (1.3–12.2)	0.01
CV death	1 (0.5)	0 (0.0)	0 (0.0)	-	-
TIA/stroke	0 (0.0)	0 (0.0)	0 (0.0)	-	-

Values are n (%).

HPR = high platelet reactivity; HR = hazard ratio; CI = confidence interval; TVR = target vessel revascularization; MI = myocardial infarction; CV = cardiovascular; TIA = transient ischaemic attack

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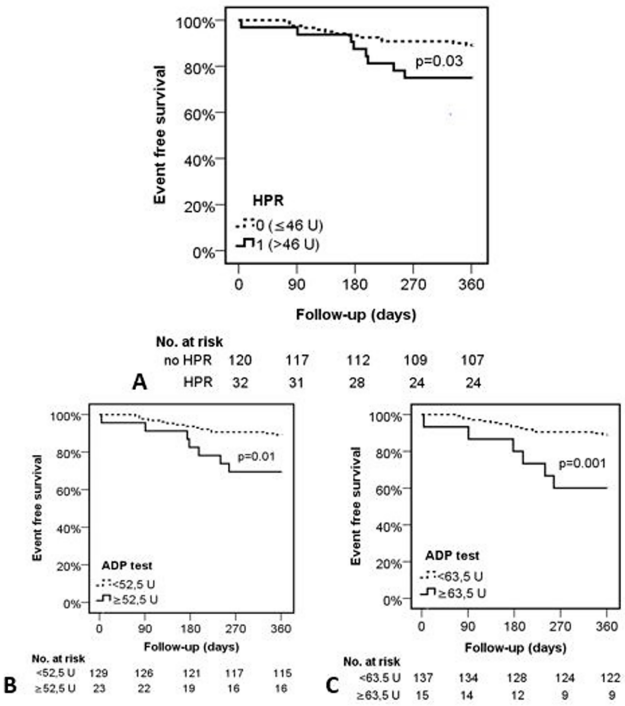

Fig 1. Event free survival of the patients based on the platelet reactivity during the follow up period. **A:** Event free survival of the patients with and without HPR based on the consensus cut-off value. **B, C:** Event free survival of the patients based on the ROC curve analysis identified two potential cut-off values. Event rates at one year are shown for each group as Kaplan-Meier estimates. HPR = high platelet reactivity; ADP = adenosine diphosphate.

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consensus cut-off value predicts the risk of later (>60 days) events, whereas, the higher cut-off values are rather predictors for the earlier cardiovascular events (Fig 1A, 1B and 1C).

Furthermore, we found a tendency of poorer outcomes associated with the total length of the DEB (HR 1.02; CI: 0.99–1.05; p = 0.06).

In order to clarify the role of platelet function testing related to other covariates of the primary endpoint multivariate models were generated to identify independent predictors.

According to the multivariate analysis, HPR and the efficacy of ADP receptor antagonist treatment as assessed by the platelet function test remained significant, independent predictor of the primary endpoint ([HPR: HR: 2.88; CI: 1.02–8.14; p = 0.04]; [ADP test, U: HR: 1.03; CI: 1.00–1.05; p = 0.04]) (Table 3). In the multivariate analysis, history of statin treatment and the total length of the DEB were significant, independent predictor of the MACE ([statin: HR: 0.28; CI: 0.09–0.84; p = 0.02]; [total DEB length: HR: 1.04; CI: 1.00–1.08; p = 0.03]) (Table 3).

Discussion

The main finding of our study is that HPR may be a predictor of adverse ischemic events in stable angina patients treated with DEB due to ISR. The higher rate of ischemic events was predominantly triggered by a higher risk for MI and repeat revascularization. In addition to HPR, total DEB length and statin treatment were shown to significantly interfere with clinical outcomes.

Several randomized studies demonstrated the safety and efficacy of DEB for the treatment of ISR.[3] [4] Based on the results of the PACCOCATH ISR [12] [3] and PEPCAD II [13]

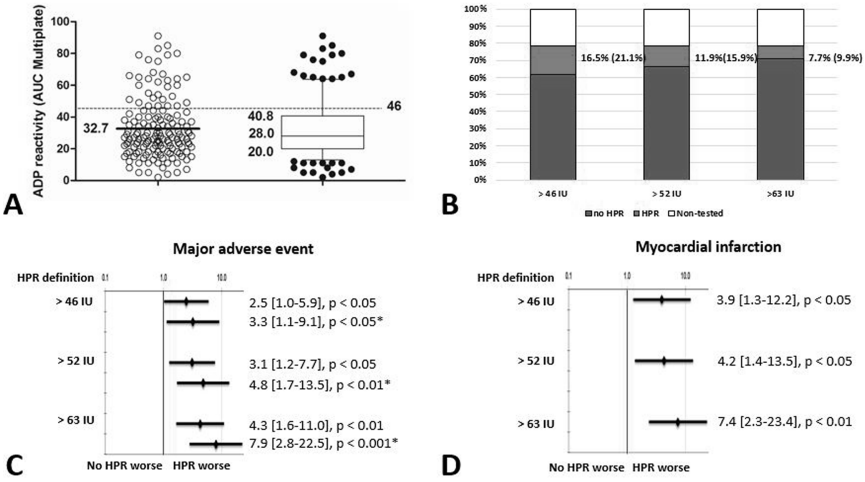

Fig 2. Results of the platelet function test, frequency of high platelet reactivity and its relation to clinical endpoints. A: A scatter plot of platelet reactivity with the Multiplate device in all patients. Values are presented as median {25% percentile, 75% percentile}, ADP reactivity presents as U. **B:** Percent of the platelet function tested cases with percent of HPR and no HPR patients in the total cohort based on the platelet reactivity values. **C:** Impact of platelet reactivity on MACE. **D:** Impact of platelet reactivity on MI. Values are presented as HR [95% CI]. *: asterisk marks hazard ratios from multivariate Cox regression analyses. ADP = adenosine diphosphate; AUC = area under the curve; HPR = high platelet reactivity; MACE = major adverse cardiovascular event; MI = myocardial infarction; HR = hazard ratio; CI = confidence interval.

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trials, the European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines for coronary revascularization gave a class IIa recommendation for this treatment modality.[4] Previous registries and studies investigated the correlation between patient and procedural characteristics and clinical outcome with heterogeneous results. Our cohort comprised a routine all-comer population with low-to-moderate risk clinical and procedural features. The incidence of the composite end point was 14% during the 1-year follow-up period, higher than in randomized trials (9% in PACCOCATH ISR I and II and in PEPCAD II),[3] [13] but similar to a multicentre prospective registry.[14] Regarding to procedural characteristics, DEB length was found to be an important predictor of adverse outcomes: the longer the DEB, the higher the risk of ischemic events. Although the length of DEB should be selected to fully cover the restenotic segment, operators should find the shortest appropriate size, without large mismatch.

After DEB PCI, patients receive dual antiplatelet therapy but the optimal intensity and length of the therapy in this patient group is not fully defined. Clopidogrel non-responsiveness and HPR is a strong independent predictor of recurrent ischemic events and mortality after coronary stent implantation [5] and may play a relevant prognostic role in patients after DEB PCI. This association is strongest in patients with ACS, likewise, more potent P2Y12-inhibitors are used to prevent thrombotic recurrences.[15]

Earlier OCT examination discovered uncovered or malapposed stent struts immediately after the DEB procedure and in all images dissections were seen throughout the DEB-dilated segment which were not visible with angiography and remained untreated.[6] Therefore, although DEB PCI was shown to be an effective treatment for ISR, it may result in a large prothrombotic surface with delayed healing consequent to the paclitaxel treatment. This represents a potential risk and may necessitate effective antiplatelet therapy to prevent adverse events.

Table 3. Clinical and procedural predictors of MACE at one year.

	Univariate Cox Proportional Hazard Model		Multivariate Cox Proportional Hazard Model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	0.98 (0.95–1.02)	0.56		
Male gender	1.28 (0.57–2.86)	0.53		
Smoking	1.07 (0.44–2.61)	0.87		
Hypertension	2.08 (0.28–15.40)	0.46		
Diabetes mellitus	0.90 (0.36–2.26)	0.83		
Statin treatment	0.49 (0.20–1.17)	0.10	0.28 (0.09–0.84)	0.02
Prior MI	2.20 (0.75–6.41)	0.13		
Prior CABG	1.03 (0.39–2.76)	0.94		
Indication of prior PCI				
• STEMI	1.52 (0.69–3.35)	0.29		
• NSTEMI	0.41 (0.05–3.04)	0.36		
• Unstable angina	0.84 (0.25–2.82)	0.78		
• Stable angina	0.88 (0.39–1.97)	0.77		
Target vessel				
• LAD	0.62 (0.27–1.43)	0.26		
• RCA	1.67 (0.78–3.57)	0.18		
• CX	1.20 (0.41–3.47)	0.73		
• Graft	0.04 (0.00–160.28)	0.26		
Drug eluting stent restenosis	0.76 (0.30–1.88)	0.55		
Type of DEB				
• SeQuent Please	0.63 (0.25–1.58)	0.32		
• Invatec In-Pact	1.39 (0.65–2.97)	0.39		
• Protege	1.42 (0.60–3.37)	0.41		
• Pantera Lux	0.54 (0.12–2.28)	0.39		
Total DEB length, mm	1.02 (0.99–1.05)	**0.06**	1.04 (1.00–1.08)	0.03
Largest DEB diameter, mm	1.01 (0.44–2.32)	0.97		
DEB count/patient	1.52 (0.75–3.05)	0.24		
Predilatation	1.24 (0.37–4.12)	0.72		
ADP-test, U	1.02 (0.99–1.04)	**0.06**	1.03 (1.00–1.05)	0.04
Prasugrel treatment	2.74 (1.04–7.26)	0.03		

HR = hazard ratio; CI = confidence interval; MI = myocardial infarction; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; LAD = left anterior descending; RCA = right coronary artery; Cx = circumflexus; DEB = drug eluting balloon; ADP = adenosine diphosphate; MACE = major adverse cardiovascular event

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In line with the intraluminal imaging findings, we found a significant association between platelet reactivity and adverse outcomes and patients with HPR had a 2.5-fold higher risk for ischemic events. The higher risk was mainly driven by MI and revascularization, while stent thrombosis (ST) and mortality were rare.

This is in line with earlier randomized trials and a multicentre registry showing a low rate of early thrombosis of the DEB treated stented segment. [14] [16] [17] In our study, there was only one diagnosed ST (0.5%) after 4 days of the procedure, in a patient with HPR.

In patients with HPR most of the repeated revascularisations were triggered by events of acute MI (75% of revascularisation and 80% of TVR), whereas, in patients without HPR 46% of revascularisations and 57% of TVR were performed because of an acute MI. In-stent restenosis can frequently present as MI [18][19][20] and angiographically, patients with MI tend to

have an aggressive pattern of restenosis and total occlusion of the target lesion. One of the most likely explanation of MI in ISR include late stent or device thrombosis, which can be caused by incomplete neointimal coverage, early termination of antiplatelet therapy and/or increased neointimal thrombogenic tissue factors such as tissue factor and collagen.[18] The average time between the DEB procedure and the appearance of adverse events was 6 months (mean 181 days) in our study. When assessed with OCT at 6 months >94%, therefore almost complete neointimal coverage was found after stent implantation postdilated with DEB [21]. Based on these findings, incomplete neointimal coverage may play a less important role in the mechanisms of late ischemic events also but supports the relevant role and importance of ineffective antiplatelet therapy and residual platelet reactivity in the mechanisms of late ST and occurrence of repeated MI.

As a consequence of paucity of relevant data corrective treatment in terms of intensification of antiplatelet therapy based on platelet function studies is not established. Currently available large scale, randomized trials showed the prognostic role of HPR in patients underwent coronary stent implantation but failed to demonstrate the clinical improvements when treatment modifications were implemented on the basis of platelet function testing in patients with elective PCI.[22] [23] [24] [25] The TRIGGER-PCI trial testing switching from clopidogrel to prasugrel in patients with HPR found the 6-month event rate after DES implantation extremely low and the study stopped prematurely due to futility. [23] In two further trials, in the GRAVITAS and ARCTIC trials, treatment modification that mainly consisted use of high-dose clopidogrel in patients with high platelet reactivity after elective PCI with DES did not reduce the rate of end points compared with standard therapy.[22] [24] Using different primary endpoint definition, we found a 14% event rate in our real-life cohort and a significantly greater rate of the composite end-point in patients with HPR compared to patients without HPR (25% vs 11%) after PCI with DEB while there were no significant differences in clinical, laboratory and treatment parameters between the HPR and NPR group. Patients treated with prasugrel because of an acute coronary event within one year had worse outcome in our study. As this difference persisted in multivariate analyses taking antiplatelet efficacy in account we hypothesize that this worse prognosis is rather explainable with the recent ACS than with the antiplatelet therapy itself. Furthermore, due to the low numbers and lack of randomized comparisons and protocolled treatment modification our data do not allow drawing conclusion regarding the efficacy of corrective treatment. According to the multivariate analysis, beside platelet reactivity, history of statin treatment and the total length of the DEB were significant, independent predictors of the cardiovascular events. The other clinical and procedural characteristics had no important influence on the outcomes. This finding is in contrast with the earlier published registry from Calé et al. In their analysis of 156 patients the predictors of poorer outcome were previous MI and CABG, acute coronary syndrome at presentation, and PCI in the LAD, while DEB length and dyslipidaemia were not predictive of one-year outcome.[14] In our study, only elective DEB treated ISR patients were recruited which cohort is dissimilar to the populations of Calé et al. with acute coronary syndrome and small vessel disease included which may explain the differences in the verified determinants of worse results.

Our analyses of the predictive value of different level residual platelet reactivity identified two potential alternative cut-off values. Using these and the consensus defined 46 U, Kaplan-Meier analyses demonstrated similarly significant higher risk of composite endpoint with higher risk but smaller at risk population with the higher cut-off values (Fig 1 A, 1B and 1C; Fig 2). Different time-distribution of end-points and separation patterns of the Kaplan Meier were observed using these values. Using the lowest consensus cut-off value, we observed a late (>60 days) occurring difference of event frequencies, whereas the higher cut-off values appeared to be better predictors for the earlier events. These findings may draw the attention

to the fact that the proposed cut-off values for platelet function tests are mainly based on stent implanted ACS populations while in different clinical scenarios the predictive value and the optimal cut-offs may differ.

Study limitations

We have to acknowledge some limitations of our registry. The most important limitations are the single-centre design and consequent small sample size and the lack of blinding. It was left to the discretion of the operator to perform platelet function testing and not all of the patients were tested. Furthermore, although our inclusion criteria allowed the inclusion of ISR patients also presenting with acute coronary syndrome all of the cases entered the registry were treated during an elective intervention. This allows only to draw conclusions regarding patients with elective DEB treatment.

Conclusion

In stable angina patients treated with DEB due to ISR, HPR is significantly associated with a higher risk for recurrent ischemic events, mostly due to a higher risk for MI and revascularization. Regarding procedural characteristics, DEB length was an independent predictor of worse outcome. Further studies may investigate the safety and efficacy of treatment modification regarding P2Y12-inhibitor therapy and the optimal duration of treatment in DEB patients with HPR.

Acknowledgments

The authors are solely responsible for the design and conduct of this study; all study analyses, the drafting and editing of the paper and its final contents.

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Optimizing $P2Y_{12}$ Receptor Inhibition in Patients With Acute Coronary Syndrome on the Basis of Platelet Function Testing

Impact of Prasugrel and High-Dose Clopidogrel

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Objectives This study sought to evaluate the impact of treatment with prasugrel and high-dose clopidogrel on the basis of platelet function testing in patients with acute coronary syndrome (ACS) who are undergoing percutaneous coronary intervention (PCI).

Background The clinical impact of treatment with prasugrel in patients with ACS who have high platelet reactivity (HPR) is unknown.

Methods Patients with ACS who were pre-treated with clopidogrel and undergoing successful PCI were enrolled in a single-center, prospective registry. Platelet function was measured 12 to 36 h after PCI with the Multiplate device (Roche Diagnostics GmbH, Mannheim, Germany). Patients with HPR (>46 U) were switched to prasugrel or treated with high-dose clopidogrel, and those without HPR continued treatment with 75 mg of clopidogrel.

Results A total of 741 consecutive patients were enrolled in the study between September 2011 and August 2012, and 219 of these patients (29.5%) had HPR. Although platelet reactivity decreased after treatment adjustments in those with HPR, prasugrel provided significantly more potent platelet inhibition compared with high-dose clopidogrel ($p < 0.0001$). Compared with patients without HPR, the risk of all-cause death, myocardial infarction, stent thrombosis, or stroke at 1 year was significantly higher in the high-dose clopidogrel group (hazard ratio [HR]: 2.27; 95% confidence interval [CI]: 1.45 to 3.55; $p < 0.0001$), and patients who were switched to prasugrel had similar outcomes (HR: 0.90; 95% CI: 0.44 to 1.81; $p = 0.76$). Bleeding Academic Research Consortium (BARC) type 3/5 bleeding was also more frequent in patients treated with high-dose clopidogrel (HR: 2.09; 95% CI: 1.05 to 4.17; $p = 0.04$) than in patients switched to prasugrel (HR: 0.45; 95% CI: 0.11 to 1.91; $p = 0.28$). In a multivariate model, HPR with high-dose clopidogrel, but not with prasugrel, was an independent predictor of the composite ischemic endpoint (HR: 1.90; 95% CI: 1.17 to 3.08; $p = 0.01$).

Conclusions Switching patients with ACS who have HPR to treatment with prasugrel reduces thrombotic and bleeding events to a level similar to that of those without HPR; however, there is a higher risk of both thrombotic and bleeding complications with high-dose clopidogrel. (J Am Coll Cardiol 2014;63:1061–70) © 2014 by the American College of Cardiology Foundation

Patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) should receive a $P2Y_{12}$ inhibitor in addition to aspirin for 1 year (1–4). Recent European guidelines favor prasugrel and ticagrelor over clopidogrel (3,4), whereas American guidelines consider these options to be possible alternatives (1,2). Although both prasugrel and ticagrelor showed a significant reduction in death, myocardial infarction, or stroke compared with

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Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
BARC = Bleeding Academic Research Consortium
CI = confidence interval
HPR = high platelet reactivity
HR = hazard ratio
PCI = percutaneous coronary intervention
RR = relative risk

clopidogrel in patients with ACS (5,6), the higher risk of major bleeding together with the higher treatment costs limit their use in routine practice.

Theoretically, platelet function assays could be useful to measure the level of platelet inhibition and guide the choice of the optimal $P2Y_{12}$ inhibitor to reduce costs and bleeding complications; however, all currently available large-scale, randomized studies failed to show clinical improvements when treatment modifications were implemented on the basis of platelet function testing (7–9). Notably, most of these studies used high-dose clopidogrel to overcome high platelet reactivity (HPR) or included patients at low risk for recurrent events, and there is a lack of evidence on the potential clinical benefits of switching patients with ACS who have HPR to treatment with prasugrel. Our aim was to evaluate the clinical and pharmacodynamic impact of using prasugrel or high-dose clopidogrel on the basis of platelet function testing in a consecutive, all-comer, single-center registry of nonelderly patients (younger than 80 years of age) with ACS after PCI.

Methods

Patient selection. As of September 2011, Hungarian health insurers have approved and provided reimbursement for treatment with prasugrel in patients with ACS undergoing PCI who have either diabetes or acute myocardial infarction, but only when assessment of platelet function verifies that the patient did not respond to treatment with clopidogrel. This regulation practically acts as a prasugrel-prescribing policy for all interventional centers because of the high costs of unreimbursed prasugrel for patients. Acknowledging the lack of evidence behind this approach, we aimed to build a single-center registry in one of the large-volume academic centers in Hungary (Heart Institute, University of Pécs, Pécs, Hungary) to evaluate the clinical impact of optimizing $P2Y_{12}$ inhibition on the basis of platelet function testing.

Starting on September 1, 2011, consecutive, high-risk patients with ACS admitted for urgent coronary angiography were enrolled in a prospective registry. All patients with ACS who were pre-treated with clopidogrel were eligible for enrollment if PCI was performed successfully with stent implantation and there was no contraindication to treatment with a $P2Y_{12}$ inhibitor for 1 year. Pre-treatment with clopidogrel was defined as either a loading dose of 600 mg before admission or long-term treatment for more than 5 days with 75 mg/day. Exclusion criteria included an indication for chronic oral anticoagulation, age older than 80 years, lack of pre-treatment with clopidogrel, or administration of other $P2Y_{12}$ inhibitors before or during PCI. Importantly, ticagrelor was not available in Hungary during enrollment in the registry. Because we aimed to recruit a real-life, high-risk, all-comer population of patients with ACS, patients with cardiogenic shock, in pulmonary edema, or who had successful resuscitation were not excluded. All patients received 60 to 80 IU/kg of unfractionated heparin for PCI, and tirofiban was given at the discretion of the operator as a 25-μg/kg bolus followed by an optional 6- to 12-h infusion. Patients gave informed consent to comply with the antiplatelet strategy offered and to be available for regular follow-ups and telephone checkups for 1 year after PCI.

Platelet function testing and choice of $P2Y_{12}$ inhibitor treatment. Platelet function testing was performed with the Multiplate analyzer (Roche Diagnostics GmbH, Mannheim, Germany) 12 to 36 h after PCI. If tirofiban was administered, assessment of platelet function was postponed until 24 h after cessation of treatment. HPR was defined according to the consensus cutoff, which was an adenosine diphosphate (ADP)-test level >46 U (10).

In patients without HPR (ADP-test ≤46 U), standard-dose (75 mg/day), generic clopidogrel was continued after PCI (no HPR group). In contrast, patients with HPR were either switched to prasugrel (HPR + prasugrel group) with a loading dose of 60 mg followed by a maintenance dose of 10 mg/day or treated with adjusted, high-dose clopidogrel (HPR + clopidogrel group) as previously described and proposed by Bonello et al. (11). Briefly, patients were treated with additional loading doses of 600 mg of clopidogrel up to 4 times on the basis of controlled Multiplate testing each day to normalize platelet reactivity below the pre-defined cutoff of HPR. According to the achieved level of platelet reactivity after the second loading dose, a maintenance dose of 75 mg/day (no HPR) or 150 mg/day (HPR) was selected.

Patients were not randomly allocated to the prasugrel or high-dose clopidogrel groups; the choice of treatment was not influenced by strict local rules but was left to the discretion of the 7 expert operators. Some operators favored a switch to prasugrel, whereas others supported the use of high-dose clopidogrel.

Clinical endpoints. The primary composite efficacy endpoint was all-cause mortality, stent thrombosis, nonfatal myocardial infarction, or stroke at 1 year. Secondary analyses were performed for each component of the primary endpoint, and rates of target vessel revascularization were also compared. The primary safety endpoint was the occurrence of major bleeding events during 1 year.

All-cause mortality was traced from hospital records, follow-up visits, and a national vital record database. The causes of fatal events were uncertain in many cases, so cardiovascular mortality was not calculated. Stent thrombosis was defined as definite or probable according to the Academic Research Consortium criteria. Nonfatal myocardial infarction was defined according to the universal definition, including type 1, 4a, and 4b. Major bleeding was defined

according to the Bleeding Academic Research Consortium (BARC) criteria, including type 3 and 5 in the analysis.

Statistical analysis. Prior data were only available for the impact of treatment with high-dose clopidogrel in HPR, so the sample size was calculated to show a clinically relevant difference in all-cause death, myocardial infarction, stent thrombosis, or stroke between the HPR + clopidogrel and the no HPR groups. On the basis of the results of a prior registry (12), we estimated a 2-fold risk (relative risk [RR]: 2.00) in the primary endpoint between groups with an estimated 1-year absolute risk of 12% for the no HPR group (5,6). Assuming a 30% rate of HPR and an equal distribution of patients with HPR treated with high-dose clopidogrel or prasugrel, 605 patients were required to detect a difference between the HPR + clopidogrel and no HPR groups with 80% power at a 2-sided alpha level of 0.05. Together with the prasugrel group, 700 patients were needed. Allowing for dropouts, we planned to enroll 750 patients in the registry.

Continuous variables with normal distribution are presented as mean ± SD, whereas non-normally distributed variables are presented as median and interquartile range. Categorical variables are expressed as frequencies and percentages. Differences between the 2 groups were assessed with the Fisher exact test for categorical variables. Unpaired Student *t* tests were used for comparisons of normally distributed continuous variables between 2 groups, whereas non-normally distributed variables were compared using the Mann-Whitney *U* test.

Time-to-event data were visualized by Kaplan-Meier curves for each group. Event rates represent Kaplan-Meier estimates. Patients with HPR were compared with the no HPR group in Cox regression models. Unadjusted hazard ratios (HRs) together with 95% confidence intervals (CIs) were determined for clinical endpoints in univariate Cox proportional models, and then a multivariable Cox proportional hazards model was used to determine independent predictors of all-cause death, myocardial infarction, stent thrombosis, or stroke at 1 year. Of the 31 different baseline clinical, procedural, pharmacological, and laboratory values collected (Table 1) for all groups, variables with a p value < 0.05 in univariate analyses were entered into a forward stepwise Cox proportional model. To test for overfitting, sensitivity analyses were performed by building multivariate models with a predictor-event ratio of 1:10. These models contained either the clinically most relevant predictors or the strongest univariate predictors of the primary endpoint. Lack of violation of the proportional hazard assumption was checked by using log minus log survival plots.

Results

Patient characteristics. Between September 1, 2011 and August 31, 2012, 1,519 patients with ACS were admitted to the Heart Institute at the University of Pécs for urgent coronary angiography. After coronary angiography, 976 patients underwent PCI with successful stenting. On the basis of the inclusion criteria, 741 patients were enrolled in the study (Fig. 1). Table 1 shows the baseline clinical, procedural, laboratory, and treatment characteristics of the recruited patients according to the treatment groups. In general, the cohort comprised a very high-risk, all-comer, consecutive cohort of patients with ACS; 85% had an acute myocardial infarction, 48% had an stent thrombosis-segment elevation myocardial infarction, and 4.5% had cardiogenic shock (Online Table 1). Patients with HPR were significantly younger and had a higher incidence of diabetes and stent thrombosis-segment elevation myocardial infarction as well as more complex coronary disease, reflected by a longer total stent length. In addition, platelet count, leukocyte count, and high-sensitivity C-reactive protein levels were significantly higher in patients with HPR compared with those without HPR (Online Table 1). In contrast, patients with HPR who were treated with prasugrel or high-dose clopidogrel had comparable baseline characteristics except for greater use of statins and beta-blockers in the prasugrel group (Table 1). No baseline clinical variables were found to predict allocation to the prasugrel group in patients with HPR; however, a trend was found for different use of prasugrel among the 7 operators (median prasugrel use: 44%; minimum: 18%; maximum: 56%; $p = 0.09$).

Platelet function results. On the basis of the Multiplate results after PCI, 219 patients (29.5%) had HPR (Figs. 1 and 2A). The 522 patients (70.5%) with normal platelet reactivity continued treatment with 75 mg/day of generic clopidogrel for 1 year. Of the 219 patients with HPR, 128 patients (58%) were treated with adjusted high-dose clopidogrel and 91 patients (42%) were switched to treatment with prasugrel (Fig. 1). In the high-dose clopidogrel group, 100%, 24%, and 7% of patients required a second, third, and fourth loading dose of 600 mg of clopidogrel, respectively. At discharge, 20% of the patients were being treated with 150 mg/day of clopidogrel and 76% were being treated with 75 mg/day. Four percent of the patients died before the maintenance dose could be established.

After PCI, there was no difference between the HPR + clopidogrel group and the prasugrel group in the level of platelet reactivity (Fig. 2B). Although both prasugrel and repeated loading doses of 600 mg of clopidogrel reduced platelet reactivity from baseline ($p < 0.0001$ for both), a single loading dose of 60 mg of prasugrel followed by a maintenance dose of 10 mg/day provided significantly more potent platelet inhibition than the repeated boluses of 600 mg of clopidogrel at discharge ($p < 0.0001$) (Fig. 2B). Although platelet reactivity significantly increased with the 10-mg/day dose of prasugrel during the maintenance phase ($p < 0.0001$), 86% of the prasugrel-treated patients still remained below the cut point for HPR. In contrast, the standard dose and the doubled maintenance dose of clopidogrel were ineffective to maintain the level

Table 1 Baseline Characteristics of the Patient Population

	HPR (n = 219)				
	Prasugrel (n = 91)	High-Dose Clopidogrel (n = 128)	p Value*	No HPR (n = 522)	p Value†
Clinical characteristics					
Age, yrs	59.3 ± 9.5	61.8 ± 11.5	0.09	62.9 ± 10.9	<0.05
Male	52 (57.1)	84 (65.6)	0.21	347 (66.5)	0.27
Type 2 diabetes mellitus	33 (36.3)	35 (27.3)	0.18	125 (23.9)	0.05
Type 2 diabetes mellitus (insulin-treated)	12 (13.2)	13 (10.2)	0.53	39 (7.5)	0.09
Hypertension	64 (70.3)	94 (73.4)	0.65	372 (71.3)	0.86
Known dyslipidemia	21 (23.1)	25 (19.5)	0.61	128 (24.5)	0.34
Smoking	16 (17.6)	25 (19.5)	0.86	105 (20.1)	0.69
Prior PCI	12 (13.2)	20 (15.6)	0.70	52 (10.0)	0.08
Prior CABG	4 (4.4)	11 (8.6)	0.28	49 (9.4)	0.32
Prior MI	14 (15.4)	25 (19.5)	0.48	76 (14.6)	0.27
Admission characteristics					
Troponin positive	81 (89.0)	111 (86.7)	0.68	434 (83.1)	0.15
STEMI	55 (60.4)	69 (53.9)	0.41	234 (44.8)	<0.01
NSTEMI	26 (28.6)	42 (32.8)	0.55	200 (38.3)	0.07
Unstable angina	10 (11.0)	17 (13.3)	0.68	88 (16.9)	0.15
Cardiogenic shock	4 (4.4)	10 (7.8)	0.41	19 (3.6)	0.12
Loading dose of 600 mg of clopidogrel	88 (96.7)	124 (96.9)	1.00	494 (94.6)	0.26
Use of clopidogrel ≥5 days before PCI	3 (3.2)	4 (3.1)		28 (5.4)	
PCI procedure					
Bare-metal stent	60 (65.9)	100 (78.1)	0.06	389 (74.5)	0.71
Total stent length, mm	32 (24–56)	36 (23–60)	0.86	30 (18.8–48)	0.01
Stent count/patient	2 (1–2)	2 (1–3)	0.52	2 (1–2)	0.06
Laboratory findings 1 day after PCI					
Hemoglobin, g/dl	13.6 ± 1.6	13.5 ± 1.9	0.91	13.5 ± 1.7	0.45
Leukocyte count, g/l	11.4 (9.0–14.7)	12.2 (9.3–15.3)	0.25	10.5 (8.2–13.3)	0.0001
Platelet count, g/l	270 (232–331)	272 (232–318.5)	0.81	245 (208–290)	<0.0001
Creatinine, μmol/l	71.5 (63–82.8)	76 (63–96)	0.29	78 (65–93)	0.19
eGFR, MDRD	90.3 ± 26.3	87.1 ± 35.0	0.48	86.7 ± 31.1	0.47
High-sensitivity C-reactive protein, mg/l	6.2 (2.6–25.2)	6.4 (2.0–36.3)	0.77	3.8 (1.5–16.2)	0.0004
Discharge medication					
Aspirin	90 (98.9)	127 (99.2)	1.00	519 (99.4)	0.64
ACE-I/ARB	70 (76.9)	98 (76.6)	1.00	405 (77.6)	0.85
Beta-blocker	77 (84.6)	92 (71.9)	0.03	402 (77.0)	1.00
Proton pump inhibitor	83 (91.2)	119 (93.0)	0.62	501 (96.0)	<0.05
Statin	87 (95.6)	110 (85.9)	0.02	465 (89.1)	0.79

Values are mean ± SD, n (%), or median (interquartile range). *Comparisons between patients with HPR treated with prasugrel and patients treated with high-dose clopidogrel. †Comparisons between patients with and without HPR.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; HPR = high platelet reactivity; MDRD = Modification of Diet in Renal Disease; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

of platelet reactivity achieved with repeated loading doses of clopidogrel, resulting in rebound platelet reactivity during the chronic phase ($p < 0.0001$), with 51% of patients returning to HPR (Fig. 2). Notably, there was no difference between the effect of 75 mg/day and 150 mg/day of clopidogrel in patients with HPR ($p = 0.42$).

Clinical outcomes. During 1-year follow-up, all-cause mortality was 8.1%. The rate of definite/probable stent thrombosis was 2.8%, and 5.3% of patients had major bleeding. When all patients in the HPR groups were pooled and compared with the no HPR group, a significant increase in all-cause mortality or stent thrombosis was observed (Fig. 3A, Online Table 2). Despite treatment adjustments, the risk of the primary composite endpoint increased 1.7-fold in the HPR group compared with the no HPR group (HR: 1.67; 95% CI: 1.11 to 2.51; $p = 0.015$), whereas there was no difference in major bleeding complications between the groups (Fig. 3B).

When the high-dose clopidogrel group was compared with patients without HPR, a significantly higher risk of thrombotic events was observed (Figs. 4A to 4C, Table 2). The risk of all-cause death, nonfatal myocardial infarction, stent thrombosis, or stroke was more than 2-fold higher in the high-dose clopidogrel group than in the no HPR group (HR: 2.27; 95% CI: 1.45 to 3.55; $p < 0.0001$). Notably, BARC type 3 or 5 major bleeding was also significantly

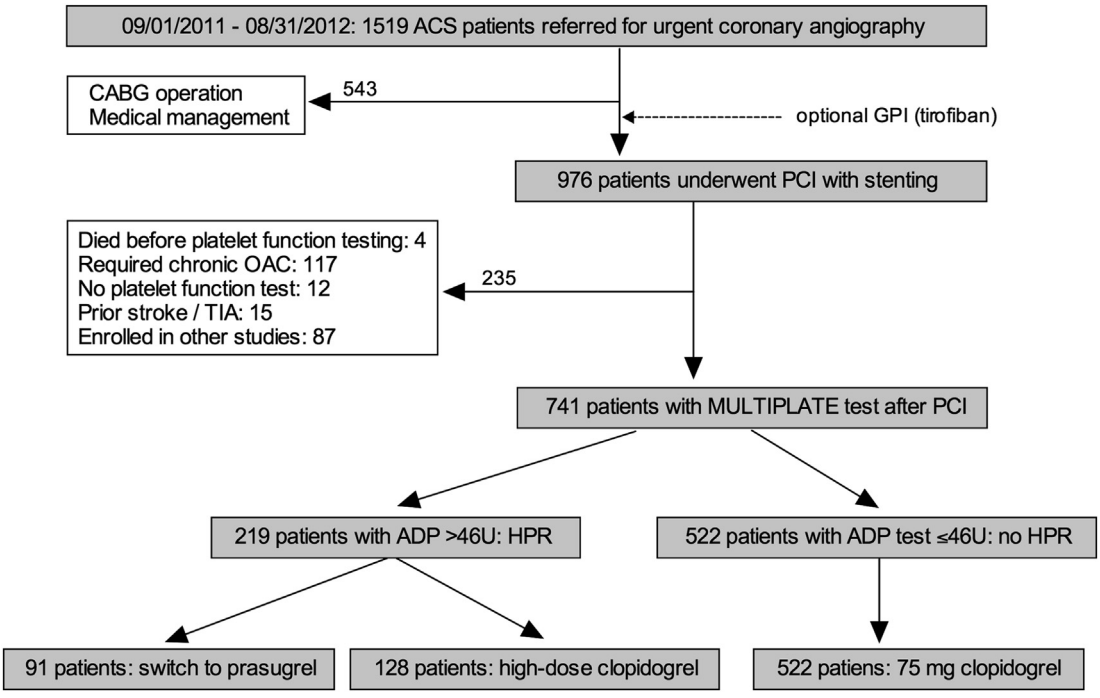

Figure 1 **Flowchart of Patient Enrollment in the Registry**

ACS = acute coronary syndrome(s); ADP = adenosine diphosphate; CABG = coronary artery bypass grafting; GPI = glycoprotein IIb/IIIa inhibitor; HPR = high platelet reactivity; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

increased (Fig. 4D, Table 2). In contrast, patients with HPR who were switched to treatment with prasugrel had rates of thrombotic complications that were similar to those in the no HPR group without any difference in all-cause death, myocardial infarction, stent thrombosis, or stroke (HR: 0.90; 95% CI: 0.44 to 1.81; p = 0.76) (Figs. 4A to 4C,

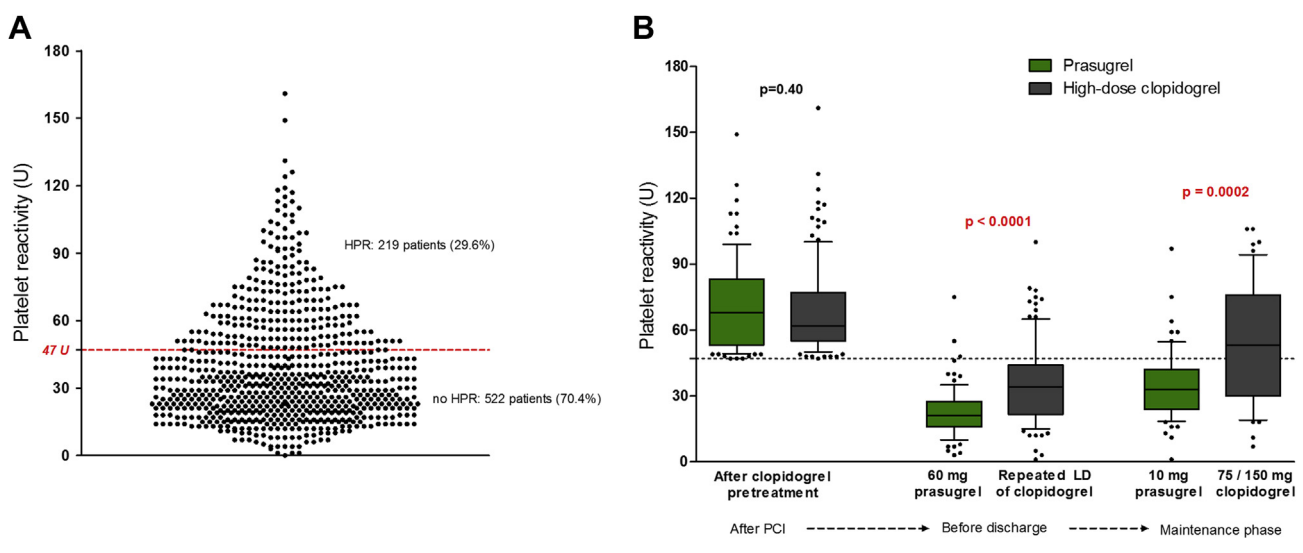

Figure 2 **Platelet Function Results Before and After $P2Y_{12}$ Inhibitor Treatment Adjustments in Patients With ACS After PCI**

(A) A scatter plot of platelet reactivity with the Multiplate device in all 741 patients after pre-treatment with clopidogrel, before treatment modification was initiated. **(B)** Changes in platelet reactivity among 219 patients with HPR who either switched to treatment with prasugrel or were treated with adjusted high-dose clopidogrel. LD = loading dose; other abbreviations as in Figure 1.

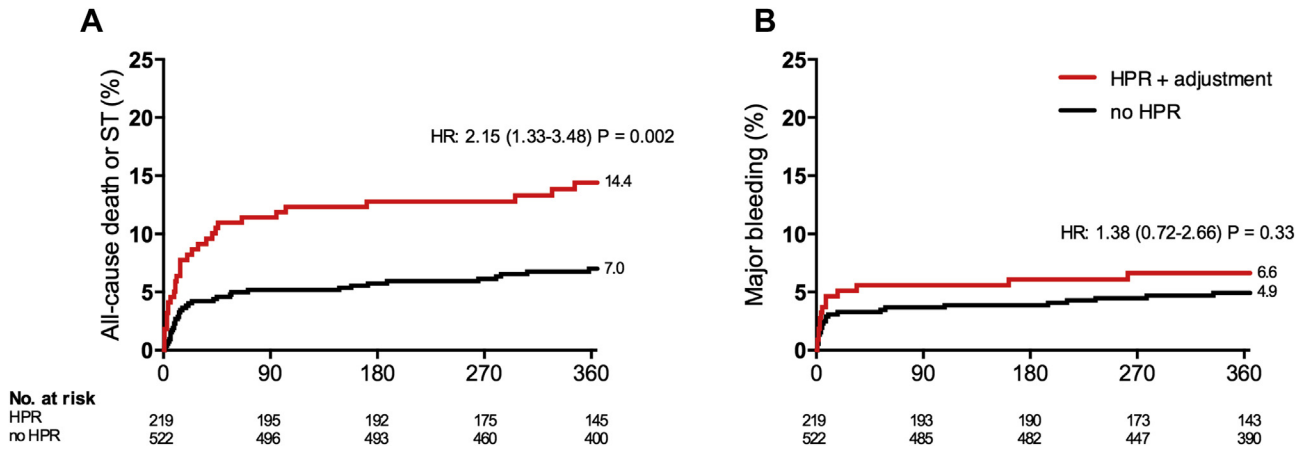

Figure 3 Thrombotic and Bleeding Complications in Patients With and Without HPR

(A) All-cause death or ST. **(B)** Major bleeding. Of note, all patients with HPR are grouped together in these comparisons regardless of whether they were treated with prasugrel or high-dose clopidogrel. HR = hazard ratio; ST = stent thrombosis; other abbreviations as in Figure 1.

Table 2). There was no excess of major bleeding after switching patients to treatment with prasugrel compared with others without HPR (Fig. 4D).

Patients in the high-dose clopidogrel group and the prasugrel group were not randomized, so all baseline characteristics were compared extensively (Table 1). After

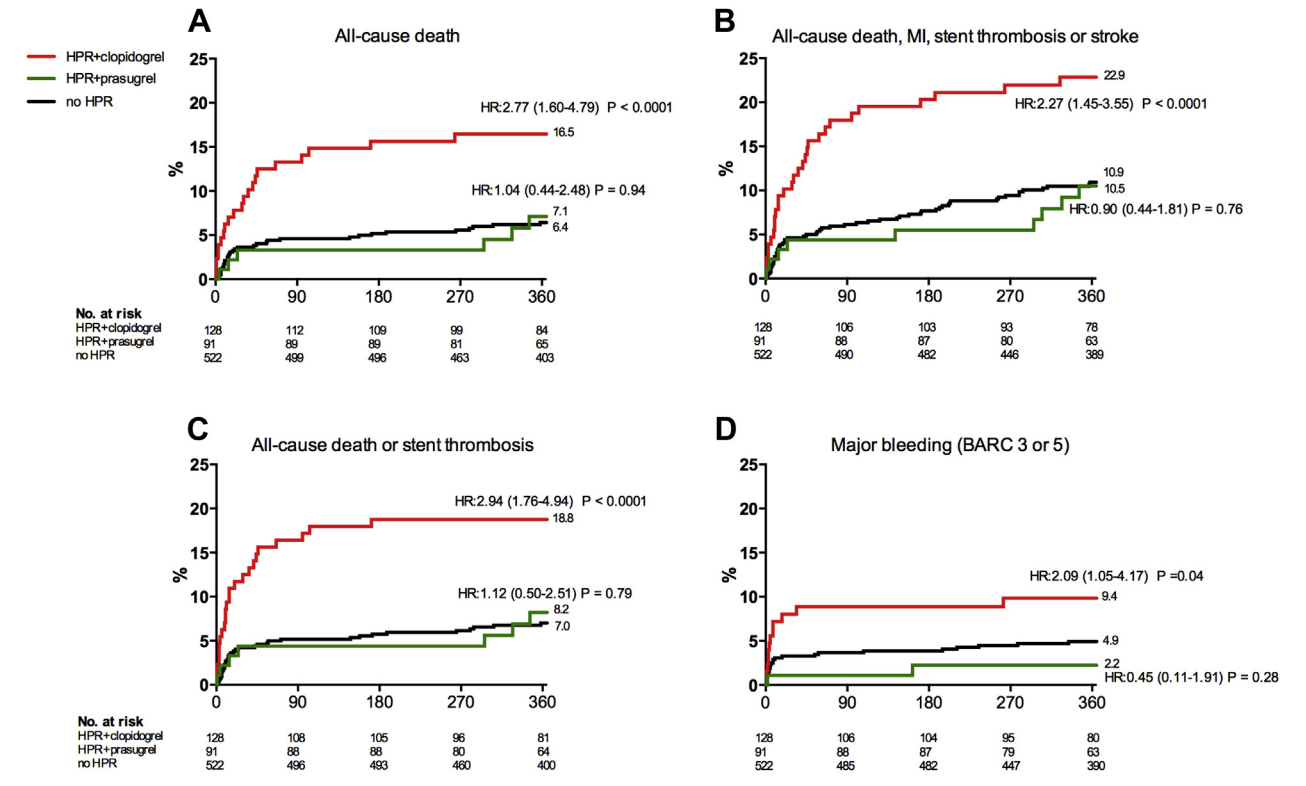

Figure 4 Impact of Prasugrel and High-Dose Clopidogrel on Thrombotic and Bleeding Events in Patients With HPR

(A) All-cause death. **(B)** All-cause death, MI, ST, or stroke. **(C)** All-cause death or ST. **(D)** Major bleeding (BARC 3 or 5). Event rates at 1 year are shown for each group as Kaplan-Meier estimates. HRs with 95% CIs were calculated in Cox proportional hazards models with the no HPR group as a reference. BARC = Bleeding Academic Research Consortium; MI = myocardial infarction; other abbreviations as in Figures 1 and 3.

Table 2 Clinical Outcomes at 12 Months Stratified According to the $P2Y_{12}$ Inhibitor Used in HPR

	No HPR (Reference) (n = 522)	HPR + Prasugrel (n = 91)	HR (95% CI)*, p Value	HPR + High-Dose Clopidogrel (n = 128)	HR (95% CI)*, p Value
Efficacy					
All-cause death	33 (6.32)	6 (6.59)	1.04 (0.44–2.48), 0.94	21 (16.41)	2.77 (1.60–4.79), <0.0001
Definite or probable stent thrombosis	10 (1.92)	3 (3.30)	1.72 (0.47–6.25), 0.41	8 (6.25)	3.48 (1.37–8.83), 0.009
MI	27 (5.17)	3 (3.30)	0.63 (0.19–2.07), 0.44	12 (9.38)	2.02 (1.02–3.99), 0.04
Stroke	3 (0.57)	0 (0.00)	N/A	1 (0.78)	1.52 (0.16–14.57), 0.72
TVR	95 (18.2)	20 (21.98)	1.02 (0.62–1.70), 0.93	22 (17.19)	1.22 (0.76–1.96), 0.40
All-cause death or stent thrombosis	36 (6.90)	7 (7.69)	1.12 (0.50–2.51), 0.79	24 (18.75)	2.94 (1.76–4.94), <0.0001
Death, MI, stent thrombosis, or stroke	57 (10.92)	9 (9.89)	0.90 (0.44–1.81), 0.76	29 (22.66)	2.27 (1.45–3.55), <0.0001
Safety					
Major bleeding (BARC 3 or 5)	25 (4.79)	2 (2.20)	0.45 (0.11–1.91), 0.28	12 (9.38)	2.09 (1.05–4.17), 0.04

Values are n (%). *Cox regression analyses using the no HPR group as a reference.
BARC = Bleeding Academic Research Consortium; CI = confidence interval; HR = hazard ratio; N/A = not available; TVR = target vessel revascularization; other abbreviations as in Table 1.

adjusting for age, diabetes, cardiogenic shock, drug-eluting stent(s), angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, beta-blocker use, statin use, and creatinine level, there was still a 2.5-fold increased risk of the primary composite endpoint in the high-dose clopidogrel group versus the prasugrel group (HR: 2.53; 95% CI: 1.08 to 5.93; p < 0.03) (Online Table 3).

Because of the clinical differences between patients with and without HPR, univariate and multivariate models were generated to identify independent predictors of the composite primary endpoint. Using univariate models, 20 baseline variables were identified that were significantly associated with all-cause death, myocardial infarction, stent thrombosis, or stroke (Table 3). According to the multivariate model, HPR with high-dose clopidogrel remained a significant, independent predictor of the primary endpoint (HR: 1.90; 95% CI: 1.17 to 3.08; p = 0.01), whereas patients with HPR who were switched to treatment with prasugrel had no increase in thrombotic events (Table 3).

When the impact of outcome events was tested on subsequent mortality, both stent thrombosis and major bleeding proved to be a strong and independent predictor of 1-year

Table 3 Clinical, Procedural, and Pharmacological Predictors of All-Cause Death, MI, Stent Thrombosis, or Stroke at 1 Year

	Univariate Cox Proportional Hazard Model		Multivariate Cox Proportional Hazard Model	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Cardiogenic shock	15.87 (9.95–25.32)	<0.0001	9.49 (5.42–16.62)	<0.0001
Acute renal failure (stage 4/5)	7.45 (4.28–12.96)	<0.0001		
High-dose clopidogrel, if HPR	2.27 (1.45–3.55)	<0.0001	1.90 (1.17–3.08)	0.01
Prasugrel, if HPR*	0.90 (0.44–1.81)	0.76*		
Leukocyte count (per 10-G/l increase)	2.39 (1.70–3.35)	<0.0001		
Type 2 diabetes mellitus (insulin-treated)	2.31 (1.35–3.95)	0.002		
Prior MI	1.92 (1.21–3.06)	0.006	2.47 (1.46–4.19)	0.001
STEMI	1.79 (1.18–2.70)	0.006		
Age (per 10-yr increase)	1.69 (1.38–2.06)	<0.0001	1.56 (1.25–1.94)	<0.0001
Type 2 diabetes mellitus	1.57 (1.03–2.39)	0.04		
No. of stents used (per 1 increase)	1.44 (1.22–1.70)	<0.0001		
Stent length (per 10-mm increase)	1.16 (1.08–1.25)	<0.0001	1.13 (1.03–1.24)	0.01
C-reactive protein (per 10-mg/l increase)	1.08 (1.05–1.11)	<0.0001		
Creatinine (per 10-μol/l increase)	1.04 (1.03–1.06)	<0.0001		
Unstable angina	0.22 (0.08–0.60)	0.003		
Drug-eluting stent (vs. bare-metal stent)	0.35 (0.19–0.66)	0.001	0.38 (0.16–0.89)	0.03
ACE-I/ARB	0.39 (0.26–0.59)	<0.0001	0.45 (0.27–0.72)	0.001
Statin	0.60 (0.33–0.96)	0.03		
Beta-blocker	0.62 (0.41–0.96)	0.03		
eGFR (per 10-ml/min/1.73 m^2 increase)	0.82 (0.77–0.88)	<0.0001		
Hemoglobin (per 10-g/l increase)	0.86 (0.76–0.97)	0.01		

*Nonsignificant variable included for demonstration.
Abbreviations as in Tables 1 and 2.

mortality (Online Table 4). Interestingly, patients with stent thrombosis had a 6-fold higher risk of major bleeding (RR: 6.23; 95% CI: 2.93 to 13.25; $p < 0.00001$), and patients with a major bleeding event had a 7-fold risk of stent thrombosis (RR: 7.20; 95% CI: 2.96 to 17.54; $p < 0.00001$).

Discussion

The main findings of this single-center registry can be summarized as follows. First, switching patients with HPR to treatment with prasugrel resulted in quicker and more potent $P2Y_{12}$ inhibition than repeating high-dose boluses of clopidogrel on the basis of platelet function testing. A lack of HPR can be maintained with 10 mg/day of prasugrel during long-term treatment, but a clear rebound in platelet reactivity occurred with maintenance doses of clopidogrel. Second, patients with ACS who had HPR and were treated with high-dose clopidogrel had an elevated risk of thrombotic events after PCI, whereas those who were switched to treatment with prasugrel had event rates that were comparable to those of patients without HPR. In addition, patients treated with high-dose clopidogrel had a higher risk of major bleeding complications. Third, in a multivariate model, use of high-dose clopidogrel in patients with HPR was an independent predictor of all-cause mortality, myocardial infarction, stent thrombosis, or stroke at 1 year, whereas switching to treatment with prasugrel was not associated with thrombotic events.

Prasugrel and ticagrelor provide more potent and more predictable $P2Y_{12}$ receptor inhibition than clopidogrel (1–4). Two large-scale randomized studies confirmed a reduction in cardiovascular death, myocardial infarction, or stroke among patients with ACS who were treated with novel $P2Y_{12}$ inhibitors as compared with clopidogrel (5,6). However, there were significant increases in major bleeding complications with both prasugrel and ticagrelor (5,6). In an era in which clopidogrel has become generic, the high treatment costs of novel $P2Y_{12}$ inhibitors together with the higher risk of bleeding limit their use in current practice.

A possible solution to these limitations might be to use prasugrel or ticagrelor selectively, that is, to restrict their use in patients with HPR on clopidogrel who are being treated with clopidogrel while continuing to treat good responders with generic clopidogrel. However, this strategy has never been tested in a randomized setting in patients with ACS. The only evidence we currently have from 2 randomized studies is that the use of platelet function testing to treat patients with high-dose clopidogrel who are at low-to-moderate risk for mortality and have HPR does not improve outcomes (7,9). However, frequent criticisms of these 2 studies are that they completely (7) or predominantly (9) used high-dose clopidogrel in patients with HPR and included patients at low risk for thrombotic events. A lack of clinical effectiveness of high-dose clopidogrel in patients with HPR was further supported by the RECLOSE-2 ACS (REsponsiveness to CLOpidogrel and Stent-related Events in Acute Coronary Syndromes) registry (12), establishing the concept that HPR may be a marker of higher risk but not a modifiable risk factor (13). However, no data are available on the clinical impact of prasugrel or ticagrelor in patients with ACS who have HPR.

In this respect, the results of our single-center, non-randomized ACS registry might be of interest for several reasons. First, we recruited a real-life patient population of all-comer, consecutive, high-risk patients with ACS, similar to the populations enrolled in TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) (5), PLATO (Study of PLATelet Inhibition and Patient Outcomes) (6), and/or the RECLOSE-2 ACS registry but not like the cohorts of prior platelet function studies (7–9). Compared with an all-cause mortality of 2% in ARCTIC (Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting) (9), <1% in GRAVITAS (Gauging Responsiveness with A VerifyNow assay–Impact on Thrombosis And Safety) (7), and 0% in TRIGGER PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) (8), we found an 8.1% all-cause mortality rate in our high-risk cohort. These differences can help explain how almost twice as many primary endpoint events occurred in a study that was one-third the size of the entire GRAVITAS study (95 vs. 50). Our results are also in line with the RECLOSE-2 ACS registry (12), which showed a more than 2-fold higher risk of all-cause death, myocardial infarction, stent thrombosis, or stroke in patients with HPR despite up-titration of the dose of clopidogrel. The only large-scale randomized study to show a benefit for high-dose clopidogrel is the CURRENT (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events) trial, which suggested a slight advantage in the subgroup of patients with ACS undergoing PCI (14). However, because the trial compared a loading dose of 300 and 600 mg of clopidogrel with and without use of a double maintenance dose for 1 week, the results are not comparable to our registry and to prior platelet function studies and prevent any meaningful conclusion on dose escalations of clopidogrel in patients receiving a loading dose of 600 mg (14).

On the basis of the discussed evidence, high-dose clopidogrel seems to have an insufficient clinical effect to overcome the higher risk of events in patients with ACS who have HPR (7,9,12). Therefore, our registry suggests that switching patients to treatment with prasugrel might decrease the risk of thrombotic events to a level similar to that of patients without HPR (Fig. 4). Platelet function results supported these findings at the pharmacodynamic level, confirming superior platelet inhibition by prasugrel (Fig. 2).

In a prior large-scale platelet function registry, Stone et al. (15) found that HPR after PCI was an independent

predictor of both stent thrombosis and major bleeding. In addition, both stent thombosis and major bleeding were independent predictors of mortality that associations were also replicated in our cohort. On the basis of this bidirectional association, they speculated that it will be impossible to reduce mortality in patients with HPR using more potent $P2Y_{12}$ inhibitor strategies, because for every stent thrombosis prevented, 4 extra major bleeds will be caused (15). Our results suggest that the impact of more potent $P2Y_{12}$ inhibitor strategies on major bleeding and stent thrombosis is more complex; the less potent clopidogrel reloading approach caused not only more stent thrombosis but also more major bleedings (Fig. 4). The lower rate of bleeding with prasugrel might be somewhat surprising in light of the results of TRITON (5); however, we administered prasugrel selectively to patients with HPR instead of a general population as analyzed in the cited trial. Although the observed differences in bleeding might be due to chance because of the low number of events or might be attributed to a less sensitive bleeding scale used during follow-up (BARC 3/5 instead of BARC $\geq$2), a recent Scandinavian registry also found a lower rate of visible bleeding with prasugrel (16). These results should not confute the higher risk of bleeding with prasugrel in a general ACS population but suggest that selected patients (such as those with HPR on clopidogrel) might tolerate more potent $P2Y_{12}$ inhibition without an excess risk of bleeding.

Study limitations. First and most importantly, the prasugrel and clopidogrel groups were not randomized. Although this might decrease the validity of our comparisons, registries are important for collecting real-life data on unselected patients. Although it was left to the discretion of the operator whether to choose prasugrel or high-dose clopidogrel, the 2 groups ended up with a very balanced distribution (42% vs. 58%) and most baseline variables were well matched between the 2 groups (Table 1). In addition, we observed similar results when adjusting for possible confounders between the HPR groups (Online Table 3). Furthermore, high-dose clopidogrel in patients with HPR prevailed as an independent predictor of the primary endpoint, corroborating the clinical relevance of our observations (Table 3). Second, it is unknown how these findings are transferable to ticagrelor because the drug was not available during the enrollment period in Hungary. Third, we only collected data on BARC type 3/5 major bleeding events, and the difference in major and minor bleeding complications remains unknown. Although BARC type 3/5 major bleeding was significantly associated with all-cause mortality (Online Table 4) and was a reliable marker of safety in TRITON (5), it might also have been a reason for a lower risk of bleeding among the prasugrel-treated patients. Finally, our results cannot be extrapolated to elderly patients (older than 80 years of age) who might require dose reduction with prasugrel but were generally excluded from our registry.

Conclusions

Treatment with prasugrel in patients with ACS who have HPR is significantly more effective than adjusted high-dose clopidogrel both after loading doses and during the maintenance phase. In parallel to the pharmacodynamic findings, treatment with prasugrel reduced thrombotic and bleeding events to a level similar to that of patients without HPR, whereas treatment with high-dose clopidogrel resulted in a higher risk of both thrombotic and bleeding complications. Further randomized studies are warranted to confirm the relevance of a platelet function-based selection of $P2Y_{12}$ inhibitors in patients with ACS after PCI, but such studies should avoid dose escalations of clopidogrel.

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Key Words: bleeding ■ high-dose clopidogrel ■ high platelet reactivity ■ mortality ■ PCI ■ platelet function testing ■ prasugrel ■ stent thrombosis.

APPENDIX

For supplemental tables, please see the online version of this article.