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Risk stratification and individualized antithrombotic therapy in patients with coronary artery disease undergoing percutaneous coronary interventions

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Dedication

To my family.

Content

Abbreviations

ACE – angiotensin-converting enzyme
ACS – acute coronary syndrome
ACT – activated clotting time
ADP – adenosine diphosphate
AMI – acute myocardial infarction
aPTT – activated partial thromboplastin time
ARBs – angiotensin receptor blockers
AUC – area under the curve aggregation units
BMI – body mass index
CABG – coronary bypass graft surgery
CAD – coronary artery disease
CrCl – creatinine clearance
DAPT – dual antiplatelet therapy
EF – ejection fraction
GPI – Glycoprotein IIb/IIIa
HPR – high on-treatment platelet reactivity
IQR – interquartile range
LMWH – low molecular weight heparin
LTA – light transmission aggregometry
LV – left ventricle/ventricular
MACE – major adverse cardiovascular events
MEA – multiple electrode aggregometry
MI – myocardial infarction
NACE – net adverse clinical events
NSTE-ACS – non-ST-elevation acute coronary syndrome
NSTEMI – non-ST-elevation myocardial infarction
PCI – percutaneous coronary intervention
PRP – platelet-rich plasma
ROC – receiver operating characteristic
SD – standard deviation

STEMI – ST-elevation myocardial infarction

TIMI – thrombolysis in myocardial infarction

UA – unstable angina

UFH – unfractionated heparin

1. Introduction

Coronary artery disease (CAD) is the major cause of mortality in developed countries (Perk et al., 2012). It is caused by atherosclerosis which results in occlusion of coronary arteries. This causes imbalance in request of blood supply and its availability. Under stress conditions, with higher demand on oxygen, it manifests as stable angina pectoris. In the case of rupture of unstable atherosclerotic plaque with sudden occlusion of coronary vessels, acute coronary syndrome (ACS) occurs. Cardiac catheterization with coronary angiography is used to diagnose the extent of the disease and allows to treat coronary lesions by percutaneous transluminal coronary angioplasty (PTCA) usually followed by coronary stent implantation, if necessary. This procedure relieves symptoms in stable patients and lowers mortality in patients with ACS. Antithrombotic therapy is an important part of management in patients with CAD. Anticoagulants inhibiting plasma coagulation system and antiplatelet agents acting against platelet aggregation are used.

Blood platelets play a crucial role for thrombus formation in ACS. Antiplatelet drugs inhibit their activation and reduce the risk of myocardial infarction (MI) and stent thrombosis. Dual antiplatelet therapy is prescribed for a particular time after percutaneous coronary intervention (PCI) to prevent stent thrombosis. In long-term treatment of patients with CAD single antiplatelet treatment lowers ischemic events and reduces mortality (Antiplatelet Trialists' Collaboration, 1994). Anticoagulants act against thrombus-formation through the inhibition of thrombin generation or activity and thus reduce thrombus formation and myocardial ischemia in the setting of ACS. Importantly, they are also necessary during elective PCI to prevent catheter associated thrombosis. On the other hand, it increases bleeding risk. Risk stratification of patients with CAD undergoing PCI is, therefore, necessary to find the best balance between risk reduction of ischemic events and low bleeding complications.

1.1 Overview and brief characteristics of antithrombotic drugs used in patients with CAD

1.1.1 Antiplatelet therapy

Aspirin

Aspirin (acetylsalicylic acid) acts through irreversible acetylation of cyclooxygenase-1. This enzyme blocks catalysis of arachidonic acid to prostaglandin G_2; and further, the formation of thromboxane-A2, which is a potent activator of platelet aggregation. As the inhibition of platelets is irreversible, it blocks platelet function for the rest of their lifetime in circulation (about 10 days). Aspirin is characterized by fast resorption and acts already after 10-20 minutes after oral application. The usual dose for the therapy of coronary artery disease is 75-100 mg once daily. In patients with ACS bolus dose of 150-500 mg is given either orally or intravenously (Droppa and Geisler, 2013).

Clopidogrel

Clopidogrel is a thienopyridine derivate which irreversible inhibits the $P2Y_{12}$-receptor receptor. It prevents binding of ADP on the receptor which is a potent platelet activator. Clopidogrel is a prodrug and has to be activated to its active metabolite (a thiol derivative of clopidogrel). This takes place in liver, in two steps mediated by cytochrome-P450-enzyme. Full therapeutic effect occurs with a delay of circa 30-60 Minutes after oral application. Clopidogrel is given in a dose of 75 mg/day. Loading dose of 600 mg is used to achieve fast and sufficient platelet inhibition (Droppa and Geisler, 2013).

Prasugrel

Prasugrel is a novel $P2Y_{12}$-receptor inhibitor. Similarly to clopidogrel it is a thienopyridine derivate, that inhibits platelets through ADP. Prasugrel is also a prodrug, but it needs only one-step biotransformation leading to much faster transformation compared to clopidogrel, allowing a therapeutic effect already

after 30 minutes. The usual treatment-dose is 10 mg pro day, the loading dose is 60 mg (Droppa and Geisler, 2013).

Ticagrelor

Ticagrelor is a nucleoside analogue, and it has a structural similarity to adenosine. Similarly to thienopyridines it blocks the $P2Y_{12}$-receptor and hence ADP-dependent pathway of platelet aggregation. In contrast to clopidogrel and prasugrel, the binding site for ticagrelor is different from ADP, and the blockage is reversible. It does not require the biotransformation from a prodrug. Its effect onsets 30 minutes after oral application. The usual treatment-dose is 90 mg twice a day, the loading dose is 180 mg (Droppa and Geisler, 2013).

Glycoprotein IIb/IIIa-Inhibitors

Platelet glycoprotein IIb/IIIa receptor allows binding of activated platelets to fibrinogen and hence platelet aggregation. Glycoprotein IIb/IIIa-inhibitors (GPI) block this pathway. There are three substances currently available – abciximab, tirofiban and eptifibatide. They differ in chemical structure and duration of their antiplatelet effect. Abciximab is a monoclonal antibody against GP IIb/IIIa receptor with a dissociation half time of 12-24 hours, tirofiban is a non-peptide antagonist with plasma lifetime of 2 hours and eptifibatide a synthetic peptide antagonist with lifetime of 2-2.5 hours (Bennett, 2001). All substances are administered intravenously. They are usually administered as a bail-out therapy in patients with ACS undergoing PCI, they are given periinterventionally and for 12-24 hours as continuous intravenous infusion after PCI. The dose is adjusted to weight and renal function.

Cangrelor

Cangrelor is a novel intravenous short acting $P2Y_{12}$-receptor inhibitor available for use in patients undergoing PCI. Possible advantages are an immediate onset of platelet inhibition in comparison to oral $P2Y_{12}$-receptor inhibitors and its short half time (minutes) allowing immediate stopping of the therapy in case of bleeding complications or necessary surgical intervention. Weight adjusted

dose is administered intravenously, as a bolus, followed by continuous infusion (Droppa and Geisler, 2013).

1.1.2 Anticoagulants

Unfractionated heparin

Unfractionated heparin (UFH) is a mixture of glycosaminoglycans in different molecular weight which inhibit thrombin through activation of antithrombin III. It is administered intravenously, as a bolus of 60-70 IU/kg, followed by an infusion of 12-15 IU/kg/h. Due to its interindividual variability and a narrow therapeutic window, monitoring using activated partial thromboplastin time (aPTT) or activated clotting time (ACT) is necessary. Half time of heparin is short, and the antagonist protamine is available making easy to antagonize anticoagulant effect in case of bleeding. Therapeutic dose should be titrated to achieve 1.5-2.5 times the upper normal limit of aPTT (50-75 s). During PCI ACT is used to control the dose of heparin. A higher bolus during PCI (70-100 IE/kg) is used, an ACT 250-350 s is intended when no glycoprotein IIb/IIIa inhibitors (GPI) are used. In case of combination with GPI inhibitors, a bolus of 50-70 IU/kg and target ACT of 200-250 s is used to guide the therapy (Authors/Task Force members et al., 2014).

Low molecular weight heparins and fondaparinux

Low molecular weight heparin (LMWH) is produced by depolymerization of UFH to molecular weight lower than 8000 Da. In contrast to UFH which inhibits both thrombin and factor Xa, LMWH inhibits factor Xa relatively selectively. It has much longer half time in plasma and more predictable pharmacokinetics. From many available LMWH, enoxaparin is approved for treatment of patients with ACS (Silvain et al., 2012a). It is dosed adjusted to body weight and renal function and administered subcutaneously or intravenously (periinterventional). Fondaparinux has similar anticoagulant effects compared to LMWH but lower bleeding risk (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators et al., 2006). It is a synthetic pentasaccharide which

selectively inhibits factor Xa by antithrombin without inhibiting thrombin. It is recommended in patients with unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI) in dose of 2.5 mg/day.

Bivalirudin

Bivalirudin is a synthetic peptide similar to hirudin. It reversibly inhibits thrombin both circulating and clot-bound. Advantages of bivalirudin are better predictable pharmacodynamics and pharmacokinetics than heparin. In contrast to heparin, it doesn't induce but inhibits platelet activation. In randomized studies bivalirudin reduced the risk of bleeding complications in comparison to heparin with GPI in patients with ST-elevation myocardial infarction (STEMI) and NSTEMI (Stone et al., 2006, 2011).

1.2 Use of antithrombotic substances in patients undergoing PCI

1.2.1 Dual antiplatelet therapy

After implantation of coronary stents dual antiplatelet treatment with aspirin and $P2Y_{12}$-receptor inhibitor is prescribed to prevent ischemic complications such as stent-thrombosis and recurrent myocardial infarction (MI). The most used $P2Y_{12}$-receptor inhibitor is clopidogrel, however significant interindividual variability of platelet inhibition exists due to its pharmacokinetics. Genetic factors especially in metabolizing of clopidogrel (variability in cytochrome P450 enzyme) are responsible. Other possible reasons are variability in intestinal absorption and interaction with other drugs. Patients with high on-treatment platelet reactivity (HPR) and hence reduced response to clopidogrel have significant higher rate of major adverse cardiovascular events after PCI (Geisler et al., 2006).

Novel $P2Y_{12}$-receptor inhibitors prasugrel and ticagrelor have advantage over clopidogrel through better platelet inhibition and lower interindividual variability. Using novel $P2Y_{12}$-inhibitors frequency of low-responders could be reduced.

Ticagrelor and prasugrel showed better platelet inhibition and reduction of ischemic adverse events in patients with ACS. Ticagrelor even lowered overall mortality in the PLATO study (Wiviott et al., 2007; Wallentin et al., 2009). Based on two large randomized studies (TRITON-TIMI-38 and PLATO) prasugrel and ticagrelor are recommended as first choice therapy in patients with ACS. Bleeding risk under prasugrel and ticagrelor seems to be slightly higher than under clopidogrel. Patients above 75 years, with body weight less than 60 kg and with a history of stroke were at higher risk for bleeding events in prasugrel treated patients. Thus, ticagrelor or clopidogrel should be the preferred option in these patients (Authors/Task Force members et al., 2014; Wiviott et al., 2007). Further, patients under oral anticoagulants shouldn't be treated with prasugrel and ticagrelor in combination with aspirin due to higher bleeding risk.

Whereas ticagrelor and prasugrel are now largely used in patients with ACS, clopidogrel is still recommended in patients with stable coronary disease. There are no large clinical randomize studies comparing clopidogrel with ticagrelor or prasugrel in low-risk patients with stable coronary disease. As mentioned above, however significant proportion of such patients may have lower response to clopidogrel and hence higher risk of adverse ischemic events. Identification of these patients could help to tailor antiplatelet treatment with more potent antiplatelet drugs.

1.2.2 Anticoagulants in patients undergoing PCI

In patients with ACS acute myocardial ischemia is caused by unstable atherosclerotic plaque with formation of thrombus and its embolization or total vessel occlusion. Anticoagulants inhibit thrombin formation and hence act again progression of present thrombus and reduce the extent of myocardial ischemia. Anticoagulants are indicated in patients with ACS immediate after establishing the diagnosis and are given continuously in the periprocedural phase during PCI. Also in elective coronary intervention in patients with stable coronary disease an effective anticoagulation is necessary to prevent intravascular and

catheter associated thrombus formation. Variety of substances are approved for periinterventional anticoagulation. For elective PCI in stable coronary disease UFH is recommended, in patients with high bleeding risk bivalirudin should be considered according to current guidelines (Authors/Task Force members et al., 2014). In patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) UFH, enoxaparin, fondaparinux or bivalirudin are recommended whereas the latter both were associated with lower bleeding events. In patients with STEMI either UFH or bivalirudin are used (Authors/Task Force members et al., 2014).

1.3 Aims

1.3.1 Risk stratification of patients with stable angina pectoris and dual antiplatelet therapy

High on-treatment platelet reactivity is common in patients treated with clopidogrel. It was shown that these patients have worse prognosis (Geisler et al., 2006). Several clinical risk factors were associated with HPR in patients treated with clopidogrel (Geisler et al., 2008). Aim of our study was to evaluate clinical risk factors which predispose to HPR in patients with stable angina pectoris. We evaluated clinical characteristics of consecutive patients admitted with stable angina pectoris and treated by PCI. Platelet reactivity was measured in all patients. Identification of the clinical risk factors would allow to predict patients with HPR and hence at risk of ischemic cardiac events. For these patients intensified antiplatelet treatment e.g. with prasugrel or ticagrelor could be considered to improve the prognosis.

1.3.2 Individual antiplatelet treatment according to platelet function analysis in clinical praxis

Large interindividual variability in response to antiplatelet therapy mainly clopidogrel raise a question of relevance of platelet function testing in clinical

practice. Several assays are commercially available to test platelet aggregation under antiplatelet treatment after stimulation by ADP. Routine testing of clopidogrel response is not recommended, however there are several clinical situations when testing of response is helpful to manage the patients. In our case report we present such a case of a patient with short-bowel syndrome and discuss pharmacokinetics and pharmacodynamics of antiplatelet substances in patients with intestinal malabsorption syndrome.

1.3.3 Optimal periinterventional anticoagulation in patients with NSTEMI undergoing PCI and its bleeding risk

Anticoagulation therapy is indicated in all patients after establishing of the diagnosis of NSTEMI. UFH, LMWH, fondaparinux and bivalirudin are approved for this indication. There were several studies which were performed to find optimal strategy for anticoagulation. An important aspect is the safety of anticoagulants in view of possible bleeding complications, which are enhanced due to combination with oral antiplatelet therapy and GPI. From the above therapies bivalirudin was proved to have very low bleeding risk in comparison with heparin in combination with GPI. According to current guidelines PCI should be performed within 24 hours in patients with intermediate risk. The impact of anticoagulation regime dependent on time from diagnosis to PCI has not been systematically studied so far. We therefore sought to analyze the impact of different antithrombotic regimens to clinical events in patients with NSTEMI randomized in large ACUITY trial.

2. Results

2.1 Evaluation of clinical risk factors to predict high on-treatment platelet reactivity and outcome in patients with stable coronary artery disease (PREDICT-STABLE). M. Droppa, D. Tschernow, K. A. L. Müller, E. Tavlaki, A. Karathanos, F. Stimpfle, E. Schaeffeler, M. Schwab, A. Tolios, J. M. Siller-Matula, M. Gawaz, T. Geisler, PLoS ONE. 2015 Mar 23;10(3):e0121620.

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RESEARCH ARTICLE

Evaluation of Clinical Risk Factors to Predict High On-Treatment Platelet Reactivity and Outcome in Patients with Stable Coronary Artery Disease (PREDICT-STABLE)

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Abstract

Objectives

This study was designed to identify the multivariate effect of clinical risk factors on high on-treatment platelet reactivity (HPR) and 12 months major adverse events (MACE) under treatment with aspirin and clopidogrel in patients undergoing non-urgent percutaneous coronary intervention (PCI).

Methods

739 consecutive patients with stable coronary artery disease (CAD) undergoing PCI were recruited. On-treatment platelet aggregation was tested by light transmittance aggregometry. Clinical risk factors and MACE during one-year follow-up were recorded. An independent population of 591 patients served as validation cohort.

Results

Degree of on-treatment platelet aggregation was influenced by different clinical risk factors. In multivariate regression analysis older age, diabetes mellitus, elevated BMI, renal function and left ventricular ejection fraction were independent predictors of HPR. After weighing these variables according to their estimates in multivariate regression model, we developed a score to predict HPR in stable CAD patients undergoing elective PCI (PREDICT-STABLE Score, ranging 0-9). Patients with a high score were significantly more likely to develop MACE within one year of follow-up, 3.4% (score 0-3), 6.3% (score 4-6) and 10.3% (score 7-9); odds ratio 3.23, P=0.02 for score 7-9 vs. 0-3. This association was confirmed in the validation cohort.

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Conclusions

Variability of on-treatment platelet function and associated outcome is mainly influenced by clinical risk variables. Identification of high risk patients (e.g. with high PREDICT-STABLE score) might help to identify risk groups that benefit from more intensified antiplatelet regimen. Additional clinical risk factor assessment rather than isolated platelet function-guided approaches should be investigated in future to evaluate personalized antiplatelet therapy in stable CAD-patients.

Introduction

Guidelines currently recommend dual platelet inhibition with aspirin and clopidogrel to prevent post-procedural adverse events after elective percutaneous coronary intervention (PCI) with stent-implantation [1]. There has been cumulative evidence in the past that interindividual variability of response to clopidogrel is high, mainly due to clinical risk factors and genetic variability of drug-metabolism [2–4]. There has been consensus that high-on-treatment platelet reactivity is associated with major adverse atherothrombotic events including stent thrombosis after PCI [5]. Presently new drugs with higher platelet inhibition and lower interindividual variability are available in clinical practice, however are not approved in stable coronary artery disease (CAD). Intensified platelet inhibition solely guided by platelet function analysis has been shown unsuccessful in reducing cardiovascular risk [6–8]. Thus, additional risk assessment is needed to identify patients with stable CAD who might benefit from enhanced platelet inhibition in the chronic phase.

Previously, we established a simple risk tool—PREDICT (Residual **P**latelet Agg**re**gation after **D**eployment of **I**ntra**c**oronary S**t**ent) score, based on clinical variables that are easily available in daily routine to identify patients at risk for high on-treatment platelet reactivity (HPR) in unselected cohort of patients undergoing PCI [9]. The score encompasses 5 different variables including acute coronary syndrome on admission, older age, diabetes mellitus, renal and left ventricular function impairment. After weighing these variables according to their effects size in multivariate analysis, the score ranged from 0–9 with higher score levels being significantly associated with both HPR and cardiovascular outcome. To date, tools to assess atherothrombotic risk after non-urgent PCI are lacking. Therefore, the aim of the present study was a) to identify clinical risk factors that are associated with on-treatment platelet reactivity and outcome and b) to investigate the added value of on-treatment platelet reactivity compared to clinical risk factor assessment in a selected population of patients with stable CAD undergoing PCI.

Methods

Study population

Patients with symptomatic coronary artery disease undergoing non-urgent coronary stent implantation were consecutively enrolled at the Department of Cardiology, University Hospital, Tübingen from March 2005 till May 2008. Inclusion criteria were age older than 18 years, planned coronary intervention and willing consent. Exclusion criteria were known platelet function disorders or indication for longterm oral anticoagulation. All patients were evaluated by platelet function analysis by Light Transmission Aggregometry (LTA) under maintenance therapy at a median of 24 hours after PCI. For the current analysis only patients with stable CAD were included and examined for clinical variables influencing HPR.

For the validation cohort, stable CAD patients with the same inclusion criteria presented between February 2011 and October 2012 at the University Hospital Tübingen, Germany (n = 354) and between March 2007 and September 2008 at the Department of Cardiology, Medical University of Vienna, Austria (n = 237) were analysed. The characteristics of the Austrian cohort are described elsewhere [10]. Platelet function was assessed using Multiple Electrode Aggretometry (MEA).

The trial was conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki. All patients gave written informed consent. Approval was obtained by the ethical committee of the University Tübingen.

Platelet function analysis

Platelet function analysis by Light Transmission Aggregometry (LTA) was performed at a median of 24 hours after a 600mg loading dose of clopidogrel was given. According to previous results, maximum platelet inhibition can be detected at this time point [9,11,12]. Venous blood samples collected in 3.8% citrate plasma were centrifuged at 150 x g for 10 minutes to obtain platelet-rich plasma (PRP). After additional centrifugation at 2000 x g for 10 minutes platelet-poor plasma (PPP) was obtained. By adding homologous PPP, platelet concentration of PRP was adjusted to 2 x 10^5 μL^{-1}. After administration of 20 μmol L^{-1} adenosine diphosphate (ADP), per cent platelet aggregation was assessed with the turbodimetric method using a ChronologLumiaggregometer with Aggro-Link Software. Platelet aggregation measured 5 min after addition of ADPwas used to determine on-treatment platelet reactivity. HPR was defined as the highest quartile of measured platelet reactivity in the examined population as reported previously [9,13–15].

In the validation cohort platelet function was analysed by Multiple Electrode Aggretometry (MEA). Samples of whole blood anticoagulated with hirudin were collected after initial clopidogrel loading. Platelet function was assessed after stimulation with 6.4 μM ADP, by a new generation impedance aggregometer (Multiplate Analyzer, VerumDiagnostica GmbH, Munich, Germany). Platelet activity was reported as area under the curve aggregation units (AUC) as described previously. A good correlation between MEA und LTA was shown before[16].

Follow-up

Patients were followed up by telephone interview 12 month after enrollment. Incidence of major cardiovascular events (MACE) including death, myocardial infarction and ischemic stroke were assessed by telephone interview. An acute myocardial infarction (AMI) was diagnosed by a rise and/or fall of cardiac biomarker values [cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit and with at least one of the following: symptoms of ischaemia, new or presumed new significant ST-segment–T-wave (ST–T) changes or new left bundle branch block, development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or identification of an intracoronary thrombus by angiography [17].Telephone interviewers were blinded with respect to the results of platelet aggregation test.

Statistical analysis

Continuous data with normal distribution are presented as mean ± SD, not normally distributed data as median and interquartile range. Categorical variables are expressed as number (%). Equality of distribution of categorical variables between subgroups was analyzed by chi-squared test. Continuous data with non-normal distribution were compared by Mann-Whitney test. For analysis of clinical predictors for HPR univariate logistic regression analysis was

used. The highest quartile of on-treatment platelet reactivity assessed by LTA was used as the dependent variable. Clinical variables available in daily routine were included in the model as independent variables. Variables included age, gender, diabetes mellitus, hypertension, hyperlipidemia, smoking history, adiposity (BMI>30), reduced left ventricular function, reduced renal function and multivessel disease. For continuous variables cut-off values with highest sensitivity and specificity were determined by receiver operating characteristic (ROC) curves. Thus categorical variables were created that were used for development of the risk score. Factors with a significance level of $P<0.1$ in univariate analysis were included into multivariate model. Multivariate analysis was used then to identify independent predictors of HPR and to create the PREDICT-STABLE score. According to effect size (odds ratio) of relevant clinical predictors for HPR in multivariate analysis, a weighed score was developed. For comparison of MACE between different score levels, Kaplan-Meier curves were constructed and groups were compared by the log-rank test. For comparison of categorical and continuous data a two-sided P value of <0.05 was considered statistically significant. All statistical tests were performed with IBM SPSS Statistics software, version 21.0.

Results

Baseline characteristics

2226 patients were consecutively enrolled in the study. In 1549 patients platelet reactivity measurement by LTA was available, from these patients 810 (52.3%) were treated for acute coronary syndrome (unstable angina pectoris, non-ST- and ST-elevation myocardial infarction) and 739 (47.7%) for stable CAD, the latter were included in the analysis. Baseline patients' characteristics are shown in Table 1. 30% of patients suffered from diabetes, 42.1% had reduced left ventricular function, 74.1% had multivessel disease. 65.7% were treated with bare metal stents, 24.5% with drug-eluting stents, 9.7% with both stent-types. Characteristics of study population according to quartiles of platelet reactivity are shown in Table 1. Patients in the highest quartile were significantly older, had a higher body mass index, had more often diabetes mellitus and renal impairment ($P<0.05$).

Risk factors of HPR and development of the risk score

For continuous variables following cut offs with best sensitivity and specificity were calculated by ROC curves: age of 63 years, left ventricular function of 55% and serum creatinin level of 1.1 g/dL. These cut offs were used to create categorical variables for the analysis. In univariate analysis, the following factors were significant predictors of HPR ($P<0.1$, Table 2) and were included in multivariate analysis: age > 63 years, female gender, diabetes mellitus, adiposity (BMI >30 kg/m^2), reduced left ventricular (LV) function (LV ejection fraction< 55%), reduced renal function (serum creatinin> 1.1 g/dL). In multivariate analysis age, diabetes mellitus, adiposity, reduced left ventricular function and reduced renal function remained significant predictors of HPR whereas female gender was no longer significant (Table 3). According to effect size (odds ratio) of relevant clinical predictors of HPR in multivariate analysis, a weighed score was developed. In detail age > 63 years was weighted by factor 3, diabetes and adiposity by factor 2, reduced left ventricular function and reduced renal function by factor 1 (odds ratios 2.11, 1.78, 1.86, 1.54 and 1.48 respectively). Thus, a score ranging from 0–9 was developed (Table 3). The prevalence for a PREDICT-STABLE score of 0–3 was 32.3%, 50% for a score of 4–6 and 17.7% for a score of 7–9. Fig. 1A shows per cent HPR in each score level: 14%, 23.7% and 43.4% for PREDICT-STABLE score 0–3, 4–6 and 7–9, respectively.

Table 1. Characteristics of the study population according to quartile of HPR.

Baseline demographics	Patients N = 739	Quartile of platelet reactivity				P*
		1	2	3	4	
Gender m/f (%)	77.5/22.5	75.5/24.5	80.7/19.3	81/19	72.8/27.2	0.081
Age (years)	69 (61–75)	67.0 (57–74)	68.0 (59.0–74.0)	70.0 (63.0–74.0)	69.0 (64.5–74.5)	0.051
Body mass index	27.4 (25.1–30.5)	26.1 (24.3–26.1)	27.1 (25.46–30.1)	28.4 (25.8–30.75)	28.3 (26.04–31.77)	0.001
Adiposity BMI>30 (%)	24.5	18.7	25.3	32.7	36.8	0.007
Hypertension (%)	82.9	80.1	81.8	86.4	87.6	0.129
Smoking history	39.0	42.4	40.8	38.9	38.1	0.536
Hyperlipidemia (%)	73.9	73.7	67.4	80.4	74.0	0.969
Diabetes mellitus (%)	30.9	22.6	27.1	34.2	41.0	0.001
Serum creatinin mg/dL	1.0 (0.9–1.2)	1.1 (0.9–1.2)	1.1 (0.9–1.3)	1.0 (0.9–1.28)	1.1 (0.9–1.4)	0.021
Left ventricular function (%)	55.7 (49–65)	55.7 (50–58)	60 (49–65)	60 (49–65)	54.5 (46–65)	0.083
Medication						
Statins (%)	88.9	87.0	90.2	91.4	86.9	0.367
ACE- Inhibitors(%)	77.4	77.6	76.8	79.3	76.0	0.615
Angiotensin receptor blockers (%)	11.6	13.7	8.5	16.5	14.9	0.514
β-blockers (%)	91.0	93.8	89.6	90.9	89.6	0.501
Multivessel disease	74.1	69.7	74.7	85.2	76.9	0.424
Bare metal stents/ drug-eluting stents/both	65.7/24.5/9.7	66.7/22.6/10.7	61.3/27.5/11.3	63.6/27.2/9.3	71.6/20.6/7.7	0.08/0.20/0.33

* for quartile 4 vs. 1–3.

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Follow-up

Follow-up was available for 686 patients (93%). MACE occurred in 42 (5.7%) of patients. Median follow up was 152 (91–400) days. There were 3.0% myocardial infarctions, 1.4% ischemic strokes and 1.9% deaths in the study population. Fig. 1B shows distribution of MACE according to PREDICT-STABLE score. There was a steady increase of MACE after 1 year follow up with higher PREDICT-STABLE score i.e. 3.4% in patients with a score of 0–3, 6.3% in patients with a score of 4–6 and 10.3% in patients with a score of 7–9 (P = 0.20 and 0.02 respectively for comparison with the score group 0–3). Patients with high PREDICT-STABLE score (7–9) had about

Table 2. Univariate analysis of risk predictors for HPR.

Quartile of platelet reactivity	1–3	4 (HPR)	Coefficient B	Odds ratio (95% CI)	P
Age (> 63 years) (%)	69.4	82.6	0.74	2.09 (1.37–3.20)	0.001
Gender m/f (%)	79.0/21.0	72.8/27.2	0.34	1.41 (0.96–2.06)	0.082
Diabetes mellitus (%)	27.9	41	0.58	1.79 (1.26–2.55)	0.001
Hypertension (%)	82.8	87.6	0.38	1.47 (0.89–2.42)	0.131
Hyperlipidemia (%)	73.9	74	0.01	1.01(0.69–1.48)	0.969
Smoking (%)	40.7	38.1	-0.11	0.54 (0.63–1.27)	0.536
Adiposity BMI>30 (%)	25.5	36.8	0.53	1.70 (1.16–2.51)	0.007
Reduced left ventricular function EF<55 (%)	41.5	51.4	0.39	1.48 (1.06–2.08)	0.02
Reduced renal function (Serumcreatinin> 1.1 g/dL in %)	46.5	61.5	0.61	1.84 (1.29–2.63)	0.001
Multivessel disease* (%)	74.9	71.9	-0.15	0.86 (0.59–1.25)	0.424

* defined as 50% or greater stenoses in at least one major epicardial vessel.

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Table 3. Multivariate analysis of risk predictors for HPR.

Variables	Coefficient B	Odds ratio (95% CI)	P	PREDICT-STABLE
Age (> 63 years)	0.745	2.11 (1.26–3.53	0.005	3
Female gender	0.381	1.46 (0.93–2.31)	0.102	-
Diabetes mellitus	0.575	1.78 (1.19–2.65)	0.005	2
Adiposity (BMI>30)	0.622	1.86 (1.22–2.86)	0.004	2
Reduced left ventricular function EF<55	0.431	1.54 (1.03–2.31)	0.037	1
Reduced renal function (Serumcreatinin> 1.1 g/dL)	0.391	1.48 (0.97–2.25)	0.067	1

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3 times higher probability to develop MACE than patients with score 0–3 (odds ratio 3.23, P = 0.02 for Score 7–9 vs. 0–3; odds ratio 1.90, P = 0.20 for Score 4–6 vs. 0–3). Early (30 days) and late outcomes are shown in Table 4. After 30 days there was numerically highest MACE rate for highest PREDICT STABLE score levels (7–9), although statistically not significant. Differences were consistent for all MACE components. Similarly, in Kaplan-Meier analysis a higher PREDICT-STABLE score level was associated with significantly higher MACE rate in comparison to a low score (Fig. 2, P = 0.01), however there was no difference in MACE between patients with HPR and patients with adequate on-treatment platelet reactivity (Fig. 3, P = 0.69).

ROC curve analysis showed that PREDICT-STABLE score improved prediction of 12-month MACE compared to on-treatment platelet reactivity alone as measured by the area under the curve (AUC 0.62, P = 0.02 versus 0.60, P = 0.04). However, there was no relevant benefit for risk prediction by combining both on-treatment platelet reactivity and PREDICT--STABLE score (AUC 0.63, P = 0.01, Fig. 4).

Validation of the PREDICT-STABLE score in an independent cohort

For validation of the PREDICT-STABLE score 591 patients with same inclusion criteria as the study population were enrolled (Table 5). Similar to the exploratory cohort we could show a significant correlation of MACE with higher PREDICT-STABLE score levels (Fig. 5A). Furthermore, we could show that patients with higher PREDICT-STABLE score have significant higher platelet reactivity assessed by MEA (Fig. 5B). In analogy to the discovery cohort, combination between on-treatment platelet reactivity assessed by MEA and the PREDICT-STABLE score did not improve risk prediction for MACE in ROC-analysis.

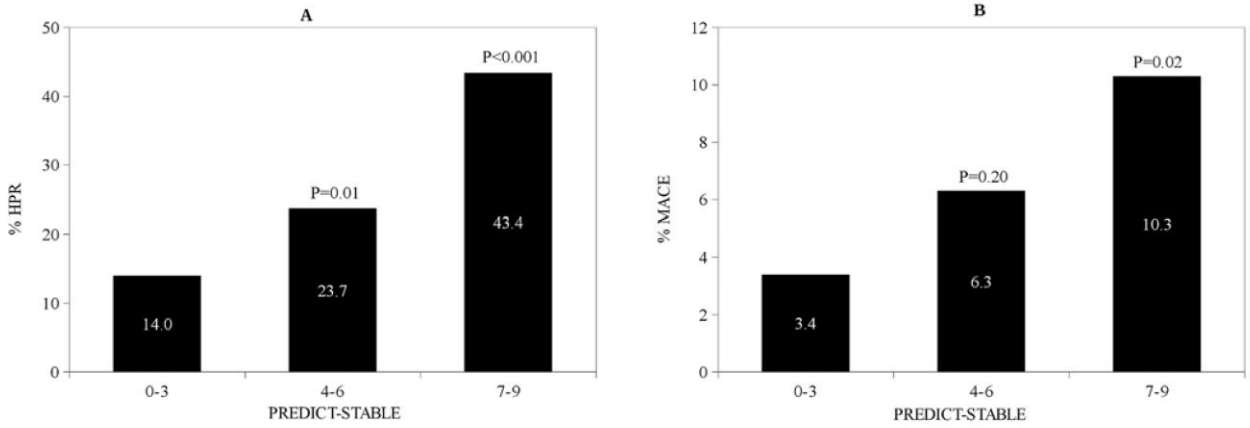

Fig 1. A Incidence of HPR (%) according to PREDICT-STABLE Score B Incidence of MACE according to PREDICT-STABLE Score. P-values for comparison with PREDICT-STABLE score 0–3

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Table 4. Clinical outcome after 30 days and 1 year of follow up according to PREDICT-STABLE Score.

30 days/1 year	N = 686	PREDICT-STABLE 0–3	PREDICT-STABLE 4–6	PREDICT-STABLE 7–9
MACE	1.8/5.7%	0.0/3.4%	1.4/6.3%	3.1/10.3%*
Myocardialinfarction	0.7/3.0%	0.0/1.7%	0.7/3.5%	1.0/5.2%
Ischemic stroke	0.3/1.4%	0.0/0.6%	0.4/1.8%	0.0/3.1%
Death	0.8/1.9%	0.0/1.1%	0.4/1.4%	2.1/4.1%
Stent thrombosis				
Definite	0.4/0.5%	0.0/0.6%	0.0/0.0%	3.1/3.1%
Probable	0.5/2.3%	0.0/0.6%	1.1/3.2%	0.0/3.1%
Possible	0.1/0.8%	0.0/0.6%	0.0/0.0%	0.1/2.1%

* $P<0.05$ in comparison with PREDICT-STABLE 0–3.

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Discussion

Variability of individual response to antiplatelet therapy remains a challenging clinical problem. There is still a significant number of patientsafter elective coronary PCI having complicating adverse cardiovascular events [18–21]. This may be partly explained by variability of response to antiplatelet therapy. According to current data there are about 40% of patients considered to be low responders to clopidogrel depending on definition and particular platelet function assay [6,7]. The prognostic impact of high on-treatment platelet reactivity (HPR) for the occurrence of serious cardiovascular events after PCI, particularly stent thrombosis has been demonstrated in several studies [12–14,22,23]. However, there is currently no evidence that platelet function guided approaches lead to improvement of clinical outcome. To date, randomized trials investigating the effect of antiplatelet therapy adjusted to the results of

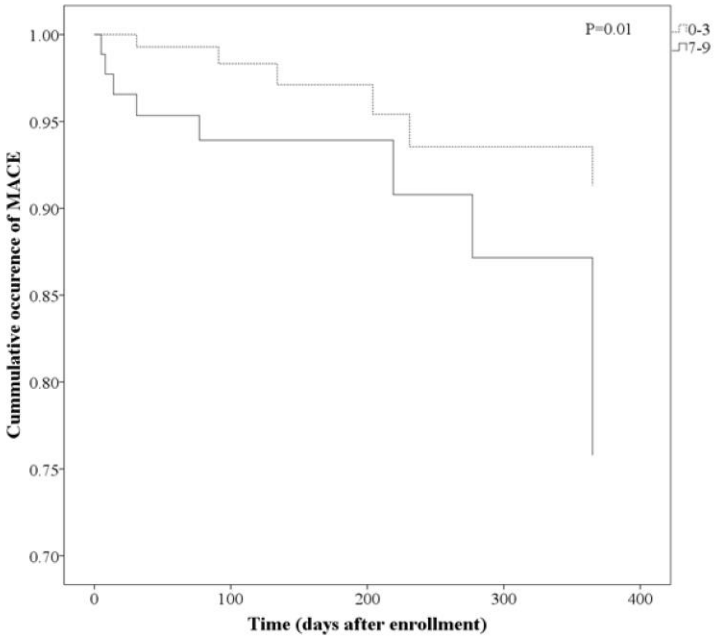

Fig 2. Kaplan-Meier analysis for incidence of MACE according PREDICT-STABLE Score (comparison of score levels 0–3 with 7–9).

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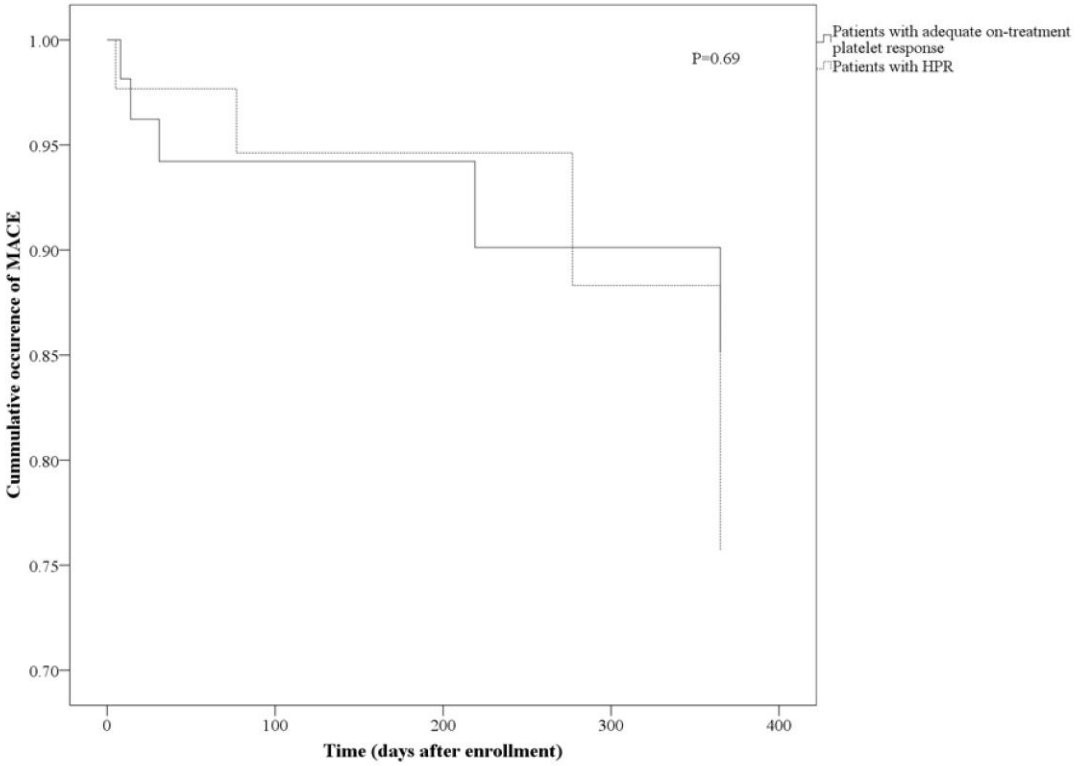

Fig 3. Kaplan-Meier analysis for incidence of MACE according platelet function analysis (comparison of HPR vs. adequate on-treatment response in Patients with high PREDICT-STABLE Score 7–9).

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platelet function testing have not shown an effect regarding improvement of outcome (GRAVITAS, TRIGGER-PCI, ARCTIC trial) either due to a weak active control arm (GRAVITAS) [6] or an overall low risk population (TRIGGER-PCI, ARCTIC) [7,8]. Therefore, the characterization of platelet function testing as a modifiable risk factor remains questionable. An association between genetic and non-genetic factors and HPR under dual antiplatelet therapy has been described previously [24–35]. Thus, it is in the focus of the on-going debate whether HPR is a "by-stander" of the overall cardiovascular risk rather than representing an independent modifiable parameter associated with clinical prognosis. Risk after elective non-urgent PCI is generally low. Some risk tools have been evaluated to characterize peri-procedural/in-hospital risk in stable CAD patients [36,37]. However, these scores have not been evaluated for their association with on-treatment platelet reactivity and long-term risk after elective PCI.

In own preliminary work we developed a score (PREDICT score) to estimate the likehood for HPR utilizing easily available non-genetic risk factors in an unselected cohort of patients with symptomatic coronary artery disease (stable CAD/ACS) [9]. The score contains distinct and easily available patient factors. In the present analysis, we were able to develop a modified score (PREDICT-STABLE Score) focusing on a sub-population of patients with stable CAD in a large retrospective cohort of patients. In our study age, adiposity defined by elevated BMI >30 kg/m2, diabetes mellitus, reduced renal function and reduced left ventricular function were associated with HPR. These findings are in line with previous studies. Influence of higher age on clopidogrel response could be demonstrated in several trials. As an explanation reduced liver function and hence slower activation of clopidogrel prodrug and higher baseline

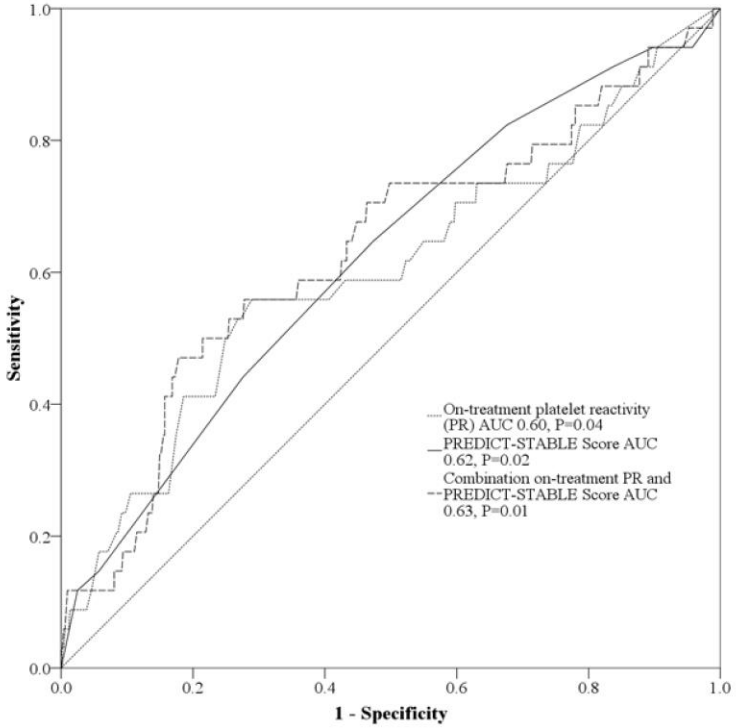

Fig 4. Comparison of predictive value for on-treatment platelet reactivity (PR), PREDICT-STABLE Score alone and in combination by ROC curve analysis.

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platelet reactivity are discussed [30,31]. In obese patients drug underdosing and decreased CYP3A4 activity is a possible explanation for lower response [32–34]. Enhanced vascular inflammation and platelet activation due to hyperglycemia, impaired lipid metabolism and oxidative stress can cause higher on-treatment platelet reactivity on antiplatelet treatment in diabetic individuals [26,27]. Some studies could demonstrate influence of reduced renal

Table 5. Baseline characteristics of the validation cohort.

Baseline demographics	N = 591
Gender m/f (%)	75/25
Age (years)	68 (59–76)
Adiposity BMI>30 (%)	28.4
Hypertension (%)	81.5
Smoking history	31.1
Hyperlipidemia (%)	69.1
Diabetes mellitus (%)	35.3
Reduced renal function (Serumcreatinin> 1.1 g/dL in %)	33.0
Reduced left ventricular function (%)	34.5
Medication	
Statins (%)	66.8
CE-Inhibitors or ARBs (%)	53.4
β-blockers (%)	67.2

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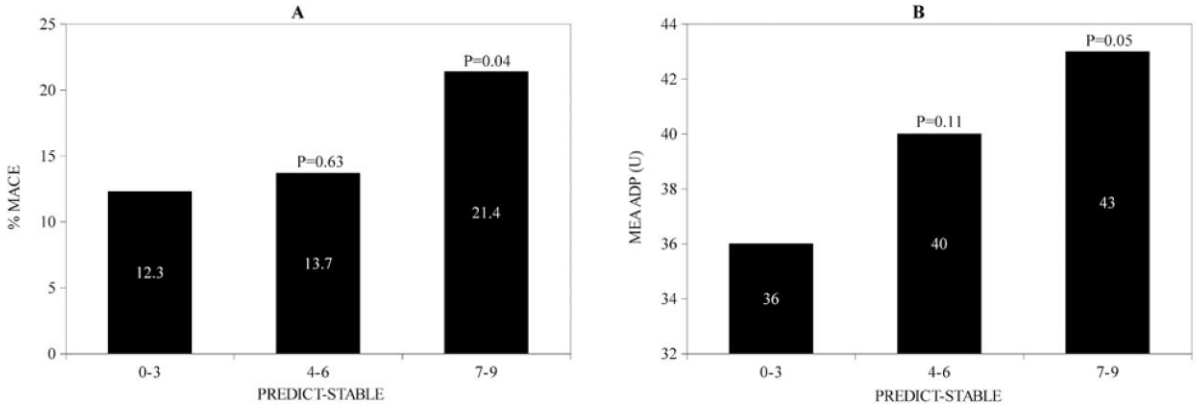

Fig 5. A Incidence of MACE according to PREDICT-STABLE Score in the validation cohort B Platelet reactivity assessed by MEA according to PREDICT-STABLE Score in the validation cohort. P-values for comparison with PREDICT-STABLE score 0–3.

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function on clopidogrel responsiveness. Altered platelet function and reduced sensitivity to antiplatelet drugs through complex disturbances (increased platelet turnover rate, impaired absorption or drug metabolism, procoagulant factors) in renal insufficient patients are supposed mechanisms [28,29,38,39]. In this context, individuals with moderate renal impairment might rather benefit from more intensified longterm P2Y12 inhibition [40]. Patients with heart failure show decreased gastrointestinal absorption of antiplatelet drugs, elevated markers of platelet activation including thromboglobulin, Platelet Factor 4, P-Selectin and platelet-derived adhesion molecules and increased platelet volume [35,41].

With the present analysis, we demonstrate that patients with a high PREDICT-STABLE Score (e.g. $>$ 6 points) have significantly increased probability of HPR and higher rate of major adverse cardiovascular events. Moreover we could validate these findings in a separate consecutive cohort of patients with stable CAD. Of note, patients with a score of $>$ 6 developed similar 12-month rate for atherothrombotic events as in clopidogrel-treated arms of recent major ACS-trials (Fig. 1B) [42,43]. Additionally, we did not find any improvement of prediction by adding on-treatment platelet reactivity to assessment of clinical risk factors for HPR and atherothrombotic events. This adds to the hypothesis that HPR represents more a bystander of overall atherothrombotic risk and partly explains the previous unsuccessful approaches to use platelet reactivity as a modifiable risk factor alone. This is especially true for long-term prognosis after PCI in stable CAD patients in contrast to the ACS setting when there is a biologically causative relationship between high platelet reactivity and early atherothrombotic events including stent thrombosis. In line with these observations are previous results from studies including stable CAD patients and medically managed ACS patients revealing that HPR has no incremental benefit for risk prediction over established clinical risk factors for MACE [44,45]. Hence, additional clinical risk factor assessment rather than isolated platelet function-guided approaches should be investigated in future to evaluate personalized antiplatelet strategies in stable patients with coronary artery disease. It is tempting to speculate, that the score might help to identify patients at high risk (e.g. patients with high PREDICT-STABLE score) that benefit not only from more intensified antiplatelet regimen (ticagrelor, prasugrel, low dose rivaroxaban or vorapaxar) [42,43,46,47] but also from a more universal strategy to modify risk profile thus reducing atherothrombotic events. Interventional studies are needed to characterize the effects of these approaches to demonstrate effects on thromboischemic and bleeding risk in selected high risk stable CAD patients.

Limitations

Antiplatelet drug response is multifactorial. In our score we assessed clinical risk variables which can be easily obtained from patients' clinical examination. Although LTA is still the gold-standard to investigate ADP-induced aggregation, antiplatelet drug response is more complex than monitored by a single platelet function test. Additionally, several genetic factors affect response to clopidogrel (polymorphisms of CYP3A4, CYP2C19, GPIa, P2Y12, GPIIIa, CES1) and these were not included in the present study. There can be more unknown factors which were not considered in the present score. On the contrary, avoiding extensive laboratory testing makes the score valuable for application in clinical situations when rapid information and risk assessment is needed.

Author Contributions

Analyzed the data: MD ES MS JS-M MG TG. Wrote the paper: MD MG TG. Acquisition of data: MD ET FS AK DT KALM JS-M AT. Critical revision of the manuscript for important intellectual content: DT KALM ET AK FS ES MS AT JS-M. Statistical analysis: MD TG. Study supervision: TG. Final approval: TG.

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2.2 Individualised dual antiplatelet therapy in a patient with short bowel syndrome after acute myocardial infarction with coronary artery stenting. Droppa M, Karathanos A, Gawaz M, Geisler T. BMJ Case Rep. 2015 Jul 6;2015.

CASE REPORT

Individualised dual antiplatelet therapy in a patient with short bowel syndrome after acute myocardial infarction with coronary artery stenting

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SUMMARY

Short bowel syndrome after extensive surgical resection of the intestine is characterised by inadequate digestion and absorption of nutrients. Additional clinical problems include impaired absorption and metabolism of diverse drugs requiring individualised medical therapy or alternative treatments. We report a case of individualised dual antiplatelet therapy in a patient who underwent an extensive intestinal resection complicated by acute myocardial infarction requiring percutaneous coronary intervention and stent implantation. Genetic testing of CYP2C19 gene polymorphisms and platelet aggregation testing were used to assess responses to aspirin, clopidogrel, prasugrel and ticagrelor. Given its unique pharmacokinetics with good absorption and without need of metabolism to an active substance, ticagrelor appears to be the best for patients with short bowel syndrome who require dual antiplatelet therapy after coronary stent implantation.

BACKGROUND

Short bowel syndrome is a rare condition characterised by intestinal failure due to inadequate length of intestine following surgical resection. Depending on the length of resected intestine and degree of adaptation in the remaining intestine, complications such as malnutrition, cachexia, electrolyte disturbances and diarrhoea occur. Additional problems include impaired absorption and metabolism of diverse drugs requiring individualised medical therapy or alternative treatments.

Patients with ST-elevation myocardial infarction are typically managed by emergency percutaneous coronary intervention (PCI) with stent implantation to open an occluded coronary artery. To prevent stent thrombosis, dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$-receptor inhibitor is indicated for at least 12 months in these patients. The three available $P2Y_{12}$-receptor inhibitors—clopidogrel, ticagrelor and prasugrel—have significant pharmacokinetic differences. Clopidogrel and prasugrel are prodrugs that must be converted to an active drug through different metabolic pathways, while ticagrelor reversibly binds to the $P2Y_{12}$ receptor on platelets. Absorption of all three drugs takes place in the stomach and intestine. However, there are no data available on absorption and effectiveness of these drugs after oral administration in patients with short bowel syndrome. Monitoring the efficacy of DAPT is crucial to prevent potentially fatal complications after PCI in this group of patients.

In our case report, we present an individualised DAPT in a patient who underwent an extensive intestinal resection, complicated by a myocardial infarction requiring PCI.

CASE PRESENTATION

A 50-year-old man presented with severe diffuse abdominal pain lasting for 2 h. His medical history was significant for chronic obstructive pulmonary disease, nicotine abuse, deep venous thrombosis and pulmonary embolism. There was no family history of thrombophilia, premature myocardial infarction or sudden cardiac death. Physical examination was notable for diffuse abdominal tenderness and guarding. The patient's symptoms and physical examination were concerning for acute peritonitis warranting emergent laparotomy. Owing to perforation of the jejunum 50 cm above the suspensory ligament of duodenum, partial jejunum resection was performed.

The postoperative course was complicated by anterior ST-segment elevation myocardial infarction 6 h after the surgery. Emergent coronary angiography demonstrated one-vessel coronary artery disease with a severe stenosis of proximal and thrombotic occlusion of middle left anterior descending coronary artery warranting ad hoc thrombus aspiration and balloon angioplasty followed by stenting with three bare metal stents. DAPT with aspirin (loading dose 500 mg) and clopidogrel (loading dose 600 mg) was started immediately.

On postoperative day 1, the patient developed recurrent abdominal discomfort with signs of severe sepsis including fever, leucocytosis, elevated C reactive protein and lactic acidosis, warranting surgical exploration. Extended small intestinal ischaemia due to thrombotic occlusion of the superior mesenteric artery was discovered, and resection of necrotised jejunum and ileum was performed. Only the duodenum and 30 cm of the proximal jejunum remained vital and were preserved after the second operation. Consequently, the patient developed short bowel syndrome.

INVESTIGATIONS

Given the multiple unexplained thromboembolic events, complementary examinations were performed: Holter monitoring demonstrated no paroxysmal atrial fibrillation. Transoesophageal echocardiogram demonstrated no intracardiac

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mass, thrombus or vegetation. Screening for inherited thrombophilias revealed heterozygosity for factor V Leiden mutation.

Given the need for prolonged DAPT and concern about insufficient drug absorption of aspirin and clopidogrel due to short bowel syndrome, on-treatment platelet aggregation was assessed by multiple electrode aggregometry (MEA) (Multiplate, Roche, Germany).[1 2] This demonstrated response to aspirin with 13 aggregation units but non-response to clopidogrel with 73 aggregation units (with a MEA value <46 units considered an adequate response).[3–5] The dose of clopidogrel was increased to 75 mg two times per day. After 5 days of continued treatment, when steady-state drug concentration should have been achieved, repeat MEA demonstrated no significant change in response to clopidogrel with 70 units. Consequently, the patient was switched from clopidogrel to prasugrel with a loading dose of 60 mg followed by a daily dose of 10 mg a day. MEA performed at 5 days after prasugrel maintenance dosing again revealed insufficient response after stimulation with ADP (64 U). Thus therapy with prasugrel was substituted by ticagrelor 90 mg two times per day with loading dose of 180 mg. After 5 days of ticagrelor therapy, MEA with ADP stimulation was again performed. Significant decrease of platelet aggregation to 35 U was observed (figure 1, table 1).

Clopidogrel is converted to its active metabolite by cytochrome P450 enzyme, which is highly polymorphic, in the liver. Testing for the most common CYP2C19 genotypes were performed.[6 7] Alleles *1, *2, *3, *17 were tested using TaqMan assay. It revealed genotype CYP2C19*1/*2, which correspond to intermediate clopidogrel metaboliser.[7]

TREATMENT

Parenteral nutrition was started. DAPT was continued with aspirin 100 mg once daily and ticagrelor 90 mg two times per day. Owing to recurrent thromboembolic events with heterozygous factor V Leiden mutation, anticoagulation was initiated with enoxaparin and, later, warfarin.

OUTCOME AND FOLLOW-UP

Four months after his initial presentation, the patient was hospitalised for severe sepsis secondary to pneumonia. Despite supportive care and broad-spectrum antibiotics, the patient died after a prolonged course in the intensive care unit. Impressively, the patient had no recurrent thromboembolic events 6 months after PCI.

Table 1 Measurement of on-treatment platelet reactivity during treatment with all tested antiplatelet drugs, values ≤46 units are considered sufficient response

Drug (mg/day)	Platelet inhibition (MEA units)
Aspirin 100	13
Clopidogrel 75	73
Clopidogrel 150	70
Prasugrel 10	64
Ticagrelor 180	35

MEA, multiple electrode aggregometry.

DISCUSSION

Short bowel syndrome is a rare condition characterised by impaired resorption of nutrients and drugs. According to current guidelines,[8] patients should be treated with DAPT for 12 month after myocardial infarction, preferably with new potent $P2Y_{12}$-receptor inhibitor (ticagrelor or prasugrel). Patients with additional indication for oral anticoagulation with vitamin K inhibitor should be prescribed clopidogrel during 'triple therapy,' due to its lowest bleeding risk. According to current consensus,[9] triple therapy after acute coronary syndrome is preferred for 6–12 month in patients with low bleeding risk (as is the case in our patient with HAS-BLED score of 1). However, in our case, clopidogrel and prasugrel were not effective in inhibiting platelets and hence would not have showed the desired therapeutic effect. Ticagrelor was the only drug known to inhibit platelets sufficiently, thus it was used in the therapeutic regimen after PCI, for our patient.

Until now, no data existed on the pharmacological activity of antiplatelet medications in patients with short bowel syndrome. Aspirin is an irreversible inhibitor cyclooxygenase-1 and prevents the thromboxane-dependent activation of platelets. Absorption of aspirin takes place in the stomach and proximal small intestine. Its pharmacological effect begins within 10–20 min as demonstrated by deactivation of thrombocytes in the portal blood.[10] As predicted, our patient had an appropriate response to aspirin given its absorption in the stomach.

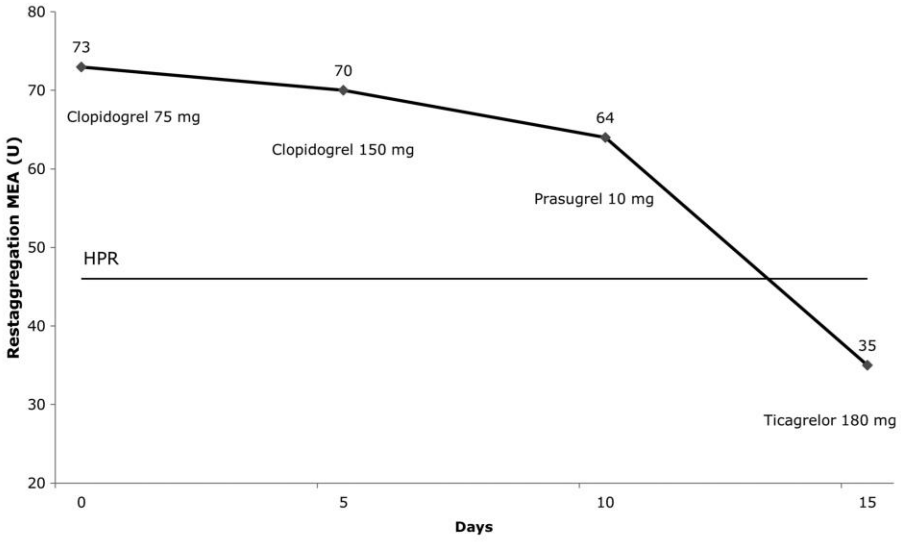

Figure 1 Measurement of on-treatment platelet reactivity during treatment with clopidogrel 75 mg, 2×75 mg, prasugrel 10 mg and ticagrelor 2×90 mg. HPR (>46 U; HPR, high on-treatment platelet reactivity; MEA, multiple electrode aggregometry).

Clopidogrel is an irreversible inhibitor of the $P2Y_{12}$ receptor. It is rapidly absorbed in the intestine. As a prodrug, clopidogrel must be transformed in two steps by cytochrome P450 enzyme to its active metabolite in the liver.[11] There is a high interindividual variability of response to clopidogrel. Patients with high platelet reactivity while on clopidogrel have increased cardiovascular risk.[12] Genetic variability in cytochrome P450 enzyme is assumed to be the main mechanism of clopidogrel non-responsiveness. Other possible mechanisms include variability of intestinal absorption and drug-drug interactions. Genotyping in our patient showed heterozygote CYP219 genotype with one loss-of-function allele (*1/*2), characterised as an intermediate clopidogrel metaboliser. Clopidogrel non-responsiveness is associated with major adverse cardiovascular events after PCI.[7] In our patient, response to clopidogrel did not change significantly despite double the maintenance dose. Thus, low intestinal absorption of clopidogrel was the likely cause of non-responsiveness in our patient.

Prasugrel is also an irreversible inhibitor of the $P2Y_{12}$ receptor. Similar to clopidogrel, it is a prodrug, but its hepatic activation is much faster. Two steps are necessary. First, hydrolysis to a thiolactone precursor is performed in the intestine. Second, cytochrome P450 enzymes located in the bowel and liver transform thiolactone into the active drug.[13] Our patient also had inadequate response to prasugrel, likely due to loss of intestinal hydrolysis.

Ticagrelor is a novel reversible $P2Y_{12}$-receptor inhibitor. In contrast to clopidogrel and prasugrel, ticagrelor does not require conversion from a prodrug.[14] It is rapidly absorbed from the small intestine. In our patient with short bowel syndrome, ticagrelor was the only $P2Y_{12}$-receptor inhibitor to effectively inhibit platelets.

High on-treatment platelet reactivity increases the risk for early and late stent thrombosis.[5] Personalised antiplatelet treatment after PCI is debated, and randomised studies failed to show its clinical benefit according to major end points.[15–17] However, it can be very helpful in cases such as our patient with short bowel syndrome. Our patient had inadequate response to two of the three available $P2Y_{12}$-receptor inhibitors, which would increase his risk of stent thrombosis while taking clopidogrel or prasugrel. Given its unique pharmacokinetics, ticagrelor seems to be a better choice for patients with short bowel syndrome.

Learning points

- Short bowel syndrome after extensive surgical resection of the intestine is characterised by inadequate digestion and absorption of nutrients and drugs.
- In patients with short bowel syndrome, standard medical therapy may be less effective, necessitating individualised dosing and monitoring of drugs.
- Owing to its unique pharmacokinetics with good resorption and without need of metabolism to an active substance, ticagrelor appears to be the best choice for patients with short bowel syndrome undergoing percutaneous coronary intervention.
- Clopidogrel, due to wide interindividual response, and prasugrel, due to need of metabolism within the intestine, appear to be less effective in patients with short bowel syndrome.

Contributors MD and AK were involved in acquisition of data. MD was responsible for drafting of the manuscript. AK, MG and TG was responsible for critical revision of the manuscript for important intellectual content. TG were involved in final approval.

Competing interests None declared.

Patient consent Obtained.

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2.3 Impact of anticoagulation regimen prior to revascularization in patients with non-ST-segment elevation acute coronary syndromes: The ACUITY trial. M. Droppa and T. Geisler, M. Gawaz, S. R. Steinhubl, M. E. Bertrand, A. M. Lincoff, A. R. Cequier, W. Desmet, L. H. Rasmussen, J. W. Hoekstra, D. Bernstein, E. N. Deliargyris, R. Mehran, and G. W. Stone. Catheter Cardiovasc Interv. 2015 Sep 2.

Original Studies

Impact of Anticoagulation Regimen Prior to Revascularization in Patients with Non-ST-Segment Elevation Acute Coronary Syndromes: The ACUITY Trial

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Aim: To evaluate the impact of antithrombotic regimens during the medical phase of treatment among 13,819 patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS) treated with an early invasive strategy in the acute catheterization and urgent intervention triage strategy (ACUITY) trial. Methods and results: Endpoints included composite major adverse cardiac events (MACE), major bleeding, and net adverse clinical events (NACE; MACE or major bleeding). The median (interquartile range) duration of antithrombin use in the medical only treatment phase was 6.5 (1.8–22.5) hours. MACE, major bleeding, and NACE during the medical only phase occurred in 63 (0.5%), 117 (0.9%), and 178 (1.3%) patients, respectively. MACE rates in the medical-treatment-only phase were not significantly different between the four randomized medical regimens used (heparin alone, bivalirudin alone, heparin plus a glycoprotein IIb/IIIa inhibitor [GPI], and bivalirudin plus GPI) ($P_{trend} = 0.65$). The lowest

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Tobias Geisler and Michal Droppa contributed equally to this work.

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rates of major bleeding and NACE during the medical treatment phase occurred in patients treated with bivalirudin alone (P_{trend} = 0.0006 and P_{trend} = 0.0004, respectively). Conclusions: In patients with NSTE-ACS undergoing an early invasive strategy, treatment with bivalirudin alone significantly reduced major bleeding and improved net clinical outcomes during the upstream medical management phase with comparable rates of MACE.

Key words: acute coronary syndrome; coronary artery disease; bivalirudin; glycoprotein IIb/IIIa inhibitors; medical management

INTRODUCTION

In-hospital antithrombotic therapy reduces ischemic complications in medically managed patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS) [1,2]. Compared with medical therapy alone, angiography followed by revascularization reduces the rates of death and myocardial infarction (MI) [3–5]. The optimal antithrombotic strategy prior to angiography and revascularization in NSTE-ACS patients treated with a routine early invasive strategy is uncertain. In the EARLY ACS trial, routine upstream administration of glycoprotein IIb/IIIa inhibitors (GPI) before angiography did not reduce adverse ischemic events compared with provisional GPI use reserved for patients undergoing percutaneous coronary intervention (PCI) after angiography, and resulted in increased major bleeding and need for transfusion [6]. Similarly, prehospital initiation of prasugrel in NSTE-ACS patients undergoing an early invasive strategy increased major bleeding without reducing ischemic event rates [7]. Major bleeding in patients with NSTE-ACS has been strongly associated with early and late mortality [8–10], and strategies that reduce bleeding have been associated with improved outcomes after revascularization [11]. Over the last decade the duration from hospital presentation to the cardiac catheterization laboratory in patients with NSTE-ACS has become increasingly shorter [12–16], and whether the choice of antithrombotic regimen within this narrow time window is important has not been studied. We therefore sought to assess the impact of different antithrombotic regimens in patients with NSTE-ACS undergoing an early invasive strategy from the ACUITY (acute catheterization and urgent intervention triage strategy) trial.

METHODS

Study Design

The study design and the principal results from the ACUITY trial have been reported [16–18]. In brief, ACUITY was a randomized, open-label, active-comparator trial, in which 13,819 patients with moderate and high-risk NSTE-ACS managed by an early invasive strategy were randomized to one of three treatments: heparin (unfractionated heparin [UFH] or enoxaparin) plus a GPI, bivalirudin plus a GPI, or bivalirudin monotherapy (with provisional GPI use allowed only for refractory thrombotic PCI complications). Patients assigned to one of the GPI arms were randomized again in a 2 × 2 factorial design to upstream GPI initiation or a deferred selective strategy, reserving GPI use only for patients triaged to PCI. Thus, prior to revascularization four medical regimens were used: heparin alone, heparin + GPI, bivalirudin alone, or bivalirudin + GPI.

Unfractionated heparin was administered as an intravenous bolus of 60 IU/kg plus an infusion of 12 IU per kg/h to achieve an activated partial thromboplastin time of 50 to 75 seconds before angiography. Alternatively, 1 mg/kg of enoxaparin was administered subcutaneously twice a day before angiography. Bivalirudin was started prior to angiography with an IV bolus of 0.1 mg/kg and an infusion of 0.25 mg/kg/hour. Standard bolus and infusion doses of GPI were administered per label, adjusted for renal insufficiency, as previously described [16–18]. Aspirin 300–325 mg PO or 250–500 mg IV was administered daily during the index hospitalization, followed by indefinite maintenance dosing of 75–325 mg daily. Dosing and timing of clopidogrel were left to investigator discretion although a loading dose ≥300 mg was strongly recommended not later than 2 hours after PCI, followed by 75 mg daily.

Endpoints

Composite major adverse cardiac events (MACE), including death from any cause, MI, and unplanned revascularization for ischemia, were recorded. Major bleeding in ACUITY was defined as intracranial bleeding, intraocular bleeding, access-site hemorrhage requiring intervention, hematoma >5 cm in diameter, reduction in hemoglobin >4 g/dL without an overt source of bleeding or >3 g/dL with an overt source of bleeding, reoperation for bleeding, or blood-product transfusion not related to coronary artery bypass graft surgery (CABG). Secondary bleeding endpoints included non-CABG-related thrombolysis in myocardial infarction (TIMI) major and minor bleeding. Net adverse clinical events (NACE) were defined as MACE or non-CABG major bleeding (protocol definition). A clinical events committee blinded to

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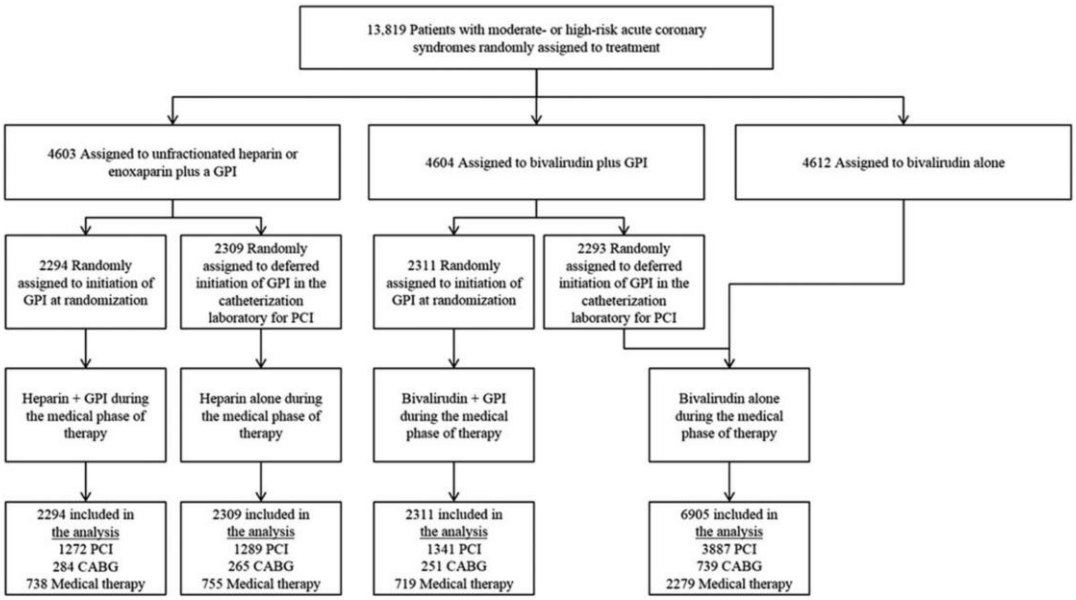

Fig. 1. Study design, randomization, and patient flow. Abbreviations: GPI, glycoprotein IIb/IIIa inhibitor; PCI, percutaneous coronary intervention.

treatment assignment adjudicated all 30-day events using original source documents.

Statistical Analysis

The present analysis was restricted to the time of upstream medical management. Thus, for the present analysis patients in whom GPI use was not started until immediately prior to or after PCI were categorized as being in the heparin or bivalirudin alone without GPI groups. Treatment outcomes were censored at the time of PCI, at the time of CABG or of study drug discontinuation prior to CABG (whichever occurred earlier), or at the conclusion of study drug in medically treated patients. Categorical variables are presented as numbers with percentages of patients and were compared with chi-square or Fisher's exact test. Continuous variables are expressed as median (interquartile range) and were compared with the nonparametric Wilcoxon rank-sum test. Time-to-event curves were displayed according to the Kaplan–Meier method and were compared with the long-rank test. All P values are two-sided, and a P-value <0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Patients

According to actual randomized treatment in the four groups during the medical only phase, 2,309 patients were treated with heparin alone, 6,905 patients were treated with bivalirudin alone, 2,294 patients were treated with heparin plus GPI, and 2,311 patients were treated with bivalirudin plus GPI (Fig. 1). Baseline clinical characteristics between treatment groups were well matched, as was medication use before angiography (Tables I and II). The median duration of antithrombin use in the medical only treatment phase was 6.5 (1.8–22.5) hours, and did not vary between the treatment groups (Table II). Angiography was performed in 98.9% of patients, after which 56.4% of patients underwent PCI, 11.1% underwent CABG, and 32.5% were treated conservatively. There were no significant differences in the use and type of revascularization across the 4 arms (Table II).

Clinical Outcomes

Event rates during the medical therapy only phase are shown in Table III and Fig. 2. MACE, protocol-defined non-CABG major bleeding and NACE during the medical therapy only phase occurred in 63 (0.5%), 117 (0.9%), and 178 (1.3%) patients respectively. There were no significant differences in MACE across the four treatment groups (Table III, Fig. 2A). The lowest rates of major bleeding and NACE during the medical treatment phase were observed in patients treated with bivalirudin alone (P_{trend}=0.0006 and 0.0004 respectively) (Table III, Fig. 2B and C).

TABLE I. Baseline Clinical Characteristics According to Randomization Arms

	Bivalirudin alone ($n=6,905$)	Heparin alone ($n=2,309$)	Bivalirudin plus GPI ($n=2,311$)	Heparin plus GPI ($n=2,294$)
Age	63.0 [54, 71]	63.0 [54, 72]	63.0 [54, 72]	63.0 [54, 72]
Female	30.6	29.7	29.7	29.2
Hypertension	67.1	66.7	67.0	66.9
Hyperlipidemia	57.1	57.6	57.6	56.8
Diabetes mellitus	28.1	29.1	27.4	27.8
Current smoker	29.3	29.5	28.5	28.5
Prior MI	31.5	32.5	30.2	30.7
Prior PCI	39.1	39.3	38.1	38.7
Prior CABG	17.7	17.6	18.0	18.8
CrCl <60 mL/min	19.1	19.0	18.7	19.4
Baseline anemia	16.6	16.6	17.7	17.2

Values are median [interquartile range] or percentage.
Abbreviations: CABG, coronary artery bypass graft surgery; CrCl, creatinine clearance; GPI, glycoprotein IIb/IIIa inhibitor; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention.

TABLE II. Medications and Treatments According to Antithrombotic Treatment

	Bivalirudin alone ($N=6,905$)	Heparin alone ($N=2,309$)	Bivalirudin + GPI ($N=2,311$)	Heparin + GPI ($N=2,294$)
Aspirin before angiography	6608 (95.9%)	2190 (95.0%)	2207 (95.7%)	2203 (96.2%)
Thienopyridine before angiography	4357 (64.2%)	1426 (62.5%)	1478 (65.2%)	1416 (63.0%)
Antithrombotic agents				
Before randomization				
Unfractionated heparin	2460/6890 (35.7%)	857/2305 (37.2%)	826/2305 (35.8%)	855/2291 (37.3%)
Low molecular weight heparin	1414/6891 (20.5%)	517/2305 (22.4%)	477/2305 (20.7%)	494/2291 (21.6%)
After randomization				
Unfractionated heparin	1009/6893 (14.6%)	1272/2304 (55.2%)	338/2304 (14.7%)	1291/2291 (56.4%)
Low molecular weight heparin	521/6893 (7.6%)	1224/2307 (53.1%)	170/2304 (7.4%)	1198/2293 (52.2%)
Bivalirudin	6804/6893 (98.7%)	28/2307 (1.2%)	2272/2308 (98.4%)	32/2293 (1.4%)
Duration of unfractionated heparin or bivalirudin infusion (hours)	17.2 ± 24.0	18.2 ± 28.5	15.9 ± 23.2	18.0 ± 27.6
Triage after angiography				
PCI	3887 (56.3%)	1289 (55.8%)	1341 (58.0%)	1272 (55.4%)
CABG	739 (10.7%)	265 (11.5%)	251 (10.9%)	284 (12.4%)
Medical therapy	2279 (33.0%)	755 (32.7%)	719 (31.1%)	738 (32.2%)

CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.

TABLE III. Event Rates During the Medical Therapy Only Phase According to Antithrombotic Treatment

	Bivalirudin alone ($N=6,905$)	Heparin alone ($N=2,309$)	Bivalirudin + GPI ($N=2,311$)	Heparin + GPI ($N=2,294$)	P value for trend
MACE	28 (0.4%)	10 (0.4%)	11 (0.5%)	14 (0.6%)	0.65
Death	2 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.0%)	
Myocardial infarction	22 (0.3%)	10 (0.4%)	9 (0.4%)	13 (0.6%)	
Unplanned revascularization	5 (0.1%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	
On-treatment major bleeding	39 (0.6%)	21 (0.9%)	24 (1.0%)	33 (1.4%)	0.0006
TIMI major or minor bleeding	55 (0.8%)	30 (1.3%)	32 (1.4%)	38 (1.7%)	0.002
TIMI major bleeding	11 (0.2%)	5 (0.2%)	5 (0.2%)	8 (0.3%)	0.40
TIMI minor bleeding	51 (0.7%)	27 (1.2%)	30 (1.3%)	35 (1.5%)	0.004
Transfusion	22 (0.3%)	9 (0.4%)	12 (0.5%)	12 (0.5%)	0.41
NACE	65 (0.9%)	31 (1.3%)	35 (1.5%)	47 (2.0%)	0.0004

Abbreviations: GPI, glycoprotein IIb/IIIa inhibitor; MACE, major adverse cardiac events; NACE, net adverse clinical events; TIMI, thrombolysis in myocardial infarction.

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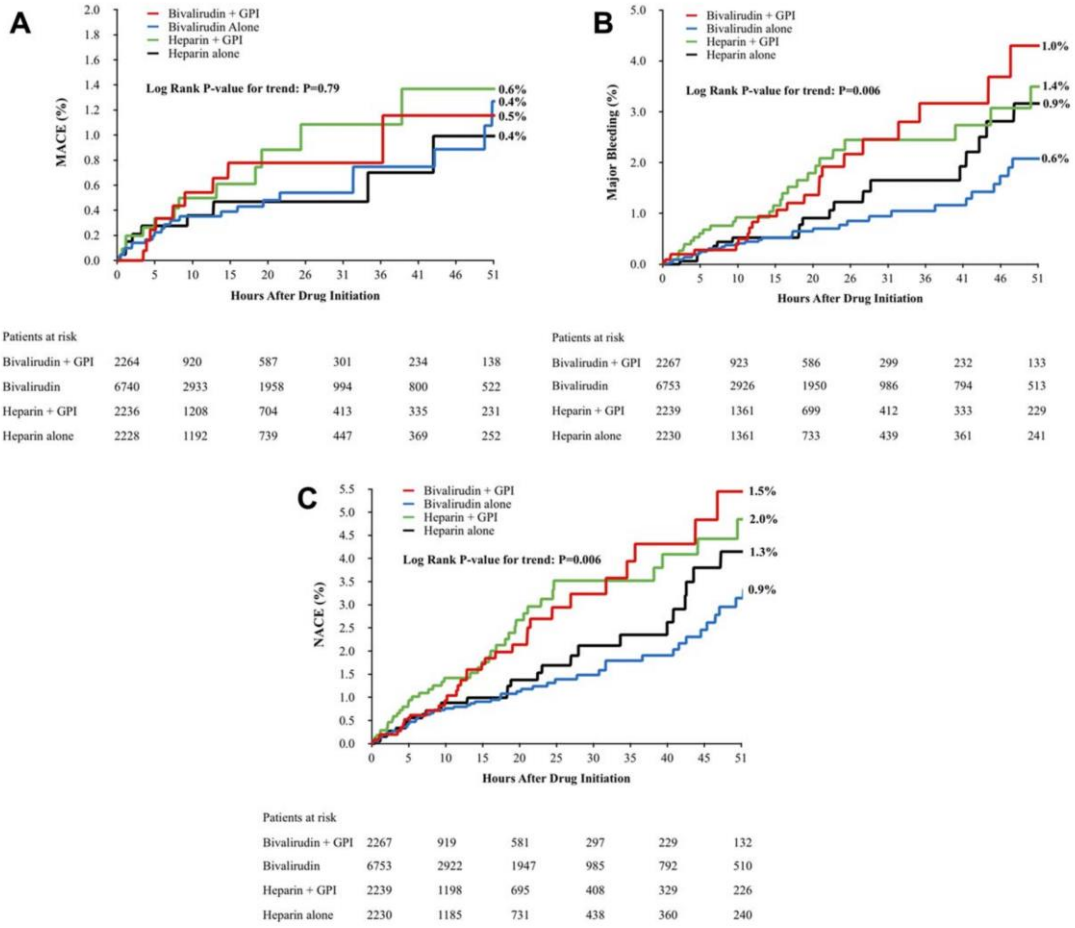

Fig. 2. Time-to-event curves for cumulative endpoints according to antithrombotic regimen during medical therapy only. A: Major adverse cardiac events (MACE), B: major bleeding not related to coronary artery bypass graft surgery (protocol definition), and C: net adverse clinical events (NACE).

DISCUSSION

Current guidelines for treatment of NSTE-ACS recommend an early invasive strategy for intermediate and high-risk patients [19,20]. While in general these recommendations allow for up to 24 hours of conservative medical therapy until angiography and subsequent triage to PCI, CABG or medical therapy, the duration from hospital admission until angiography in patients with NSTE-ACS is becoming increasingly shorter, from 4 to 6 days in the late 1990's [12,13] to 19.7 hours in the ACUITY trial (enrolled in 2003-2005), [16] to 5–7 hours in the recent CHAMPION trials [14,15]. Antithrombotic medications (anticoagulants and anti-platelet agents) are indicated during the upstream treatment period to inhibit thrombin generation and platelet activation. However, all such agents are associated with an increased risk of bleeding, necessitating balancing their risks and benefits. At 30 days in the ACUITY trial, randomization of moderate and high-risk NSTE-ACS patients to bivalirudin plus GPI, heparin plus GPI, or bivalirudin alone resulted in comparable rates of ischemic MACE, whereas bivalirudin monotherapy resulted in significantly reduced major bleeding and thus NACE [16]. No prior study, however, has examined the outcomes of different antithrombin regimens during the medical therapy only phase in NSTE-ACS patients undergoing an early invasive strategy. In the present post-hoc analysis, we observed significant differences in the risk of major bleeding according to the antithrombotic regimen used in the medical treatment only phase. Despite the relatively brief duration of antithrombin use in the medical only treatment phase (median 6.5 hours), the lowest rates of bleeding were observed in patients treated with

bivalirudin only rather than either heparin alone or heparin or bivalirudin plus a GPI.

The timing of GPI therapy in patients with NSTE-ACS undergoing PCI has been studied in several trials [6,18]. Based on these studies current guidelines do not support routine upstream therapy with GPI [19,20]. In both the ACUITY Timing and EARLY ACS trials [6,18] routine upstream use in comparison to deferred selective GPI therapy was not superior in preventing ischemic events but was associated with substantially greater bleeding. Similarly, in the present analysis, the addition of GPI to either heparin or bivalirudin during the medical management phase did not reduce ischemic events but increased bleeding.

Bivalirudin is a direct thrombin inhibitor with distinct pharmacologic advantages over heparin that include predictable pharmacokinetic and pharmacodynamic profiles, the ability to inhibit both circulating and clot-bound thrombin, and importantly the ability to inhibit rather than induce platelet activation [21,22]. Bivalirudin has consistently outperformed the combination of heparin plus GPI across the spectrum of patients undergoing PCI, with lower rates of bleeding and comparable ischemic protection [16,21–24]. Bivalirudin also significantly reduced mortality through 3 years in STEMI patients undergoing primary PCI in the multicenter HORIZONS-AMI randomized trial [24,25]. The multicenter, randomized EUROMAX and BRIGHT trials found that bivalirudin resulted in marked reductions in 30-day major bleeding compared with heparin with or without GPI in STEMI patients undergoing primary PCI [26,27]. Comparable rates of MACE occurred with bivalirudin and heparin + GPI in both the ACUITY and ISAR-REACT 4 trials (collectively 15,540 randomized NSTE-ACS patients), with marked reductions in bleeding at 30 days [16,28]. The present analysis, coupled with the principal results of ACUITY and ISAR-REACT 4 [16,28], thus supports the safety benefits of upstream bivalirudin as part of an early invasive management strategy prior to the catheterization laboratory in patients with NSTE-ACS.

The present analysis has several limitations. First, as a post hoc subgroup analysis from a major randomized trial, the results should be considered hypothesis-generating. Although the initial pharmacologic assignment was randomized and the baseline characteristics were well balanced, treatment duration in the 4 groups was censored according to revascularization modality, a post randomization decision. However, the triaged therapies (PCI vs. CABG vs. medical therapy only) were used in similar proportion between the groups, and it is unlikely that this factor importantly contributed to the differences observed. Second, the event rates during the short upstream medical therapy period were modest and not sufficiently powered to evaluate small differences in ischemic MACE or mortality. Finally, clopidogrel and ticlopidine were the only ADP antagonists available during enrollment in ACUITY. In the current era of more potent ADP antagonists (prasugrel, ticagrelor), non-CABG-related bleeding rates have increased [29,30], and as such the differences observed in the present study may be even more relevant.

In conclusion, the present analysis from the large-scale ACUITY trial suggests that among patients with moderate and high-risk NSTE-ACS undergoing an early invasive strategy, treatment with bivalirudin alone during the upstream medical therapy only phase (prior to PCI, CABG or drug discontinuation) results in the lowest rates of major bleeding and NACE, with comparable suppression of adverse ischemic events compared with either heparin with or without a GPI, or bivalirudin with a GPI.

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3. Discussion

Antithrombotic therapy is an important part of treatment for patients with CAD undergoing PCI. It reduces ischemic complications and improves prognosis. In our work we evaluated specific aspects of choosing the appropriate antithrombotic treatment. First, we evaluated clinical risk predictors for HPR in patients with stable CAD. We developed a risk score, which allows to identify patients with higher risk for HPR and MACE. Second, we discussed clinical indications of individual platelet aggregation testing in a case-report of a challenging patient with a malabsorption syndrome. Finally, we evaluated 4 anticoagulation regimens in patients with NSTEMI during medical phase of treatment prior to revascularization. Risk stratification of patients according to clinical characteristics helps to find the best individual treatment under consideration of the efficacy-safety profile of the chosen agent.

3.1 Risk stratification of patients with stable angina pectoris treated with dual antiplatelet treatment after PCI

After PCI dual antiplatelet therapy is necessary to prevent adverse cardiac events such as stent thrombosis. However, interindividual variability in response to clopidogrel remains a challenging clinical problem. Patients after PCI with HPR have worse prognosis, regarding ischemic cardiac events, than patients with sufficient platelet inhibition (Geisler et al., 2006). Platelet function testing allows identification of non-responders, however, its routinely administration failed to improve outcome in some clinical trials, likely due to low-risk studied population (Price et al., 2011; Collet et al., 2012; Trenk et al., 2012). Further, clinical risk stratification may be a useful tool to identify patients at high-risk for HPR, and so a means of predicting clinical adverse events. We evaluated clinical characteristics, platelet function and clinical events after 12 month of follow up in 739 patients with stable coronary disease undergoing PCI. In our study, age, adiposity, diabetes mellitus, reduced renal function and reduced left ventricular function were associated with HPR. Accordingly, we have developed

a risk score depending on effect size of the clinical variables on HPR – PREDICT-STABLE Score, ranging from 0 to 9. We could show that patients with higher score (7-9) had significant higher MACE in 12 month of follow up (10.3% versus 3.4% in patients with score 0-3). We have validated these findings on an independent cohort of patients with stable coronary disease. This simple score allows to identify patients at higher risk, who may profit from more intensive antiplatelet therapy i.e. prasugrel or ticagrelor.

3.2 Individual antiplatelet therapy in selected patients in clinical praxis

Despite variable response rates to antiplatelet therapy mainly under clopidogrel medication, measuring of platelet function was not established routinely in patients undergoing PCI. However, in clinical practice the testing of platelet response can be sometimes crucial for appropriate therapy. In our case report, we could show an example of a difficult clinical situation during treatment of a patient with malabsorption due to short-bowel syndrome. The efficacy of the medication, in such cases, is not simply predictable due to reduced absorption surface of the intestine, and pharmacological testing may be warranted. In our patient there was reduced response to both clopidogrel and prasugrel. The reason for that are specific pharmacokinetics and metabolism of these drugs with an important involvement of intestinal mucosa as discussed above. The best choice for our patient was the therapy with ticagrelor, which doesn´t need metabolic transformation to active metabolite and is very good absorbed from intestinal tract. These findings could be transferred to similar patients with malabsorption syndrome and could help to choose the best antiplatelet therapy.

There are more possible indications of platelet response testing in clinical practice. First, patients under clopidogrel treatment after PCI with high risk, such as stentthrombosis in medical history, diabetes mellitus or performed complex coronary interventions e.g. left main PCI or long stent lesions, could be considered for platelet reactivity testing. Second, patients with unpredictable

pharmacokinetics such as massive adiposity, liver or intestinal diseases could also profit from platelet aggregation testing.

3.3 Anticoagulation in patients with NSTEMI

Anticoagulation is necessary during medical treatment period in patients with NSTEMI as it inhibits thrombin generation and reduces ischemic events. On the other hand, it is associated with increased bleeding risk. Bleeding is associated with increased mortality in patients with NSTEMI necessitating balanced anticoagulation treatment (Manoukian et al., 2007; Doyle et al., 2009). We investigated anticoagulation regimes in patients with NSTEMI during medical treatment before PCI. We could show that bivalirudin had the best net clinical benefit of all studied combinations – heparin, heparin plus GPI and bivalirudin plus GPI. This difference was mainly driven by lower bleeding risk.

Bivalirudin binds directly to thrombin and inhibits both circulating and clot-bound thrombin. Moreover, in contrast to heparin it doesn´t activate but inhibits platelets. It has more predictable pharmacokinetics in comparison to UFH. Bivalirudin was shown to reduce bleeding risk in several randomized clinical trials. In patients with STEMI it reduced bleeding events by comparable MACE in HORIZONS-AMI (Stone et al., 2008, 2011), EUROMAX (Steg et al., 2013) and BRIGHT (Han et al., 2015) trials. The same could be shown in patients with NSTEMI in ACUITY (Stone et al., 2006, 2007b) and ISAR-REACT 4 (Kastrati et al., 2011) trials where patients treated with bivalirudin had lower bleeding rates with comparable MACE. Direct comparison of UFH and bivalirudin was investigated in ISAR-REACT 3 (Kastrati et al., 2008) and HEAT-PPCI (Shahzad et al., 2014) trials. In ISAR-REACT 3 trial, patients with stable CAD and biomarker negative ACS were randomized. Bivalirudin showed comparable ischemic events and mortality but lower bleeding risk. In the HEAT-PPCI there was no difference in bleeding events between UFH and bivalirudin, however, bivalirudin was associated with higher catheter thromboembolic events in patients with STEMI undergoing primary PCI. Another trial MATRIX included

patients with STEMI and NSTEMI, it showed reduced bleeding events and slightly higher rate of stentthrombosis in bivalirudin arm. Our analysis adds knowledge to upstream anticoagulant treatment of NSTEMI patients. It shows that bivalirudin has a good safety profile during medical phase of treatment according to bleeding events which is in line with previous studies. It implicates that bivalirudin should be considered in patients with higher bleeding risk.

3.4 Implication of the findings for praxis

According to current guidelines novel $P2Y_{12}$-receptor inhibitors i.e. prasugrel and ticagrelor are first-line therapy for patients with ACS. Prasugrel was clinically tested in large TRITON-TIMI-38 trial, stentthrombosis and MI were significantly reduced in comparison with clopidogrel. Similarly, PLATO trial showed that patients treated with ticagrelor have reduced ischemic events (death, MI, ischemic stroke) and reduced mortality. Explanation of these findings are better pharmacokinetics and pharmacodynamics of those drugs allowing better predictable effect, higher platelet inactivation and less interindividual variability. In patients with stable angina pectoris who are in lower risk clopidogrel is still recommended. However, interindividual variability of metabolism of clopidogrel and hence significant proportion of non-responders may be problematic in some patients. Till now, large randomized clinical trials comparing clopidogrel and novel $P2Y_{12}$-recetor inhibitors in patients with stable angina pectoris are missing. Thus, individual clinical risk stratification may help to identify patients who would profit from more intensive antiplatelet treatment. In our work, we could identify several clinical variables and develop a score which could help to identify patients at higher risk for adverse ischemic events. Patients with higher score levels had significant worse prognosis measured by MACE. Mainly patients with diabetes mellitus, adiposity, renal- and heart-failure could be considered to more intensive treatment. Except these factors interventional aspects of PCI should be taken to account, i.e. patients with long stents lesions with higher risk of stent thrombosis or patients after left main PCI

are also possible candidates to more potent antiplatelet treatment. Alternatively, individual platelet aggregation testing may be performed.

Direct measuring of platelet aggregation remains indicated in special clinical conditions. We could show one example where individual platelet reactivity testing offered advantage to standard therapy. In our patient with short-bowel syndrome, drug absorption and effectiveness was questionable due to massively reduced intestinal mucosa after extensive intestine resection. Even use of novel high effective $P2Y_{12}$-receptor inhibitor prasugrel didn't show an expected effect. Using of platelet testing allowed to manage medical therapy and prevent ischemic events. Patients with similar clinical problems such as unpredictable pharmacodynamics and pharmacokinetics or patients at high risk for ischemic events may be considered for individual platelet aggregation testing.

Anticoagulation prior and during PCI inhibits thrombin formation and hence prevents progression of ischemia and trombusformation on catheter devices. In stable patients with NSTEMI, general recommendations allow for up to 24 hours of conservative medical therapy until angiography and subsequent triage to PCI, CABG or medical therapy. During the upstream treatment period anticoagulants are indicated to inhibit thrombin generation and platelet activation. Variety of anticoagulation agents are approved in patients with NSTEMI prior and during PCI. Probably, the most common is the UFH because of its availability, short plasmatic half-life, low cost and broad experience with its use under medical professionals. Alternatively, bivalirudin can be used. Bivalirudin is direct thrombin inhibitor which was extensively tested in large randomized trials and has been shown to have low risk of bleeding. We evaluated bleeding and ischemic events in the upstream period and could show that bivalirudin significantly reduces bleeding in comparison with UFH with or without GPI. This is in line with other studies and indicates that bivalirudin should be preferred in patients with higher bleeding risk. Fondaparinux and enoxaparin are further options of anticoagulation prior to PCI. Fondaparinux has

very good safety profile according to bleeding events. However, it has long elimination half-life (17 hours) and no available antagonist, which can be problematic in case of urgent coronary bypass surgery or bleeding complications. Other strategies mainly use of radial access for catheterization are warranted to reduce bleeding events.

4. Conclusion

Antithrombotic therapy is an important part of management in patients with CAD undergoing PCI. It prevents thrombus progression and hence reduces ischemia in patients with ACS. During coronary intervention it protects against thrombus formation on used devices such as coronary catheters, balloons and stents. After stent deployment dual platelet therapy prevents stentthrombosis till endothelialisation process of the implanted device is finalized. However, antithrombotic agents are associated with an increased risk of bleeding, necessitating balancing their risks and benefits. Risk stratification of patients is crucial to decide which antithrombotic therapy is the best option for individual patient.

After PCI dual antiplatelet therapy with aspirin and $P2Y_{12}$-receptor inhibitor is indicated. Novel $P2Y_{12}$-receptor inhibitors i.e. ticagrelor and prasugrel are first-line therapy for patients with ACS. Better platelet inhibiting effect, lower interindividual variability in response to the therapy and reduction of ischemic events was proved in large randomized control trials. Clopidogrel is recommended for patients with stable angina pectoris. There is a high interindividual variability of response to clopidogrel, whereas lower response predisposes to higher rate of ischemic events. We could show that HPR could be predicted by distinct clinical variables and developed a PREDICT-STABLE Score which helps to identify patients in risk for MACE. We could validate the score in an independent cohort of patients. Patients at high risk could be considered to more intensive antiplatelet treatment, for example, with novel $P2Y_{12}$-receptor inhibitors.

Platelet reactivity testing allows to evaluate individual response to antiplatelet treatment. This tool could be used in selected high-risk patients to guide the therapy. In our case-report we could prove this concept of individual therapy in high-risk patient with extended malabsorption after intestine resection. We could show that ticagrelor, because of its favorable pharmacokinetics, was the best choice for effective $P2Y_{12}$-receptor inhibition in this clinical setting.

There are several options of approved anticoagulation in patients with NSTEMI during medical therapy before revascularization. We analyzed data of large randomized clinical trial (ACUITY) on ischemic and bleeding rates during medical therapy. We compared four anticoagulation regimes – UFH alone, UFH plus GPI, bivalirudin alone and bivalirudin plus GPI. We could show that bivalirudin alone has the lowest bleeding events by similar rates of ischemic events, and hence the best net clinical benefit during medical treatment before PCI. This should be taken into account when choosing the treatment of NSTEMI, mainly in patients at higher risk for bleeding events.

5. Zusammenfassung

Die antithrombotische Therapie ist ein wichtiger Teil des Managements bei Patienten mit koronarer Herzerkrankung. Sie verhindert die Thrombusprogression und reduziert damit die Ischämie bei den Patienten mit einem akuten Koronarsyndrom. Während der koronaren Intervention verhindert die antithrombotische Therapie eine Thrombusformation auf den benutzten Kathetern, Ballons und Stents. Zur Verhinderung der Stentthrombose wird nach der koronaren Intervention die duale Plättchenhemmung bis zum Abschluss der Stentendothelialisierung fortgeführt. Die antithrombotische Therapie ist jedoch mit einem erhöhten Blutungsrisiko assoziiert. Deshalb ist es notwendig, Nutzen und Risiko bei jedem Patienten sorgfältig abzuwägen. Klinische Stratifizierungen des Risikos ermöglichen die individuelle Entscheidung für die zu verordnende antithrombotische Therapie.

Nach der koronaren Intervention ist eine duale Plätchenhemmung mit Acetylsalicylsäure und P2Y12-Receptor Inhibitor indiziert. Bei den Patienten mit einem akuten Koronarsyndrom werden in der ersten Linie die neuen P2Y12-Receptor Inhibitoren – Ticagrelor und Prasugrel eingesetzt. In den großen randomisierten Studien konnte hier ein Vorteil bezüglich einer besseren Plättcheninhibition, niedrigerer interindividueller Variabilität in der Wirkung, sowie Reduktion von ischämischen Ereignissen gezeigt werden. Bei den Patienten mit stabiler Angina pectoris wird Clopidogrel empfohlen. Die Patienten unter Clopidogreltherapie weisen jedoch eine hohe interindividuelle Variabilität in der Plätchenhemmung auf. Die Patienten mit verminderter Plätchenhemmung sind für ischämische Folgeereignisse prädisponiert. Wir konnten zeigen dass die hohe Plättchenreaktivität unter Clopidogreltherapie bei den Patienten mit stabiler Angina pectoris von verschiedenen klinischen Faktoren beeinflusst wird. Wir entwickelten den PREDICT-STABLE Score. Dieser hilft die Patienten mit erhöhtem ischämischem Risiko zu identifizieren. Ebenso, validierten wir den Score in einer unabhängigen Patientenpopulation. Patienten mit erhöhtem Risiko können von einer intensivierten plättchenhemmenden Therapie, z.B. mit neuen P2Y12-Receptor Inhibitoren profitieren.

Plättchenaggregationstests ermöglichen die Evaluation des individuellen Ansprechens auf die plättchenhemmende Therapie. Sie können bei selektierten Hochrisikopatienten zur Steuerung der Therapie eingesetzt werden. In unserem Fallbeispiel zeigen wir die Bedeutung dieses Konzeptes bei einem Patienten mit ausgeprägter Malabsorption nach Darmresektion. Dank seiner günstigen Pharmakokinetik war Ticagrelor der überlegene P2Y12-Receptor Inhibitor für eine effektive Plätchenhemmung in dieser anspruchsvollen klinischen Situation.

Mehrere Antikoagulantien sind für Patienten mit NSTEMI vor der Revaskularisation zugelassen. Wir haben die Daten einer großen randomisierten klinischen Studie (ACUITY) in Bezug auf Blutungsrisiko und

ischämische Ereignisse analysiert. Wir haben 4 Antikoagulationsregime (unfraktioniertes Heparin mit und ohne Glycoprotein IIb/IIIa-Inhibitoren sowie Bivalirudin mit und ohne Glycoprotein IIb/IIIa-Inhibitoren) verglichen. Während der medikamentösen Therapie zeigte Bivalirudin alleine die niedrigste Häufigkeit von Blutungskomplikationen ohne die ischämischen Ereignisse zu erhöhen. Bivalirudin sollte daher vor allem bei NSTEMI-Patienten mit erhöhtem Blutungsrisiko bevorzugt werden.

6. References

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7. Declaration of authorship

I hereby certify that this dissertation has been composed by me and is based on my own work, unless stated otherwise. No other person's work has been used without due acknowledgement in this thesis. All references have been quoted, and all sources of information have been specifically acknowledged. Authors' contributions of included publications are listed below:

7.1 Droppa M, Tschernow D, Müller KAL, Tavlaki E, Karathanos A, Stimpfle F, Schaeffeler E, Schwab M, Tolios A, Siller-Matula JM, Gawaz M, Geisler T. Evaluation of clinical risk factors to predict high on-treatment platelet reactivity and outcome in patients with stable coronary artery disease (PREDICT-STABLE). PLoS ONE 2015 Mar 23;10(3):e0121620.

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Analysis and interpretation of data	Droppa, Geisler, Schaeffeler, Schwab, Siller-Matula, Gawaz
Statistical analysis	Droppa, Geisler
Drafting of the manuscript	Droppa
Critical revision of the manuscript for important intellectual content	Tschernow, Müller, Tavlaki, Karathanos, Stimpfle, Schaeffeler, Schwab, Tolios, Siller-Matula, Gawaz
Study supervision	Geisler
Final approval	Geisler

7.2 Droppa M, Karathanos A, Gawaz M, Geisler T. Individualised dual antiplatelet therapy in a patient with short bowel syndrome after acute myocardial infarction with coronary artery stenting. BMJ Case Rep 2015 Jul 6;2015.

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7.3 Geisler T[*], Droppa M[*], Gawaz M, Steinhubl SR, Bertrand ME, Lincoff AM, Cequier AR, Desmet W, Rasmussen LH, Hoekstra JW, Bernstein D, Deliargyris EN, Mehran R, Stone GW. Impact of anticoagulation regimen prior to revascularization in patients with non-ST-segment elevation acute coronary syndromes: The ACUITY trial. Catheter Cardiovasc Interv 2015 Sep 2.

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