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Complete List of Authors:	Christ, Günter; 5th Medical Department of Cardiology, Kaiser Franz Josef Hospital, Siller-Matula, Jolanta; Medical University, Department of Cardiology Francesconi, Marcel; 5th Medical Department of Cardiology, Kaiser Franz Josef Hospital, Dechant, Cornelia; 5th Medical Department of Cardiology, Kaiser Franz Josef Hospital, Grohs, Katharina; Clinical Institute for Laboratory Medicine, Kaiser Franz Josef Hospital, Podczeck-Schweighofer, Andrea; 5th Medical Department of Cardiology, Kaiser Franz Josef Hospital,
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Individualizing Dual Antiplatelet Therapy after Percutaneous Coronary Intervention: The IDEAL-PCI Registry.

Günter Christ* MD, Jolanta M. Siller-Matula† MD PhD, Marcel Francesconi* MD, Cornelia Dechant* MD, Katharina Grohs‡ MD and Andrea Podczeck-Schweighofer* MD for the IDEAL-PCI investigators.

* 5th Medical Department with Cardiology, Kaiser Franz Josef Hospital, Vienna, Austria

† Department of Cardiology, Medical University of Vienna, Austria

‡ Clinical Institute for Laboratory Medicine, Kaiser Franz Josef Hospital, Vienna, Austria

Correspondence: Prof. Günter Christ, MD

5th Medical Department with Cardiology, Kaiser Franz Josef Hospital

Kundratstr. 3, 1100 Vienna, Austria

Tel.: +43-1-60191-2508

Fax: +43-1-60191-2509

E-mail: guenter.christ@wienkav.at

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Abstract

Introduction: The clinical utility of individualizing dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) has been tested in lower risk patients, with equivocal results. Its value in an all-comers PCI population, including ST-elevation myocardial infarction (STEMI) patients, is unknown.

Methods and Results: A prospective, single-centre registry of 1008 consecutive PCI patients with individualization of DAPT guided by multiple electrode aggregometry (MEA) was compiled. Overall, 53% of patients presented with acute coronary syndrome (9% STEMI, 44% non-ST-elevation). High on-treatment platelet reactivity (HPR) to adenosine diphosphate (ADP)-induced aggregation (≥50 U) after 600 mg clopidogrel loading occurred in 30% of patients (73±19 U vs. 28±11 U; p<0.001) and was treated by prasugrel or ticagrelor (73%) or clopidogrel (27%) reloading (22±12 U; p<0.001). HPR to prasugrel occurred in 2% of patients (82±26 U vs. 19±10 U; p<0.001) and was treated with ticagrelor (34±15 U; p=0.02). The efficacy endpoint definite stent thrombosis (ST) at 30 days occurred in 0.09% of patients (n=1); probable ST, myocardial infarction and cardiovascular death occurred in 0.19% (n=2), 0.09% (n=1) and 1.8% (n=18) of patients. The safety endpoints TIMI major and minor bleeding did not differ between patients without HPR and individualized patients (2.6% for both).

Conclusions: Individualization of DAPT with MEA minimizes early thrombotic events in an all-comers PCI population to an unreported degree without increasing bleeding. A randomized multicenter trial utilizing MEA seems warranted.

Clinical Trial Registration: URL: http://www.clinicaltrials.gov; Unique identifier: NCT01515345

Keywords: percutaneous coronary intervention, platelet function testing, dual antiplatelet therapy

Article summary

Strengths and limitations of this study

The strengths of our study are, at first the real world percutaneous coronary intervention setting with inclusion of every consecutive patient, without any exclusion criteria. Second, the consequent and efficient peri-interventional individualization of dual antiplatelet therapy, leaving only 0.3% of patients on high on-treatment platelet reactivity to adenosine diphosphate at the time of hospital discharge. Third, the minimization of ischemic events within 30 days by nearly abolishing early definite stent thrombosis, without increasing bleeding complications.

Limitations of our study are the non randomised and monocentric registry design without control group concerning ischemic events.

Introduction

High on-treatment platelet reactivity (HPR) to adenosine diphosphate (ADP) represents one of the strongest independent risk factors for post-percutaneous coronary intervention (PCI) ischemic events in patients given dual antiplatelet therapy (DAPT), according to numerous observational studies using various platelet function tests [1-3].

Whether HPR represents only a marker of higher risk or a modifiable risk factor is still a matter of debate [2], as prospective randomized trials evaluating personalized antiplatelet therapy aiming to overcome HPR resulted in conflicting data. Smaller randomized trials [4], as well as non-randomized studies [5] and a recent meta-analysis [6] suggested a significant

clinical benefit, but three randomized studies failed to do so [7-9]. However, each of these trials, utilizing the VerifyNow™ assay, was afflicted with major limitations potentially masking the real value of individualizing DAPT after PCI in daily practice [1, 10]. Their low-risk population and primarily the high selection bias in GRAVITAS [7] and TRIGGER-PCI [9], with patient inclusion more than 12 hours after PCI, seems to cloud the potential importance of optimizing platelet inhibition at the time of PCI. By contrast, the very recent CHAMPION Phoenix trial [11] provides a more realistic scenario of expectable ischemic complications during and after PCI. More than 11,000 patients with oral clopidogrel loading, including the whole clinical PCI spectrum [56% stable coronary artery disease (CAD), 26% non-ST-elevation acute coronary syndrome (NSTE-ACS), 18% ST-elevation myocardial infarction (STEMI)], were pre-interventionally randomized to receive an intravenous (i.v.) bolus and infusion of cangrelor, a fast acting reversible ADP receptor blocker. Ischemic complications in the whole study cohort occurred in 5.3%, including a definite stent thrombosis (ST) rate of 1.1% during the first 48 hours. Notably, the majority of events occurred within 6 hours after PCI.

HPR to acetylic salicylic acid (ASA) is less well studied and its clinical relevance is unclear. The ADAPT-DES registry [3] found no difference in response to ASA, measured by the VerifyNow™ assay, between patients with and without ST. Data from our group, however, suggested that dual HPR to both ADP- and arachidonic acid- (AA; reflecting response to ASA) induced aggregation, measured by multiple electrode aggregometry (MEA), predisposes patients to a higher ischemic risk than single HPR [12]. Furthermore, MEA has been shown to effectively assess the risk of HPR to ADP after PCI [13] with higher accuracy than the vasodilator-stimulated phosphoprotein phosphorylation (VASP) assay [14] utilized in the Bonello studies.

Therefore, our registry aimed to evaluate the impact of individualizing DAPT with MEA in an all-comers population, including STEMI patients without exclusion criteria, by peri-interventional treatment of HPR to both ADP and AA.

Methods

Patient population

This was a prospective, single-centre cohort observation of consecutive PCI patients, including all forms of ACS (including cardiogenic shock) and all stable CAD, with stent implantation or drug eluting balloon dilatation, and without exclusion criteria. Peri-interventional individualization of platelet inhibition was performed according to the protocol shown in Figure 1 and described in detail below. The local Ethics Committee approved the study protocol in accordance with the Declaration of Helsinki. Participants were included between November 2008 and June 2012. Informed consent was obtained after PCI, either from the patient or from the guardian in cases of critically ill conditions. Follow-up information was obtained by either direct outpatient visit or telephone contact at 30 days.

Study endpoints

The primary efficacy endpoint was definite ST during a 30 days follow-up. The secondary efficacy outcome parameters were probable ST, myocardial infarction and cardiovascular death. Definite and probable ST were defined according to the Academic Research Consortium (ARC) [15]. The primary safety end point was the incidence of TIMI bleeding complications [16]. TIMI major bleeding was defined as intracranial bleeding or overt

bleeding with a decrease in haemoglobin ≥5 g/dL. TIMI minor bleeding was defined as observed bleeding with decrease in haemoglobin ≥3 to <5 g/dL.

Individualization of dual antiplatelet therapy

Individualization of ADP receptor blocker treatment was performed according to the algorithm presented in Figure 1. After an initial clopidogrel loading dose of 600 mg, on-treatment platelet reactivity was measured the next day by MEA, at the earliest after 12 hours and at the latest at the time of diagnostic angiography. HPR was defined as ≥50 U ADP-induced aggregation. This cut-off represents the mean of published data from Sibbing and our group [13, 14]. From November 2008 to May 2009, patients with HPR were reloaded with clopidogrel 600 mg up to three times according to the Bonello protocol [4]. After prasugrel [17] became available in June 2009, HPR to clopidogrel was treated with prasugrel (Efient/Effient®) loading, depending on the degree of the residual ADP-induced platelet reactivity. Cases where ADP >80 U received 60 mg, ADP 60–79 U 30 mg, and ADP 50–59 U 10 mg of prasugrel. In patients older than 75 years or weighing less than 60 kg, the maintenance dose (MD) of prasugrel was reduced to 5 mg according to the manufacturer's specification, with MEA testing 1 week later and dose adjustments if necessary. In cases of contraindications to prasugrel (history of stroke), clopidogrel reloadings were performed, until ticagrelor (Brilique/Brilinta®) became available. STEMI patients younger than 75 years and weighing more than 60 kg without history of stroke were primarily loaded with 60 mg prasugrel due to the local standard operating procedure of the Viennese STEMI network. After ticagrelor [18] became available in March 2011, HPR to prasugrel and HPR to clopidogrel in patients with contraindications to prasugrel were treated with 180 mg ticagrelor loading. In cases of contraindications to ticagrelor (history of intracranial

haemorrhage), clopidogrel reloadings were performed. Special care was taken to limit the possibility of HPR at the time of PCI by clopidogrel loading at least 12 hours prior to PCI, with reloading if necessary either prior PCI in case MEA testing was already known, or the latest 1–2 hours after PCI. In case no oral ADP receptor blocker loading, or only within 4–6 hours pre-PCI was given [e.g., STEMI or urgent invasive non-STEMI (NSTEMI) patients], bolus-only administration of a glycoprotein IIbIIIa inhibitor (GPI) was performed [intracoronary (i.c.) abciximab (0.25 mg/kg; Reopro®) or i.v. eptifibatide (180 µg/kg, Integrilin®)]. Thereafter, serial MEA measurements were performed up to 7 days to allow determination of the level of oral ADP receptor inhibition. Details of this blocking and bridging strategy have been published previously [19]. At discharge all patients should be within the therapeutic range of platelet inhibition (i.e., no-HPR).

Individualization of ASA treatment was conducted as follows. Stable patients without chronic ASA treatment were loaded with 300 mg ASA p.o. the day before angiography. ACS patients were loaded with ASA i.v.: 500 mg was used in ASA naïve patients and 250 mg was used in cases of chronic ASA treatment. HPR to ASA was defined as >35 U AA-induced aggregation. This cut-off represents a mean derived from published data (12, 20) and the MEA manufacturer's recommendations. ASA reloading was performed with either 300 mg p.o or 250 mg i.v. In cases of HPR to both ADP and ASA, first ADP receptor blocker reloading was performed with ASA reloading if necessary after MEA testing the next day.

PCI was performed according to current standard guidelines. The type of stent implanted was at the discretion of the interventional cardiologist. In cases of drug eluting stent (DES) implantation, only 2nd generation DES were used (Biolimus-eluting: Biomatrix™; Everolimus-eluting: Promus Element™ and Xience™; Zotarolimus-eluting: Resolute™). All patients

received 100 IU/kg of unfractionated heparin, with adjustments according to measurements of activated clotting time, except in cases of GPI bolus administration where only 70 IU/kg were given.

Impedance aggregometry

Whole blood aggregation was determined using MEA, a new-generation impedance aggregometer (Multiplate™ Analyzer, Roche, Munich, Germany). The system detects the electrical impedance change due to the adhesion and aggregation of platelets on two independent electrode-set surfaces in the test cuvette, with a low rate of intra-and interassay variability [21]. ADP and AA were used as agonists. A 1:2 dilution of whole blood anticoagulated with hirudin and 0.9% NaCl was stirred at 37°C for 3 min in the test cuvette. ADP (6.4 µM) and AA (0.5 mM) were added, and the increase in electrical impedance was continuously recorded for 6 min. The mean values of the two independent determinations were expressed as the area under the curve (AUC) of the aggregation tracing. AUC is reported herein in units (U), as described previously [22].

Statistical analysis

Data are expressed as mean ± standard deviation (SD). Statistical comparisons were performed with the Mann Whitney U test, the paired and unpaired Student t-test and chi-squared test. COX regression analysis was performed to compare the event rates between the no-HPR group and the individualized treatment group, and was adjusted for gender, body mass index, diabetes, hyperlipidemia, use of calcium channel blockers (CCB) and proton pump inhibitors (PPI), clinical presentation, platelet count and cardiogenic shock. All statistical calculations were performed using commercially available statistics analysis software (SPSS Version 21; Chicago).

Sample size

We estimated that the sample size of 1008 patients would provide 80% power to demonstrate a reduction in the incidence of ST by individualization of antiplatelet therapy, on the basis of assumptions of ST rates during one month follow-up. We expected a 0.2% rate of ST at 1 month in patients without HPR, as compared to a 1.9% rate in a historical group of patients with HPR [3, 5, 13]. Thus, if the hazard ratio (HR) for ST was 3.0–4.0-fold lower in patients without HPR than in those with HPR (3), the study would have more than 80% power to demonstrate that individualized antiplatelet therapy in patients with HPR reduces the rate of ST.

Results

Patient inclusion and baseline characteristics

Of 1043 consecutive PCI patients, only those with unsuccessful reopening of a chronic total occlusion or with conventional balloon-only PCI were excluded (n=35), leaving 1008 participants (Figure 2). At 30 days, one patient (0.09%), a French tourist, was lost to follow-up. Table 1 shows the demographic variables of our patient cohort and differences between the group without HPR after clopidogrel loading (no-HPR) and the individualized group (i.e., ADP receptor blocker reloading and primary prasugrel or ticagrelor loading).

Table 1 **Baseline characteristics**

	Total (n=1008)	**No-HPR** (n=665; 66%)	**Individualized** (n=343; 34%)	
Age	65±12	65±12	64±12	ns
Women	303 (30%)	183 (28%)	120 (35%)	0.01
Body Mass Index (kg/m^2)	28±5	28±5	29±5	0.001
Diabetes	321 (32%)	196 (30%)	125 (36%)	0.03
Insulin treatment	84 (8%)	41 (6%)	43 (13%)	0.001
Oral medication	237 (24%)	155 (23%)	82 (24%)	ns

Smoker	504 (50%)	334 (50%)	170 (50%)	ns
Hypertension	842 (84%)	557 (84%)	285 (83%)	ns
Hyperlipidemia	855 (85%)	552 (83%)	303 (88%)	0.03
Family history	272 (27%)	181 (27%)	91 (27%)	ns
History of myocardial infarction	212 (21%)	139 (21%)	73 (21%)	ns
History of PCI	190 (19%)	130 (20%)	60 (18%)	ns
History of CABG	60 (6%)	42 (6%)	18 (5%)	ns
Cerebrovascular disease	115 (11%)	71 (11%)	44 (13%)	ns
Peripheral vascular disease	133 (13%)	92 (14%)	41 (12%)	ns
Clinical presentation				<0.001
STEMI	93 (9%)	31 (5%)	62 (18%)	
NSTE-ACS	447 (44%)	304 (46%)	143 (41%)	
NSTEMI	393 (39%)	261 (39%)	132 (38%)	
Unstable Angina	54 (5%)	43 (7%)	11 (3%)	
Stable angina	468 (47%)	330 (50%)	138 (41%)	
Cardiogenic shock	26 (3%)	8 (1%)	18 (5%)	<0.001
Platelet count x10^3/µl	251±81	239±74	276±88	<0.001
Co-medication				
Statin	929 (92%)	612 (92%)	317 (92%)	ns
Proton pump inhibitor	649 (64%)	397 (60%)	252 (74%)	<0.001
Calcium channel blocker	195 (19%)	116 (17%)	79 (23%)	0.03
Betablocker	771 (77%)	515 (77%)	256 (75%)	ns
ACE-I/ARB	764 (76%)	494 (74%)	270 (79%)	ns

Patients in the individualized group were more frequently of female gender (p=0.01), had higher bodyweight (p=0.001), and a greater incidence of diabetes (p=0.003), especially insulin dependent (p=0.001), STEMI and cardiogenic shock (p<0.001). Higher platelet counts (p<0.001), and co-medication with PPI (p<0.001) and CCB (p=0.03), were also significantly associated with individualization of DAPT.

Angiographic and interventional details

Table 2 shows angiographic and procedural characteristics according to platelet inhibition (no-HPR versus individualized group).

Table 2	Angiographic and interventional details			
	Total (n=1008)	**No-HPR** (n=665; 66%)	**Individualized** (n=343; 34%)	**p**
Type of intervention				ns
Stent	1000 (99%)	661 (99%)	339 (99%)	
Drug Eluting	948 (94%)	625 (94%)	323 (94%)	
Bare Metal	52 (5%)	36 (5%)	16 (5%)	
Balloon (Drug Eluting)	8 (1%)	4 (1%)	4 (1%)	
Access site				ns
femoral	867 (86%)	571 (86%)	296 (86%)	
radial	117 (12%)	77 (12%)	40 (12%)	
both	24 (2%)	17 (2%)	7 (2%)	
Lesion location				ns
Left Main	114 (11%)	78 (12%)	36 (11%)	
Left anterior descending	585 (58%)	391 (59%)	194 (57%)	
Left circumflex	401 (40%)	277 (42%)	124 (36%)	
Right coronary artery	443 (44%)	285 (43%)	158 (46%)	
Bypass graft	18 (2%)	12 (2%)	6 (2%)	
AHA/ACC Type b2/c	739 (73%)	490 (74%)	249 (73%)	ns
Stent length total (mm; range)	43±33 (8–241)	44±32 (8–241)	43±33 (8–217)	ns
Stents/patient (range)	2.2±1.5 (1–12)	2.2±1.5 (1–12)	2.1±1.6 (1–12)	ns
Multivessel disease	655 (65%)	428 (64%)	227 (66%)	ns

The rate of DES implantation was high (94%), and of these 20% were biolimus-eluting, 49% everolimus-eluting and 25% zotarolimus-eluting. Multivessel disease was present in 65% of patients, with a high proportion of complex lesion morphology (Type b2/c: 73%), including 11% left main and 58% left anterior descending artery lesions, resulting in 2.2±1.5 implanted stents/patient (mean stent length 43±33 mm). The rate of use of a femoral access site for PCI during the registry period was high (86%). All parameters showed no differences between groups.

Primary ADP receptor blocker loading and individualization of ADP receptor blocker therapy.

As shown in Figure 3A, 94.8% of patients were primarily loaded with 600 mg clopidogrel, 5% with 60 mg prasugrel (STEMI patients <75 years and >60 kg without history of stroke) and 0.2% with 180 mg ticagrelor (known clopidogrel allergy). Of the clopidogrel loaded patients, 30% showed HPR. Clopidogrel reloadings of 600 mg were performed up to three times in 27% of patients with HPR, leaving five patients with persisting HPR, of whom three were finally switched to prasugrel during the observation period, as it became available. Prasugrel reloading was performed in 70% of patients with HPR. Of the prasugrel loaded patients, 2% showed HPR, which was successfully treated with ticagrelor reloading; this was also performed in 3% of patients with HPR to clopidogrel and contraindications to prasugrel. Only three patients remained in HPR during the observation period, and were put on a higher MD (two on clopidogrel 150 mg, one on prasugrel 20 mg as ticagrelor was not yet available). For patients older than 75 years or weighing less than 60 kg, prasugrel 5 mg was primarily prescribed (15% of prasugrel patients, n=37). After MEA testing 1 week later, 14% (n=5) were switched to 10 mg.

ASA-dependent platelet aggregation and reloading

After ASA and ADP receptor blocker loading, 9% of our patients showed a HPR to AA-induced aggregation (68±28 U vs. 16±8 U; p<0.001). As shown in Figure 3B, HPR to AA was significantly more prevalent in patients with HPR to ADP (22% vs. 4%; p<0.001). HPR to AA without HPR to ADP (63±29 U) was treated by ASA reloading successfully in all patients (14±6 U; p<0.001). In patients with HPR to ADP, the HPR to AA was influenced by the extent of the residual AA-induced platelet aggregation, as follows. In patients with intermediate HPR to

AA (<60 U), only ADP receptor blocker reloading was sufficient to treat HPR to AA as well (from 45±7 U to 15±10 U; p<0.001). In patients with high HPR to AA (≥60 U) an additional ASA reloading was necessary to significantly reduce AA-induced aggregation from 92±21 U to 20±16 U (p<0.001). Six of these patients showed persisting HPR to AA and were discharged on 300 mg ASA.

Platelet aggregation in clopidogrel and prasugrel loaded patients and effect of reloading.

ADP-induced aggregation after 600 mg clopidogrel loading was significantly higher in patients with HPR (= non-responder: 73±19 U) than without (= responder: 28±11 U; p<0.001) (Figure 4A). Reloading effectively treated HPR (22±12 U; p<0.001), except in two patients for whom prasugrel was not yet available. ADP-induced aggregation after 60 mg prasugrel loading was significantly higher in patients with HPR (= non-responder: 82±26 U) than without (= responder: 19±10 U; p<0.001), and was successfully treated with ticagrelor reloading (34±15 U; p=0.02) (Figure 4B).

Glycoprotein IIbIIIa inhibitor (GPI) treatment

GPI was given to 61% (n=57) of STEMI patients, with an i.c. abciximab bolus only in 91% (n=52) and an i.v. eptifibatide bolus only in 9% (n=5). Non-STEMI (NSTEMI) patients received a GPI treatment in 11% (n=47) of cases, with an i.c. abciximab bolus only in 72% (n=34) and an i.v. eptifibatide bolus only in 28% (n=13).

Clinical outcome at 30 days

Table 3 shows the clinical outcome of the overall patient cohort.

Table 3	**Thirty day clinical outcome**			
	Total	**No-HPR**	**Individualized**	**HR (95%CI) p**

Overall cohort	1007	664 (66%)	343 (34%)	
Cardiovascular Death	18 (1.8%)	9 (1.4%)	9 (2.6%)	0.67 (0.23–2.03) 0.5
non-shock	8 (0.8%)	4 (0.6%)	4 (1.2%)	
cardiogenic shock (n=shock patients;% of shock)	10 (26; 38%)	5 (8; 62%)	5 (18; 28%)	
Myocardial Infarction	1 (0.09%)	1 (0.15%)	0 (0%)	0.00 (0.00–1.38) 0.972
Stent thrombosis				
definite and probable	3 (0.29%)	3 (0.45%)	0 (0%)	0.00 (0.00–5.71) 0.966
definite	1 (0.09%)	1 (0.15%)	0 (0%)	
probable	2 (0.19%)	2 (0.3%)	0 (0%)	
Bleeding				
TIMI major and minor	26 (2.6%)	17 (2.6%)	9 (2.6%)	0.78 (0.33–1.85) 0.574
TIMI major	10 (1.0%)	6 (0.9%)	4 (1.2%)	
TIMI minor	16 (1.6%)	11 (1.7%)	5 (1.5%)	
Type				
Instrumented	14 (1.4%)	10 (1.5%)	4 (1.2%)	
Spontaneous	12 (1.2%)	7 (1.1%)	5 (1.5%)	

Only one definite ST, which also accounted for the only myocardial infarction, occurred within 30 days (0.09%). This patient had multivessel PCI for NSTEMI, and developed diarrhea and Gram negative sepsis. On the seventh day post PCI, an attempted resuscitation was unsuccessful. Acute thrombosis of the circumflex artery stent was confirmed at autopsy. Two sudden deaths without autopsy occurred after discharge in NSTEMI patients, which have been classified as probable ST according to the ARC criteria. However, both patients also suffered from ischemic cardiomyopathy, which would suggest a primary rhythmogenic cause for their sudden deaths. Cardiovascular death (n=18; 1.8%) was primarily due to cardiogenic shock (88%), without differences in groups [HR 0.67 (0.23–2.03); p=0.5]. Concerning bleeding complications, no increase in individualized patients occurred [HR 0.78 (0.33–1.85); p=0.574]. Slightly more than half of the bleeding complications (54%, n=14) were related to the access site ("instrumented"), requiring surgical intervention in three

cases (21% of instrumented complications; 0.3% of patients). The majority of spontaneous bleeding complications were gastrointestinal (67%, n=8). One intracranial haemorrhage occurred under standard DAPT with clopidogrel 17 days after PCI for NSTEMI in an 86 year old patient.

Table 4 shows 30-day outcomes for the STEMI-, NSTE-ACS- and stable CAD cohorts.

Table 4 **Thirty day clinical outcome of clinical subgroups**

	Total	No-HPR	Individualized	HR (95%CI) p
STEMI cohort	93	31 (33%)	62 (67%)	
Cardiovascular Death	8 (8.6%)	4 (12.9%)	4 (6.5%)	0.16 (0.62–0.91) 0.04
non-shock	1 (1.1%)	1 (3.2%)	0 (0%)	
cardiogenic shock (n=shock patients;% of shock)	7 (17; 41%)	3 (6; 50%)	4 (11; 36%)	
Myocardial Infarction	0 (0%)	0 (0%)	0 (0%)	
Stent thrombosis				
definite	0 (0%)	0 (0%)	0 (0%)	
probable	0 (0%)	0 (0%)	0 (0%)	
Bleeding				
TIMI major and minor	6 (6.5%)	3 (9.7%)	3 (4.8%)	0.59 (0.10–3.42) 0.55
TIMI major	4 (4.3%)	2 (6.5%)	2 (3.2%)	
TIMI minor	2 (2.2%)	1 (3.2%)	1 (1.6%)	
Type				
Instrumented	5 (5.4%)	3 (9.7%)	2 (3.2%)	
Spontaneous	1 (1.1%)	0 (0%)	1 (1.6%)	
NSTE-ACS cohort	446	303 (68%)	143 (32%)	
Cardiovascular Death	10 (2.2%)	5 (1.7%)	5 (3.5%)	1.33 (0.33–5.26) 0.69
non-shock	7 (1.6%)	3 (1.0%)	4 (2.8%)	
cardiogenic shock (n=shock patients;% of shock)	3 (9; 33%)	2 (2; 100%)	1 (7; 14%)	
Myocardial Infarction	1 (0.2%)	1 (0.3%)	0 (0%)	0.00 (0–4.89E+261) 0.97

Stent thrombosis				
definite	1 (0.2%)	1 (0.3%)	0 (0%)	
probable	2 (0.4%)	2 (0.7%)	0 (0%)	
Bleeding				
TIMI major and minor	13 (2.9%)	9 (3.0%)	4 (2.8%)	0.58 (0.15–2.21) 0.42
TIMI major	4 (0.9%)	2 (0.7%)	2 (1.4%)	
TIMI minor	9 (2.0%)	7 (2.3%)	2 (1.4%)	
Type				
Instrumented	5 (1.1%)	4 (1.3%)	1 (0.7%)	
Spontaneous	8 (1.8%)	5 (1.7%)	3 (2.1%)	
Stable CAD cohort	468	330 (70%)	138 (30%)	
Cardiovascular Death	0 (0%)	0 (0%)	0 (0%)	
Myocardial Infarction	0 (0%)	0 (0%)	0 (0%)	
Stent thrombosis				
definite	0 (0%)	0 (0%)	0 (0%)	
probable	0 (0%)	0 (0%)	0 (0%)	
Bleeding				
TIMI major and minor	7 (1.5%)	5 (1.5%)	2 (1.4%)	0.99 (0.17–5.94) 0.99
TIMI major	2 (0.4%)	2 (0.6%)	0 (0%)	
TIMI minor	5 (1.1%)	3 (0.9%)	2 (1.4%)	
Type				
Instrumented	4 (0.8%)	3 (0.9%)	1 (0.7%)	
Spontaneous	3 (0.6%)	2 (0.6%)	1 (0.7%)	

No ischemic event occurred either in the STEMI cohort, with a required high rate of individualization (67%), or in the stable CAD cohort, with a sufficient lower rate of individualization (30%). The safety endpoint of combined TIMI major and minor bleeding risk was 2× higher in NSTE-ACS patients and 4× higher in STEMI patients than in stable CAD patients (2.9% vs. 6.5% vs. 1.5%; p=0.02), without an increase associated with individualization in any subgroup.

Discussion

The main findings of our study are as follows. Firstly, routine efficient peri-interventional individualization of DAPT with MEA, incorporating the newer generations of ADP receptor blocker (prasugrel and ticagrelor), is able to minimize early ischemic events after PCI in an all-comers population including STEMI patients by nearly abolishing early definite stent thrombosis as compared to the historical group. Secondly, intensifying platelet inhibition in patients with HPR does not increase bleeding complications compared to patients without HPR under DAPT. Thirdly, there is indirect evidence for synergistic roles of ADP- and ASA-dependent platelet activation.

For the interpretation of the very low ischemic complication rate observed during the 30 days after PCI, the most recent literature on the incidence of real world early ST in PCI for all-comers [23] and STEMI patients [24,25], as well as the complication rate in the randomized CHAMPION Phoenix trial [11], should be considered. We could show that adjusting the level of platelet inhibition reduced the rate of early definite ST to 0.09%, which is about 7-fold lower than observed in PCI for all-comers [23] and about 25- to 35-fold lower than in primary PCI for STEMI [24, 25], even with contemporary 2nd generation DES. Monitored intensification of platelet inhibition by bolus-only administration of GPI and individualized DAPT resulted in a yet more favourable outcome in our STEMI population, as no early thrombotic events occurred. Furthermore, even under randomized study conditions like the CHAMPION Phoenix trial [11], the definite ST rate after clopidogrel loading was 1.4% within 48 hours, or about 14-fold higher than in our study. Immediate ADP receptor blockade with cangrelor, however, showed a benefit with reduction to 0.8% (p=0.01), which is still about 8-fold higher than what achieved with our individualization protocol. In addition, ischemic complications were not only not driven by urgent ACS patients (4.1%), but were also

numerically higher in stable CAD (7.4%). By contrast, individualization of DAPT in our stable CAD cohort, with 600 mg clopidogrel loading the day before PCI and MEA guided individualization (the latest within 2 hours after PCI), resulted in no early ischemic events. As the "first do no harm" principle should be generally applied, optimization of platelet inhibition at the time of PCI seems also of importance in this patient population, thus questioning the negative recommendation on the role of platelet function testing in stable CAD patients [2].

Three randomized multicenter trials [7-9] failed to show a clinical benefit of individualizing DAPT with the VerifyNow™ assay. Among the most common raised limitations, those in study design, protocol implementation and efficacy of platelet inhibition are the most important. Concerning study design, the late randomization of patients, more than 12 hours after PCI, in GRAVITAS [7] and TRIGGER-PCI [9] excluded acute procedural complications attributable to insufficient platelet inhibition. This occurred even in stable CAD patients, as impressively shown in CHAMPION Phoenix [11]. Concerning protocol implementation, the ARCTIC trial [8] discharged 1.3% of patients in the active study arm without any ADP receptor blocker medication, and lost nearly 9% of patients to follow-up. TRIGGER-PCI [9] was stopped prematurely, leaving an underpowered study population. Concerning efficacy of platelet inhibition, 40% of patients in GRAVITAS [7] and 16% in ARCTIC [8] remained in HPR due to primary reloading with clopidogrel (100% in GRAVITAS and 90% in ARCTIC). By contrast, 100% of our patients were included prior to PCI and discharged with DAPT, 99.9% could be followed at 30 days and only 0.3% remained in HPR. Together, this resulted in a 1.7-fold lower rate of ST (definite and probable) than in the high dose clopidogrel arm of

GRAVITAS [7] and a 3.5-fold lower rate than in the monitored arm of ARCTIC [8], despite our higher risk population, including STEMI patients.

Concerning bleeding complications, our concept of using the newer generations of ADP receptor blockers, primarily for intensifying platelet inhibition in patients with HPR to clopidogrel rather than upfront for all ACS patients without contraindications, seems beneficial. In contrast to TRITON [17] and PLATO [18], which featured significantly increased non-CABG related bleeding rates under prasugrel and ticagrelor, no increased bleeding occurred in the individualized patients compared to those on clopidogrel without HPR. The observed 1.5% TIMI major bleeding rate in our ACS cohort compares favourably to the non-CABG related TIMI major bleeding rates in the clopidogrel arms of TRITON (1.8%) and PLATO (2.2%). Furthermore, even in the highest bleeding risk group, the STEMI patients, our blocking and bridging strategy with GPI bolus-only administration resulted in fewer TIMI major and minor bleeds (6.4%) than in the GPI arm with bolus and infusion (9.6%) of the HORIZON AMI trial [26]. Although our number of patients is admittedly far too low to draw this conclusion, GPI bolus-only administration seems suggestively comparable to the bivalirudin arm (5.9%).

Concerning the regulation of platelet activation, it is already known that thrombin- (via the protease activated receptor-1) and ADP- (via the $P2Y_{12}$ receptor) mediated platelet activation play a synergistic role in hemostasis and thrombosis [19, 27, 28]. Herein, we provide indirect evidence for a synergistic role of ADP- and ASA- (cyclooxygenase) dependent platelet activation. We observed an interplay between AA- and ADP- induced platelet aggregability, as HPR to AA was significantly associated with HPR to ADP, and

solitary reloading with ADP receptor blocker in patients with HPR to ADP and AA was able to successfully resolve intermediate levels of HPR to AA without ASA reloading.

Limitations of our study include primarily the observational, non-randomized nature of the registry without a control group concerning efficacy, and the monocentric design.

In conclusion, our data strongly suggest that HPR represents a modifiable risk factor that can be used for tailoring treatment in PCI patients, rather than a marker of higher risk only. Effective individualization of DAPT for PCI under MEA guidance is able to minimize early ischemic complications to a so far unreported degree. Further properly designed randomized multicenter trials utilizing MEA seem warranted.

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Contributorship statement

G. Christ: concept and design, analysis and interpretation of data; writing; JM Siller-Matula: analysis and interpretation of data; revising the intellectual content, critical writing; M. Francesconi: concept and design, C. Dechant: analysis and interpretation of data, K. Grohs: analysis of data and revising the intellectual content, A. Podczeck-Schweighofer: revising the intellectual content

Data sharing statement:

No additional data available

Disclosures

None

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Figures

Figure 1: Algorithm of ADP receptor blocker treatment

ADP = adenosine diphosphate, CAD = coronary artery disease, GPI = glycoprotein IIbIIIa inhibitor, MEA = multiple electrode aggregometry, NSTE-ACS = non-ST-elevation acute coronary syndrome, STEMI = ST-elevation myocardial infarction.

* loading in stable patients the day before angiography; ** platelet testing not earlier than 12 hours after loading, and at the latest at the time of diagnostic angiography, after GPI administration serial testing up to 7 days; *** platelet testing the day after angiography; **** platelet testing 1 week after starting 5 mg prasugrel; # up to three clopidogrel reloadings; ## prasugrel reloading dependent on residual reactivity: ADP >80: 60 mg, ADP 60–79: 30 mg, ADP 50–59: 10mg; ### in patients <60 kg and/or >75 years

Figure 2: Flow chart of study patients

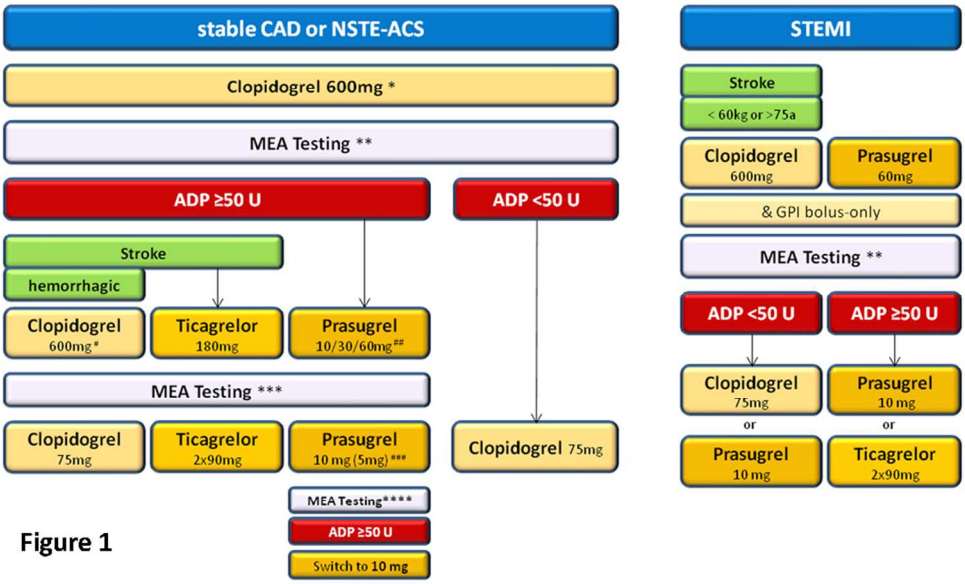
CTO = chronic total occlusion, PCI = percutaneous coronary intervention

Figure 3: Flow chart of primary ADP receptor blocker and ASA loading and reloading

A) ADP receptor blocker loading. Only 0.3% of patients (n=3) showed persisting HPR to ADP (≥50 U): two patients after 4 × 600 mg clopidogrel loading (as prasugrel was not yet available) and one patient on prasugrel (as ticagrelor was not yet available). B) HPR to AA-induced aggregation (>35 U) occurred to a significant higher proportion in patients with HPR to ADP (ADP ≥50 U). In patients with HPR to ADP and intermediate HPR to AA (AA <60 U) only ADP receptor blocker reloading successfully treated also HPR to AA. AA = Arachidonic Acid, ADP = adenosine diphosphate, ASA = acetylic salicylic acid.

Figure 4: ADP-induced aggregation after 600 mg Clopidogrel or 60 mg Prasugrel loading and effect of reloading

A) Of clopidogrel loaded patients, 30% showed a high on-treatment platelet reactivity (= non-responder), effectively treated by reloading (except for two patients as prasugrel and ticagrelor had not yet been available). B) Of prasugrel loaded patients, 2% showed a high on-treatment platelet reactivity (= non-responder), effectively treated by ticagrelor.



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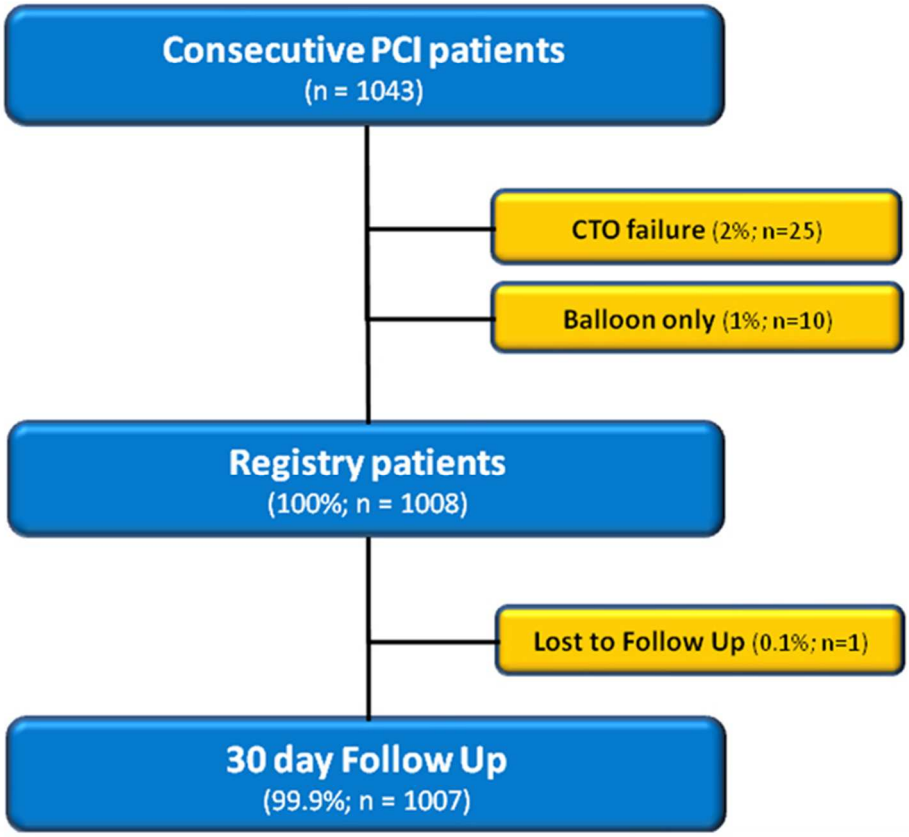

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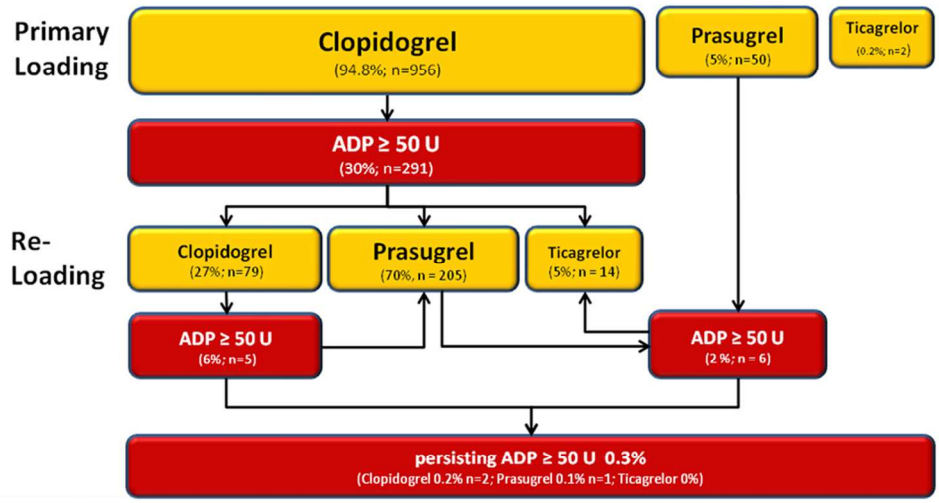

Figure 3A

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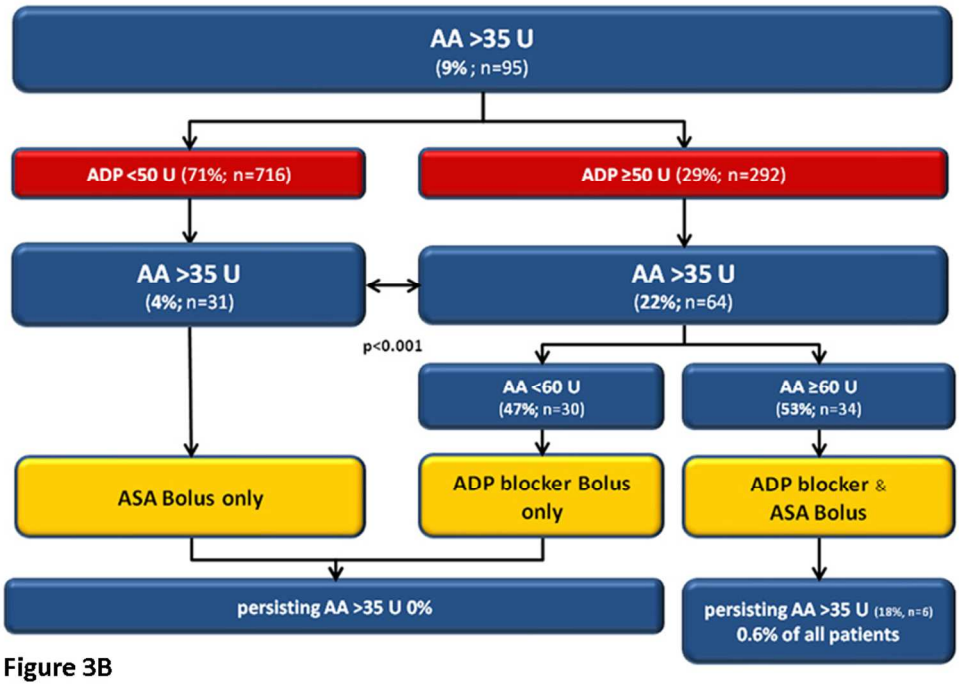

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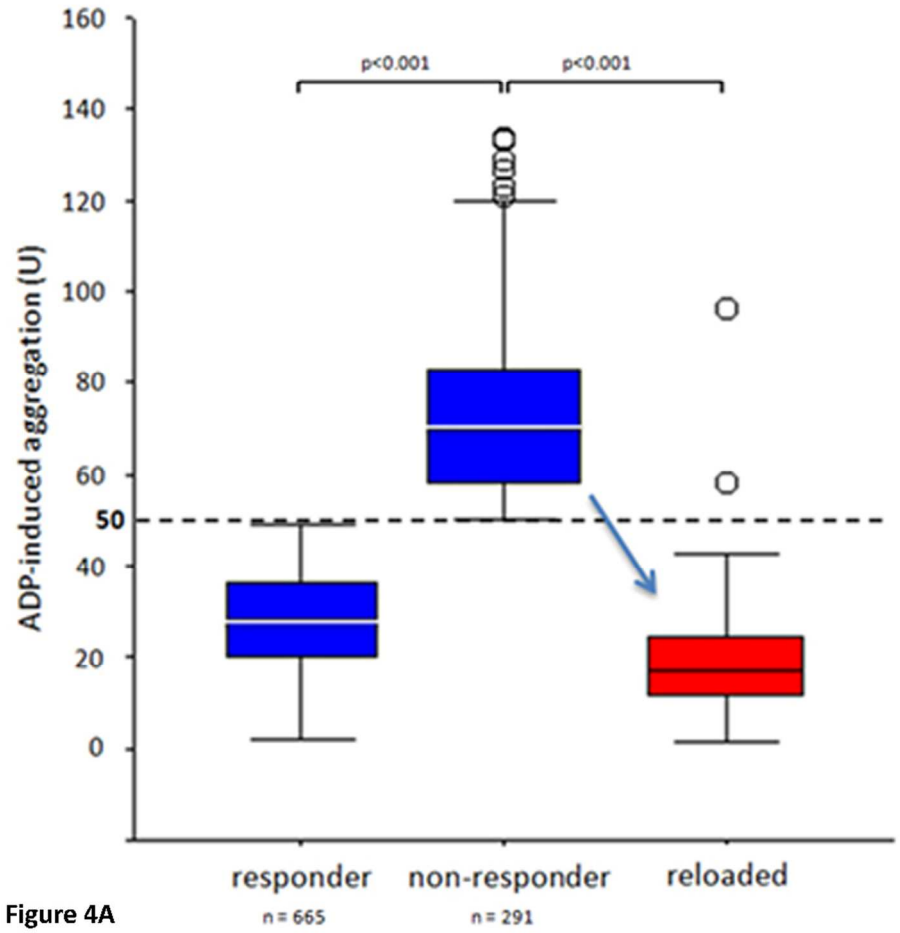

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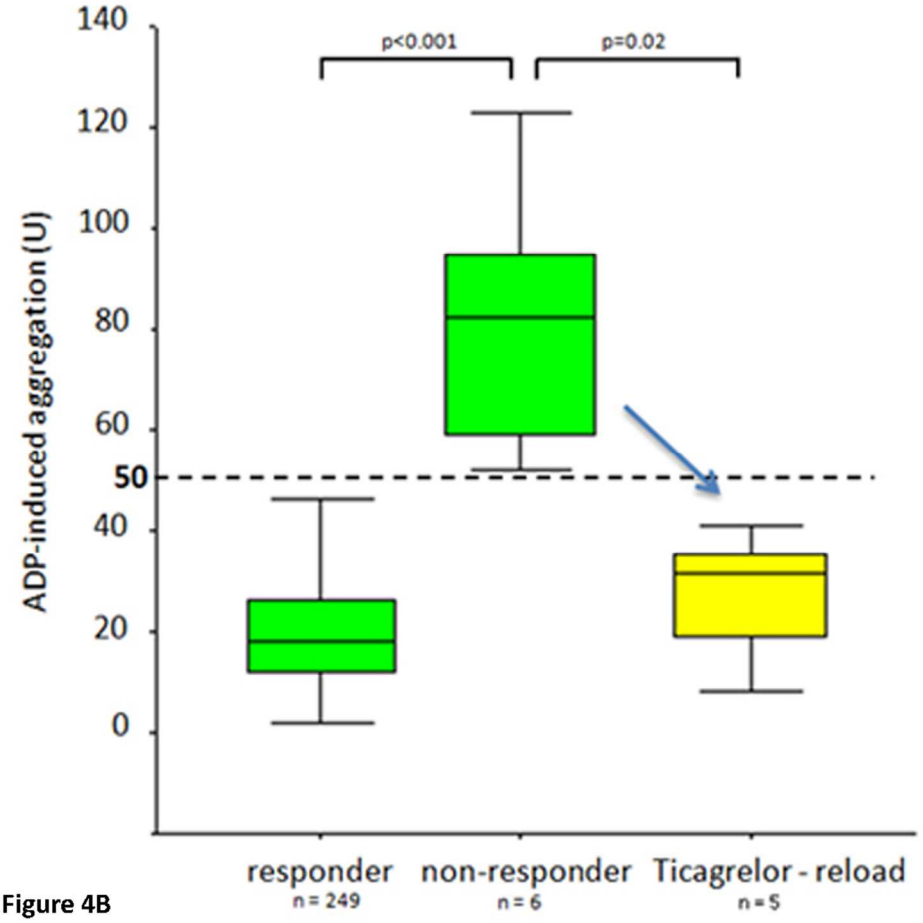

Figure 4B

Figure 4: ADP-induced aggregation after 600 mg Clopidogrel or 60 mg Prasugrel loading and effect of reloading B) Of prasugrel loaded patients, 2% showed a high on-treatment platelet reactivity (= non-responder), effectively treated by ticagrelor.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*11*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**:1453-7

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Individualizing Dual Antiplatelet Therapy after Percutaneous Coronary Intervention: The IDEAL-PCI Registry.

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Keywords:	Adult cardiology < CARDIOLOGY, Coronary heart disease < CARDIOLOGY, Coronary intervention < CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY

Individualizing Dual Antiplatelet Therapy after Percutaneous Coronary Intervention: The IDEAL-PCI Registry.

Günter Christ* MD, Jolanta M. Siller-Matula† MD PhD, Marcel Francesconi* MD, Cornelia Dechant* MD, Katharina Grohs‡ MD and Andrea Podczeck-Schweighofer* MD

* 5th Medical Department with Cardiology, Kaiser Franz Josef Hospital, Vienna, Austria

† Department of Cardiology, Medical University of Vienna, Austria

‡ Clinical Institute for Laboratory Medicine, Kaiser Franz Josef Hospital, Vienna, Austria

Correspondence: Prof. Günter Christ, MD

5th Medical Department with Cardiology, Kaiser Franz Josef Hospital

Kundratstr. 3, 1100 Vienna, Austria

Tel.: +43-1-60191-2508

Fax: +43-1-60191-2509

E-mail: guenter.christ@wienkav.at

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Abstract

Objective: To evaluate the clinical utility of individualizing dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) in an all-comers population, including ST-elevation myocardial infarction (STEMI) patients.

Setting: Tertiary care single centre registry

Participants: 1008 consecutive PCI patients with stent implantation, without exclusion criteria.

Intervention: Periinterventional individualization of DAPT, guided by multiple electrode aggregometry (MEA), to overcome high on-treatment platelet reactivity (HPR) to adenosine diphosphate (ADP)- (≥50 U) and arachidonic acid (AA)-induced aggregation (>35 U).

Outcome measures: The primary efficacy endpoint was definite stent thrombosis (ST) at 30 days. The primary safety endpoint was TIMI major and minor bleeding. Secondary endpoints were probable ST, myocardial infarction, cardiovascular death and the combined endpoint major cardiac adverse event (MACE).

Results: 53% of patients presented with acute coronary syndrome (9% STEMI, 44% non-ST-elevation). HPR to ADP after 600 mg clopidogrel loading occurred in 30% of patients (73±19 U vs. 28±11 U; p<0.001) and was treated by prasugrel or ticagrelor (73%) or clopidogrel (27%) reloading (22±12 U; p<0.001). HPR to ADP after prasugrel loading occurred in 2% of patients (82±26 U vs. 19±10 U; p<0.001) and was treated with ticagrelor (34±15 U; p=0.02). HPR to AA occurred in 9% of patients with a significant higher proportion in patients with HPR to ADP (22% vs. 4%, p<0.001) and was treated with aspirin reloading. Definite ST occurred in 0.09% of patients (n=1); probable ST, myocardial infarction, cardiovascular death and MACE occurred in 0.19% (n=2), 0.09% (n=1) and 1.8% (n=18) of patients. TIMI major and

minor bleeding did not differ between patients without HPR and individualized patients (2.6% for both).

Conclusions: Individualization of DAPT with MEA minimizes early thrombotic events in an all-comers PCI population to an unreported degree without increasing bleeding. A randomized multicenter trial utilizing MEA seems warranted.

Trial Registration: http://www.clinicaltrials.gov; NCT01515345

Keywords: percutaneous coronary intervention, platelet function testing, dual antiplatelet therapy

Article summary

Strengths and limitations of this study

The strengths of our study are, at first the real world percutaneous coronary intervention setting with inclusion of every consecutive patient with stent implantation, without any exclusion criteria. Second, the consequent and efficient peri-interventional individualization of dual antiplatelet therapy, leaving only 0.3% of patients on high on-treatment platelet reactivity to adenosine diphosphate at the time of hospital discharge. Third, the minimization of ischemic events within 30 days by nearly abolishing early definite stent thrombosis, without increasing bleeding complications.

Limitations of our study are the non randomised and monocentric registry design without control group concerning ischemic events.

Introduction

High on-treatment platelet reactivity (HPR) to adenosine diphosphate (ADP) represents one of the strongest independent risk factors for post-percutaneous coronary intervention

(PCI) ischemic events in patients given dual antiplatelet therapy (DAPT), according to numerous observational studies using various platelet function tests [1-3].

Whether HPR represents only a marker of higher risk or a modifiable risk factor is still a matter of debate [2], as prospective randomized trials evaluating personalized antiplatelet therapy aiming to overcome HPR resulted in conflicting data. Smaller randomized trials [4], as well as non-randomized studies [5] and a recent meta-analysis [6] suggested a significant clinical benefit, but three randomized studies failed to do so [7-9]. However, each of these trials, utilizing the VerifyNow™ assay, was afflicted with major limitations potentially masking the real value of individualizing DAPT after PCI in daily practice [1, 10]. Their low-risk population and primarily the high selection bias in GRAVITAS [7] and TRIGGER-PCI [9], with patient inclusion more than 12 hours after PCI, seems to cloud the potential importance of optimizing platelet inhibition at the time of PCI. By contrast, the very recent CHAMPION Phoenix trial [11] provides a more realistic scenario of expectable ischemic complications during and after PCI. More than 11,000 patients with oral clopidogrel loading, including the whole clinical PCI spectrum [56% stable coronary artery disease (CAD), 26% non-ST-elevation acute coronary syndrome (NSTE-ACS), 18% ST-elevation myocardial infarction (STEMI)], were pre-interventionally randomized to receive an intravenous (i.v.) bolus and infusion of cangrelor, a fast acting reversible ADP receptor blocker. Ischemic complications in the whole study cohort occurred in 5.3%, including a definite stent thrombosis (ST) rate of 1.1% during the first 48 hours. Notably, the majority of events occurred within 6 hours after PCI.

HPR to acetylic salicylic acid (ASA) is less well studied and its clinical relevance is unclear. The ADAPT-DES registry [3] found no difference in response to ASA, measured by the VerifyNow™ assay, between patients with and without ST. Data not only from our group,

however, suggested that dual HPR to both ADP- and arachidonic acid- (AA; reflecting response to ASA) induced aggregation, measured by multiple electrode aggregometry (MEA) [12] or the VerifyNow assay [13], predisposes patients to a higher ischemic risk than single HPR. Furthermore, MEA has been shown to effectively assess the risk of HPR to ADP after PCI [14] with higher accuracy than the vasodilator-stimulated phosphoprotein phosphorylation (VASP) assay [15] utilized in the Bonello studies.

Therefore, our registry aimed to evaluate the impact of individualizing DAPT with MEA in an all-comers population, including STEMI patients without exclusion criteria, by peri-interventional treatment of HPR to both ADP and AA.

Methods

Patient population

This was a prospective, single-centre cohort observation of consecutive PCI patients, including all forms of ACS (including cardiogenic shock) and all stable CAD, with stent implantation or drug eluting balloon dilatation (for treatment of instent restenosis), and without exclusion criteria (secondary causes for ACS, like anaemia had to be corrected according to standard patient care, but did not represent an exclusion criterion, nor did thrombocytopenia or liver dysfunction once the indication for an invasive approach was given). Patients without stent implantation (i.e. unsuccessful reopening of a chronic total occlusion or balloon dilatation only) were not included. Peri-interventional individualization of platelet inhibition was performed according to the protocol shown in Figure 1 and described in detail below. The local Ethics Committee approved the study protocol in accordance with the Declaration of Helsinki. Participants were included between November 2008 and June 2012. Informed consent was obtained after PCI, either from the patient or

from the guardian in cases of critically ill conditions. Follow-up information was obtained by either direct outpatient visit or telephone contact at 30 days.

Study endpoints

The primary efficacy endpoint was definite ST during a 30 days follow-up. The secondary efficacy outcome parameters were probable ST, myocardial infarction and cardiovascular death, as well as the combination of the above mentioned endpoints as major cardiac adverse events (MACE). Definite and probable ST were defined according to the Academic Research Consortium (ARC) [16]. The primary safety end point was the incidence of TIMI bleeding complications [17]. TIMI major bleeding was defined as intracranial bleeding or overt bleeding with a decrease in haemoglobin ≥5 g/dL. TIMI minor bleeding was defined as observed bleeding with decrease in haemoglobin ≥3 to <5 g/dL.

Individualization of dual antiplatelet therapy

Individualization of ADP receptor blocker treatment was performed according to the algorithm presented in Figure 1. After an initial clopidogrel loading dose of 600 mg, on-treatment platelet reactivity was measured the next day by MEA, at the earliest after 12 hours and at the latest at the time of diagnostic angiography. HPR was defined as ≥50 U ADP-induced aggregation. This cut-off represents the mean of published data from Sibbing and our group [14, 15]. From November 2008 to May 2009, patients with HPR were reloaded with clopidogrel 600 mg up to three times according to the Bonello protocol [4]. After prasugrel [18] became available in June 2009, HPR to clopidogrel was treated with prasugrel (Efient/Effient®) loading, depending on the degree of the residual ADP-induced platelet reactivity: Cases with ADP >80 U received 60 mg, ADP 60–79 U 30 mg, and ADP 50–59 U 10

mg of prasugrel. This staged approach was chosen in order to avoid potential bleeding complications due to the observed overresponse (i.e. very "flat" ADP and ASPI curves, <10-15 U) after a routine prasugrel 60mg loading in patients with borderline clopidogrel response (ADP 50-60 U). In patients older than 75 years or weighing less than 60 kg, the maintenance dose (MD) of prasugrel was reduced to 5 mg according to the manufacturer's specification, with MEA testing 1 week later and dose adjustments if necessary. In cases of contraindications to prasugrel (history of stroke), clopidogrel reloadings were performed, until ticagrelor (Brilique/Brilinta®) became available. STEMI patients younger than 75 years and weighing more than 60 kg without history of stroke were primarily loaded with 60 mg prasugrel due to the local standard operating procedure of the Viennese STEMI network. After ticagrelor [19] became available in March 2011, HPR to prasugrel and HPR to clopidogrel in patients with contraindications to prasugrel were treated with 180 mg ticagrelor loading. In cases of contraindications to ticagrelor (history of intracranial haemorrhage), clopidogrel reloadings were performed. Special care was taken to limit the possibility of HPR at the time of PCI by clopidogrel loading at least 12 hours prior to PCI, with reloading if necessary either prior PCI in case MEA testing was already known, or the latest 1–2 hours after PCI. In case no oral ADP receptor blocker loading, or only within 4–6 hours pre-PCI was given [e.g., STEMI or urgent invasive non-STEMI (NSTEMI) patients], bolus-only administration of a glycoprotein IIbIIIa inhibitor (GPI) was performed [intracoronary (i.c.) abciximab (0.25 mg/kg; Reopro®) or i.v. eptifibatide (180 µg/kg, Integrilin®)]. Thereafter, serial MEA measurements were performed up to 7 days to allow determination of the level of oral ADP receptor inhibition. Details of this blocking and bridging strategy have been

published previously [20]. At discharge all patients should be within the therapeutic range of platelet inhibition (i.e., non-HPR).

Individualization of ASA treatment was conducted as follows. Stable patients without chronic ASA treatment were loaded with 300 mg ASA p.o. the day before angiography. ACS patients were loaded with ASA i.v.: 500 mg was used in ASA naïve patients and 250 mg was used in cases of chronic ASA treatment. HPR to ASA was defined as >35 U AA-induced aggregation. This cut-off represents a mean derived from published data [12, 21] and the MEA manufacturer's recommendations. ASA reloading was performed with either 300 mg p.o or 250 mg i.v. In cases of HPR to both ADP and ASA, first ADP receptor blocker reloading was performed with ASA reloading if necessary after MEA testing the next day.

PCI was performed according to current standard guidelines. The type of stent implanted was at the discretion of the interventional cardiologist. In cases of drug eluting stent (DES) implantation, only 2nd generation DES were used (Biolimus-eluting: Biomatrix™; Everolimus-eluting: Promus Element™ and Xience™; Zotarolimus-eluting: Resolute™). All patients received 100 IU/kg of unfractionated heparin, with adjustments according to measurements of activated clotting time, except in cases of GPI bolus administration where only 70 IU/kg were given.

Impedance aggregometry

Whole blood aggregation was determined using MEA, a new-generation impedance aggregometer (Multiplate™ Analyzer, Roche, Munich, Germany). The system detects the electrical impedance change due to the adhesion and aggregation of platelets on two independent electrode-set surfaces in the test cuvette, with a low rate of intra-and interassay variability [22]. ADP and AA were used as agonists. A 1:2 dilution of whole blood

anticoagulated with hirudin and 0.9% NaCl was stirred at 37°C for 3 min in the test cuvette. ADP (6.4 µM) and AA (0.5 mM) were added, and the increase in electrical impedance was continuously recorded for 6 min. The mean values of the two independent determinations were expressed as the area under the curve (AUC) of the aggregation tracing. AUC is reported herein in units (U), as described previously [23].

Statistical analysis

Data are expressed as mean ± standard deviation (SD). Statistical comparisons were performed with the Mann Whitney U test, the paired and unpaired Student t-test and chi-squared test. COX regression analysis was performed to compare event rates between the non-HPR group and the individualized treatment group. As the power of the study was limited due to the low event rate, we provide crude and adjusted HR. The adjustment was done for gender, body mass index, diabetes, hyperlipidemia, use of calcium channel blockers (CCB) and proton pump inhibitors (PPI), clinical presentation, platelet count and cardiogenic shock. All statistical calculations were performed using commercially available statistics analysis software (SPSS Version 21; Chicago).

Sample size

We estimated that the sample size of 1008 patients would provide 80% power to demonstrate a reduction in the incidence of ST by individualization of antiplatelet therapy, on the basis of assumptions of ST rates during one month follow-up. We expected a 0.2% rate of ST at 1 month in patients without HPR, as compared to a 1.9% rate in a historical group of patients with HPR [3, 5, 14]. Thus, if the hazard ratio (HR) for ST was 3.0–4.0-fold lower in patients without HPR than in those with HPR [3], the study would have more than

80% power to demonstrate that individualized antiplatelet therapy in patients with HPR reduces the rate of ST.

Results

Patient inclusion and baseline characteristics

Of 1043 consecutive PCI patients, only those with unsuccessful reopening of a chronic total occlusion or with conventional balloon-only PCI were excluded (n=35), leaving 1008 participants (Figure 2). All STEMI patients received a primary PCI. At 30 days, one patient (0.09%), a French tourist, was lost to follow-up. Table 1 shows the demographic variables of our patient cohort and differences between the group without HPR after clopidogrel loading (non-HPR) and the individualized group (i.e., ADP receptor blocker reloading and primary prasugrel or ticagrelor loading).

Table 1 **Baseline characteristics**

	Total (n=1008)	**Non-HPR** (n=665; 66%)	**Individualized** (n=343; 34%)	
Age	64.7±11.8	65.1±11.7	63.9±11.9	ns
Women	303 (30%)	183 (28%)	120 (35%)	0.01
Body Mass Index (kg/m^2)	28.4±4.6	28.1±4.5	29.1±4.8	0.001
Diabetes	321 (32%)	196 (30%)	125 (36%)	0.03
Insulin treatment	84 (8%)	41 (6%)	43 (13%)	0.001
Oral medication	237 (24%)	155 (23%)	82 (24%)	ns
Smoker	504 (50%)	334 (50%)	170 (50%)	ns
Hypertension	842 (84%)	557 (84%)	285 (83%)	ns
Hyperlipidemia	855 (85%)	552 (83%)	303 (88%)	0.03
Family history	272 (27%)	181 (27%)	91 (27%)	ns
History of myocardial infarction	212 (21%)	139 (21%)	73 (21%)	ns
History of PCI	190 (19%)	130 (20%)	60 (18%)	ns
History of CABG	60 (6%)	42 (6%)	18 (5%)	ns
Cerebrovascular disease	115 (11%)	71 (11%)	44 (13%)	ns
Peripheral vascular disease	133 (13%)	92 (14%)	41 (12%)	ns

Clinical presentation				<0.001
STEMI	93 (9%)	31 (5%)	62 (18%)	
NSTE-ACS	447 (44%)	304 (46%)	143 (41%)	
NSTEMI	393 (39%)	261 (39%)	132 (38%)	
Unstable Angina	54 (5%)	43 (7%)	11 (3%)	
Stable angina	468 (47%)	330 (50%)	138 (41%)	
Cardiogenic shock	26 (3%)	8 (1%)	18 (5%)	<0.001
Platelet count x10^3/µl	251±81	239±74	276±88	<0.001
Co-medication				
Statin	929 (92%)	612 (92%)	317 (92%)	ns
Proton pump inhibitor	649 (64%)	397 (60%)	252 (74%)	<0.001
Calcium channel blocker	195 (19%)	116 (17%)	79 (23%)	0.03
Betablocker	771 (77%)	515 (77%)	256 (75%)	ns
ACE-I/ARB	764 (76%)	494 (74%)	270 (79%)	ns

(ACE-I = Angiotensin converting enzyme inhibitor; ARB = Angiotensin receptor blocker; CABG = coronary artery bypass graft; HPR = high on-treatment platelet reactivity; NSTE-ACS = Non ST-elevation acute coronary syndrome; NSTEMI = Non ST-Elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction)

Patients in the individualized group were more frequently of female gender (p=0.01), had higher bodyweight (p=0.001), and a greater incidence of diabetes (p=0.003), especially insulin dependent (p=0.001), STEMI and cardiogenic shock (p<0.001). Higher platelet counts (p<0.001), and co-medication with PPI (p<0.001) and CCB (p=0.03), were also significantly associated with individualization of DAPT.

Angiographic and interventional details

Table 2 shows angiographic and procedural characteristics according to platelet inhibition (non-HPR versus individualized group).

Table 2	**Angiographic and interventional details**			
	Total (n=1008)	**Non-HPR** (n=665; 66%)	**Individualized** (n=343; 34%)	**p**

Type of intervention				ns
Stent	1000 (99%)	661 (99%)	339 (99%)	
Drug Eluting	948 (94%)	625 (94%)	323 (94%)	
Bare Metal	52 (5%)	36 (5%)	16 (5%)	
Balloon (Drug Eluting)	8 (1%)	4 (1%)	4 (1%)	
Access site				ns
femoral	867 (86%)	571 (86%)	296 (86%)	
radial	117 (12%)	77 (12%)	40 (12%)	
Both	24 (2%)	17 (2%)	7 (2%)	
Lesion location				ns
Left Main	114 (11%)	78 (12%)	36 (11%)	
Left anterior descending	585 (58%)	391 (59%)	194 (57%)	
Left circumflex	401 (40%)	277 (42%)	124 (36%)	
Right coronary artery	443 (44%)	285 (43%)	158 (46%)	
Bypass graft	18 (2%)	12 (2%)	6 (2%)	
AHA/ACC Type b2/c	739 (73%)	490 (74%)	249 (73%)	ns
Stent length total (mm; range)	43±33 (8–241)	44±32 (8–241)	43±33 (8–217)	ns
Stents/patient (range)	2.2±1.5 (1–12)	2.2±1.5 (1–12)	2.1±1.6 (1–12)	ns
Multivessel disease	655 (65%)	428 (64%)	227 (66%)	ns

The rate of DES implantation was high (94%), and of these 20% were biolimus-eluting, 49% everolimus-eluting and 25% zotarolimus-eluting. Multivessel disease was present in 65% of patients, with a high proportion of complex lesion morphology (Type b2/c: 73%), including 11% left main and 58% left anterior descending artery lesions, resulting in 2.2±1.5 implanted stents/patient (mean stent length 43±33 mm). The rate of use of a femoral access site for PCI during the registry period was high (86%). All parameters showed no differences between groups.

Primary ADP receptor blocker loading and individualization of ADP receptor blocker therapy.

As shown in Figure 3A, 94.8% of patients were primarily loaded with 600 mg clopidogrel, 5% with 60 mg prasugrel (STEMI patients <75 years and >60 kg without history of stroke) and 0.2% with 180 mg ticagrelor (known clopidogrel allergy). Of the clopidogrel loaded patients, 30% showed HPR. Clopidogrel reloadings of 600 mg were performed up to three times in 27% of patients with HPR, leaving five patients with persisting HPR, of whom three were finally switched to prasugrel during the observation period, as it became available. Prasugrel reloading was performed in 70% of patients with HPR. Of the prasugrel loaded patients, 2% showed HPR, which was successfully treated with ticagrelor reloading; this was also performed in 3% of patients with HPR to clopidogrel and contraindications to prasugrel. Only three patients remained in HPR during the observation period, and were put on a higher MD (two on clopidogrel 150 mg, one on prasugrel 20 mg as ticagrelor was not yet available). For patients older than 75 years or weighing less than 60 kg, prasugrel 5 mg was primarily prescribed (15% of prasugrel patients, n=37). After MEA testing 1 week later, 14% (n=5) were switched to 10 mg.

ASA-dependent platelet aggregation and reloading

After ASA and ADP receptor blocker loading, 9% of our patients showed a HPR to AA-induced aggregation (68±28 U vs. 16±8 U; p<0.001). As shown in Figure 3B, HPR to AA was significantly more prevalent in patients with HPR to ADP (22% vs. 4%; p<0.001). HPR to AA without HPR to ADP (63±29 U) was treated by ASA reloading successfully in all patients (14±6 U; p<0.001). In patients with HPR to ADP, the HPR to AA was influenced by the extent of the residual AA-induced platelet aggregation, as follows. In patients with intermediate HPR to AA (<60 U), only ADP receptor blocker reloading was sufficient to treat HPR to AA as well (from 45±7 U to 15±10 U; p<0.001). In patients with high HPR to AA (≥60 U) an additional

ASA reloading was necessary to significantly reduce AA-induced aggregation from 92±21 U to 20±16 U (p<0.001). Six of these patients showed persisting HPR to AA and were discharged on 300 mg ASA.

Platelet aggregation in clopidogrel and prasugrel loaded patients and effect of reloading.

ADP-induced aggregation after 600 mg clopidogrel loading was significantly higher in patients with HPR (= non-responder: 73±19 U) than without (= responder: 28±11 U; p<0.001) (Figure 4A). Reloading effectively treated HPR (22±12 U; p<0.001), except in two patients for whom prasugrel was not yet available. ADP-induced aggregation after 60 mg prasugrel loading was significantly higher in patients with HPR (= non-responder: 82±26 U) than without (= responder: 19±10 U; p<0.001), and was successfully treated with ticagrelor reloading (34±15 U; p=0.02) (Figure 4B).

Glycoprotein IIbIIIa inhibitor (GPI) treatment

GPI was given to 61% (n=57) of STEMI patients, with an i.c. abciximab bolus only in 91% (n=52) and an i.v. eptifibatide bolus only in 9% (n=5). Non-STEMI (NSTEMI) patients received a GPI treatment in 11% (n=47) of cases, with an i.c. abciximab bolus only in 72% (n=34) and an i.v. eptifibatide bolus only in 28% (n=13).

Clinical outcome at 30 days

Table 3 shows the clinical outcome of the overall patient cohort.

Table 3	**Thirty day clinical outcome**				
	Total (n=1007)	**Non-HPR** (n=664, 66%)	**Individualized** (n=343, 34%)	**adj. HR** (95%CI) **p**	**crude HR** (95%CI) **p**
MACE (Cardiovascular Death, Myocardial Infarction, Stent thrombosis)	18 (1.8%)	9 (1.4%)	9 (2.6%)	0.67 (0.23–2.03) 0.5	0.51 (0.20–1.30) 0.16

Cardiovascular Death	18 (1.8%)	9 (1.4%)	9 (2.6%)		
non-shock	8 (0.8%)	4 (0.6%)	4 (1.2%)		
cardiogenic shock (n=shock patients; % of shock)	10 (26; 38%)	5 (8; 62%)	5 (18; 28%)		
Myocardial Infarction	1 (0.09%)	1 (0.15%)	0 (0%)		
Stent thrombosis					
definite and probable	3 (0.29%)	3 (0.45%)	0 (0%)		
definite	1 (0.09%)	1 (0.15%)	0 (0%)		
probable	2 (0.19%)	2 (0.3%)	0 (0%)		
Bleeding					
TIMI major and minor	26 (2.6%)	17 (2.6%)	9 (2.6%)	0.78 (0.33–1.85) 0.574	0.96 (0.42–2.20) 0.914
TIMI major	10 (1.0%)	6 (0.9%)	4 (1.2%)		
TIMI minor	16 (1.6%)	11 (1.7%)	5 (1.5%)		
Type					
Instrumented	14 (1.4%)	10 (1.5%)	4 (1.2%)		
Spontaneous	12 (1.2%)	7 (1.1%)	5 (1.5%)		

(MACE = major adverse cardiac event)

No acute ST occurred within 24 hours in the whole patient cohort. 3 patients died in cardiogenic shock within 24 hours after successful PCI without evidence of ST at autopsy. Only one subacute definite ST, which also accounted for the only myocardial infarction, occurred within 30 days (0.09%). This patient had multivessel PCI for NSTEMI, and developed diarrhea and Gram negative sepsis. On the seventh day post PCI, an attempted resuscitation was unsuccessful. Acute thrombosis of the circumflex artery stent was confirmed at autopsy. Two sudden deaths without autopsy occurred after discharge in NSTEMI patients, which have been classified as probable ST according to the ARC criteria. However, both patients also suffered from ischemic cardiomyopathy, which would suggest a primary rhythmogenic cause for their sudden deaths. MACE number equals cardiovascular deaths (n=18; 1.8%) as all three cases of ST died. Cardiogenic shock was the cause of cardiovascular deaths in the majority of cases (88%), without differences in groups. Concerning bleeding complications,

no increase in individualized patients occurred (2.6% TIMI major and minor bleedings in both groups). Slightly more than half of the bleeding complications (54%, n=14) were related to the access site ("instrumented"), requiring surgical intervention in three cases (21% of instrumented complications; 0.3% of patients). The majority of spontaneous bleeding complications were gastrointestinal (67%, n=8). One intracranial haemorrhage occurred under standard DAPT with clopidogrel 17 days after PCI for NSTEMI in an 86 year old patient.

Table 4 shows 30-day outcomes for the STEMI-, NSTE-ACS- and stable CAD cohorts.

Table 4. Descriptive Statistics for 30 days outcome in clinical subgroups.

	Total	Non-HPR	Individualized
STEMI cohort	93	31 (33%)	62 (67%)
Cardiovascular Death	8 (8.6%)	4 (12.9%)	4 (6.5%)
non-shock	1 (1.1%)	1 (3.2%)	0 (0%)
cardiogenic shock (n=shock patients; % of shock)	7 (17; 41%)	3 (6; 50%)	4 (11; 36%)
Myocardial Infarction	0 (0%)	0 (0%)	0 (0%)
Stent thrombosis			
definite	0 (0%)	0 (0%)	0 (0%)
probable	0 (0%)	0 (0%)	0 (0%)
Bleeding			
TIMI major and minor	6 (6.5%)	3 (9.7%)	3 (4.8%)
TIMI major	4 (4.3%)	2 (6.5%)	2 (3.2%)
TIMI minor	2 (2.2%)	1 (3.2%)	1 (1.6%)
Type			
Instrumented	5 (5.4%)	3 (9.7%)	2 (3.2%)
Spontaneous	1 (1.1%)	0 (0%)	1 (1.6%)
NSTE-ACS cohort	446	303 (68%)	143 (32%)
Cardiovascular Death	10 (2.2%)	5 (1.7%)	5 (3.5%)
non-shock	7 (1.6%)	3 (1.0%)	4 (2.8%)
cardiogenic shock (n=shock patients;% of shock)	3 (9; 33%)	2 (2; 100%)	1 (7; 14%)
Myocardial Infarction	1 (0.2%)	1 (0.3%)	0 (0%)
Stent thrombosis			

definite	1 (0.2%)	1 (0.3%)	0 (0%)
probable	2 (0.4%)	2 (0.7%)	0 (0%)
Bleeding			
TIMI major and minor	13 (2.9%)	9 (3.0%)	4 (2.8%)
TIMI major	4 (0.9%)	2 (0.7%)	2 (1.4%)
TIMI minor	9 (2.0%)	7 (2.3%)	2 (1.4%)
Type			
Instrumented	5 (1.1%)	4 (1.3%)	1 (0.7%)
Spontaneous	8 (1.8%)	5 (1.7%)	3 (2.1%)
Stable CAD cohort	468	330 (70%)	138 (30%)
Cardiovascular Death	0 (0%)	0 (0%)	0 (0%)
Myocardial Infarction	0 (0%)	0 (0%)	0 (0%)
Stent thrombosis			
definite	0 (0%)	0 (0%)	0 (0%)
probable	0 (0%)	0 (0%)	0 (0%)
Bleeding			
TIMI major and minor	7 (1.5%)	5 (1.5%)	2 (1.4%)
TIMI major	2 (0.4%)	2 (0.6%)	0 (0%)
TIMI minor	5 (1.1%)	3 (0.9%)	2 (1.4%)
Type			
Instrumented	4 (0.8%)	3 (0.9%)	1 (0.7%)
Spontaneous	3 (0.6%)	2 (0.6%)	1 (0.7%)

No ischemic event occurred either in the STEMI cohort, with a required high rate of individualization (67%), or in the stable CAD cohort, with a sufficient lower rate of individualization (30%). The safety endpoint of combined TIMI major and minor bleeding risk was 2× higher in NSTE-ACS patients and 4× higher in STEMI patients than in stable CAD patients (2.9% vs. 6.5% vs. 1.5%; p=0.02), without an increase associated with individualization in any subgroup.

Discussion

The main findings of our study are as follows. Firstly, routine efficient peri-interventional individualization of DAPT with MEA, incorporating the newer generations of ADP receptor blocker (prasugrel and ticagrelor), is able to minimize early ischemic events after PCI in an

all-comers population including STEMI patients by nearly abolishing early definite stent thrombosis. Secondly, intensifying platelet inhibition in patients with HPR does not increase bleeding complications compared to patients without HPR under DAPT. Thirdly, there is indirect evidence for synergistic roles of ADP- and ASA- dependent platelet activation.

For the interpretation of the very low ischemic complication rate observed during the 30 days after PCI, the most recent literature on the incidence of real world early ST in PCI for all-comers [24] and STEMI patients [25,26], as well as the complication rate in the randomized CHAMPION Phoenix trial [11], should be considered. We could show that adjusting the level of platelet inhibition reduced the rate of early definite ST to 0.09%, which is about 7-fold lower than observed in PCI for all-comers [24] and about 25- to 35-fold lower than in primary PCI for STEMI [25, 26], even with contemporary 2nd generation DES. Monitored intensification of platelet inhibition by bolus-only administration of GPI and individualized DAPT resulted in a yet more favourable outcome in our STEMI population, as no early thrombotic events occurred. Furthermore, even under randomized study conditions like the CHAMPION Phoenix trial [11], the definite ST rate after clopidogrel loading was 1.4% within 48 hours, or about 14-fold higher than in our study. Immediate ADP receptor blockade with cangrelor, however, showed a benefit with reduction to 0.8% (p=0.01), which is still about 8-fold higher than what achieved with our individualization protocol. In addition, ischemic complications were not only not driven by urgent ACS patients (4.1%), but were also numerically higher in stable CAD (7.4%). By contrast, individualization of DAPT in our stable CAD cohort, with 600 mg clopidogrel loading the day before PCI and MEA guided individualization (the latest within 2 hours after PCI), resulted in no early ischemic events. As the “first do no harm” principle should be generally applied, optimization of platelet

inhibition at the time of PCI seems also of importance in this patient population, thus questioning the negative recommendation on the role of platelet function testing in stable CAD patients [2].

Three randomized multicenter trials [7-9] failed to show a clinical benefit of individualizing DAPT with the VerifyNow™ assay. Among the most common raised limitations, those in study design, protocol implementation and efficacy of platelet inhibition are the most important. Concerning study design, the late randomization of patients, more than 12 hours after PCI, in GRAVITAS [7] and TRIGGER-PCI [9] excluded acute procedural complications attributable to insufficient platelet inhibition. This occurred even in stable CAD patients, as impressively shown in CHAMPION Phoenix [11]. Concerning protocol implementation, the ARCTIC trial [8] discharged 1.3% of patients in the active study arm without any ADP receptor blocker medication, and lost nearly 9% of patients to follow-up. TRIGGER-PCI [9] was stopped prematurely, leaving an underpowered study population. Concerning efficacy of platelet inhibition, 40% of patients in GRAVITAS [7] and 16% in ARCTIC [8] remained in HPR due to primary reloading with clopidogrel (100% in GRAVITAS and 90% in ARCTIC). By contrast, 100% of our patients were included prior to PCI and discharged with DAPT, 99.9% could be followed at 30 days and only 0.3% remained in HPR. Together, this resulted in a 1.7-fold lower rate of ST (definite and probable) than in the high dose clopidogrel arm of GRAVITAS [7] and a 3.5-fold lower rate than in the monitored arm of ARCTIC [8], despite our higher risk population, including STEMI patients.

Concerning bleeding complications, our concept of using the newer generations of ADP receptor blockers, primarily for intensifying platelet inhibition in patients with HPR to clopidogrel rather than upfront for all ACS patients without contraindications, seems

beneficial. In contrast to TRITON [18] and PLATO [19], which featured significantly increased non-CABG related bleeding rates under prasugrel and ticagrelor, no increased bleeding occurred in the individualized patients compared to those on clopidogrel without HPR. The observed 1.5% TIMI major bleeding rate in our ACS cohort compares favourably to the non-CABG related TIMI major bleeding rates in the clopidogrel arms of TRITON (1.8%) and PLATO (2.2%). Furthermore, even in the highest bleeding risk group, the STEMI patients, our blocking and bridging strategy with GPI bolus-only administration resulted in fewer TIMI major and minor bleeds (6.4%) than in the GPI arm with bolus and infusion (9.6%) of the HORIZON AMI trial [27]. Although our number of patients is admittedly far too low to draw this conclusion, GPI bolus-only administration seems suggestively comparable to the bivalirudin arm (5.9%).

Concerning the regulation of platelet activation, it is already known that thrombin- (via the protease activated receptor-1) and ADP- (via the $P2Y_{12}$ receptor) mediated platelet activation play a synergistic role in hemostasis and thrombosis [20, 28, 29]. Herein, we provide indirect evidence for a synergistic role of ADP- and ASA- (cyclooxygenase) dependent platelet activation. We observed an interplay between AA- and ADP- induced platelet aggregability, as HPR to AA was significantly associated with HPR to ADP, and solitary reloading with ADP receptor blocker in patients with HPR to ADP and AA was able to successfully resolve intermediate levels of HPR to AA without ASA reloading.

Limitations of our study include primarily the observational, non-randomized nature of the registry without a control group concerning efficacy, and the monocentric design.

In conclusion, our data strongly suggest that HPR represents a modifiable risk factor that can be used for tailoring treatment in PCI patients, rather than a marker of higher risk only.

Effective individualization of DAPT for PCI under MEA guidance is able to minimize early ischemic complications to a so far unreported degree. Further properly designed randomized multicenter trials utilizing MEA seem warranted.

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Contributorship statement

G. Christ: conception and design of the registry; acquisition, analysis and interpretation of data, drafting and revising the manuscript critically for important intellectual content; final approval of the version to be published; J.M. Siller-Matula: design of the registry, analysis and interpretation of data, revising the manuscript critically for important intellectual content; final approval of the version to be published; M. Francesconi: design of the registry, acquisition and analysis of data, revising the manuscript critically for important intellectual content; final approval of the version to be published; C. Dechant: design of the registry, acquisition and analysis of data, revising the manuscript critically for important intellectual content; final approval of the version to be published; K. Grohs: design of the registry, analysis of data, revising the manuscript critically for important intellectual content; final approval of the version to be published; A. Podczeck-Schweighofer: design of the registry; interpretation of data, revising the manuscript critically for important intellectual content; final approval of the version to be published. All authors agreed to be accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data sharing statement:

No additional data available

Disclosures

None

Figures

Figure 1: Algorithm of ADP receptor blocker treatment

ADP = adenosine diphosphate, CAD = coronary artery disease, GPI = glycoprotein IIbIIIa inhibitor, MEA = multiple electrode aggregometry, NSTE-ACS = non-ST-elevation acute coronary syndrome, STEMI = ST-elevation myocardial infarction.

* loading in stable patients the day before angiography; ** platelet testing not earlier than 12 hours after loading, and at the latest at the time of diagnostic angiography, after GPI administration serial testing up to 7 days; *** platelet testing the day after reloading; **** platelet testing 1 week after starting 5 mg prasugrel; # up to three clopidogrel reloadings; ## prasugrel reloading dependent on residual reactivity: ADP >80: 60 mg, ADP 60–79: 30 mg, ADP 50–59: 10mg; ### in patients <60 kg and/or >75 years

Figure 2: Flow chart of study patients

CTO = chronic total occlusion, PCI = percutaneous coronary intervention

Figure 3: Flow chart of primary ADP receptor blocker and ASA loading and reloading

A) ADP receptor blocker loading. Only 0.3% of patients (n=3) showed persisting HPR to ADP (≥50 U): two patients after 4 × 600 mg clopidogrel loading (as prasugrel was not yet available) and one patient on prasugrel (as ticagrelor was not yet available). B) HPR to AA-induced aggregation (>35 U) occurred to a significant higher proportion in patients with HPR to ADP (ADP ≥50 U). In patients with HPR to ADP and intermediate HPR to AA (AA <60 U) only ADP receptor blocker reloading successfully treated also HPR to AA. AA = Arachidonic Acid, ADP = adenosine diphosphate, ASA = acetylic salicylic acid.

Figure 4: ADP-induced aggregation after 600 mg Clopidogrel or 60 mg Prasugrel loading and effect of reloading

A) Of clopidogrel loaded patients, 30% showed a high on-treatment platelet reactivity (= non-responder), effectively treated by reloading (except for two patients as prasugrel and ticagrelor had not yet been available). B) Of prasugrel loaded patients, 2% showed a high on-treatment platelet reactivity (= non-responder), effectively treated by ticagrelor.

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Individualizing Dual Antiplatelet Therapy after Percutaneous Coronary Intervention: The IDEAL-PCI Registry.

Günter Christ* MD, Jolanta M. Siller-Matula† MD PhD, Marcel Francesconi* MD, Cornelia Dechant* MD, Katharina Grohs‡ MD and Andrea Podczeck-Schweighofer* MD ~~for the IDEAL-PCI investigators.~~

* 5th Medical Department with Cardiology, Kaiser Franz Josef Hospital, Vienna, Austria

† Department of Cardiology, Medical University of Vienna, Austria

‡ Clinical Institute for Laboratory Medicine, Kaiser Franz Josef Hospital, Vienna, Austria

Correspondence: Prof. Günter Christ, MD

5th Medical Department with Cardiology, Kaiser Franz Josef Hospital

Kundratstr. 3, 1100 Vienna, Austria

Tel.: +43-1-60191-2508

Fax: +43-1-60191-2509

E-mail: guenter.christ@wienkav.at

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Abstract

~~**Introduction**~~**Objective:** To evaluate ~~T~~the clinical utility of individualizing dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) in an all-comers population, including ST-elevation myocardial infarction (STEMI) patients. ~~has been tested in lower risk patients, with equivocal results. Its value in an all-comers PCI population, including ST-elevation myocardial infarction (STEMI) patients, is unknown.~~

Setting: Tertiary care single centre registry

~~**Methods and Results:**~~**Participants:** ~~A prospective, single-centre registry of~~ 1008 consecutive PCI patients with stent implantation, without exclusion criteria.

Intervention: Perinterventional ~~i~~individualization of DAPT, guided by multiple electrode aggregometry (MEA), to overcome high on-treatment platelet reactivity (HPR) to adenosine diphosphate (ADP)- (≥50 U) and arachidonic acid (AA)-induced aggregation (>35 U). ~~was compiled.~~

Outcome measures: The primary efficacy endpoint was definite stent thrombosis (ST) at 30 days. The primary safety endpoint was TIMI major and minor bleeding. Secondary endpoints were probable ST, myocardial infarction, cardiovascular death and the combined endpoint major cardiac adverse event (MACE).

Results: ~~Overall,~~ 53% of patients presented with acute coronary syndrome (9% STEMI, 44% non-ST-elevation). ~~High on-treatment platelet reactivity (HPR) to adenosine diphosphate (ADP) induced aggregation (≥50 U)~~ HPR to ADP after 600 mg clopidogrel loading occurred in 30% of patients (73±19 U vs. 28±11 U; p<0.001) and was treated by prasugrel or ticagrelor (73%) or clopidogrel (27%) reloading (22±12 U; p<0.001). HPR to ADP after~~to~~ prasugrel loading occurred in 2% of patients (82±26 U vs. 19±10 U; p<0.001) and was treated with

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ticagrelor (34±15 U; p=0.02). HPR to AA occurred in 9% of patients with a significant higher proportion in patients with HPR to ADP (22% vs. 4%, p<0.001) and was treated with aspirin reloading. The efficacy endpoint d Definite stent thrombosis (ST) at 30 days occurred in 0.09% of patients (n=1); probable ST, myocardial infarction and, cardiovascular death and MACE occurred in 0.19% (n=2), 0.09% (n=1) and 1.8% (n=18) of patients. The safety endpoints TIMI major and minor bleeding did not differ between patients without HPR and individualized patients (2.6% for both).

Conclusions: Individualization of DAPT with MEA minimizes early thrombotic events in an all-comers PCI population to an unreported degree without increasing bleeding. A randomized multicenter trial utilizing MEA seems warranted.

Clinical Trial Registration: URL: http://www.clinicaltrials.gov; Unique identifier: NCT01515345

Keywords: percutaneous coronary intervention, platelet function testing, dual antiplatelet therapy

Article summary

Strengths and limitations of this study

The strengths of our study are, at first the real world percutaneous coronary intervention setting with inclusion of every consecutive patient with stent implantation, without any exclusion criteria. Second, the consequent and efficient peri-interventional individualization of dual antiplatelet therapy, leaving only 0.3% of patients on high on-treatment platelet reactivity to adenosine diphosphate at the time of hospital discharge. Third, the minimization of ischemic events within 30 days by nearly abolishing early definite stent thrombosis, without increasing bleeding complications.

Limitations of our study are the non randomised and monocentric registry design without control group concerning ischemic events.

Introduction

High on-treatment platelet reactivity (HPR) to adenosine diphosphate (ADP) represents one of the strongest independent risk factors for post-percutaneous coronary intervention (PCI) ischemic events in patients given dual antiplatelet therapy (DAPT), according to numerous observational studies using various platelet function tests [1-3].

Whether HPR represents only a marker of higher risk or a modifiable risk factor is still a matter of debate [2], as prospective randomized trials evaluating personalized antiplatelet therapy aiming to overcome HPR resulted in conflicting data. Smaller randomized trials [4], as well as non-randomized studies [5] and a recent meta-analysis [6] suggested a significant clinical benefit, but three randomized studies failed to do so [7-9]. However, each of these trials, utilizing the VerifyNow™ assay, was afflicted with major limitations potentially masking the real value of individualizing DAPT after PCI in daily practice [1, 10]. Their low-risk population and primarily the high selection bias in GRAVITAS [7] and TRIGGER-PCI [9], with patient inclusion more than 12 hours after PCI, seems to cloud the potential importance of optimizing platelet inhibition at the time of PCI. By contrast, the very recent CHAMPION Phoenix trial [11] provides a more realistic scenario of expectable ischemic complications during and after PCI. More than 11,000 patients with oral clopidogrel loading, including the whole clinical PCI spectrum [56% stable coronary artery disease (CAD), 26% non-ST-elevation acute coronary syndrome (NSTE-ACS), 18% ST-elevation myocardial infarction (STEMI)], were pre-interventionally randomized to receive an intravenous (i.v.) bolus and infusion of

cangrelor, a fast acting reversible ADP receptor blocker. Ischemic complications in the whole study cohort occurred in 5.3%, including a definite stent thrombosis (ST) rate of 1.1% during the first 48 hours. Notably, the majority of events occurred within 6 hours after PCI.

HPR to acetylic salicylic acid (ASA) is less well studied and its clinical relevance is unclear. The ADAPT-DES registry [3] found no difference in response to ASA, measured by the VerifyNow™ assay, between patients with and without ST. Data not only from our group, however, suggested that dual HPR to both ADP- and arachidonic acid- (AA; reflecting response to ASA) induced aggregation, measured by multiple electrode aggregometry (MEA) [12] or the VerifyNow assay [13], predisposes patients to a higher ischemic risk than single HPR ~~[12].~~ Furthermore, MEA has been shown to effectively assess the risk of HPR to ADP after PCI [143] with higher accuracy than the vasodilator-stimulated phosphoprotein phosphorylation (VASP) assay [154] utilized in the Bonello studies.

Therefore, our registry aimed to evaluate the impact of individualizing DAPT with MEA in an all-comers population, including STEMI patients without exclusion criteria, by peri-interventional treatment of HPR to both ADP and AA.

Methods

Patient population

This was a prospective, single-centre cohort observation of consecutive PCI patients, including all forms of ACS (including cardiogenic shock) and all stable CAD, with stent implantation or drug eluting balloon dilatation (for treatment of instent restenosis), and without exclusion criteria (secondary causes for ACS, like anaemia had to be corrected according to standard patient care, but did not represent an exclusion criterion, nor did thrombocytopenia or liver dysfunction once the indication for an invasive approach was

given). Patients without stent implantation (i.e. unsuccessful reopening of a chronic total occlusion or balloon dilatation only) were not included. Peri-interventional individualization of platelet inhibition was performed according to the protocol shown in Figure 1 and described in detail below. The local Ethics Committee approved the study protocol in accordance with the Declaration of Helsinki. Participants were included between November 2008 and June 2012. Informed consent was obtained after PCI, either from the patient or from the guardian in cases of critically ill conditions. Follow-up information was obtained by either direct outpatient visit or telephone contact at 30 days.

Study endpoints

The primary efficacy endpoint was definite ST during a 30 days follow-up. The secondary efficacy outcome parameters were probable ST, myocardial infarction and cardiovascular death, as well as the combination of the above mentioned endpoints as major cardiac adverse events (MACE). Definite and probable ST were defined according to the Academic Research Consortium (ARC) [165]. The primary safety end point was the incidence of TIMI bleeding complications [176]. TIMI major bleeding was defined as intracranial bleeding or overt bleeding with a decrease in haemoglobin ≥5 g/dL. TIMI minor bleeding was defined as observed bleeding with decrease in haemoglobin ≥3 to <5 g/dL.

Individualization of dual antiplatelet therapy

Individualization of ADP receptor blocker treatment was performed according to the algorithm presented in Figure 1. After an initial clopidogrel loading dose of 600 mg, on-treatment platelet reactivity was measured the next day by MEA, at the earliest after 12 hours and at the latest at the time of diagnostic angiography. HPR was defined as ≥50 U

ADP-induced aggregation. This cut-off represents the mean of published data from Sibbing and our group [143, 154]. From November 2008 to May 2009, patients with HPR were reloaded with clopidogrel 600 mg up to three times according to the Bonello protocol [4]. After prasugrel [187] became available in June 2009, HPR to clopidogrel was treated with prasugrel (Efient/Effient®) loading, depending on the degree of the residual ADP-induced platelet reactivity. Cases where ADP >80 U received 60 mg, ADP 60–79 U 30 mg, and ADP 50–59 U 10 mg of prasugrel. This staged approach was chosen in order to avoid potential bleeding complications due to the observed overresponse (i.e. very "flat" ADP and ASPI curves, <10-15U) after a routine 60 mg prasugrel loading in patients with borderline clopidogrel response (ADP 50-60 U). In patients older than 75 years or weighing less than 60 kg, the maintenance dose (MD) of prasugrel was reduced to 5 mg according to the manufacturer's specification, with MEA testing 1 week later and dose adjustments if necessary. In cases of contraindications to prasugrel (history of stroke), clopidogrel reloadings were performed, until ticagrelor (Brilique/Brilinta®) became available. STEMI patients younger than 75 years and weighing more than 60 kg without history of stroke were primarily loaded with 60 mg prasugrel due to the local standard operating procedure of the Viennese STEMI network. After ticagrelor [198] became available in March 2011, HPR to prasugrel and HPR to clopidogrel in patients with contraindications to prasugrel were treated with 180 mg ticagrelor loading. In cases of contraindications to ticagrelor (history of intracranial haemorrhage), clopidogrel reloadings were performed. Special care was taken to limit the possibility of HPR at the time of PCI by clopidogrel loading at least 12 hours prior to PCI, with reloading if necessary either prior PCI in case MEA testing was already known, or the latest 1–2 hours after PCI. In case no oral ADP receptor blocker loading, or only within 4–

6 hours pre-PCI was given [e.g., STEMI or urgent invasive non-STEMI (NSTEMI) patients], bolus-only administration of a glycoprotein IIbIIIa inhibitor (GPI) was performed [intracoronary (i.c.) abciximab (0.25 mg/kg; Reopro®) or i.v. eptifibatide (180 µg/kg, Integrilin®)]. Thereafter, serial MEA measurements were performed up to 7 days to allow determination of the level of oral ADP receptor inhibition. Details of this blocking and bridging strategy have been published previously [~~19~~20]. At discharge all patients should be within the therapeutic range of platelet inhibition (i.e., non-HPR).

Individualization of ASA treatment was conducted as follows. Stable patients without chronic ASA treatment were loaded with 300 mg ASA p.o. the day before angiography. ACS patients were loaded with ASA i.v.: 500 mg was used in ASA naïve patients and 250 mg was used in cases of chronic ASA treatment. HPR to ASA was defined as >35 U AA-induced aggregation. This cut-off represents a mean derived from published data [~~(~~12, 2~~10)~~] and the MEA manufacturer's recommendations. ASA reloading was performed with either 300 mg p.o or 250 mg i.v. In cases of HPR to both ADP and ASA, first ADP receptor blocker reloading was performed with ASA reloading if necessary after MEA testing the next day.

PCI was performed according to current standard guidelines. The type of stent implanted was at the discretion of the interventional cardiologist. In cases of drug eluting stent (DES) implantation, only 2nd generation DES were used (Biolimus-eluting: Biomatrix™; Everolimus-eluting: Promus Element™ and Xience™; Zotarolimus-eluting: Resolute™). All patients received 100 IU/kg of unfractionated heparin, with adjustments according to measurements of activated clotting time, except in cases of GPI bolus administration where only 70 IU/kg were given.

Impedance aggregometry

Whole blood aggregation was determined using MEA, a new-generation impedance aggregometer (Multiplate™ Analyzer, Roche, Munich, Germany). The system detects the electrical impedance change due to the adhesion and aggregation of platelets on two independent electrode-set surfaces in the test cuvette, with a low rate of intra-and interassay variability [221]. ADP and AA were used as agonists. A 1:2 dilution of whole blood anticoagulated with hirudin and 0.9% NaCl was stirred at 37°C for 3 min in the test cuvette. ADP (6.4 µM) and AA (0.5 mM) were added, and the increase in electrical impedance was continuously recorded for 6 min. The mean values of the two independent determinations were expressed as the area under the curve (AUC) of the aggregation tracing. AUC is reported herein in units (U), as described previously [232].

Statistical analysis

Data are expressed as mean ± standard deviation (SD). Statistical comparisons were performed with the Mann Whitney U test, the paired and unpaired Student t-test and chi-squared test. COX regression analysis was performed to compare the event rates between the non-HPR group and the individualized treatment group. As the power of the study was limited due to the low event rate, we provide crude and adjusted HR., and was adjustedThe adjustment was done for gender, body mass index, diabetes, hyperlipidemia, use of calcium channel blockers (CCB) and proton pump inhibitors (PPI), clinical presentation, platelet count and cardiogenic shock. All statistical calculations were performed using commercially available statistics analysis software (SPSS Version 21; Chicago).

Sample size

We estimated that the sample size of 1008 patients would provide 80% power to demonstrate a reduction in the incidence of ST by individualization of antiplatelet therapy,

on the basis of assumptions of ST rates during one month follow-up. We expected a 0.2% rate of ST at 1 month in patients without HPR, as compared to a 1.9% rate in a historical group of patients with HPR [3, 5, 143]. Thus, if the hazard ratio (HR) for ST was 3.0–4.0-fold lower in patients without HPR than in those with HPR [(3)], the study would have more than 80% power to demonstrate that individualized antiplatelet therapy in patients with HPR reduces the rate of ST.

Results

Patient inclusion and baseline characteristics

Of 1043 consecutive PCI patients, only those with unsuccessful reopening of a chronic total occlusion or with conventional balloon-only PCI were excluded (n=35), leaving 1008 participants (Figure 2). All STEMI patients received a primary PCI. At 30 days, one patient (0.09%), a French tourist, was lost to follow-up. Table 1 shows the demographic variables of our patient cohort and differences between the group without HPR after clopidogrel loading (no-HPR) and the individualized group (i.e., ADP receptor blocker reloading and primary prasugrel or ticagrelor loading).

Table 1 **Baseline characteristics**

	Total (n=1008)	**Non-HPR** (n=665; 66%)	**Individualized** (n=343; 34%)	
Age	64.75±11.82	65.1±11.72	63.94±11.92	ns
Women	303 (30%)	183 (28%)	120 (35%)	0.01
Body Mass Index (kg/m^2)	28.4±4.65	28.1±4.55	29.1±4.85	0.001
Diabetes	321 (32%)	196 (30%)	125 (36%)	0.03
Insulin treatment	84 (8%)	41 (6%)	43 (13%)	0.001
Oral medication	237 (24%)	155 (23%)	82 (24%)	ns
Smoker	504 (50%)	334 (50%)	170 (50%)	ns
Hypertension	842 (84%)	557 (84%)	285 (83%)	ns
Hyperlipidemia	855 (85%)	552 (83%)	303 (88%)	0.03

Family history	272 (27%)	181 (27%)	91 (27%)	ns
History of myocardial infarction	212 (21%)	139 (21%)	73 (21%)	ns
History of PCI	190 (19%)	130 (20%)	60 (18%)	ns
History of CABG	60 (6%)	42 (6%)	18 (5%)	ns
Cerebrovascular disease	115 (11%)	71 (11%)	44 (13%)	ns
Peripheral vascular disease	133 (13%)	92 (14%)	41 (12%)	ns
Clinical presentation				<0.001
STEMI	93 (9%)	31 (5%)	62 (18%)	
NSTE-ACS	447 (44%)	304 (46%)	143 (41%)	
NSTEMI	393 (39%)	261 (39%)	132 (38%)	
Unstable Angina	54 (5%)	43 (7%)	11 (3%)	
Stable angina	468 (47%)	330 (50%)	138 (41%)	
Cardiogenic shock	26 (3%)	8 (1%)	18 (5%)	<0.001
Platelet count x10^3/µl	251±81	239±74	276±88	<0.001
Co-medication				
Statin	929 (92%)	612 (92%)	317 (92%)	ns
Proton pump inhibitor	649 (64%)	397 (60%)	252 (74%)	<0.001
Calcium channel blocker	195 (19%)	116 (17%)	79 (23%)	0.03
Betablocker	771 (77%)	515 (77%)	256 (75%)	ns
ACE-I/ARB	764 (76%)	494 (74%)	270 (79%)	ns

(ACE-I = Angiotensin converting enzyme inhibitor; ARB = Angiotensin receptor blocker; CABG = coronary artery bypass graft; HPR = high on-treatment platelet reactivity; NSTE-ACS = Non ST-elevation acute coronary syndrome; NSTEMI = Non ST-Elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction)

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Patients in the individualized group were more frequently of female gender (p=0.01), had higher bodyweight (p=0.001), and a greater incidence of diabetes (p=0.003), especially insulin dependent (p=0.001), STEMI and cardiogenic shock (p<0.001). Higher platelet counts (p<0.001), and co-medication with PPI (p<0.001) and CCB (p=0.03), were also significantly associated with individualization of DAPT.

Angiographic and interventional details

Table 2 shows angiographic and procedural characteristics according to platelet inhibition (non-HPR versus individualized group).

Table 2	**Angiographic and interventional details**			
	Total (n=1008)	**Non-HPR** (n=665; 66%)	**Individualized** (n=343; 34%)	**p**
Type of intervention				ns
Stent	1000 (99%)	661 (99%)	339 (99%)	
Drug Eluting	948 (94%)	625 (94%)	323 (94%)	
Bare Metal	52 (5%)	36 (5%)	16 (5%)	
Balloon (Drug Eluting)	8 (1%)	4 (1%)	4 (1%)	
Access site				ns
femoral	867 (86%)	571 (86%)	296 (86%)	
radial	117 (12%)	77 (12%)	40 (12%)	
both	24 (2%)	17 (2%)	7 (2%)	
Lesion location				ns
Left Main	114 (11%)	78 (12%)	36 (11%)	
Left anterior descending	585 (58%)	391 (59%)	194 (57%)	
Left circumflex	401 (40%)	277 (42%)	124 (36%)	
Right coronary artery	443 (44%)	285 (43%)	158 (46%)	
Bypass graft	18 (2%)	12 (2%)	6 (2%)	
AHA/ACC Type b2/c	739 (73%)	490 (74%)	249 (73%)	ns
Stent length total (mm; range)	43±33 (8–241)	44±32 (8–241)	43±33 (8–217)	ns
Stents/patient (range)	2.2±1.5 (1–12)	2.2±1.5 (1–12)	2.1±1.6 (1–12)	ns
Multivessel disease	655 (65%)	428 (64%)	227 (66%)	ns

The rate of DES implantation was high (94%), and of these 20% were biolimus-eluting, 49% everolimus-eluting and 25% zotarolimus-eluting. Multivessel disease was present in 65% of patients, with a high proportion of complex lesion morphology (Type b2/c: 73%), including 11% left main and 58% left anterior descending artery lesions, resulting in 2.2±1.5 implanted stents/patient (mean stent length 43±33 mm). The rate of use of a femoral access site for

PCI during the registry period was high (86%). All parameters showed no differences between groups.

Primary ADP receptor blocker loading and individualization of ADP receptor blocker therapy.

As shown in Figure 3A, 94.8% of patients were primarily loaded with 600 mg clopidogrel, 5% with 60 mg prasugrel (STEMI patients <75 years and >60 kg without history of stroke) and 0.2% with 180 mg ticagrelor (known clopidogrel allergy). Of the clopidogrel loaded patients, 30% showed HPR. Clopidogrel reloadings of 600 mg were performed up to three times in 27% of patients with HPR, leaving five patients with persisting HPR, of whom three were finally switched to prasugrel during the observation period, as it became available. Prasugrel reloading was performed in 70% of patients with HPR. Of the prasugrel loaded patients, 2% showed HPR, which was successfully treated with ticagrelor reloading; this was also performed in 3% of patients with HPR to clopidogrel and contraindications to prasugrel. Only three patients remained in HPR during the observation period, and were put on a higher MD (two on clopidogrel 150 mg, one on prasugrel 20 mg as ticagrelor was not yet available). For patients older than 75 years or weighing less than 60 kg, prasugrel 5 mg was primarily prescribed (15% of prasugrel patients, n=37). After MEA testing 1 week later, 14% (n=5) were switched to 10 mg.

ASA-dependent platelet aggregation and reloading

After ASA and ADP receptor blocker loading, 9% of our patients showed a HPR to AA-induced aggregation (68±28 U vs. 16±8 U; p<0.001). As shown in Figure 3B, HPR to AA was significantly more prevalent in patients with HPR to ADP (22% vs. 4%; p<0.001). HPR to AA without HPR to ADP (63±29 U) was treated by ASA reloading successfully in all patients (14±6

U; p<0.001). In patients with HPR to ADP, the HPR to AA was influenced by the extent of the residual AA-induced platelet aggregation, as follows. In patients with intermediate HPR to AA (<60 U), only ADP receptor blocker reloading was sufficient to treat HPR to AA as well (from 45±7 U to 15±10 U; p<0.001). In patients with high HPR to AA (≥60 U) an additional ASA reloading was necessary to significantly reduce AA-induced aggregation from 92±21 U to 20±16 U (p<0.001). Six of these patients showed persisting HPR to AA and were discharged on 300 mg ASA.

Platelet aggregation in clopidogrel and prasugrel loaded patients and effect of reloading.

ADP-induced aggregation after 600 mg clopidogrel loading was significantly higher in patients with HPR (= non-responder: 73±19 U) than without (= responder: 28±11 U; p<0.001) (Figure 4A). Reloading effectively treated HPR (22±12 U; p<0.001), except in two patients for whom prasugrel was not yet available. ADP-induced aggregation after 60 mg prasugrel loading was significantly higher in patients with HPR (= non-responder: 82±26 U) than without (= responder: 19±10 U; p<0.001), and was successfully treated with ticagrelor reloading (34±15 U; p=0.02) (Figure 4B).

Glycoprotein IIbIIIa inhibitor (GPI) treatment

GPI was given to 61% (n=57) of STEMI patients, with an i.c. abciximab bolus only in 91% (n=52) and an i.v. eptifibatide bolus only in 9% (n=5). Non-STEMI (NSTEMI) patients received a GPI treatment in 11% (n=47) of cases, with an i.c. abciximab bolus only in 72% (n=34) and an i.v. eptifibatide bolus only in 28% (n=13).

Clinical outcome at 30 days

Table 3 shows the clinical outcome of the overall patient cohort.

Table 3 Thirty day clinical outcome

	Total (n=1007)	Non-HPR (n= 664, (66%)	Individualized (n= 343, (34%)	adj. HR (95%CI) p	crude HR (95%CI) p
MACE (Cardiovascular Death, Myocardial Infarction, Stent thrombosis) ~~**Overall cohort**~~	18 (1.8%) ~~107~~	9 (1.4%) ~~664 (66%)~~	9 (2.6%) ~~343 (34%)~~	0.67 (0.23–2.03) 0.5	0.51 (0.20–1.30) 0.16
Cardiovascular Death	18 (1.8%)	9 (1.4%)	9 (2.6%)	~~0.67 (0.23–2.03) 0.5~~	
non-shock	8 (0.8%)	4 (0.6%)	4 (1.2%)		
cardiogenic shock -(n=shock patients; % of shock)	10 (26; 38%)	5 (8; 62%)	5 (18; 28%)		
Myocardial Infarction	1 (0.09%)	1 (0.15%)	0 (0%)	~~0.00 (0.00–1.38) 0.972~~	
Stent thrombosis					
definite and probable	3 (0.29%)	3 (0.45%)	0 (0%)	~~0.00 (0.00–5.71) 0.966~~	
definite	1 (0.09%)	1 (0.15%)	0 (0%)		
probable	2 (0.19%)	2 (0.3%)	0 (0%)		
Bleeding					
TIMI major and minor	26 (2.6%)	17 (2.6%)	9 (2.6%)	0.78 (0.33–1.85) 0.574	0.96 (0.42–2.20) 0.914
TIMI major	10 (1.0%)	6 (0.9%)	4 (1.2%)		
TIMI minor	16 (1.6%)	11 (1.7%)	5 (1.5%)		
Type					
Instrumented	14 (1.4%)	10 (1.5%)	4 (1.2%)		
Spontaneous	12 (1.2%)	7 (1.1%)	5 (1.5%)		

(MACE = major adverse cardiac event)

No acute ST occurred within 24 hours in the whole patient cohort. 3 patients died in cardiogenic shock within 24 hours after successful PCI without evidence of ST at autopsy.

Only one subacute definite ST, which also accounted for the only myocardial infarction,

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occurred within 30 days (0.09%). This patient had multivessel PCI for NSTEMI, and developed diarrhea and Gram negative sepsis. On the seventh day post PCI, an attempted resuscitation was unsuccessful. Acute thrombosis of the circumflex artery stent was confirmed at autopsy. Two sudden deaths without autopsy occurred after discharge in NSTEMI patients, which have been classified as probable ST according to the ARC criteria. However, both patients also suffered from ischemic cardiomyopathy, which would suggest a primary rhythmogenic cause for their sudden deaths.

MACE number equals cardiovascular deaths (n=18; 1.8%) as all three cases of ST died. Cardiogenic shock was the cause of cardiovascular deaths in the majority of cases (88%), without differences in groups. ~~Cardiovascular death (n=18; 1.8%) was primarily due to cardiogenic shock (88%), without differences in groups [HR 0.67 (0.23–2.03); p=0.5].~~ Concerning bleeding complications, no increase in individualized patients occurred [HR 0.78 (0.33–1.85); p=0.574]. Slightly more than half of the bleeding complications (54%, n=14) were related to the access site ("instrumented"), requiring surgical intervention in three cases (21% of instrumented complications; 0.3% of patients). The majority of spontaneous bleeding complications were gastrointestinal (67%, n=8). One intracranial haemorrhage occurred under standard DAPT with clopidogrel 17 days after PCI for NSTEMI in an 86 year old patient.

Table 4 shows 30-day outcomes for the STEMI-, NSTE-ACS- and stable CAD cohorts.

Table 4	**Descriptive Statistics for 30 days outcome in clinical subgroups.** ~~**Thirty day clinical outcome of clinical subgroups**~~			
	Total	**Non-HPR**	**Individualized**	~~**HR (95%CI) p**~~
STEMI cohort	93	31 (33%)	62 (67%)	
Cardiovascular Death	8 (8.6%)	4 (12.9%)	4 (6.5%)	~~0.16 (0.62–0.91)~~

				~~0.04~~
non-shock	1 (1.1%)	1 (3.2%)	0 (0%)	
cardiogenic shock (n=shock patients;% of shock)	7 (17; 41%)	3 (6; 50%)	4 (11; 36%)	
Myocardial Infarction	0 (0%)	0 (0%)	0 (0%)	
Stent thrombosis				
definite	0 (0%)	0 (0%)	0 (0%)	
probable	0 (0%)	0 (0%)	0 (0%)	
Bleeding				
TIMI major and minor	6 (6.5%)	3 (9.7%)	3 (4.8%)	~~0.59 (0.10–3.42) 0.55~~
TIMI major	4 (4.3%)	2 (6.5%)	2 (3.2%)	
TIMI minor	2 (2.2%)	1 (3.2%)	1 (1.6%)	
Type				
Instrumented	5 (5.4%)	3 (9.7%)	2 (3.2%)	
Spontaneous	1 (1.1%)	0 (0%)	1 (1.6%)	
NSTE-ACS cohort	446	303 (68%)	143 (32%)	
Cardiovascular Death	10 (2.2%)	5 (1.7%)	5 (3.5%)	~~1.33 (0.33–5.26) 0.69~~
non-shock	7 (1.6%)	3 (1.0%)	4 (2.8%)	
cardiogenic shock (n=shock patients;% of shock)	3 (9; 33%)	2 (2; 100%)	1 (7; 14%)	
Myocardial Infarction	1 (0.2%)	1 (0.3%)	0 (0%)	~~0.00 (0–4.89E+261) 0.97~~
Stent thrombosis				
definite	1 (0.2%)	1 (0.3%)	0 (0%)	
probable	2 (0.4%)	2 (0.7%)	0 (0%)	
Bleeding				
TIMI major and minor	13 (2.9%)	9 (3.0%)	4 (2.8%)	~~0.58 (0.15–2.21) 0.42~~
TIMI major	4 (0.9%)	2 (0.7%)	2 (1.4%)	
TIMI minor	9 (2.0%)	7 (2.3%)	2 (1.4%)	
Type				
Instrumented	5 (1.1%)	4 (1.3%)	1 (0.7%)	
Spontaneous	8 (1.8%)	5 (1.7%)	3 (2.1%)	
Stable CAD cohort	468	330 (70%)	138 (30%)	
Cardiovascular Death	0 (0%)	0 (0%)	0 (0%)	
Myocardial Infarction	0 (0%)	0 (0%)	0 (0%)	
Stent thrombosis				
definite	0 (0%)	0 (0%)	0 (0%)	

probable	0 (0%)	0 (0%)	0 (0%)	
Bleeding				
TIMI major and minor	7 (1.5%)	5 (1.5%)	2 (1.4%)	~~0.99 (0.17–5.94)~~ ~~0.99~~
TIMI major	2 (0.4%)	2 (0.6%)	0 (0%)	
TIMI minor	5 (1.1%)	3 (0.9%)	2 (1.4%)	
Type				
Instrumented	4 (0.8%)	3 (0.9%)	1 (0.7%)	
Spontaneous	3 (0.6%)	2 (0.6%)	1 (0.7%)	

No ischemic event occurred either in the STEMI cohort, with a required high rate of individualization (67%), or in the stable CAD cohort, with a sufficient lower rate of individualization (30%). The safety endpoint of combined TIMI major and minor bleeding risk was 2× higher in NSTE-ACS patients and 4× higher in STEMI patients than in stable CAD patients (2.9% vs. 6.5% vs. 1.5%; p=0.02), without an increase associated with individualization in any subgroup.

Discussion

The main findings of our study are as follows. Firstly, routine efficient peri-interventional individualization of DAPT with MEA, incorporating the newer generations of ADP receptor blocker (prasugrel and ticagrelor), is able to minimize early ischemic events after PCI in an all-comers population including STEMI patients by nearly abolishing early definite stent thrombosis ~~as compared to the historical group~~. Secondly, intensifying platelet inhibition in patients with HPR does not increase bleeding complications compared to patients without HPR under DAPT. Thirdly, there is indirect evidence for synergistic roles of ADP- and ASA-dependent platelet activation.

For the interpretation of the very low ischemic complication rate observed during the 30 days after PCI, the most recent literature on the incidence of real world early ST in PCI for all-

comers [2324] and STEMI patients [2425,2526], as well as the complication rate in the randomized CHAMPION Phoenix trial [11], should be considered. We could show that adjusting the level of platelet inhibition reduced the rate of early definite ST to 0.09%, which is about 7-fold lower than observed in PCI for all-comers [243] and about 25- to 35-fold lower than in primary PCI for STEMI [254, 265], even with contemporary 2nd generation DES. Monitored intensification of platelet inhibition by bolus-only administration of GPI and individualized DAPT resulted in a yet more favourable outcome in our STEMI population, as no early thrombotic events occurred. Furthermore, even under randomized study conditions like the CHAMPION Phoenix trial [11], the definite ST rate after clopidogrel loading was 1.4% within 48 hours, or about 14-fold higher than in our study. Immediate ADP receptor blockade with cangrelor, however, showed a benefit with reduction to 0.8% (p=0.01), which is still about 8-fold higher than what achieved with our individualization protocol. In addition, ischemic complications were not only not driven by urgent ACS patients (4.1%), but were also numerically higher in stable CAD (7.4%). By contrast, individualization of DAPT in our stable CAD cohort, with 600 mg clopidogrel loading the day before PCI and MEA guided individualization (the latest within 2 hours after PCI), resulted in no early ischemic events. As the “first do no harm” principle should be generally applied, optimization of platelet inhibition at the time of PCI seems also of importance in this patient population, thus questioning the negative recommendation on the role of platelet function testing in stable CAD patients [2].

Three randomized multicenter trials [7-9] failed to show a clinical benefit of individualizing DAPT with the VerifyNow™ assay. Among the most common raised limitations, those in study design, protocol implementation and efficacy of platelet inhibition are the most

important. Concerning study design, the late randomization of patients, more than 12 hours after PCI, in GRAVITAS [7] and TRIGGER-PCI [9] excluded acute procedural complications attributable to insufficient platelet inhibition. This occurred even in stable CAD patients, as impressively shown in CHAMPION Phoenix [11]. Concerning protocol implementation, the ARCTIC trial [8] discharged 1.3% of patients in the active study arm without any ADP receptor blocker medication, and lost nearly 9% of patients to follow-up. TRIGGER-PCI [9] was stopped prematurely, leaving an underpowered study population. Concerning efficacy of platelet inhibition, 40% of patients in GRAVITAS [7] and 16% in ARCTIC [8] remained in HPR due to primary reloading with clopidogrel (100% in GRAVITAS and 90% in ARCTIC). By contrast, 100% of our patients were included prior to PCI and discharged with DAPT, 99.9% could be followed at 30 days and only 0.3% remained in HPR. Together, this resulted in a 1.7-fold lower rate of ST (definite and probable) than in the high dose clopidogrel arm of GRAVITAS [7] and a 3.5-fold lower rate than in the monitored arm of ARCTIC [8], despite our higher risk population, including STEMI patients.

Concerning bleeding complications, our concept of using the newer generations of ADP receptor blockers, primarily for intensifying platelet inhibition in patients with HPR to clopidogrel rather than upfront for all ACS patients without contraindications, seems beneficial. In contrast to TRITON [187] and PLATO [198], which featured significantly increased non-CABG related bleeding rates under prasugrel and ticagrelor, no increased bleeding occurred in the individualized patients compared to those on clopidogrel without HPR. The observed 1.5% TIMI major bleeding rate in our ACS cohort compares favourably to the non-CABG related TIMI major bleeding rates in the clopidogrel arms of TRITON (1.8%) and PLATO (2.2%). Furthermore, even in the highest bleeding risk group, the STEMI patients,

our blocking and bridging strategy with GPI bolus-only administration resulted in fewer TIMI major and minor bleeds (6.4%) than in the GPI arm with bolus and infusion (9.6%) of the HORIZON AMI trial [276]. Although our number of patients is admittedly far too low to draw this conclusion, GPI bolus-only administration seems suggestively comparable to the bivalirudin arm (5.9%).

Concerning the regulation of platelet activation, it is already known that thrombin- (via the protease activated receptor-1) and ADP- (via the $P2Y_{12}$ receptor) mediated platelet activation play a synergistic role in hemostasis and thrombosis [1920, 2728, 2829]. Herein, we provide indirect evidence for a synergistic role of ADP- and ASA- (cyclooxygenase) dependent platelet activation. We observed an interplay between AA- and ADP- induced platelet aggregability, as HPR to AA was significantly associated with HPR to ADP, and solitary reloading with ADP receptor blocker in patients with HPR to ADP and AA was able to successfully resolve intermediate levels of HPR to AA without ASA reloading.

Limitations of our study include primarily the observational, non-randomized nature of the registry without a control group concerning efficacy, and the monocentric design.

In conclusion, our data strongly suggest that HPR represents a modifiable risk factor that can be used for tailoring treatment in PCI patients, rather than a marker of higher risk only. Effective individualization of DAPT for PCI under MEA guidance is able to minimize early ischemic complications to a so far unreported degree. Further properly designed randomized multicenter trials utilizing MEA seem warranted.

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Contributorship statement

G. Christ: conception and design of the registry; acquisition, analysis and interpretation of data, drafting and revising the manuscript critically for important intellectual content; final approval of the version to be published; J.M. Siller-Matula: design of the registry, analysis and interpretation of data, revising the manuscript critically for important intellectual content; final approval of the version to be published; M. Francesconi: design of the registry, acquisition and analysis of data, revising the manuscript critically for important intellectual content; final approval of the version to be published; C. Dechant: design of the registry, acquisition and analysis of data, revising the manuscript critically for important intellectual content; final approval of the version to be published; K. Grohs: design of the registry, analysis of data, revising the manuscript critically for important intellectual content; final approval of the version to be published; A. Podczeck-Schweighofer: design of the registry; interpretation of data, revising the manuscript critically for important intellectual content; final approval of the version to be published;

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. ~~G. Christ: concept and design, analysis and interpretation of data; writing; JM Siller-Matula: analysis and interpretation of data; revising the intellectual content, critical~~

~~writing; M. Francesconi: concept and design, C. Dechant: analysis and interpretation of data, K. Grohs: analysis of data and revising the intellectual content, A. Podczeck-Schweighofer: revising the intellectual content~~

Data sharing statement:

No additional data available

Disclosures

None

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Figures

Figure 1: Algorithm of ADP receptor blocker treatment

ADP = adenosine diphosphate, CAD = coronary artery disease, GPI = glycoprotein IIbIIIa inhibitor, MEA = multiple electrode aggregometry, NSTE-ACS = non-ST-elevation acute coronary syndrome, STEMI = ST-elevation myocardial infarction.

* loading in stable patients the day before angiography; ** platelet testing not earlier than 12 hours after loading, and at the latest at the time of diagnostic angiography, after GPI administration serial testing up to 7 days; *** platelet testing the day after ~~angiography~~reloading; **** platelet testing 1 week after starting 5 mg prasugrel; # up to three clopidogrel reloadings; ## prasugrel reloading dependent on residual reactivity: ADP >80: 60 mg, ADP 60–79: 30 mg, ADP 50–59: 10mg; ### in patients <60 kg and/or >75 years

Figure 2: Flow chart of study patients

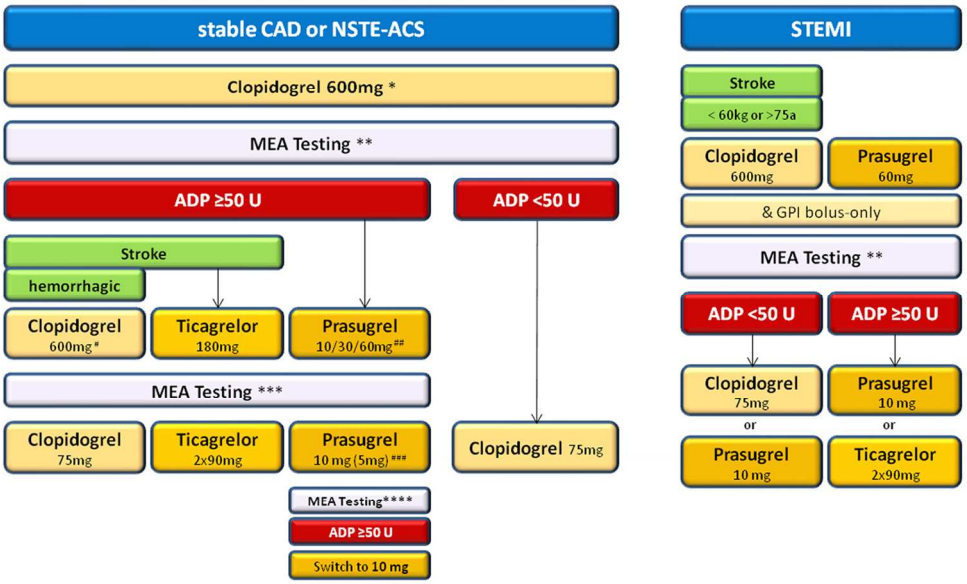
CTO = chronic total occlusion, PCI = percutaneous coronary intervention

Figure 3: Flow chart of primary ADP receptor blocker and ASA loading and reloading

A) ADP receptor blocker loading. Only 0.3% of patients (n=3) showed persisting HPR to ADP (≥50 U): two patients after 4 × 600 mg clopidogrel loading (as prasugrel was not yet available) and one patient on prasugrel (as ticagrelor was not yet available). B) HPR to AA-induced aggregation (>35 U) occurred to a significant higher proportion in patients with HPR to ADP (ADP ≥50 U). In patients with HPR to ADP and intermediate HPR to AA (AA <60 U) only ADP receptor blocker reloading successfully treated also HPR to AA. AA = Arachidonic Acid, ADP = adenosine diphosphate, ASA = acetylic salicylic acid.

Figure 4: ADP-induced aggregation after 600 mg Clopidogrel or 60 mg Prasugrel loading and effect of reloading

A) Of clopidogrel loaded patients, 30% showed a high on-treatment platelet reactivity (= non-responder), effectively treated by reloading (except for two patients as prasugrel and ticagrelor had not yet been available). B) Of prasugrel loaded patients, 2% showed a high on-treatment platelet reactivity (= non-responder), effectively treated by ticagrelor.



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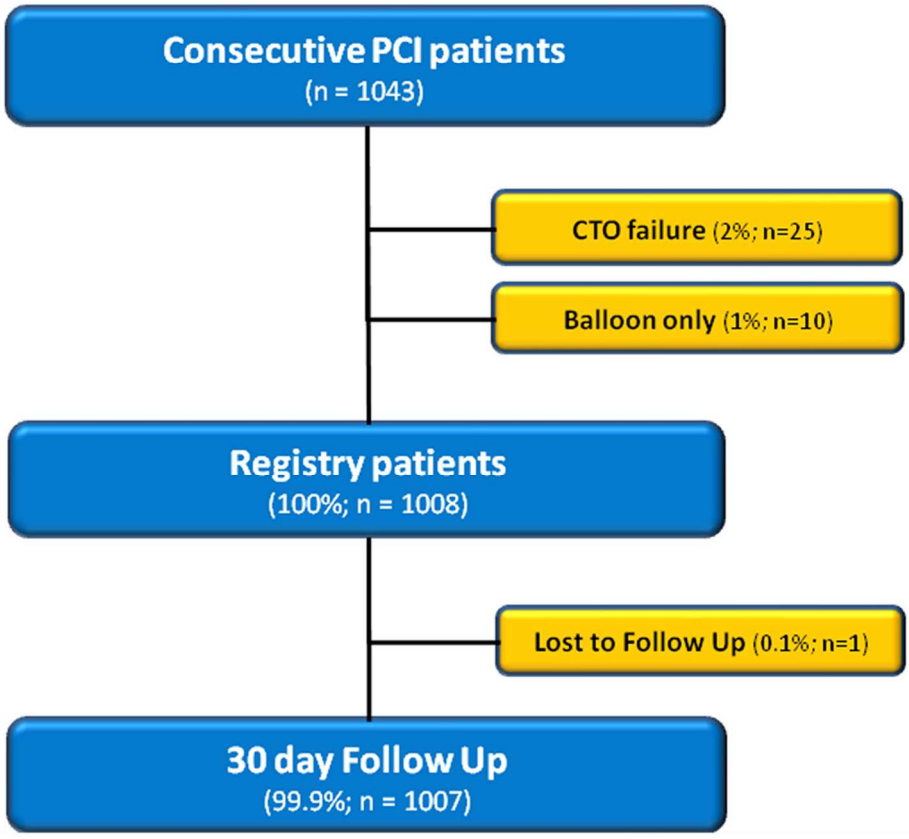

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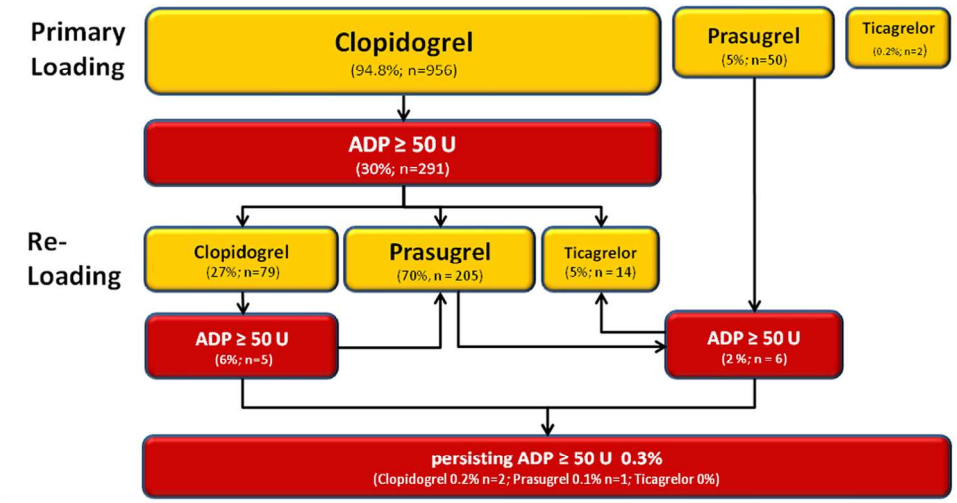

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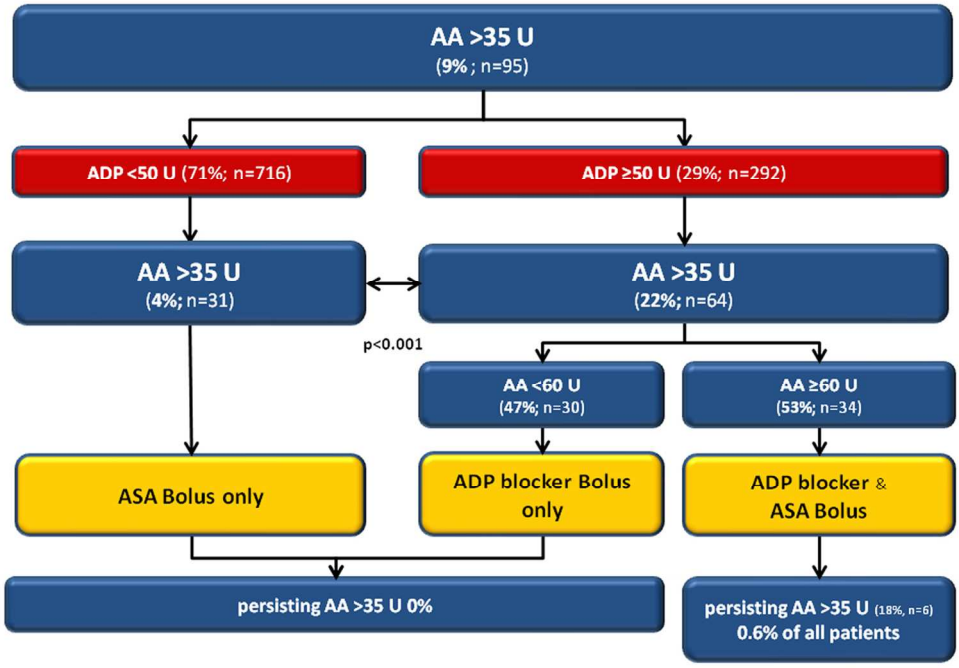

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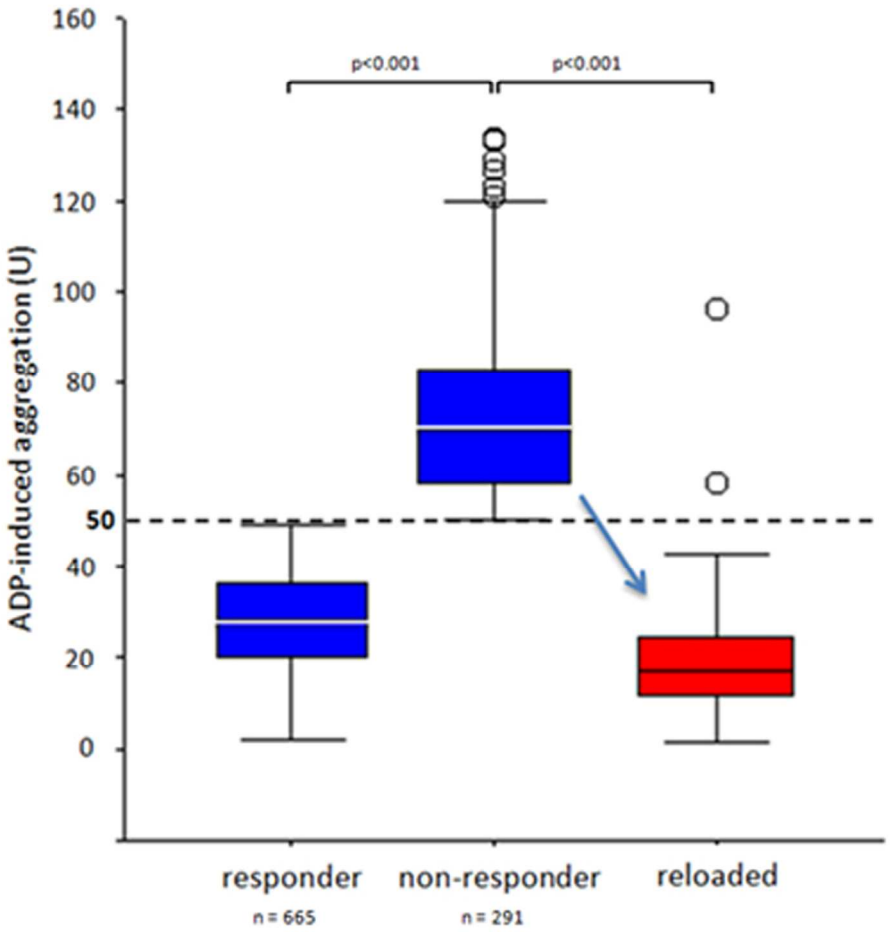

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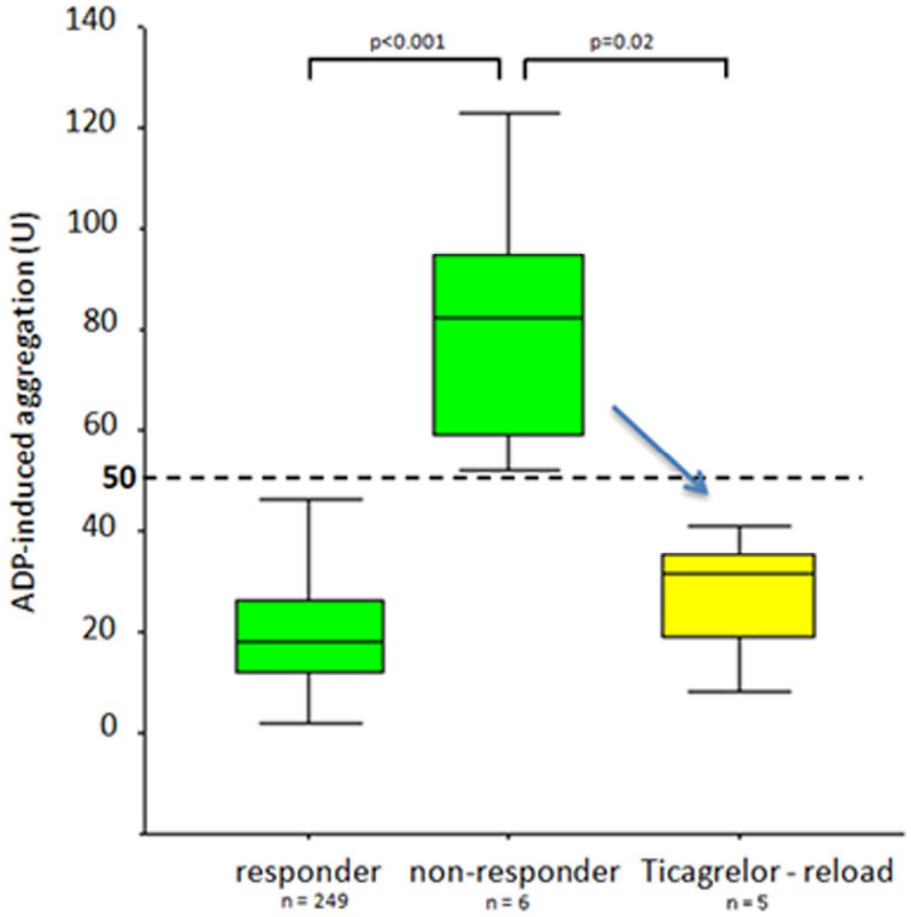

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B) Of prasugrel loaded patients, 2% showed a high on-treatment platelet reactivity (= non-responder), effectively treated by ticagrelor.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*11*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**:1453-7

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Individualizing Dual Antiplatelet Therapy after Percutaneous Coronary Intervention: The IDEAL-PCI Registry.

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Individualizing Dual Antiplatelet Therapy after Percutaneous Coronary Intervention: The IDEAL-PCI Registry.

Günter Christ* MD, Jolanta M. Siller-Matula† MD PhD, Marcel Francesconi* MD, Cornelia Dechant* MD, Katharina Grohs‡ MD and Andrea Podczeck-Schweighofer* MD

* 5th Medical Department with Cardiology, Kaiser Franz Josef Hospital, Vienna, Austria

† Department of Cardiology, Medical University of Vienna, Austria

‡ Clinical Institute for Laboratory Medicine, Kaiser Franz Josef Hospital, Vienna, Austria

Correspondence: Prof. Günter Christ, MD

5th Medical Department with Cardiology, Kaiser Franz Josef Hospital

Kundratstr. 3, 1100 Vienna, Austria

Tel.: +43-1-60191-2508

Fax: +43-1-60191-2509

E-mail: guenter.christ@wienkav.at

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Abstract

Objective: To evaluate the clinical utility of individualizing dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) in an all-comers population, including ST-elevation myocardial infarction (STEMI) patients.

Setting: Tertiary care single centre registry

Participants: 1008 consecutive PCI patients with stent implantation, without exclusion criteria.

Intervention: Periinterventional individualization of DAPT, guided by multiple electrode aggregometry (MEA), to overcome high on-treatment platelet reactivity (HPR) to adenosine diphosphate (ADP)- (≥50 U) and arachidonic acid (AA)-induced aggregation (>35 U).

Outcome measures: The primary efficacy endpoint was definite stent thrombosis (ST) at 30 days. The primary safety endpoint was TIMI major and minor bleeding. Secondary endpoints were probable ST, myocardial infarction, cardiovascular death and the combined endpoint major cardiac adverse event (MACE).

Results: 53% of patients presented with acute coronary syndrome (9% STEMI, 44% non-ST-elevation). HPR to ADP after 600 mg clopidogrel loading occurred in 30% of patients (73±19 U vs. 28±11 U; p<0.001) and was treated by prasugrel or ticagrelor (73%) or clopidogrel (27%) reloading (22±12 U; p<0.001). HPR to ADP after prasugrel loading occurred in 2% of patients (82±26 U vs. 19±10 U; p<0.001) and was treated with ticagrelor (34±15 U; p=0.02). HPR to AA occurred in 9% of patients with a significant higher proportion in patients with HPR to ADP (22% vs. 4%, p<0.001) and was treated with aspirin reloading. Definite ST occurred in 0.09% of patients (n=1); probable ST, myocardial infarction, cardiovascular death and MACE occurred in 0.19% (n=2), 0.09% (n=1) and 1.8% (n=18) of patients. TIMI major and

minor bleeding did not differ between patients without HPR and individualized patients (2.6% for both).

Conclusions: Individualization of DAPT with MEA minimizes early thrombotic events in an all-comers PCI population to an unreported degree without increasing bleeding. A randomized multicenter trial utilizing MEA seems warranted.

Trial Registration: http://www.clinicaltrials.gov; NCT01515345

Keywords: percutaneous coronary intervention, platelet function testing, dual antiplatelet therapy

Article summary

Strengths and limitations of this study

The strengths of our study are, at first the real world percutaneous coronary intervention setting with inclusion of every consecutive patient with stent implantation, without any exclusion criteria. Second, the consequent and efficient peri-interventional individualization of dual antiplatelet therapy, leaving only 0.3% of patients on high on-treatment platelet reactivity to adenosine diphosphate at the time of hospital discharge. Third, the minimization of ischemic events within 30 days by nearly abolishing early definite stent thrombosis, without increasing bleeding complications.

Limitations of our study are the non randomised and monocentric registry design without control group concerning ischemic events.

Introduction

High on-treatment platelet reactivity (HPR) to adenosine diphosphate (ADP) represents one of the strongest independent risk factors for post-percutaneous coronary intervention

(PCI) ischemic events in patients given dual antiplatelet therapy (DAPT), according to numerous observational studies using various platelet function tests [1-3].

Whether HPR represents only a marker of higher risk or a modifiable risk factor is still a matter of debate [2], as prospective randomized trials evaluating personalized antiplatelet therapy aiming to overcome HPR resulted in conflicting data. Smaller randomized trials [4], as well as non-randomized studies [5] and a recent meta-analysis [6] suggested a significant clinical benefit, but three randomized studies failed to do so [7-9]. However, each of these trials, utilizing the VerifyNow™ assay, was afflicted with major limitations potentially masking the real value of individualizing DAPT after PCI in daily practice [1, 10]. Their low-risk population and primarily the high selection bias in GRAVITAS [7] and TRIGGER-PCI [9], with patient inclusion more than 12 hours after PCI, seems to cloud the potential importance of optimizing platelet inhibition at the time of PCI. By contrast, the very recent CHAMPION Phoenix trial [11] provides a more realistic scenario of expectable ischemic complications during and after PCI. More than 11,000 patients with oral clopidogrel loading, including the whole clinical PCI spectrum [56% stable coronary artery disease (CAD), 26% non-ST-elevation acute coronary syndrome (NSTE-ACS), 18% ST-elevation myocardial infarction (STEMI)], were pre-interventionally randomized to receive an intravenous (i.v.) bolus and infusion of cangrelor, a fast acting reversible ADP receptor blocker. Ischemic complications in the whole study cohort occurred in 5.3%, including a definite stent thrombosis (ST) rate of 1.1% during the first 48 hours. Notably, the majority of events occurred within 6 hours after PCI.

HPR to acetylic salicylic acid (ASA) is less well studied and its clinical relevance is unclear. The ADAPT-DES registry [3] found no difference in response to ASA, measured by the VerifyNow™ assay, between patients with and without ST. Data not only from our group,

however, suggested that dual HPR to both ADP- and arachidonic acid- (AA; reflecting response to ASA) induced aggregation, measured by multiple electrode aggregometry (MEA) [12] or the VerifyNow assay [13], predisposes patients to a higher ischemic risk than single HPR. Furthermore, MEA has been shown to effectively assess the risk of HPR to ADP after PCI [14] with higher accuracy than the vasodilator-stimulated phosphoprotein phosphorylation (VASP) assay [15] utilized in the Bonello studies.

Therefore, our registry aimed to evaluate the impact of individualizing DAPT with MEA in an all-comers population, including STEMI patients without exclusion criteria, by peri-interventional treatment of HPR to both ADP and AA.

Methods

Patient population

This was a prospective, single-centre cohort observation of consecutive PCI patients, including all forms of ACS (including cardiogenic shock) and all stable CAD, with stent implantation or drug eluting balloon dilatation (for treatment of instent restenosis), and without exclusion criteria (secondary causes for ACS, like anaemia had to be corrected according to standard patient care, but did not represent an exclusion criterion, nor did thrombocytopenia or liver dysfunction once the indication for an invasive approach was given). Patients without stent implantation (i.e. unsuccessful reopening of a chronic total occlusion or balloon dilatation only) were not included. Peri-interventional individualization of platelet inhibition was performed according to the protocol shown in Figure 1 and described in detail below. The local Ethics Committee approved the study protocol in accordance with the Declaration of Helsinki. Participants were included between November 2008 and June 2012. Informed consent was obtained after PCI, either from the patient or

from the guardian in cases of critically ill conditions. Follow-up information was obtained by either direct outpatient visit or telephone contact at 30 days.

Study endpoints

The primary efficacy endpoint was definite ST during a 30 days follow-up. The secondary efficacy outcome parameters were probable ST, myocardial infarction and cardiovascular death, as well as the combination of the above mentioned endpoints as major cardiac adverse events (MACE). Definite and probable ST were defined according to the Academic Research Consortium (ARC) [16] and diagnosed by the authors without blinded adjudication. The primary safety end point was the incidence of TIMI bleeding complications [17]. TIMI major bleeding was defined as intracranial bleeding or overt bleeding with a decrease in haemoglobin ≥5 g/dL. TIMI minor bleeding was defined as observed bleeding with decrease in haemoglobin ≥3 to <5 g/dL.

Individualization of dual antiplatelet therapy

Individualization of ADP receptor blocker treatment was performed according to the algorithm presented in Figure 1. After an initial clopidogrel loading dose of 600 mg, on-treatment platelet reactivity was measured the next day by MEA, at the earliest after 12 hours and at the latest at the time of diagnostic angiography. HPR was defined as ≥50 U ADP-induced aggregation. This cut-off represents the mean of published data from Sibbing and our group [14, 15]. From November 2008 to May 2009, patients with HPR were reloaded with clopidogrel 600 mg up to three times according to the Bonello protocol [4]. After prasugrel [18] became available in June 2009, HPR to clopidogrel was treated with prasugrel (Efient/Effient®) loading, depending on the degree of the residual ADP-induced platelet

reactivity: Cases with ADP >80 U received 60 mg, ADP 60–79 U 30 mg, and ADP 50–59 U 10 mg of prasugrel. This staged approach was chosen in order to avoid potential bleeding complications due to the observed overresponse (i.e. very "flat" ADP and ASPI curves, <10-15 U) after a routine prasugrel 60mg loading in patients with borderline clopidogrel response (ADP 50-60 U). In patients older than 75 years or weighing less than 60 kg, the maintenance dose (MD) of prasugrel was reduced to 5 mg according to the manufacturer's specification, with MEA testing 1 week later and dose adjustments if necessary. In cases of contraindications to prasugrel (history of stroke), clopidogrel reloadings were performed, until ticagrelor (Brilique/Brilinta®) became available. STEMI patients younger than 75 years and weighing more than 60 kg without history of stroke were primarily loaded with 60 mg prasugrel due to the local standard operating procedure of the Viennese STEMI network. After ticagrelor [19] became available in March 2011, HPR to prasugrel and HPR to clopidogrel in patients with contraindications to prasugrel were treated with 180 mg ticagrelor loading. In cases of contraindications to ticagrelor (history of intracranial haemorrhage), clopidogrel reloadings were performed. Special care was taken to limit the possibility of HPR at the time of PCI by clopidogrel loading at least 12 hours prior to PCI, with reloading if necessary either prior PCI in case MEA testing was already known, or the latest 1–2 hours after PCI. In case no oral ADP receptor blocker loading, or only within 4–6 hours pre-PCI was given [e.g., STEMI or urgent invasive non-STEMI (NSTEMI) patients], bolus-only administration of a glycoprotein IIbIIIa inhibitor (GPI) was performed [intracoronary (i.c.) abciximab (0.25 mg/kg; Reopro®) or i.v. eptifibatide (180 µg/kg, Integrilin®)]. Thereafter, serial MEA measurements were performed up to 7 days to allow determination of the level of oral ADP receptor inhibition. Details of this blocking and bridging strategy have been

published previously [20]. At discharge all patients should be within the therapeutic range of platelet inhibition (i.e., non-HPR).

Individualization of ASA treatment was conducted as follows. Stable patients without chronic ASA treatment were loaded with 300 mg ASA p.o. the day before angiography. ACS patients were loaded with ASA i.v.: 500 mg was used in ASA naïve patients and 250 mg was used in cases of chronic ASA treatment. HPR to ASA was defined as >35 U AA-induced aggregation. This cut-off represents a mean derived from published data [12, 21] and the MEA manufacturer's recommendations. ASA reloading was performed with either 300 mg p.o or 250 mg i.v. In cases of HPR to both ADP and ASA, first ADP receptor blocker reloading was performed with ASA reloading if necessary after MEA testing the next day.

PCI was performed according to current standard guidelines. The type of stent implanted was at the discretion of the interventional cardiologist. In cases of drug eluting stent (DES) implantation, only 2nd generation DES were used (Biolimus-eluting: Biomatrix™; Everolimus-eluting: Promus Element™ and Xience™; Zotarolimus-eluting: Resolute™). All patients received 100 IU/kg of unfractionated heparin, with adjustments according to measurements of activated clotting time, except in cases of GPI bolus administration where only 70 IU/kg were given.

Impedance aggregometry

Whole blood aggregation was determined using MEA, a new-generation impedance aggregometer (Multiplate™ Analyzer, Roche, Munich, Germany). The system detects the electrical impedance change due to the adhesion and aggregation of platelets on two independent electrode-set surfaces in the test cuvette, with a low rate of intra-and interassay variability [22]. ADP and AA were used as agonists. A 1:2 dilution of whole blood

anticoagulated with hirudin and 0.9% NaCl was stirred at 37°C for 3 min in the test cuvette. ADP (6.4 µM) and AA (0.5 mM) were added, and the increase in electrical impedance was continuously recorded for 6 min. The mean values of the two independent determinations were expressed as the area under the curve (AUC) of the aggregation tracing. AUC is reported herein in units (U), as described previously [23].

Statistical analysis

Data are expressed as mean ± standard deviation (SD). Statistical comparisons were performed with the Mann Whitney U test, the paired and unpaired Student t-test and chi-squared test. COX regression analysis was performed to compare event rates between the non-HPR group and the individualized treatment group. As the power of the study was limited due to the low event rate, we provide crude and adjusted HR. The adjustment was done for gender, body mass index, diabetes, hyperlipidemia, use of calcium channel blockers (CCB) and proton pump inhibitors (PPI), clinical presentation, platelet count and cardiogenic shock. All statistical calculations were performed using commercially available statistics analysis software (SPSS Version 21; Chicago).

Sample size

We estimated that the sample size of 1008 patients would provide 80% power to demonstrate a reduction in the incidence of ST by individualization of antiplatelet therapy, on the basis of assumptions of ST rates during one month follow-up. We expected a 0.2% rate of ST at 1 month in patients without HPR, as compared to a 1.9% rate in a historical group of patients with HPR [3, 5, 14]. Thus, if the hazard ratio (HR) for ST was 3.0–4.0-fold lower in patients without HPR than in those with HPR [3], the study would have more than

80% power to demonstrate that individualized antiplatelet therapy in patients with HPR reduces the rate of ST.

Results

Patient inclusion and baseline characteristics

Of 1043 consecutive PCI patients, only those with unsuccessful reopening of a chronic total occlusion or with conventional balloon-only PCI were excluded (n=35), leaving 1008 participants (Figure 2). All STEMI patients received a primary PCI. At 30 days, one patient (0.09%), a French tourist, was lost to follow-up. Table 1 shows the demographic variables of our patient cohort and differences between the group without HPR after clopidogrel loading (non-HPR) and the individualized group (i.e., ADP receptor blocker reloading and primary prasugrel or ticagrelor loading).

Table 1 **Baseline characteristics**

	Total (n=1008)	**Non-HPR** (n=665; 66%)	**Individualized** (n=343; 34%)	
Age	64.7±11.8	65.1±11.7	63.9±11.9	ns
Women	303 (30%)	183 (28%)	120 (35%)	0.01
Body Mass Index (kg/m^2)	28.4±4.6	28.1±4.5	29.1±4.8	0.001
Diabetes	321 (32%)	196 (30%)	125 (36%)	0.03
Insulin treatment	84 (8%)	41 (6%)	43 (13%)	0.001
Oral medication	237 (24%)	155 (23%)	82 (24%)	ns
Smoker	504 (50%)	334 (50%)	170 (50%)	ns
Hypertension	842 (84%)	557 (84%)	285 (83%)	ns
Hyperlipidemia	855 (85%)	552 (83%)	303 (88%)	0.03
Family history	272 (27%)	181 (27%)	91 (27%)	ns
History of myocardial infarction	212 (21%)	139 (21%)	73 (21%)	ns
History of PCI	190 (19%)	130 (20%)	60 (18%)	ns
History of CABG	60 (6%)	42 (6%)	18 (5%)	ns
Cerebrovascular disease	115 (11%)	71 (11%)	44 (13%)	ns
Peripheral vascular disease	133 (13%)	92 (14%)	41 (12%)	ns

Clinical presentation				<0.001
STEMI	93 (9%)	31 (5%)	62 (18%)	
NSTE-ACS	447 (44%)	304 (46%)	143 (41%)	
NSTEMI	393 (39%)	261 (39%)	132 (38%)	
Unstable Angina	54 (5%)	43 (7%)	11 (3%)	
Stable angina	468 (47%)	330 (50%)	138 (41%)	
Cardiogenic shock	26 (3%)	8 (1%)	18 (5%)	<0.001
Platelet count x10^3/µl	251±81	239±74	276±88	<0.001
Co-medication				
Statin	929 (92%)	612 (92%)	317 (92%)	ns
Proton pump inhibitor	649 (64%)	397 (60%)	252 (74%)	<0.001
Calcium channel blocker	195 (19%)	116 (17%)	79 (23%)	0.03
Betablocker	771 (77%)	515 (77%)	256 (75%)	ns
ACE-I/ARB	764 (76%)	494 (74%)	270 (79%)	ns

(ACE-I = Angiotensin converting enzyme inhibitor; ARB = Angiotensin receptor blocker; CABG = coronary artery bypass graft; HPR = high on-treatment platelet reactivity; NSTE-ACS = Non ST-elevation acute coronary syndrome; NSTEMI = Non ST-Elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction)

Patients in the individualized group were more frequently of female gender (p=0.01), had higher bodyweight (p=0.001), and a greater incidence of diabetes (p=0.003), especially insulin dependent (p=0.001), STEMI and cardiogenic shock (p<0.001). Higher platelet counts (p<0.001), and co-medication with PPI (p<0.001) and CCB (p=0.03), were also significantly associated with individualization of DAPT.

Angiographic and interventional details

Table 2 shows angiographic and procedural characteristics according to platelet inhibition (non-HPR versus individualized group).

Table 2	**Angiographic and interventional details**			
	Total (n=1008)	**Non-HPR** (n=665; 66%)	**Individualized** (n=343; 34%)	**p**

Type of intervention				ns
Stent	1000 (99%)	661 (99%)	339 (99%)	
Drug Eluting	948 (94%)	625 (94%)	323 (94%)	
Bare Metal	52 (5%)	36 (5%)	16 (5%)	
Balloon (Drug Eluting)	8 (1%)	4 (1%)	4 (1%)	
Access site				ns
femoral	867 (86%)	571 (86%)	296 (86%)	
radial	117 (12%)	77 (12%)	40 (12%)	
Both	24 (2%)	17 (2%)	7 (2%)	
Lesion location				ns
Left Main	114 (11%)	78 (12%)	36 (11%)	
Left anterior descending	585 (58%)	391 (59%)	194 (57%)	
Left circumflex	401 (40%)	277 (42%)	124 (36%)	
Right coronary artery	443 (44%)	285 (43%)	158 (46%)	
Bypass graft	18 (2%)	12 (2%)	6 (2%)	
AHA/ACC Type b2/c	739 (73%)	490 (74%)	249 (73%)	ns
Stent length total (mm; range)	43±33 (8–241)	44±32 (8–241)	43±33 (8–217)	ns
Stents/patient (range)	2.2±1.5 (1–12)	2.2±1.5 (1–12)	2.1±1.6 (1–12)	ns
Multivessel disease	655 (65%)	428 (64%)	227 (66%)	ns

The rate of DES implantation was high (94%), and of these 20% were biolimus-eluting, 49% everolimus-eluting and 25% zotarolimus-eluting. Multivessel disease was present in 65% of patients, with a high proportion of complex lesion morphology (Type b2/c: 73%), including 11% left main and 58% left anterior descending artery lesions, resulting in 2.2±1.5 implanted stents/patient (mean stent length 43±33 mm). The rate of use of a femoral access site for PCI during the registry period was high (86%). All parameters showed no differences between groups.

Primary ADP receptor blocker loading and individualization of ADP receptor blocker therapy.

As shown in Figure 3A, 94.8% of patients were primarily loaded with 600 mg clopidogrel, 5% with 60 mg prasugrel (STEMI patients <75 years and >60 kg without history of stroke) and 0.2% with 180 mg ticagrelor (known clopidogrel allergy). Of the clopidogrel loaded patients, 30% showed HPR. Clopidogrel reloadings of 600 mg were performed up to three times in 27% of patients with HPR, leaving five patients with persisting HPR, of whom three were finally switched to prasugrel during the observation period, as it became available. Prasugrel reloading was performed in 70% of patients with HPR. Of the prasugrel loaded patients, 2% showed HPR, which was successfully treated with ticagrelor reloading; this was also performed in 3% of patients with HPR to clopidogrel and contraindications to prasugrel. Only three patients remained in HPR during the observation period, and were put on a higher MD (two on clopidogrel 150 mg, one on prasugrel 20 mg as ticagrelor was not yet available). For patients older than 75 years or weighing less than 60 kg, prasugrel 5 mg was primarily prescribed (15% of prasugrel patients, n=37). After MEA testing 1 week later, 14% (n=5) were switched to 10 mg.

ASA-dependent platelet aggregation and reloading

After ASA and ADP receptor blocker loading, 9% of our patients showed a HPR to AA-induced aggregation (68±28 U vs. 16±8 U; p<0.001). As shown in Figure 3B, HPR to AA was significantly more prevalent in patients with HPR to ADP (22% vs. 4%; p<0.001). HPR to AA without HPR to ADP (63±29 U) was treated by ASA reloading successfully in all patients (14±6 U; p<0.001). In patients with HPR to ADP, the HPR to AA was influenced by the extent of the residual AA-induced platelet aggregation, as follows. In patients with intermediate HPR to AA (<60 U), only ADP receptor blocker reloading was sufficient to treat HPR to AA as well (from 45±7 U to 15±10 U; p<0.001). In patients with high HPR to AA (≥60 U) an additional

ASA reloading was necessary to significantly reduce AA-induced aggregation from 92±21 U to 20±16 U (p<0.001). Six of these patients showed persisting HPR to AA and were discharged on 300 mg ASA.

Platelet aggregation in clopidogrel and prasugrel loaded patients and effect of reloading.

ADP-induced aggregation after 600 mg clopidogrel loading was significantly higher in patients with HPR (= non-responder: 73±19 U) than without (= responder: 28±11 U; p<0.001) (Figure 4A). Reloading effectively treated HPR (22±12 U; p<0.001), except in two patients for whom prasugrel was not yet available. ADP-induced aggregation after 60 mg prasugrel loading was significantly higher in patients with HPR (= non-responder: 82±26 U) than without (= responder: 19±10 U; p<0.001), and was successfully treated with ticagrelor reloading (34±15 U; p=0.02) (Figure 4B).

Glycoprotein IIbIIIa inhibitor (GPI) treatment

GPI was given to 61% (n=57) of STEMI patients, with an i.c. abciximab bolus only in 91% (n=52) and an i.v. eptifibatide bolus only in 9% (n=5). Non-STEMI (NSTEMI) patients received a GPI treatment in 11% (n=47) of cases, with an i.c. abciximab bolus only in 72% (n=34) and an i.v. eptifibatide bolus only in 28% (n=13).

Clinical outcome at 30 days

Table 3 shows the clinical outcome of the overall patient cohort.

Table 3	**Thirty day clinical outcome**				
	Total (n=1007)	**Non-HPR** (n=664, 66%)	**Individualized** (n=343, 34%)	**adj. HR** (95%CI) **p**	**crude HR** (95%CI) **p**
MACE (Cardiovascular Death, Myocardial Infarction, Stent thrombosis)	18 (1.8%)	9 (1.4%)	9 (2.6%)	0.67 (0.23–2.03) 0.5	0.51 (0.20–1.30) 0.16

Cardiovascular Death	18 (1.8%)	9 (1.4%)	9 (2.6%)		
non-shock	8 (0.8%)	4 (0.6%)	4 (1.2%)		
cardiogenic shock (n=shock patients; % of shock)	10 (26; 38%)	5 (8; 62%)	5 (18; 28%)		
Myocardial Infarction	1 (0.09%)	1 (0.15%)	0 (0%)		
Stent thrombosis					
definite and probable	3 (0.29%)	3 (0.45%)	0 (0%)		
definite	1 (0.09%)	1 (0.15%)	0 (0%)		
probable	2 (0.19%)	2 (0.3%)	0 (0%)		
Bleeding					
TIMI major and minor	26 (2.6%)	17 (2.6%)	9 (2.6%)	0.78 (0.33–1.85) 0.574	0.96 (0.42–2.20) 0.914
TIMI major	10 (1.0%)	6 (0.9%)	4 (1.2%)		
TIMI minor	16 (1.6%)	11 (1.7%)	5 (1.5%)		
Type					
Instrumented	14 (1.4%)	10 (1.5%)	4 (1.2%)		
Spontaneous	12 (1.2%)	7 (1.1%)	5 (1.5%)		

(MACE = major adverse cardiac event)

No acute ST occurred within 24 hours in the whole patient cohort. 3 patients died in cardiogenic shock within 24 hours after successful PCI without evidence of ST at autopsy. Only one subacute definite ST, which also accounted for the only myocardial infarction, occurred within 30 days (0.09%). This patient had multivessel PCI for NSTEMI, and developed diarrhea and Gram negative sepsis. On the seventh day post PCI, an attempted resuscitation was unsuccessful. Acute thrombosis of the circumflex artery stent was confirmed at autopsy. Two sudden deaths without autopsy occurred after discharge in NSTEMI patients, which have been classified as probable ST according to the ARC criteria. However, both patients also suffered from ischemic cardiomyopathy, which would suggest a primary rhythmogenic cause for their sudden deaths. MACE number equals cardiovascular deaths (n=18; 1.8%) as all three cases of ST died. Cardiogenic shock was the cause of cardiovascular deaths in the majority of cases (88%), without differences in groups. Concerning bleeding complications,

no increase in individualized patients occurred (2.6% TIMI major and minor bleedings in both groups). Slightly more than half of the bleeding complications (54%, n=14) were related to the access site ("instrumented"), requiring surgical intervention in three cases (21% of instrumented complications; 0.3% of patients). The majority of spontaneous bleeding complications were gastrointestinal (67%, n=8). One intracranial haemorrhage occurred under standard DAPT with clopidogrel 17 days after PCI for NSTEMI in an 86 year old patient.

Table 4 shows 30-day outcomes for the STEMI-, NSTE-ACS- and stable CAD cohorts.

Table 4. Descriptive Statistics for 30 days outcome in clinical subgroups.

	Total	Non-HPR	Individualized
STEMI cohort	93	31 (33%)	62 (67%)
Cardiovascular Death	8 (8.6%)	4 (12.9%)	4 (6.5%)
non-shock	1 (1.1%)	1 (3.2%)	0 (0%)
cardiogenic shock (n=shock patients; % of shock)	7 (17; 41%)	3 (6; 50%)	4 (11; 36%)
Myocardial Infarction	0 (0%)	0 (0%)	0 (0%)
Stent thrombosis			
definite	0 (0%)	0 (0%)	0 (0%)
probable	0 (0%)	0 (0%)	0 (0%)
Bleeding			
TIMI major and minor	6 (6.5%)	3 (9.7%)	3 (4.8%)
TIMI major	4 (4.3%)	2 (6.5%)	2 (3.2%)
TIMI minor	2 (2.2%)	1 (3.2%)	1 (1.6%)
Type			
Instrumented	5 (5.4%)	3 (9.7%)	2 (3.2%)
Spontaneous	1 (1.1%)	0 (0%)	1 (1.6%)
NSTE-ACS cohort	446	303 (68%)	143 (32%)
Cardiovascular Death	10 (2.2%)	5 (1.7%)	5 (3.5%)
non-shock	7 (1.6%)	3 (1.0%)	4 (2.8%)
cardiogenic shock (n=shock patients;% of shock)	3 (9; 33%)	2 (2; 100%)	1 (7; 14%)
Myocardial Infarction	1 (0.2%)	1 (0.3%)	0 (0%)
Stent thrombosis			

definite	1 (0.2%)	1 (0.3%)	0 (0%)
probable	2 (0.4%)	2 (0.7%)	0 (0%)
Bleeding			
TIMI major and minor	13 (2.9%)	9 (3.0%)	4 (2.8%)
TIMI major	4 (0.9%)	2 (0.7%)	2 (1.4%)
TIMI minor	9 (2.0%)	7 (2.3%)	2 (1.4%)
Type			
Instrumented	5 (1.1%)	4 (1.3%)	1 (0.7%)
Spontaneous	8 (1.8%)	5 (1.7%)	3 (2.1%)
Stable CAD cohort	468	330 (70%)	138 (30%)
Cardiovascular Death	0 (0%)	0 (0%)	0 (0%)
Myocardial Infarction	0 (0%)	0 (0%)	0 (0%)
Stent thrombosis			
definite	0 (0%)	0 (0%)	0 (0%)
probable	0 (0%)	0 (0%)	0 (0%)
Bleeding			
TIMI major and minor	7 (1.5%)	5 (1.5%)	2 (1.4%)
TIMI major	2 (0.4%)	2 (0.6%)	0 (0%)
TIMI minor	5 (1.1%)	3 (0.9%)	2 (1.4%)
Type			
Instrumented	4 (0.8%)	3 (0.9%)	1 (0.7%)
Spontaneous	3 (0.6%)	2 (0.6%)	1 (0.7%)

No ischemic event occurred either in the STEMI cohort, with a required high rate of individualization (67%), or in the stable CAD cohort, with a sufficient lower rate of individualization (30%). The safety endpoint of combined TIMI major and minor bleeding risk was 2× higher in NSTE-ACS patients and 4× higher in STEMI patients than in stable CAD patients (2.9% vs. 6.5% vs. 1.5%; p=0.02), without an increase associated with individualization in any subgroup.

Discussion

The main findings of our study are as follows. Firstly, routine efficient peri-interventional individualization of DAPT with MEA, incorporating the newer generations of ADP receptor blocker (prasugrel and ticagrelor), is able to minimize early ischemic events after PCI in an

all-comers population including STEMI patients by nearly abolishing early definite stent thrombosis. Secondly, intensifying platelet inhibition in patients with HPR does not increase bleeding complications compared to patients without HPR under DAPT. Thirdly, there is indirect evidence for synergistic roles of ADP- and ASA- dependent platelet activation.

For the interpretation of the very low ischemic complication rate observed during the 30 days after PCI, the most recent literature on the incidence of real world early ST in PCI for all-comers [24] and STEMI patients [25,26], as well as the complication rate in the randomized CHAMPION Phoenix trial [11], should be considered. We could show that adjusting the level of platelet inhibition reduced the rate of early definite ST to 0.09%, which is about 7-fold lower than observed in PCI for all-comers [24] and about 25- to 35-fold lower than in primary PCI for STEMI [25, 26], even with contemporary 2nd generation DES. Monitored intensification of platelet inhibition by bolus-only administration of GPI and individualized DAPT resulted in a yet more favourable outcome in our STEMI population, as no early thrombotic events occurred. Furthermore, even under randomized study conditions like the CHAMPION Phoenix trial [11], the definite ST rate after clopidogrel loading was 1.4% within 48 hours, or about 14-fold higher than in our study. Immediate ADP receptor blockade with cangrelor, however, showed a benefit with reduction to 0.8% (p=0.01), which is still about 8-fold higher than what achieved with our individualization protocol. In addition, ischemic complications were not only not driven by urgent ACS patients (4.1%), but were also numerically higher in stable CAD (7.4%). By contrast, individualization of DAPT in our stable CAD cohort, with 600 mg clopidogrel loading the day before PCI and MEA guided individualization (the latest within 2 hours after PCI), resulted in no early ischemic events.

Three randomized multicenter trials [7-9] failed to show a clinical benefit of individualizing DAPT with the VerifyNow™ assay. Among the most common raised limitations, those in study design, protocol implementation and efficacy of platelet inhibition are the most important. Concerning study design, the late randomization of patients, more than 12 hours after PCI, in GRAVITAS [7] and TRIGGER-PCI [9] excluded acute procedural complications attributable to insufficient platelet inhibition. This occurred even in stable CAD patients, as impressively shown in CHAMPION Phoenix [11]. Concerning protocol implementation, the ARCTIC trial [8] discharged 1.3% of patients in the active study arm without any ADP receptor blocker medication, and lost nearly 9% of patients to follow-up. TRIGGER-PCI [9] was stopped prematurely, leaving an underpowered study population. Concerning efficacy of platelet inhibition, 40% of patients in GRAVITAS [7] and 16% in ARCTIC [8] remained in HPR due to primary reloading with clopidogrel (100% in GRAVITAS and 90% in ARCTIC). By contrast, 100% of our patients were included prior to PCI and discharged with DAPT, 99.9% could be followed at 30 days and only 0.3% remained in HPR. Together, this resulted in a 1.7-fold lower rate of ST (definite and probable) than in the high dose clopidogrel arm of GRAVITAS [7] and a 3.5-fold lower rate than in the monitored arm of ARCTIC [8], despite our higher risk population, including STEMI patients.

Concerning bleeding complications, our concept of using the newer generations of ADP receptor blockers, primarily for intensifying platelet inhibition in patients with HPR to clopidogrel rather than upfront for all ACS patients without contraindications, seems beneficial. In contrast to TRITON [18] and PLATO [19], which featured significantly increased non-CABG related bleeding rates under prasugrel and ticagrelor, no increased bleeding occurred in the individualized patients compared to those on clopidogrel without HPR. The

observed 1.5% TIMI major bleeding rate in our ACS cohort compares favourably to the non-CABG related TIMI major bleeding rates in the clopidogrel arms of TRITON (1.8%) and PLATO (2.2%). Furthermore, even in the highest bleeding risk group, the STEMI patients, our blocking and bridging strategy with GPI bolus-only administration resulted in fewer TIMI major and minor bleeds (6.4%) than in the GPI arm with bolus and infusion (9.6%) of the HORIZON AMI trial [27]. Although our number of patients is admittedly far too low to draw this conclusion, GPI bolus-only administration seems suggestively comparable to the bivalirudin arm (5.9%).

Concerning the regulation of platelet activation, it is already known that thrombin- (via the protease activated receptor-1) and ADP- (via the $P2Y_{12}$ receptor) mediated platelet activation play a synergistic role in hemostasis and thrombosis [20, 28, 29]. Herein, we provide indirect evidence for a synergistic role of ADP- and ASA- (cyclooxygenase) dependent platelet activation. We observed an interplay between AA- and ADP- induced platelet aggregability, as HPR to AA was significantly associated with HPR to ADP, and solitary reloading with ADP receptor blocker in patients with HPR to ADP and AA was able to successfully resolve intermediate levels of HPR to AA without ASA reloading.

Limitations of our study include primarily the non-randomized nature of the registry without a control group concerning efficacy, and the monocentric design, leading to the need for a high number of indirect comparisons, with all its known shortcomings, in order to discuss and put our findings in perspective.

In conclusion, our data strongly suggest that HPR represents a modifiable risk factor that can be used for tailoring treatment in PCI patients, rather than a marker of higher risk only. Effective individualization of DAPT for PCI under MEA guidance is able to minimize early

ischemic complications to a so far unreported degree. Further properly designed randomized multicenter trials utilizing MEA seem warranted.

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Contributorship statement

G. Christ: conception and design of the registry; acquisition, analysis and interpretation of data, drafting and revising the manuscript critically for important intellectual content; final approval of the version to be published; J.M. Siller-Matula: design of the registry, analysis and interpretation of data, revising the manuscript critically for important intellectual content; final approval of the version to be published; M. Francesconi: design of the registry, acquisition and analysis of data, revising the manuscript critically for important intellectual content; final approval of the version to be published; C. Dechant: design of the registry, acquisition and analysis of data, revising the manuscript critically for important intellectual content; final approval of the version to be published; K. Grohs: design of the registry, analysis of data, revising the manuscript critically for important intellectual content; final approval of the version to be published; A. Podczeck-Schweighofer: design of the registry; interpretation of data, revising the manuscript critically for important intellectual content; final approval of the version to be published. All authors agreed to be accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data sharing statement:

No additional data available

Disclosures

None

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Figures

Figure 1: Algorithm of ADP receptor blocker treatment

ADP = adenosine diphosphate, CAD = coronary artery disease, GPI = glycoprotein IIbIIIa inhibitor, MEA = multiple electrode aggregometry, NSTE-ACS = non-ST-elevation acute coronary syndrome, STEMI = ST-elevation myocardial infarction.

* loading in stable patients the day before angiography; ** platelet testing not earlier than 12 hours after loading, and at the latest at the time of diagnostic angiography, after GPI administration serial testing up to 7 days; *** platelet testing the day after reloading; **** platelet testing 1 week after starting 5 mg prasugrel; # up to three clopidogrel reloadings; ## prasugrel reloading dependent on residual reactivity: ADP >80: 60 mg, ADP 60–79: 30 mg, ADP 50–59: 10mg; ### in patients <60 kg and/or >75 years

Figure 2: Flow chart of study patients

CTO = chronic total occlusion, PCI = percutaneous coronary intervention

Figure 3: Flow chart of primary ADP receptor blocker and ASA loading and reloading

A) ADP receptor blocker loading. Only 0.3% of patients (n=3) showed persisting HPR to ADP (≥50 U): two patients after 4 × 600 mg clopidogrel loading (as prasugrel was not yet available) and one patient on prasugrel (as ticagrelor was not yet available). B) HPR to AA-induced aggregation (>35 U) occurred to a significant higher proportion in patients with HPR to ADP (ADP ≥50 U). In patients with HPR to ADP and intermediate HPR to AA (AA <60 U) only ADP receptor blocker reloading successfully treated also HPR to AA. AA = Arachidonic Acid, ADP = adenosine diphosphate, ASA = acetylic salicylic acid.

Figure 4: ADP-induced aggregation after 600 mg Clopidogrel or 60 mg Prasugrel loading and effect of reloading

A) Of clopidogrel loaded patients, 30% showed a high on-treatment platelet reactivity (= non-responder), effectively treated by reloading (except for two patients as prasugrel and ticagrelor had not yet been available). B) Of prasugrel loaded patients, 2% showed a high on-treatment platelet reactivity (= non-responder), effectively treated by ticagrelor.

Individualizing Dual Antiplatelet Therapy after Percutaneous Coronary Intervention: The IDEAL-PCI Registry.

Günter Christ* MD, Jolanta M. Siller-Matula† MD PhD, Marcel Francesconi* MD, Cornelia Dechant* MD, Katharina Grohs‡ MD and Andrea Podczeck-Schweighofer* MD

* 5th Medical Department with Cardiology, Kaiser Franz Josef Hospital, Vienna, Austria

† Department of Cardiology, Medical University of Vienna, Austria

‡ Clinical Institute for Laboratory Medicine, Kaiser Franz Josef Hospital, Vienna, Austria

Correspondence: Prof. Günter Christ, MD

5th Medical Department with Cardiology, Kaiser Franz Josef Hospital

Kundratstr. 3, 1100 Vienna, Austria

Tel.: +43-1-60191-2508

Fax: +43-1-60191-2509

E-mail: guenter.christ@wienkav.at

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Abstract

Objective: To evaluate the clinical utility of individualizing dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) in an all-comers population, including ST-elevation myocardial infarction (STEMI) patients.

Setting: Tertiary care single centre registry

Participants: 1008 consecutive PCI patients with stent implantation, without exclusion criteria.

Intervention: Periinterventional individualization of DAPT, guided by multiple electrode aggregometry (MEA), to overcome high on-treatment platelet reactivity (HPR) to adenosine diphosphate (ADP)- (≥50 U) and arachidonic acid (AA)-induced aggregation (>35 U).

Outcome measures: The primary efficacy endpoint was definite stent thrombosis (ST) at 30 days. The primary safety endpoint was TIMI major and minor bleeding. Secondary endpoints were probable ST, myocardial infarction, cardiovascular death and the combined endpoint major cardiac adverse event (MACE).

Results: 53% of patients presented with acute coronary syndrome (9% STEMI, 44% non-ST-elevation). HPR to ADP after 600 mg clopidogrel loading occurred in 30% of patients (73±19 U vs. 28±11 U; p<0.001) and was treated by prasugrel or ticagrelor (73%) or clopidogrel (27%) reloading (22±12 U; p<0.001). HPR to ADP after prasugrel loading occurred in 2% of patients (82±26 U vs. 19±10 U; p<0.001) and was treated with ticagrelor (34±15 U; p=0.02). HPR to AA occurred in 9% of patients with a significant higher proportion in patients with HPR to ADP (22% vs. 4%, p<0.001) and was treated with aspirin reloading. Definite ST occurred in 0.09% of patients (n=1); probable ST, myocardial infarction, cardiovascular death and MACE occurred in 0.19% (n=2), 0.09% (n=1) and 1.8% (n=18) of patients. TIMI major and

minor bleeding did not differ between patients without HPR and individualized patients (2.6% for both).

Conclusions: Individualization of DAPT with MEA minimizes early thrombotic events in an all-comers PCI population to an unreported degree without increasing bleeding. A randomized multicenter trial utilizing MEA seems warranted.

Trial Registration: http://www.clinicaltrials.gov; NCT01515345

Keywords: percutaneous coronary intervention, platelet function testing, dual antiplatelet therapy

Article summary

Strengths and limitations of this study

The strengths of our study are, at first the real world percutaneous coronary intervention setting with inclusion of every consecutive patient with stent implantation, without any exclusion criteria. Second, the consequent and efficient peri-interventional individualization of dual antiplatelet therapy, leaving only 0.3% of patients on high on-treatment platelet reactivity to adenosine diphosphate at the time of hospital discharge. Third, the minimization of ischemic events within 30 days by nearly abolishing early definite stent thrombosis, without increasing bleeding complications.

Limitations of our study are the non randomised and monocentric registry design without control group concerning ischemic events.

Introduction

High on-treatment platelet reactivity (HPR) to adenosine diphosphate (ADP) represents one of the strongest independent risk factors for post-percutaneous coronary intervention

(PCI) ischemic events in patients given dual antiplatelet therapy (DAPT), according to numerous observational studies using various platelet function tests [1-3].

Whether HPR represents only a marker of higher risk or a modifiable risk factor is still a matter of debate [2], as prospective randomized trials evaluating personalized antiplatelet therapy aiming to overcome HPR resulted in conflicting data. Smaller randomized trials [4], as well as non-randomized studies [5] and a recent meta-analysis [6] suggested a significant clinical benefit, but three randomized studies failed to do so [7-9]. However, each of these trials, utilizing the VerifyNow™ assay, was afflicted with major limitations potentially masking the real value of individualizing DAPT after PCI in daily practice [1, 10]. Their low-risk population and primarily the high selection bias in GRAVITAS [7] and TRIGGER-PCI [9], with patient inclusion more than 12 hours after PCI, seems to cloud the potential importance of optimizing platelet inhibition at the time of PCI. By contrast, the very recent CHAMPION Phoenix trial [11] provides a more realistic scenario of expectable ischemic complications during and after PCI. More than 11,000 patients with oral clopidogrel loading, including the whole clinical PCI spectrum [56% stable coronary artery disease (CAD), 26% non-ST-elevation acute coronary syndrome (NSTE-ACS), 18% ST-elevation myocardial infarction (STEMI)], were pre-interventionally randomized to receive an intravenous (i.v.) bolus and infusion of cangrelor, a fast acting reversible ADP receptor blocker. Ischemic complications in the whole study cohort occurred in 5.3%, including a definite stent thrombosis (ST) rate of 1.1% during the first 48 hours. Notably, the majority of events occurred within 6 hours after PCI.

HPR to acetylic salicylic acid (ASA) is less well studied and its clinical relevance is unclear. The ADAPT-DES registry [3] found no difference in response to ASA, measured by the VerifyNow™ assay, between patients with and without ST. Data not only from our group,

however, suggested that dual HPR to both ADP- and arachidonic acid- (AA; reflecting response to ASA) induced aggregation, measured by multiple electrode aggregometry (MEA) [12] or the VerifyNow assay [13], predisposes patients to a higher ischemic risk than single HPR. Furthermore, MEA has been shown to effectively assess the risk of HPR to ADP after PCI [14] with higher accuracy than the vasodilator-stimulated phosphoprotein phosphorylation (VASP) assay [15] utilized in the Bonello studies.

Therefore, our registry aimed to evaluate the impact of individualizing DAPT with MEA in an all-comers population, including STEMI patients without exclusion criteria, by peri-interventional treatment of HPR to both ADP and AA.

Methods

Patient population

This was a prospective, single-centre cohort observation of consecutive PCI patients, including all forms of ACS (including cardiogenic shock) and all stable CAD, with stent implantation or drug eluting balloon dilatation (for treatment of instent restenosis), and without exclusion criteria (secondary causes for ACS, like anaemia had to be corrected according to standard patient care, but did not represent an exclusion criterion, nor did thrombocytopenia or liver dysfunction once the indication for an invasive approach was given). Patients without stent implantation (i.e. unsuccessful reopening of a chronic total occlusion or balloon dilatation only) were not included. Peri-interventional individualization of platelet inhibition was performed according to the protocol shown in Figure 1 and described in detail below. The local Ethics Committee approved the study protocol in accordance with the Declaration of Helsinki. Participants were included between November 2008 and June 2012. Informed consent was obtained after PCI, either from the patient or

from the guardian in cases of critically ill conditions. Follow-up information was obtained by either direct outpatient visit or telephone contact at 30 days.

Study endpoints

The primary efficacy endpoint was definite ST during a 30 days follow-up. The secondary efficacy outcome parameters were probable ST, myocardial infarction and cardiovascular death, as well as the combination of the above mentioned endpoints as major cardiac adverse events (MACE). Definite and probable ST were defined according to the Academic Research Consortium (ARC) [16] and diagnosed by the authors without blinded adjudication. The primary safety end point was the incidence of TIMI bleeding complications [17]. TIMI major bleeding was defined as intracranial bleeding or overt bleeding with a decrease in haemoglobin ≥5 g/dL. TIMI minor bleeding was defined as observed bleeding with decrease in haemoglobin ≥3 to <5 g/dL.

Individualization of dual antiplatelet therapy

Individualization of ADP receptor blocker treatment was performed according to the algorithm presented in Figure 1. After an initial clopidogrel loading dose of 600 mg, on-treatment platelet reactivity was measured the next day by MEA, at the earliest after 12 hours and at the latest at the time of diagnostic angiography. HPR was defined as ≥50 U ADP-induced aggregation. This cut-off represents the mean of published data from Sibbing and our group [14, 15]. From November 2008 to May 2009, patients with HPR were reloaded with clopidogrel 600 mg up to three times according to the Bonello protocol [4]. After prasugrel [18] became available in June 2009, HPR to clopidogrel was treated with prasugrel (Efient/Effient®) loading, depending on the degree of the residual ADP-induced platelet

reactivity: Cases with ADP >80 U received 60 mg, ADP 60–79 U 30 mg, and ADP 50–59 U 10 mg of prasugrel. This staged approach was chosen in order to avoid potential bleeding complications due to the observed overresponse (i.e. very "flat" ADP and ASPI curves, <10-15 U) after a routine prasugrel 60mg loading in patients with borderline clopidogrel response (ADP 50-60 U). In patients older than 75 years or weighing less than 60 kg, the maintenance dose (MD) of prasugrel was reduced to 5 mg according to the manufacturer's specification, with MEA testing 1 week later and dose adjustments if necessary. In cases of contraindications to prasugrel (history of stroke), clopidogrel reloadings were performed, until ticagrelor (Brilique/Brilinta®) became available. STEMI patients younger than 75 years and weighing more than 60 kg without history of stroke were primarily loaded with 60 mg prasugrel due to the local standard operating procedure of the Viennese STEMI network. After ticagrelor [19] became available in March 2011, HPR to prasugrel and HPR to clopidogrel in patients with contraindications to prasugrel were treated with 180 mg ticagrelor loading. In cases of contraindications to ticagrelor (history of intracranial haemorrhage), clopidogrel reloadings were performed. Special care was taken to limit the possibility of HPR at the time of PCI by clopidogrel loading at least 12 hours prior to PCI, with reloading if necessary either prior PCI in case MEA testing was already known, or the latest 1–2 hours after PCI. In case no oral ADP receptor blocker loading, or only within 4–6 hours pre-PCI was given [e.g., STEMI or urgent invasive non-STEMI (NSTEMI) patients], bolus-only administration of a glycoprotein IIbIIIa inhibitor (GPI) was performed [intracoronary (i.c.) abciximab (0.25 mg/kg; Reopro®) or i.v. eptifibatide (180 µg/kg, Integrilin®)]. Thereafter, serial MEA measurements were performed up to 7 days to allow determination of the level of oral ADP receptor inhibition. Details of this blocking and bridging strategy have been

published previously [20]. At discharge all patients should be within the therapeutic range of platelet inhibition (i.e., non-HPR).

Individualization of ASA treatment was conducted as follows. Stable patients without chronic ASA treatment were loaded with 300 mg ASA p.o. the day before angiography. ACS patients were loaded with ASA i.v.: 500 mg was used in ASA naïve patients and 250 mg was used in cases of chronic ASA treatment. HPR to ASA was defined as >35 U AA-induced aggregation. This cut-off represents a mean derived from published data [12, 21] and the MEA manufacturer's recommendations. ASA reloading was performed with either 300 mg p.o or 250 mg i.v. In cases of HPR to both ADP and ASA, first ADP receptor blocker reloading was performed with ASA reloading if necessary after MEA testing the next day.

PCI was performed according to current standard guidelines. The type of stent implanted was at the discretion of the interventional cardiologist. In cases of drug eluting stent (DES) implantation, only 2nd generation DES were used (Biolimus-eluting: Biomatrix™; Everolimus-eluting: Promus Element™ and Xience™; Zotarolimus-eluting: Resolute™). All patients received 100 IU/kg of unfractionated heparin, with adjustments according to measurements of activated clotting time, except in cases of GPI bolus administration where only 70 IU/kg were given.

Impedance aggregometry

Whole blood aggregation was determined using MEA, a new-generation impedance aggregometer (Multiplate™ Analyzer, Roche, Munich, Germany). The system detects the electrical impedance change due to the adhesion and aggregation of platelets on two independent electrode-set surfaces in the test cuvette, with a low rate of intra-and interassay variability [22]. ADP and AA were used as agonists. A 1:2 dilution of whole blood

anticoagulated with hirudin and 0.9% NaCl was stirred at 37°C for 3 min in the test cuvette. ADP (6.4 µM) and AA (0.5 mM) were added, and the increase in electrical impedance was continuously recorded for 6 min. The mean values of the two independent determinations were expressed as the area under the curve (AUC) of the aggregation tracing. AUC is reported herein in units (U), as described previously [23].

Statistical analysis

Data are expressed as mean ± standard deviation (SD). Statistical comparisons were performed with the Mann Whitney U test, the paired and unpaired Student t-test and chi-squared test. COX regression analysis was performed to compare event rates between the non-HPR group and the individualized treatment group. As the power of the study was limited due to the low event rate, we provide crude and adjusted HR. The adjustment was done for gender, body mass index, diabetes, hyperlipidemia, use of calcium channel blockers (CCB) and proton pump inhibitors (PPI), clinical presentation, platelet count and cardiogenic shock. All statistical calculations were performed using commercially available statistics analysis software (SPSS Version 21; Chicago).

Sample size

We estimated that the sample size of 1008 patients would provide 80% power to demonstrate a reduction in the incidence of ST by individualization of antiplatelet therapy, on the basis of assumptions of ST rates during one month follow-up. We expected a 0.2% rate of ST at 1 month in patients without HPR, as compared to a 1.9% rate in a historical group of patients with HPR [3, 5, 14]. Thus, if the hazard ratio (HR) for ST was 3.0–4.0-fold lower in patients without HPR than in those with HPR [3], the study would have more than

80% power to demonstrate that individualized antiplatelet therapy in patients with HPR reduces the rate of ST.

Results

Patient inclusion and baseline characteristics

Of 1043 consecutive PCI patients, only those with unsuccessful reopening of a chronic total occlusion or with conventional balloon-only PCI were excluded (n=35), leaving 1008 participants (Figure 2). All STEMI patients received a primary PCI. At 30 days, one patient (0.09%), a French tourist, was lost to follow-up. Table 1 shows the demographic variables of our patient cohort and differences between the group without HPR after clopidogrel loading (non-HPR) and the individualized group (i.e., ADP receptor blocker reloading and primary prasugrel or ticagrelor loading).

Table 1	**Baseline characteristics**			
	Total (n=1008)	**Non-HPR** (n=665; 66%)	**Individualized** (n=343; 34%)	
Age	64.7±11.8	65.1±11.7	63.9±11.9	ns
Women	303 (30%)	183 (28%)	120 (35%)	0.01
Body Mass Index (kg/m^2)	28.4±4.6	28.1±4.5	29.1±4.8	0.001
Diabetes	321 (32%)	196 (30%)	125 (36%)	0.03
Insulin treatment	84 (8%)	41 (6%)	43 (13%)	0.001
Oral medication	237 (24%)	155 (23%)	82 (24%)	ns
Smoker	504 (50%)	334 (50%)	170 (50%)	ns
Hypertension	842 (84%)	557 (84%)	285 (83%)	ns
Hyperlipidemia	855 (85%)	552 (83%)	303 (88%)	0.03
Family history	272 (27%)	181 (27%)	91 (27%)	ns
History of myocardial infarction	212 (21%)	139 (21%)	73 (21%)	ns
History of PCI	190 (19%)	130 (20%)	60 (18%)	ns
History of CABG	60 (6%)	42 (6%)	18 (5%)	ns
Cerebrovascular disease	115 (11%)	71 (11%)	44 (13%)	ns
Peripheral vascular disease	133 (13%)	92 (14%)	41 (12%)	ns

Clinical presentation				<0.001
STEMI	93 (9%)	31 (5%)	62 (18%)	
NSTE-ACS	447 (44%)	304 (46%)	143 (41%)	
NSTEMI	393 (39%)	261 (39%)	132 (38%)	
Unstable Angina	54 (5%)	43 (7%)	11 (3%)	
Stable angina	468 (47%)	330 (50%)	138 (41%)	
Cardiogenic shock	26 (3%)	8 (1%)	18 (5%)	<0.001
Platelet count x10^3/µl	251±81	239±74	276±88	<0.001
Co-medication				
Statin	929 (92%)	612 (92%)	317 (92%)	ns
Proton pump inhibitor	649 (64%)	397 (60%)	252 (74%)	<0.001
Calcium channel blocker	195 (19%)	116 (17%)	79 (23%)	0.03
Betablocker	771 (77%)	515 (77%)	256 (75%)	ns
ACE-I/ARB	764 (76%)	494 (74%)	270 (79%)	ns

(ACE-I = Angiotensin converting enzyme inhibitor; ARB = Angiotensin receptor blocker; CABG = coronary artery bypass graft; HPR = high on-treatment platelet reactivity; NSTE-ACS = Non ST-elevation acute coronary syndrome; NSTEMI = Non ST-Elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction)

Patients in the individualized group were more frequently of female gender (p=0.01), had higher bodyweight (p=0.001), and a greater incidence of diabetes (p=0.003), especially insulin dependent (p=0.001), STEMI and cardiogenic shock (p<0.001). Higher platelet counts (p<0.001), and co-medication with PPI (p<0.001) and CCB (p=0.03), were also significantly associated with individualization of DAPT.

Angiographic and interventional details

Table 2 shows angiographic and procedural characteristics according to platelet inhibition (non-HPR versus individualized group).

Table 2	**Angiographic and interventional details**			
	Total (n=1008)	**Non-HPR** (n=665; 66%)	**Individualized** (n=343; 34%)	**p**

Type of intervention				ns
Stent	1000 (99%)	661 (99%)	339 (99%)	
Drug Eluting	948 (94%)	625 (94%)	323 (94%)	
Bare Metal	52 (5%)	36 (5%)	16 (5%)	
Balloon (Drug Eluting)	8 (1%)	4 (1%)	4 (1%)	
Access site				ns
femoral	867 (86%)	571 (86%)	296 (86%)	
radial	117 (12%)	77 (12%)	40 (12%)	
Both	24 (2%)	17 (2%)	7 (2%)	
Lesion location				ns
Left Main	114 (11%)	78 (12%)	36 (11%)	
Left anterior descending	585 (58%)	391 (59%)	194 (57%)	
Left circumflex	401 (40%)	277 (42%)	124 (36%)	
Right coronary artery	443 (44%)	285 (43%)	158 (46%)	
Bypass graft	18 (2%)	12 (2%)	6 (2%)	
AHA/ACC Type b2/c	739 (73%)	490 (74%)	249 (73%)	ns
Stent length total (mm; range)	43±33 (8–241)	44±32 (8–241)	43±33 (8–217)	ns
Stents/patient (range)	2.2±1.5 (1–12)	2.2±1.5 (1–12)	2.1±1.6 (1–12)	ns
Multivessel disease	655 (65%)	428 (64%)	227 (66%)	ns

The rate of DES implantation was high (94%), and of these 20% were biolimus-eluting, 49% everolimus-eluting and 25% zotarolimus-eluting. Multivessel disease was present in 65% of patients, with a high proportion of complex lesion morphology (Type b2/c: 73%), including 11% left main and 58% left anterior descending artery lesions, resulting in 2.2±1.5 implanted stents/patient (mean stent length 43±33 mm). The rate of use of a femoral access site for PCI during the registry period was high (86%). All parameters showed no differences between groups.

Primary ADP receptor blocker loading and individualization of ADP receptor blocker therapy.

As shown in Figure 3A, 94.8% of patients were primarily loaded with 600 mg clopidogrel, 5% with 60 mg prasugrel (STEMI patients <75 years and >60 kg without history of stroke) and 0.2% with 180 mg ticagrelor (known clopidogrel allergy). Of the clopidogrel loaded patients, 30% showed HPR. Clopidogrel reloadings of 600 mg were performed up to three times in 27% of patients with HPR, leaving five patients with persisting HPR, of whom three were finally switched to prasugrel during the observation period, as it became available. Prasugrel reloading was performed in 70% of patients with HPR. Of the prasugrel loaded patients, 2% showed HPR, which was successfully treated with ticagrelor reloading; this was also performed in 3% of patients with HPR to clopidogrel and contraindications to prasugrel. Only three patients remained in HPR during the observation period, and were put on a higher MD (two on clopidogrel 150 mg, one on prasugrel 20 mg as ticagrelor was not yet available). For patients older than 75 years or weighing less than 60 kg, prasugrel 5 mg was primarily prescribed (15% of prasugrel patients, n=37). After MEA testing 1 week later, 14% (n=5) were switched to 10 mg.

ASA-dependent platelet aggregation and reloading

After ASA and ADP receptor blocker loading, 9% of our patients showed a HPR to AA-induced aggregation (68±28 U vs. 16±8 U; p<0.001). As shown in Figure 3B, HPR to AA was significantly more prevalent in patients with HPR to ADP (22% vs. 4%; p<0.001). HPR to AA without HPR to ADP (63±29 U) was treated by ASA reloading successfully in all patients (14±6 U; p<0.001). In patients with HPR to ADP, the HPR to AA was influenced by the extent of the residual AA-induced platelet aggregation, as follows. In patients with intermediate HPR to AA (<60 U), only ADP receptor blocker reloading was sufficient to treat HPR to AA as well (from 45±7 U to 15±10 U; p<0.001). In patients with high HPR to AA (≥60 U) an additional

ASA reloading was necessary to significantly reduce AA-induced aggregation from 92±21 U to 20±16 U (p<0.001). Six of these patients showed persisting HPR to AA and were discharged on 300 mg ASA.

Platelet aggregation in clopidogrel and prasugrel loaded patients and effect of reloading.

ADP-induced aggregation after 600 mg clopidogrel loading was significantly higher in patients with HPR (= non-responder: 73±19 U) than without (= responder: 28±11 U; p<0.001) (Figure 4A). Reloading effectively treated HPR (22±12 U; p<0.001), except in two patients for whom prasugrel was not yet available. ADP-induced aggregation after 60 mg prasugrel loading was significantly higher in patients with HPR (= non-responder: 82±26 U) than without (= responder: 19±10 U; p<0.001), and was successfully treated with ticagrelor reloading (34±15 U; p=0.02) (Figure 4B).

Glycoprotein IIbIIIa inhibitor (GPI) treatment

GPI was given to 61% (n=57) of STEMI patients, with an i.c. abciximab bolus only in 91% (n=52) and an i.v. eptifibatide bolus only in 9% (n=5). Non-STEMI (NSTEMI) patients received a GPI treatment in 11% (n=47) of cases, with an i.c. abciximab bolus only in 72% (n=34) and an i.v. eptifibatide bolus only in 28% (n=13).

Clinical outcome at 30 days

Table 3 shows the clinical outcome of the overall patient cohort.

Table 3	**Thirty day clinical outcome**				
	Total (n=1007)	**Non-HPR** (n=664, 66%)	**Individualized** (n=343, 34%)	**adj. HR** (95%CI) **p**	**crude HR** (95%CI) **p**
MACE (Cardiovascular Death, Myocardial Infarction, Stent thrombosis)	18 (1.8%)	9 (1.4%)	9 (2.6%)	0.67 (0.23–2.03) 0.5	0.51 (0.20–1.30) 0.16

Cardiovascular Death	18 (1.8%)	9 (1.4%)	9 (2.6%)		
non-shock	8 (0.8%)	4 (0.6%)	4 (1.2%)		
cardiogenic shock (n=shock patients; % of shock)	10 (26; 38%)	5 (8; 62%)	5 (18; 28%)		
Myocardial Infarction	1 (0.09%)	1 (0.15%)	0 (0%)		
Stent thrombosis					
definite and probable	3 (0.29%)	3 (0.45%)	0 (0%)		
Definite	1 (0.09%)	1 (0.15%)	0 (0%)		
probable	2 (0.19%)	2 (0.3%)	0 (0%)		
Bleeding					
TIMI major and minor	26 (2.6%)	17 (2.6%)	9 (2.6%)	0.78 (0.33–1.85) 0.574	0.96 (0.42–2.20) 0.914
TIMI major	10 (1.0%)	6 (0.9%)	4 (1.2%)		
TIMI minor	16 (1.6%)	11 (1.7%)	5 (1.5%)		
Type					
Instrumented	14 (1.4%)	10 (1.5%)	4 (1.2%)		
Spontaneous	12 (1.2%)	7 (1.1%)	5 (1.5%)		

(MACE = major adverse cardiac event)

No acute ST occurred within 24 hours in the whole patient cohort. 3 patients died in cardiogenic shock within 24 hours after successful PCI without evidence of ST at autopsy. Only one subacute definite ST, which also accounted for the only myocardial infarction, occurred within 30 days (0.09%). This patient had multivessel PCI for NSTEMI, and developed diarrhea and Gram negative sepsis. On the seventh day post PCI, an attempted resuscitation was unsuccessful. Acute thrombosis of the circumflex artery stent was confirmed at autopsy. Two sudden deaths without autopsy occurred after discharge in NSTEMI patients, which have been classified as probable ST according to the ARC criteria. However, both patients also suffered from ischemic cardiomyopathy, which would suggest a primary rhythmogenic cause for their sudden deaths. MACE number equals cardiovascular deaths (n=18; 1.8%) as all three cases of ST died. Cardiogenic shock was the cause of cardiovascular deaths in the majority of cases (88%), without differences in groups. Concerning bleeding complications,

no increase in individualized patients occurred (2.6% TIMI major and minor bleedings in both groups). Slightly more than half of the bleeding complications (54%, n=14) were related to the access site ("instrumented"), requiring surgical intervention in three cases (21% of instrumented complications; 0.3% of patients). The majority of spontaneous bleeding complications were gastrointestinal (67%, n=8). One intracranial haemorrhage occurred under standard DAPT with clopidogrel 17 days after PCI for NSTEMI in an 86 year old patient.

Table 4 shows 30-day outcomes for the STEMI-, NSTE-ACS- and stable CAD cohorts.

Table 4. Descriptive Statistics for 30 days outcome in clinical subgroups.

	Total	Non-HPR	Individualized
STEMI cohort	93	31 (33%)	62 (67%)
Cardiovascular Death	8 (8.6%)	4 (12.9%)	4 (6.5%)
non-shock	1 (1.1%)	1 (3.2%)	0 (0%)
cardiogenic shock (n=shock patients; % of shock)	7 (17; 41%)	3 (6; 50%)	4 (11; 36%)
Myocardial Infarction	0 (0%)	0 (0%)	0 (0%)
Stent thrombosis			
Definite	0 (0%)	0 (0%)	0 (0%)
probable	0 (0%)	0 (0%)	0 (0%)
Bleeding			
TIMI major and minor	6 (6.5%)	3 (9.7%)	3 (4.8%)
TIMI major	4 (4.3%)	2 (6.5%)	2 (3.2%)
TIMI minor	2 (2.2%)	1 (3.2%)	1 (1.6%)
Type			
Instrumented	5 (5.4%)	3 (9.7%)	2 (3.2%)
Spontaneous	1 (1.1%)	0 (0%)	1 (1.6%)
NSTE-ACS cohort	446	303 (68%)	143 (32%)
Cardiovascular Death	10 (2.2%)	5 (1.7%)	5 (3.5%)
non-shock	7 (1.6%)	3 (1.0%)	4 (2.8%)
cardiogenic shock (n=shock patients;% of shock)	3 (9; 33%)	2 (2; 100%)	1 (7; 14%)
Myocardial Infarction	1 (0.2%)	1 (0.3%)	0 (0%)
Stent thrombosis			

Definite	1 (0.2%)	1 (0.3%)	0 (0%)
probable	2 (0.4%)	2 (0.7%)	0 (0%)
Bleeding			
TIMI major and minor	13 (2.9%)	9 (3.0%)	4 (2.8%)
TIMI major	4 (0.9%)	2 (0.7%)	2 (1.4%)
TIMI minor	9 (2.0%)	7 (2.3%)	2 (1.4%)
Type			
Instrumented	5 (1.1%)	4 (1.3%)	1 (0.7%)
Spontaneous	8 (1.8%)	5 (1.7%)	3 (2.1%)
Stable CAD cohort	468	330 (70%)	138 (30%)
Cardiovascular Death	0 (0%)	0 (0%)	0 (0%)
Myocardial Infarction	0 (0%)	0 (0%)	0 (0%)
Stent thrombosis			
Definite	0 (0%)	0 (0%)	0 (0%)
probable	0 (0%)	0 (0%)	0 (0%)
Bleeding			
TIMI major and minor	7 (1.5%)	5 (1.5%)	2 (1.4%)
TIMI major	2 (0.4%)	2 (0.6%)	0 (0%)
TIMI minor	5 (1.1%)	3 (0.9%)	2 (1.4%)
Type			
Instrumented	4 (0.8%)	3 (0.9%)	1 (0.7%)
Spontaneous	3 (0.6%)	2 (0.6%)	1 (0.7%)

No ischemic event occurred either in the STEMI cohort, with a required high rate of individualization (67%), or in the stable CAD cohort, with a sufficient lower rate of individualization (30%). The safety endpoint of combined TIMI major and minor bleeding risk was 2× higher in NSTE-ACS patients and 4× higher in STEMI patients than in stable CAD patients (2.9% vs. 6.5% vs. 1.5%; p=0.02), without an increase associated with individualization in any subgroup.

Discussion

The main findings of our study are as follows. Firstly, routine efficient peri-interventional individualization of DAPT with MEA, incorporating the newer generations of ADP receptor blocker (prasugrel and ticagrelor), is able to minimize early ischemic events after PCI in an

all-comers population including STEMI patients by nearly abolishing early definite stent thrombosis. Secondly, intensifying platelet inhibition in patients with HPR does not increase bleeding complications compared to patients without HPR under DAPT. Thirdly, there is indirect evidence for synergistic roles of ADP- and ASA- dependent platelet activation.

For the interpretation of the very low ischemic complication rate observed during the 30 days after PCI, the most recent literature on the incidence of real world early ST in PCI for all-comers [24] and STEMI patients [25,26], as well as the complication rate in the randomized CHAMPION Phoenix trial [11], should be considered. We could show that adjusting the level of platelet inhibition reduced the rate of early definite ST to 0.09%, which is about 7-fold lower than observed in PCI for all-comers [24] and about 25- to 35-fold lower than in primary PCI for STEMI [25, 26], even with contemporary 2nd generation DES. Monitored intensification of platelet inhibition by bolus-only administration of GPI and individualized DAPT resulted in a yet more favourable outcome in our STEMI population, as no early thrombotic events occurred. Furthermore, even under randomized study conditions like the CHAMPION Phoenix trial [11], the definite ST rate after clopidogrel loading was 1.4% within 48 hours, or about 14-fold higher than in our study. Immediate ADP receptor blockade with cangrelor, however, showed a benefit with reduction to 0.8% (p=0.01), which is still about 8-fold higher than what achieved with our individualization protocol. In addition, ischemic complications were not only not driven by urgent ACS patients (4.1%), but were also numerically higher in stable CAD (7.4%). By contrast, individualization of DAPT in our stable CAD cohort, with 600 mg clopidogrel loading the day before PCI and MEA guided individualization (the latest within 2 hours after PCI), resulted in no early ischemic events. ~~As the "first do no harm" principle should be generally applied, optimization of platelet~~

~~inhibition at the time of PCI seems also of importance in this patient population, thus questioning the negative recommendation on the role of platelet function testing in stable CAD patients [2].~~

Three randomized multicenter trials [7-9] failed to show a clinical benefit of individualizing DAPT with the VerifyNow™ assay. Among the most common raised limitations, those in study design, protocol implementation and efficacy of platelet inhibition are the most important. Concerning study design, the late randomization of patients, more than 12 hours after PCI, in GRAVITAS [7] and TRIGGER-PCI [9] excluded acute procedural complications attributable to insufficient platelet inhibition. This occurred even in stable CAD patients, as impressively shown in CHAMPION Phoenix [11]. Concerning protocol implementation, the ARCTIC trial [8] discharged 1.3% of patients in the active study arm without any ADP receptor blocker medication, and lost nearly 9% of patients to follow-up. TRIGGER-PCI [9] was stopped prematurely, leaving an underpowered study population. Concerning efficacy of platelet inhibition, 40% of patients in GRAVITAS [7] and 16% in ARCTIC [8] remained in HPR due to primary reloading with clopidogrel (100% in GRAVITAS and 90% in ARCTIC). By contrast, 100% of our patients were included prior to PCI and discharged with DAPT, 99.9% could be followed at 30 days and only 0.3% remained in HPR. Together, this resulted in a 1.7-fold lower rate of ST (definite and probable) than in the high dose clopidogrel arm of GRAVITAS [7] and a 3.5-fold lower rate than in the monitored arm of ARCTIC [8], despite our higher risk population, including STEMI patients.

Concerning bleeding complications, our concept of using the newer generations of ADP receptor blockers, primarily for intensifying platelet inhibition in patients with HPR to clopidogrel rather than upfront for all ACS patients without contraindications, seems

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beneficial. In contrast to TRITON [18] and PLATO [19], which featured significantly increased non-CABG related bleeding rates under prasugrel and ticagrelor, no increased bleeding occurred in the individualized patients compared to those on clopidogrel without HPR. The observed 1.5% TIMI major bleeding rate in our ACS cohort compares favourably to the non-CABG related TIMI major bleeding rates in the clopidogrel arms of TRITON (1.8%) and PLATO (2.2%). Furthermore, even in the highest bleeding risk group, the STEMI patients, our blocking and bridging strategy with GPI bolus-only administration resulted in fewer TIMI major and minor bleeds (6.4%) than in the GPI arm with bolus and infusion (9.6%) of the HORIZON AMI trial [27]. Although our number of patients is admittedly far too low to draw this conclusion, GPI bolus-only administration seems suggestively comparable to the bivalirudin arm (5.9%).

Concerning the regulation of platelet activation, it is already known that thrombin- (via the protease activated receptor-1) and ADP- (via the $P2Y_{12}$ receptor) mediated platelet activation play a synergistic role in hemostasis and thrombosis [20, 28, 29]. Herein, we provide indirect evidence for a synergistic role of ADP- and ASA- (cyclooxygenase) dependent platelet activation. We observed an interplay between AA- and ADP- induced platelet aggregability, as HPR to AA was significantly associated with HPR to ADP, and solitary reloading with ADP receptor blocker in patients with HPR to ADP and AA was able to successfully resolve intermediate levels of HPR to AA without ASA reloading.

Limitations of our study include primarily the ~~observational,~~ non-randomized nature of the registry without a control group concerning efficacy, and the monocentric design, leading to the need for a higher number of indirect comparisons, with all its known shortcomings, in order to discuss and put our findings in perspective.

In conclusion, our data strongly suggest that HPR represents a modifiable risk factor that can be used for tailoring treatment in PCI patients, rather than a marker of higher risk only. Effective individualization of DAPT for PCI under MEA guidance is able to minimize early ischemic complications to a so far unreported degree. Further properly designed randomized multicenter trials utilizing MEA seem warranted.

Acknowledgments

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Contributorship statement

G. Christ: conception and design of the registry; acquisition, analysis and interpretation of data, drafting and revising the manuscript critically for important intellectual content; final approval of the version to be published; J.M. Siller-Matula: design of the registry, analysis and interpretation of data, revising the manuscript critically for important intellectual content; final approval of the version to be published; M. Francesconi: design of the registry, acquisition and analysis of data, revising the manuscript critically for important intellectual content; final approval of the version to be published; C. Dechant: design of the registry, acquisition and analysis of data, revising the manuscript critically for important intellectual content; final approval of the version to be published; K. Grohs: design of the registry, analysis of data, revising the manuscript critically for important intellectual content; final approval of the version to be published; A. Podczeck-Schweighofer: design of the registry;

interpretation of data, revising the manuscript critically for important intellectual content; final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data sharing statement:

No additional data available

Disclosures

None

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Figures

Figure 1: Algorithm of ADP receptor blocker treatment

ADP = adenosine diphosphate, CAD = coronary artery disease, GPI = glycoprotein IIbIIIa inhibitor, MEA = multiple electrode aggregometry, NSTE-ACS = non-ST-elevation acute coronary syndrome, STEMI = ST-elevation myocardial infarction.

* loading in stable patients the day before angiography; ** platelet testing not earlier than 12 hours after loading, and at the latest at the time of diagnostic angiography, after GPI administration serial testing up to 7 days; *** platelet testing the day after reloading; **** platelet testing 1 week after starting 5 mg prasugrel; # up to three clopidogrel reloadings; ## prasugrel reloading dependent on residual reactivity: ADP >80: 60 mg, ADP 60–79: 30 mg, ADP 50–59: 10mg; ### in patients <60 kg and/or >75 years

Figure 2: Flow chart of study patients

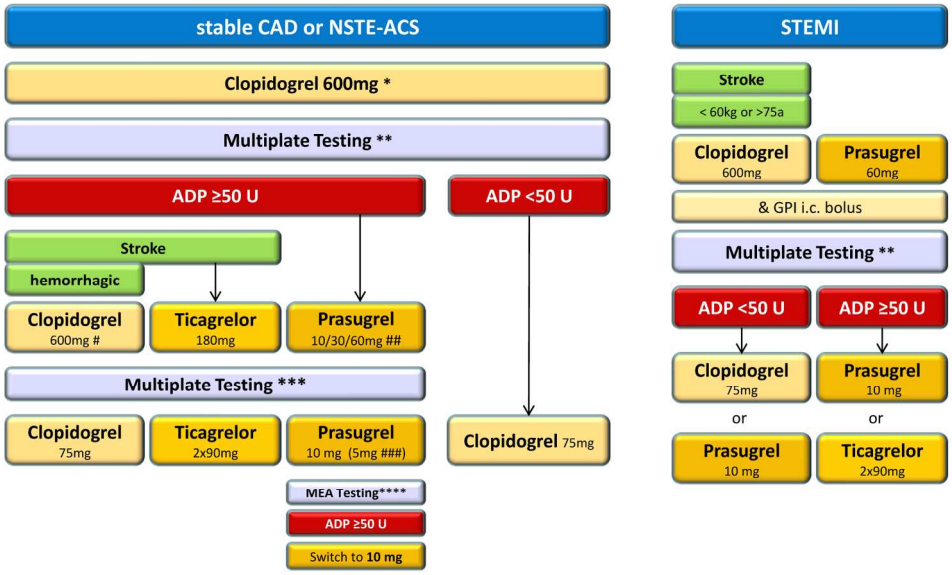
CTO = chronic total occlusion, PCI = percutaneous coronary intervention

Figure 3: Flow chart of primary ADP receptor blocker and ASA loading and reloading

A) ADP receptor blocker loading. Only 0.3% of patients (n=3) showed persisting HPR to ADP (≥50 U): two patients after 4 × 600 mg clopidogrel loading (as prasugrel was not yet available) and one patient on prasugrel (as ticagrelor was not yet available). B) HPR to AA-induced aggregation (>35 U) occurred to a significant higher proportion in patients with HPR to ADP (ADP ≥50 U). In patients with HPR to ADP and intermediate HPR to AA (AA <60 U) only ADP receptor blocker reloading successfully treated also HPR to AA. AA = Arachidonic Acid, ADP = adenosine diphosphate, ASA = acetylic salicylic acid.

Figure 4: ADP-induced aggregation after 600 mg Clopidogrel or 60 mg Prasugrel loading and effect of reloading

A) Of clopidogrel loaded patients, 30% showed a high on-treatment platelet reactivity (= non-responder), effectively treated by reloading (except for two patients as prasugrel and ticagrelor had not yet been available). B) Of prasugrel loaded patients, 2% showed a high on-treatment platelet reactivity (= non-responder), effectively treated by ticagrelor.



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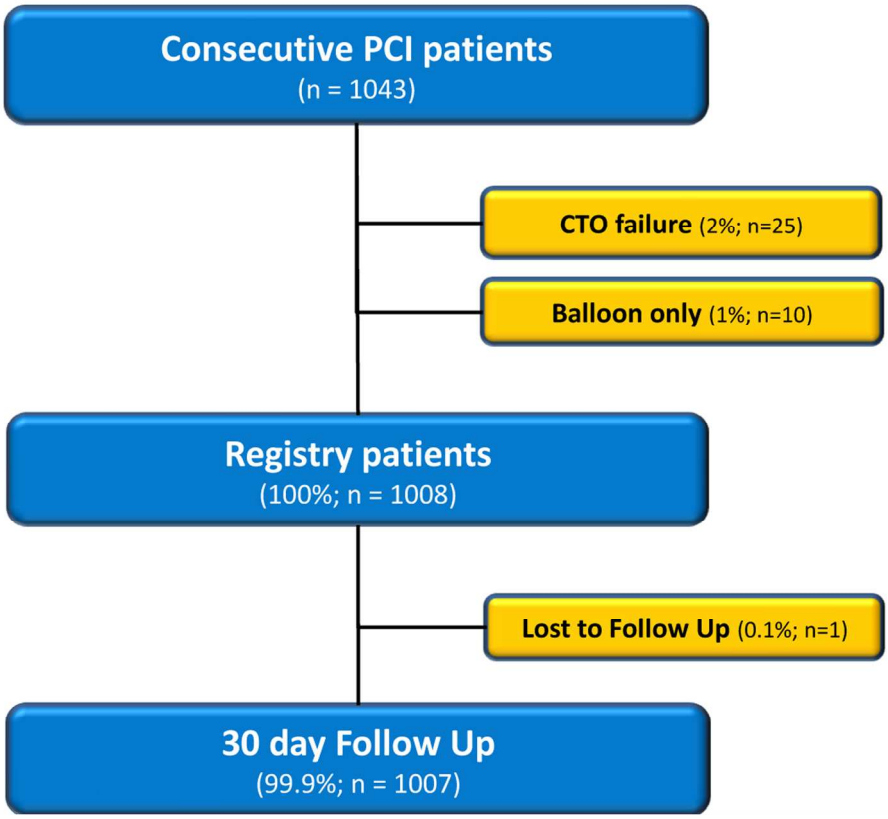

Figure 2: Flow chart of study patients
CTO = chronic total occlusion, PCI = percutaneous coronary intervention

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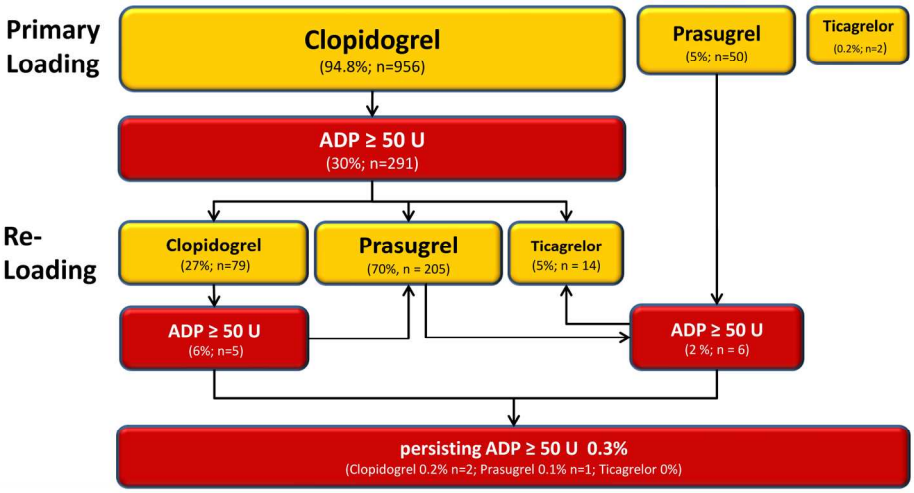

Figure 3: Flow chart of primary ADP receptor blocker and ASA loading and reloading
A) ADP receptor blocker loading. Only 0.3% of patients (n=3) showed persisting HPR to ADP (≥50 U): two patients after 4 × 600 mg clopidogrel loading (as prasugrel was not yet available) and one patient on prasugrel (as ticagrelor was not yet available).
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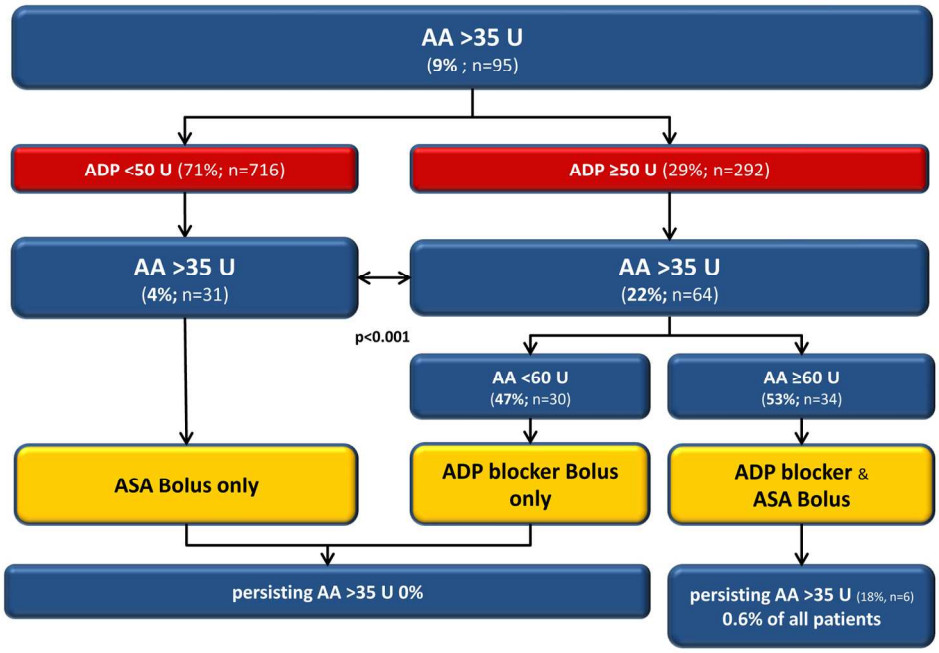

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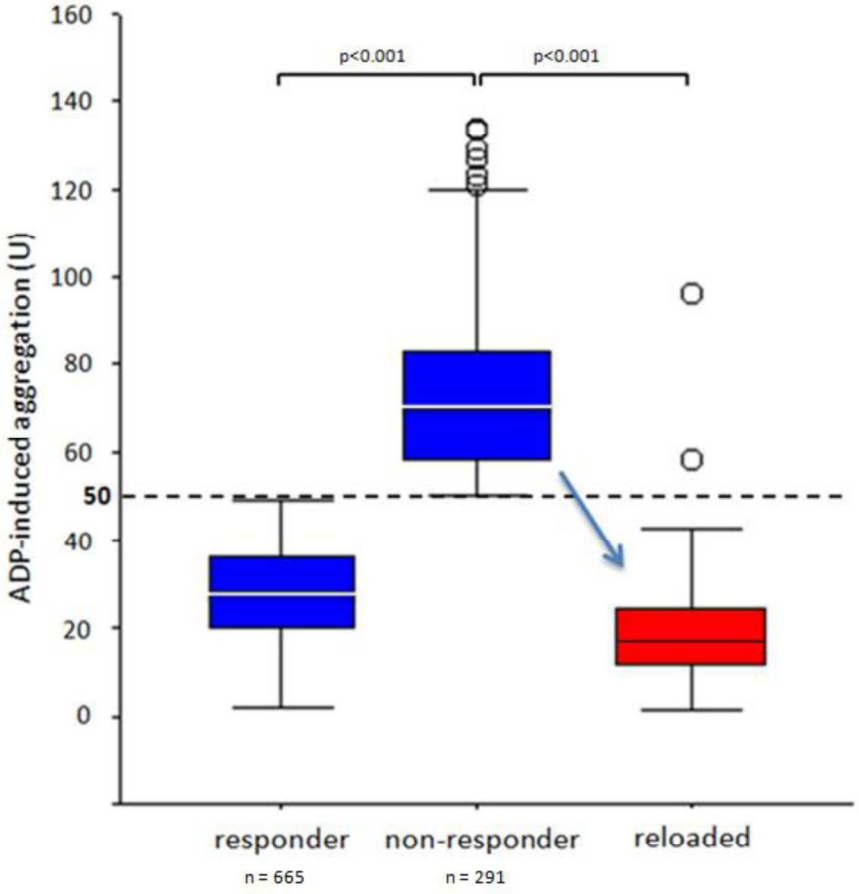

Figure 4: ADP-induced aggregation after 600 mg Clopidogrel or 60 mg Prasugrel loading and effect of reloading
A) Of clopidogrel loaded patients, 30% showed a high on-treatment platelet reactivity (= non-responder), effectively treated by reloading (except for two patients as prasugrel and ticagrelor had not yet been available).
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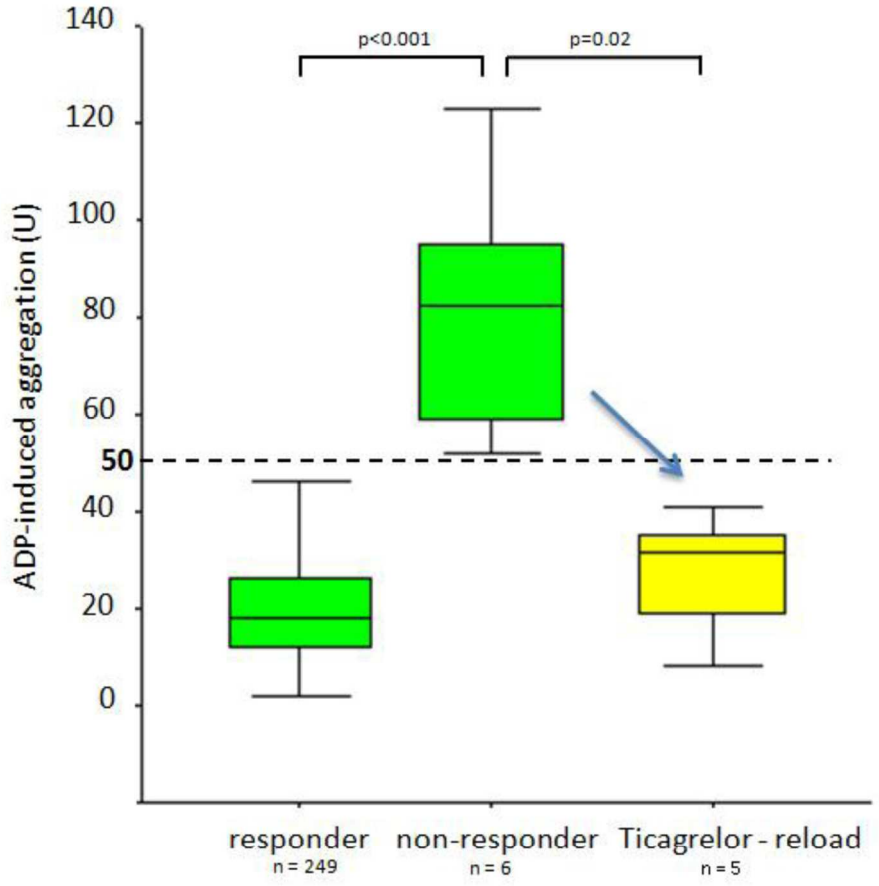

Figure 4: ADP-induced aggregation after 600 mg Clopidogrel or 60 mg Prasugrel loading and effect of reloading
B) Of prasugrel loaded patients, 2% showed a high on-treatment platelet reactivity (= non-responder), effectively treated by ticagrelor.

170x173mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*11*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**:1453-7