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

Ph.D. thesis

by

Adrienn Tornyos MD

Supervisor:

András Komócsi MD PhD DSc

Dániel Aradi MD PhD

Leader of the Doctoral School:

Lajos Bogár MD PhD

Program Leader:

István Szokodi MD PhD DSc

OGYDHT Pécs

University of Pécs, Faculty of medicine

Heart Centre

2021

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. 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. 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. 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.

Platelet function results

Based on the Multiplate results after PCI and clopidogrel pre-treatment, 219 patients (29.5%) had HPR. 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. 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. 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 ($p < 0.0001$). 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. 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. There was a significant increase in all-cause mortality or stent thrombosis in the pooled HPR group compared to the patients without HPR. 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.

Compared the high-dose clopidogrel group with the no HPR patient group, a significantly higher risk of thrombotic events was observed. 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. 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). There was no excess of major bleeding after switching patients to treatment with prasugrel compared with patients without HPR. 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. 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.

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).

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.

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.

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. 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.

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).

Predictors of ischemic events

According to the Cox regression analyses HPR (HR: 2.45; CI: 1.01–5.92; p = 0.03), 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. 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. 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]). 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]).

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. Platelet function results supported these findings at the pharmacodynamic level, confirming superior platelet inhibition by prasugrel.

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. 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.

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. 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.

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.

References

1. Guerra E, Ndrepepa G, Schulz S, Byrne R, Hoppmann P, Kufner S, et al. Impact of inhospital stent thrombosis and cerebrovascular accidents on long-term prognosis after percutaneous coronary intervention. Am Heart J. 2014 Dec;168(6):862–868.e1.

2. Wiviott SD, Braunwald E, McCabe CH, Horvath I, Keltai M, Herrman J-PR, et al. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. Lancet Lond Engl. 2008 Apr 19;371(9621):1353–63.

3. Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Grüntzig Lecture ESC 2014. Eur Heart J. 2015 Dec 14;36(47):3320–31.

4. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es G-A, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007 May 1;115(17):2344–51.

5. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med. 1998 Dec 3;339(23):1665–71.

6. Schömig A, Neumann FJ, Kastrati A, Schühlen H, Blasini R, Hadamitzky M, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med. 1996 Apr 25;334(17):1084–9.

7. Urban P, Macaya C, Rupprecht HJ, Kiemeneij F, Emanuelsson H, Fontanelli A, et al. Randomized evaluation of anticoagulation versus antiplatelet therapy after coronary stent implantation in high-risk patients: the multicenter aspirin and ticlopidine trial after intracoronary stenting (MATTIS). Circulation. 1998 Nov 17;98(20):2126–32.

8. Bertrand ME, Legrand V, Boland J, Fleck E, Bonnier J, Emmanuelson H, et al. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting. The full anticoagulation versus aspirin and ticlopidine (fantastic) study. Circulation. 1998 Oct 20;98(16):1597–603.

9. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014 Dec 4;371(23):2155–66.

10. Steg PG, Harrington RA, Emanuelsson H, Katus HA, Mahaffey KW, Meier B, et al. Stent thrombosis with ticagrelor versus clopidogrel in patients with acute coronary

syndromes: an analysis from the prospective, randomized PLATO trial. Circulation. 2013 Sep 3;128(10):1055–65.

11. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018 Jan 14;39(3):213–60.

12. Davì G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med. 2007 Dec 13;357(24):2482–94.

13. Virmani R, Farb A. Pathology of in-stent restenosis. Curr Opin Lipidol. 1999 Dec;10(6):499–506.

14. Farb A, Weber DK, Kolodgie FD, Burke AP, Virmani R. Morphological predictors of restenosis after coronary stenting in humans. Circulation. 2002 Jun 25;105(25):2974–80.

15. Singh M, Gersh BJ, McClelland RL, Ho KKL, Willerson JT, Penny WF, et al. Clinical and angiographic predictors of restenosis after percutaneous coronary intervention: insights from the Prevention of Restenosis With Tranilast and Its Outcomes (PRESTO) trial. Circulation. 2004 Jun 8;109(22):2727–31.

16. Nayak AK, Kawamura A, Nesto RW, Davis G, Jarbeau J, Pyne CT, et al. Myocardial infarction as a presentation of clinical in-stent restenosis. Circ J Off J Jpn Circ Soc. 2006 Aug;70(8):1026–9.

17. Bossi I, Klersy C, Black AJ, Cortina R, Choussat R, Cassagneau B, et al. In-stent restenosis: long-term outcome and predictors of subsequent target lesion revascularization after repeat balloon angioplasty. J Am Coll Cardiol. 2000 May;35(6):1569–76.

18. Walters DL, Harding SA, Walsh CR, Wong P, Pomerantsev E, Jang IK. Acute coronary syndrome is a common clinical presentation of in-stent restenosis. Am J Cardiol. 2002 Mar 1;89(5):491–4.

19. Byrne RA, Serruys PW, Baumbach A, Escaned J, Fajadet J, James S, et al. Report of a European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions task force on the evaluation of coronary stents in Europe: executive summary. Eur Heart J. 2015 Oct 7;36(38):2608–20.

20. Scheller B, Hehrlein C, Bocksch W, Rutsch W, Haghi D, Dietz U, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. N Engl J Med. 2006 Nov 16;355(20):2113–24.

21. Scheller B, Clever YP, Kelsch B, Hehrlein C, Bocksch W, Rutsch W, et al. Long-term follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. JACC Cardiovasc Interv. 2012 Mar;5(3):323–30.

22. Habara S, Iwabuchi M, Inoue N, Nakamura S, Asano R, Nanto S, et al. A multicenter randomized comparison of paclitaxel-coated balloon catheter with conventional balloon angioplasty in patients with bare-metal stent restenosis and drug-eluting stent restenosis. Am Heart J. 2013 Sep;166(3):527–33.

23. Unverdorben M, Vallbracht C, Cremers B, Heuer H, Hengstenberg C, Maikowski C, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. Circulation. 2009 Jun 16;119(23):2986–94.

24. Rittger H, Brachmann J, Sinha A-M, Waliszewski M, Ohlow M, Brugger A, et al. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study. J Am Coll Cardiol. 2012 Apr 10;59(15):1377–82.

25. Habara S, Mitsudo K, Kadota K, Goto T, Fujii S, Yamamoto H, et al. Effectiveness of paclitaxel-eluting balloon catheter in patients with sirolimus-eluting stent restenosis. JACC Cardiovasc Interv. 2011 Feb;4(2):149–54.

26. Byrne RA, Neumann F-J, Mehilli J, Pinieck S, Wolff B, Tiroch K, et al. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. Lancet Lond Engl. 2013 Feb 9;381(9865):461–7.

27. Indermuehle A, Bahl R, Lansky AJ, Froehlich GM, Knapp G, Timmis A, et al. Drug-eluting balloon angioplasty for in-stent restenosis: a systematic review and meta-analysis of randomised controlled trials. Heart Br Card Soc. 2013 Mar;99(5):327–33.

28. Wallentin L. P2Y(12) inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. Eur Heart J. 2009 Aug;30(16):1964–77.

29. Foye WO, Lemke TL, Williams DA, editors. Foye's principles of medicinal chemistry. 7th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2013. 1500 p.

30. Damman P, Woudstra P, Kuijt WJ, de Winter RJ, James SK. P2Y12 platelet inhibition in clinical practice. J Thromb Thrombolysis. 2012 Feb;33(2):143–53.

31. Farid NA, Kurihara A, Wrighton SA. Metabolism and disposition of the thienopyridine antiplatelet drugs ticlopidine, clopidogrel, and prasugrel in humans. J Clin Pharmacol. 2010 Feb;50(2):126–42.

32. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, CLASSICS Investigators. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin

after coronary stenting : the clopidogrel aspirin stent international cooperative study (CLASSICS). Circulation. 2000 Aug 8;102(6):624–9.

33. Campo G, Valgimigli M, Gemmati D, Percoco G, Catozzi L, Frangione A, et al. Poor responsiveness to clopidogrel: drug-specific or class-effect mechanism? Evidence from a clopidogrel-to-ticlopidine crossover study. J Am Coll Cardiol. 2007 Sep 18;50(12):1132–7.

34. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Alfonso F, Macaya C, Bass TA, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. J Am Coll Cardiol. 2007 Apr 10;49(14):1505–16.

35. Damman P, Woudstra P, Kuijt WJ, de Winter RJ, James SK. P2Y12 platelet inhibition in clinical practice. J Thromb Thrombolysis. 2012 Feb;33(2):143–53.

36. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Méneveau N, et al. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med. 2009 Jan 22;360(4):363–75.

37. Juurlink DN, Gomes T, Ko DT, Szmitko PE, Austin PC, Tu JV, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ Can Med Assoc J J Assoc Medicale Can. 2009 Mar 31;180(7):713–8.

38. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet Lond Engl. 1996 Nov 16;348(9038):1329–39.

39. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001 Aug 16;345(7):494–502.

40. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med. 2005 Mar 24;352(12):1179–89.

41. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet Lond Engl. 2005 Nov 5;366(9497):1607–21.

42. Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH, et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J. 2011 Dec;32(23):2933–44.

43. Wiviott SD, Antman EM, Gibson CM, Montalescot G, Riesmeyer J, Weerakkody G, et al. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel

Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). Am Heart J. 2006 Oct;152(4):627–35.

44. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018 Jan 14;39(3):213–60.

45. Brandt JT, Close SL, Iturria SJ, Payne CD, Farid NA, Ernest CS, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. J Thromb Haemost JTH. 2007 Dec;5(12):2429–36.

46. Aradi D, Komócsi A, Kancz S, Nagy GG, Kiss RG, Merkely B. Trombocitaaggregáció-gátlás akut koronária szindrómán átesett betegek magas kockázatú alcsoportjaiban. Cardiol Hung. 2019;49(4):267–77.

47. Storey RF, Becker RC, Harrington RA, Husted S, James SK, Cools F, et al. Characterization of dyspnoea in PLATO study patients treated with ticagrelor or clopidogrel and its association with clinical outcomes. Eur Heart J. 2011 Dec;32(23):2945–53.

48. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation. 2003 Jun 17;107(23):2908–13.

49. von Beckerath N, Taubert D, Pogatsa-Murray G, Schömig E, Kastrati A, Schömig A. Absorption, metabolization, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel: results of the ISAR-CHOICE (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) Trial. Circulation. 2005 Nov 8;112(19):2946–50.

50. Price MJ, Coleman JL, Steinhubl SR, Wong GB, Cannon CP, Teirstein PS. Onset and offset of platelet inhibition after high-dose clopidogrel loading and standard daily therapy measured by a point-of-care assay in healthy volunteers. Am J Cardiol. 2006 Sep 1;98(5):681–4.

51. Wallentin L, Varenhorst C, James S, Erlinge D, Braun OO, Jakubowski JA, et al. Prasugrel achieves greater and faster P2Y12receptor-mediated platelet inhibition than clopidogrel due to more efficient generation of its active metabolite in aspirin-treated patients with coronary artery disease. Eur Heart J. 2008 Jan;29(1):21–30.

52. Verstuyft C, Simon T, Kim RB. Personalized medicine and antiplatelet therapy: ready for prime time? Eur Heart J. 2009 Aug;30(16):1943–63.

53. Aradi D, Komócsi A, Vorobcsuk A, Rideg O, Tokés-Füzesi M, Magyarlaki T, et al. Prognostic significance of high on-clopidogrel platelet reactivity after percutaneous

coronary intervention: systematic review and meta-analysis. Am Heart J. 2010 Sep;160(3):543–51.

54. Price MJ, Berger PB, Teirstein PS, Tanguay J-F, Angiolillo DJ, Spriggs D, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA. 2011 Mar 16;305(11):1097–105.

55. Tantry US, Bonello L, Aradi D, Price MJ, Jeong Y-H, Angiolillo DJ, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol. 2013 Dec 17;62(24):2261–73.

56. Bonello L, Camoin-Jau L, Arques S, Boyer C, Panagides D, Wittenberg O, et al. Adjusted clopidogrel loading doses according to vasodilator-stimulated phosphoprotein phosphorylation index decrease rate of major adverse cardiovascular events in patients with clopidogrel resistance: a multicenter randomized prospective study. J Am Coll Cardiol. 2008 Apr 8;51(14):1404–11.

57. Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013 Oct;34(38):2949–3003.

58. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation. 2012 Oct 16;126(16):2020–35.

59. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke. 2009 Jun;40(6):2276–93.

60. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJB, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013 Jul;44(7):2064–89.

61. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011 Jun 14;123(23):2736–47.

62. Parodi G, Marcucci R, Valenti R, Gori AM, Migliorini A, Giusti B, et al. High Residual Platelet Reactivity After Clopidogrel Loading and Long-term Cardiovascular Events

Among Patients With Acute Coronary Syndromes Undergoing PCI. JAMA. 2011 Sep 21;306(11):1215.

63. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med. 2009 Sep 10;361(11):1045–57.

64. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med. 2007 Nov 15;357(20):2001–15.

65. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Jan 29;61(4):e78–140.

66. Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2012 Aug 14;60(7):645–81.

67. Hamm CW, Bassand J-P, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011 Dec;32(23):2999–3054.

68. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012 Oct;33(20):2569–619.

69. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007 Nov 15;357(20):2001–15.

70. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation. 2003 Jun 17;107(23):2908–13.

71. von Beckerath N, Taubert D, Pogatsa-Murray G, Schömig E, Kastrati A, Schömig A. Absorption, metabolization, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel: results of the ISAR-CHOICE (Intracoronary Stenting and

Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) Trial. Circulation. 2005 Nov 8;112(19):2946–50.

72. Price MJ, Coleman JL, Steinhubl SR, Wong GB, Cannon CP, Teirstein PS. Onset and offset of platelet inhibition after high-dose clopidogrel loading and standard daily therapy measured by a point-of-care assay in healthy volunteers. Am J Cardiol. 2006 Sep 1;98(5):681–4.

73. Aradi D, Komócsi A, Vorobcsuk A, Rideg O, Tokés-Füzesi M, Magyarlaki T, et al. Prognostic significance of high on-clopidogrel platelet reactivity after percutaneous coronary intervention: systematic review and meta-analysis. Am Heart J. 2010 Sep;160(3):543–51.

74. Bonello L, Tantry US, Marcucci R, Blindt R, Angiolillo DJ, Becker R, et al. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol. 2010 Sep 14;56(12):919–33.

75. Price MJ, Berger PB, Teirstein PS, Tanguay J-F, Angiolillo DJ, Spriggs D, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA. 2011 Mar 16;305(11):1097–105.

76. Collet J-P, Cuisset T, Rangé G, Cayla G, Elhadad S, Pouillot C, et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med. 2012 Nov 29;367(22):2100–9.

77. Trenk D, Stone GW, Gawaz M, Kastrati A, Angiolillo DJ, Müller U, et al. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) study. J Am Coll Cardiol. 2012 Jun 12;59(24):2159–64.

78. Angiolillo DJ. Applying platelet function testing in clinical practice: what are the unmet needs? JAMA. 2011 Sep 21;306(11):1260–1.

79. CURRENT-OASIS 7 Investigators, Mehta SR, Bassand J-P, Chrolavicius S, Diaz R, Eikelboom JW, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med. 2010 Sep 2;363(10):930–42.

80. Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann F-J, Metzger DC, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. Lancet Lond Engl. 2013 Aug 17;382(9892):614–23.

81. Damman P, Varenhorst C, Koul S, Eriksson P, Erlinge D, Lagerqvist B, et al. Treatment patterns and outcomes in patients undergoing percutaneous coronary intervention treated with prasugrel or clopidogrel (from the Swedish Coronary Angiography and Angioplasty Registry [SCAAR]). Am J Cardiol. 2014 Jan 1;113(1):64–9.

82. Cayla G, Cuisset T, Silvain J, Leclercq F, Manzo-Silberman S, Saint-Etienne C, et al. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. Lancet Lond Engl. 2016 Oct 22;388(10055):2015–22.

83. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet Lond Engl. 2017 Oct 14;390(10104):1747–57.

84. Antman EM, Wiviott SD, Murphy SA, Voitk J, Hasin Y, Widimsky P, et al. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. J Am Coll Cardiol. 2008 May 27;51(21):2028–33.

85. Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH, et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J. 2011 Dec;32(23):2933–44.

86. Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, García del Blanco B, García-Touchard A, López-Minguéz JR, et al. A Prospective Randomized Trial of Drug-Eluting Balloons Versus Everolimus-Eluting Stents in Patients With In-Stent Restenosis of Drug-Eluting Stents: The RIBS IV Randomized Clinical Trial. J Am Coll Cardiol. 2015 Jul 7;66(1):23–33.

87. Xu B, Gao R, Wang J, Yang Y, Chen S, Liu B, et al. A prospective, multicenter, randomized trial of paclitaxel-coated balloon versus paclitaxel-eluting stent for the treatment of drug-eluting stent in-stent restenosis: results from the PEPCAD China ISR trial. JACC Cardiovasc Interv. 2014 Feb;7(2):204–11.

88. Agostoni P, Belkacemi A, Voskuil M, Nathoe HM, Doevendans PA, Stella PR. Serial morphological and functional assessment of drug-eluting balloon for in-stent restenotic lesions: mechanisms of action evaluated with angiography, optical coherence tomography, and fractional flow reserve. JACC Cardiovasc Interv. 2013 Jun;6(6):569–76.

89. Calé R, Sousa PJ, Pereira E, Araújo Gonçalves P, Vitorino S, Vinhas H, et al. One-year clinical outcomes of percutaneous treatment with drug-eluting balloons: results from a multicenter registry. Rev Port Cardiol Orgao Of Soc Port Cardiol Port J Cardiol Off J Port Soc Cardiol. 2013 May;32(5):361–9.

90. Fröhlich GM, Lansky AJ, Ko DT, Archangelidi O, De Palma R, Timmis A, et al. Drug eluting balloons for de novo coronary lesions - a systematic review and meta-analysis. BMC Med. 2013 May 8;11:123.

91. Poerner TC, Otto S, Gassdorf J, Nitsche K, Janiak F, Scheller B, et al. Stent coverage and neointimal proliferation in bare metal stents postdilated with a Paclitaxel-eluting balloon versus everolimus-eluting stents: prospective randomized study using optical coherence tomography at 6-month follow-up. Circ Cardiovasc Interv. 2014 Dec;7(6):760–7.

92. Scheller B, Hehrlein C, Bocksch W, Rutsch W, Haghi D, Dietz U, et al. Two year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. Clin Res Cardiol Off J Ger Card Soc. 2008 Oct;97(10):773–81.

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.
   IF: 2.766
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.
   IF: 16.503

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*
2. **Tornyos A**, Vorobcsuk A, Kupó P, Aradi D, Kehl D, Komócsi A. Apixaban and risk of myocardial infarction: meta-analysis of randomized controlled trials. J Thromb Thrombolysis. 2015 Jul; 40(1):1-11. *IF: 1.884*
3. Komócsi A, **Tornyos A**, Kehl D, Aradi D, Vorobcsuk A. Mortality after transradial approach in ST-segment elevation myocardial infarction. Do we see the forest for the trees? Int J Cardiol. 2013 Oct 3; 168(3):3050-3. *IF: 4,036*
4. Komócsi A, Aradi D, Kehl D, Ungi I, Thury A, Pintér T, Di Nicolantonio JJ, **Tornyos A**, Vorobcsuk A. Meta-analysis of randomized trials on access site selection for percutaneous coronary intervention in ST-segment elevation myocardial infarction. Arch Med Sci. 2014 May 12; 10(2):203-12. *IF: 2.03*
5. Kiss T, Kovacs K, Komocsi A, **Tornyos A**, Zalan P, Sumegi B, Gallyas F Jr, Kovacs K. Novel mechanisms of sildenafil in pulmonary hypertension involving

cytokines/chemokines, MAP kinases and Akt. PLoS One. 2014 Aug 18; 9(8):e104890. *IF: 3.234*

6. Költő G, Vuolteenaho O, Szokodi I, Faludi R, **Tornyos A**, Ruskoaho H, Minier T, Czirják L, Komócsi A. Prognostic value of N-terminal natriuretic peptides in systemic sclerosis: a single centre study. Clin Exp Rheumatol. 2014 Nov-Dec; 32(6 Suppl 86):S-75-81. *IF: 2.724*
7. Kupó P, Aradi D, **Tornyos A**, Tőkés-Füzesi M, Komócsi A. Assessment of platelet function in patients receiving tirofiban early after primary coronary intervention. Interv Med Appl Sci. 2016 Dec; 8(4):135-140. *IF: 0.203*
8. Oldham WM, Oliveira RKF, Wang RS, Opotowsky AR, Rubins DM, Hainer J, Wertheim BM, Alba GA, Choudhary G, **Tornyos A**, MacRae CA, Loscalzo J, Leopold JA, Waxman AB, Olschewski H, Kovacs G, Systrom DM, Maron BA. Network Analysis to Risk Stratify Patients With Exercise Intolerance. Circ Res. 2018 Mar 16; 122(6):864-876. *IF: 15.211*
9. Nagy BM, Kovacs G, **Tornyos A**, Svehlikova E, Foris V, Nagaraj C, Kwapiszewska G, Pieber TR, Olschewski A, Olschewski H. No indication of insulin resistance in idiopathic pulmonary arterial hypertension with preserved physical activity. Eur Respir J. 2020 Jun 11;55(6):1901228. *IF: 12.339*

Cumulative impact factor: 62,842

International abstracts and poster presentations

1. **Tornyos A**, Komócsi A, Vorobcsuk A, Kehl D. Risk of myocardial infarction in patients treated with oral anticoagulation, a Bayesian network meta-analysis. ESC 2014; Barcelona, Spain
2. **Tornyos A**, Komócsi A, Aradi D, Vorobcsuk A, Kehl D. No signal for higher risk of myocardial infarction with apixaban: meta-analysis of randomized controlled trials. ESC 2014; Barcelona, Spain
3. **Tornyos A**, Trinker M, Foris V, Pfeiffer S, Odler B, Douschan P, Avian A, Olschewski A, Kovacs G, Olschewski H. Pulmonary Hypertension in Hypersensitivity

Pneumonitis. 15th International Pulmonary Hypertension Forum 2016; Barcelona, Spain

4. **Tornyos A**, Trinker M, Foris V, Pfeiffer S, Odler B, Douschan P, Avian A, Olschewski A, Kovacs G, Olschewski H. Pulmonary Hypertension in Hypersensitivity Pneumonitis. (ERS 2016; London, UK) Eur Respir J. 2016 48: PA2450
5. **Tornyos A**, Trinker M, Foris V, Pfeiffer S, Odler B, Douschan P, Avian A, Olschewski A, Kovacs G, Olschewski H. Pulmonary Hypertension in Hypersensitivity Pneumonitis. (ÖGP Annual Meeting 2016; Vienna, Austria) Wien Klin Wochenschr. 2016; 128 (19-20):766-766.
6. **Tornyos A**, Trinker M, Foris V, Pfeiffer S, Odler B, Douschan P, Avian A, Olschewski A, Kovacs G, Olschewski H. Pulmonary Hypertension in Hypersensitivity Pneumonitis. LBG Meeting for Health Sciences 2016; Vienna, Austria
7. **Tornyos A**, Trinker M, Foris V, Pfeiffer S, Odler B, Douschan P, Avian A, Olschewski A, Kovacs G, Olschewski H. Pulmonary Hypertension in Hypersensitivity Pneumonitis. 17th International Pulmonary Hypertension Forum 2018; Madrid, Spain
8. **Tornyos A**, Trinker M, Foris V, Pfeiffer S, Odler B, Douschan P, Avian A, Olschewski A, Kovacs G, Olschewski H. Pulmonary Hypertension in Hypersensitivity Pneumonitis. (ERS 2018; Paris, France) Eur Respir J. 2018 52: PA3100
9. **Tornyos A**, Trinker M, Foris V, Pfeiffer S, Odler B, Douschan P, Avian A, Olschewski A, Kovacs G, Olschewski H. Pulmonary Hypertension in Hypersensitivity Pneumonitis. (ÖGP Annual Meeting 2018; Linz, Austria) Wien Klin Wochenschr. 2018; 130 (19-20):621-621.-42.
10. Komócsi A, **Tornyos A**, Kupó P, Tokés-Füzesi M, Rideg O, Aradi D. Impact of platelet volume and platelet reactivity on thrombotic events in ACS patients on clopidogrel or prasugrel after PCI. EuroPCR 2014 Paris, France 2014 May 20-23 Euro14A-OP089 Eurointervention 2014; 10 (Suppl.) 80.
11. Odler B, Douschan P, Pfeiffer S, Foris V, **Tornyos A**, Avian A, Olschewski A, Olschewski H, Kovacs G. Diffusion capacity for nitric oxide: a novel marker for pulmonary hemodynamics and exercise capacity? (ÖGP Annual Meeting 2016; Vienna, Austria) Wien Klin Wochenschr. 2016 128 (19-20):768-768.

12. Odler B, Reiter U, Reiter G, Fuchsjäger M, Foris V, **Tornyos A**, Douschan P, Pfeiffer S, Olschewski A, Olschewski H, Kovacs G. Validation of cardiac MR parameters in the assessment of pulmonary hemodynamics. (ERS 2017; Milan, Italy) Eur Respir J. 50 (suppl 61) PA2441
13. Odler B, Reiter U, Reiter G, Fuchsjäger M, Foris V, **Tornyos A**, Douschan P, Pfeiffer S, Olschewski A, Olschewski H, Kovacs G. Cardiac magnetic resonance parameters in the assessment of pulmonary hemodynamics: a validation study. (ÖGP Annual Meeting 2017; Insbruck, Austria) Wien Klin Wochenschr. 2017 129(19-20):768-768.
14. Nagy B, Bordag N, Nagaraj C, Foris V, **Tornyos A**, Narath S, Gander E, Magnes C, Kovacs G, Klepetko W, Pieber TR, Kwapiszewska G, Olschewski H, Olschewski A. Metabolic fingerprinting in pulmonary hypertension. (ÖGP Annual Meeting 2018; Linz, Austria) Wien Klin Wochenschr. 2018; 130 (19-20):604-605.
15. Nagy B, Bordag N, Nagaraj C, Foris V, **Tornyos A**, Narath S, Gander E, Magnes C, Kovacs G, Klepetko W, Pieber TR, Kwapiszewska G, Olschewski H, Olschewski A. Metabolic fingerprinting in pulmonary hypertension. Keystone Symposia 2018; Hannover, Germany.

Hungarian abstracts

1. **Tornyos A**, Komócsi A, Kónyi A, Vorobcsuk A, Magyari B, Márton L, Horváth IG, Pintér T. A konvencionális kardiovaszkuláris rizikófaktorok és a procedurális jellemzők hatása a klinikai kimenetelre DEB kezelést követően. Balatonfüred, 2014. Cardiologia Hungarica 2014; 44 : E76
2. **Tornyos A**, Kiss T, Kovács K, Komócsi A, Zalán P, Sümegi B, Ifj. Gallyas F, Kovács K. A szildenafil új terápiás mechanizmusai a pulmonális hipertóniában (Novel mechanisms of sildenafil in pulmonary hypertension) Balatonfüred 2015. Cardiologia Hungarica
3. **Tornyos A**, Trinker M, Foris V, Pfeiffer S, Odler B, Douschan P, Avian A, Olschewski A, Kovacs G, Olschewski H. A pulmonalis hypertonia gyakorisága és prognosztikai jelentősége exogén allergiás alveolitiszben. (MTT 2016) Medicina Thoracalis 2016; 69 (3): 171

4. Komócsi A, **Tornyos A**, Vorobcsuk A. Új generációs antikoagulánsok biztonságossága és hatékonysága akut koronária szindrómában. Az MKT és a Magyar Haemorrheológiai társaság kongresszusa. Pécs 2013
5. Költő Gy, Szokodi I, Faludi R, **Tornyos A**, Ruskoaho H, Vuolteenaho O, Minier T, Czirják L, Komócsi A. Nátriuretikus peptidek prediktív szerepe szisztémás sclerosisban. Balatonfüred, 2014. Cardiologia Hungarica 2014; 44 : E29
6. Odler B, Avian A, Nora W, Hafner F, Moazedi-Fuerst F, Aberer E, Brodmann M, Graninger W, Foris V, **Tornyos A**, Olschewski A, Olschewski H, Kovács G. Terheléses pulmonalis hemodinamikai változások szisztémás sclerosisos betegekben. (MTT 2016) Medicina Thoracalis 2016; 69 (3): 160