EuroIntervention

Antiplatelet response to the 150-mg maintenance dose of clopidogrel in patients with insufficient platelet inhibition after clopidogrel loading for elective coronary stent placement

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The authors have no conflict of interest to declare.

Abstract

Aims: Our prospective study sought to investigate whether inadequate platelet responses to clopidogrel can be corrected by increasing the daily maintenance dose from 75 mg to 150 mg.

Methods and results: In 117 patients with elective PCI after loading with 600 mg clopidogrel, we determined residual platelet aggregation in response to 5 µmol/l ADP (RPA) by optical aggregometry after the first 75 mg maintenance dose (baseline), and at days 14 and 28. In patients with RPA >14% at baseline, we increased the daily dose to 150 mg. Fifty-seven additional patients without dose adjustment served as historic control. In 39 patients with baseline RPA >14%, the increase in maintenance dose to 150 mg reduced median RPA significantly (P<0.001) from 24% [interquartile range: 18-32%] at baseline to 14% [8-20%] at 14 days without any further significant change. In patients with RPA ≤ 14%, who continued on 75 mg clopidogrel, RPA increased during the first 14 days by 4.5% (0-14%; P<0.001). At 14 days, the study group with selective dose adjustment had a significantly lower RPA than the control group without dose adjustment (10.0% [4-20%] versus 17.0% [9-32%], P<0.001).

Conclusions: In patients with a low initial response to clopidogrel, platelet inhibition can be improved by increasing the maintenance dose to 150 mg.

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Introduction

Platelet inhibition by clopidogrel shows a broad variability, both after loading and during maintenance therapy[1-4]. Several independent studies suggested that the risk of adverse cardiac events after percutaneous coronary intervention (PCI) critically depends on the level of platelet inhibition achieved in response to clopidogrel[5-9]. Specifically, the Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate (EXCELSIOR) study showed a more than 3-fold increase in the risk of death and myocardial infarction during the first year after stent placement, if residual platelet aggregation in response to 5 µmol/l adenosine diphosphate (ADP) was above 14% after the first 75-mg maintenance dose of clopidogrel following loading with 600 mg one day before[10].

Platelet aggregation after stimulation with ADP is blocked incompletely after administration of loading doses up to 600 mg clopidogrel[11] or during maintenance dosing regimens[12]. This observation has been attributed to an incomplete inhibition of the ADP-binding sites at the $P2Y_{12}$ receptor[13]. Previous studies showed that clopidogrel as well as ticlopidine produced only partial inhibition of [^{3}H]-2-methylthio-ADP binding to platelets[14,15]. High on-treatment platelet reactivity after clopidogrel may be related to a total or partial inability to convert clopidogrel into the active metabolite[16] or an increased baseline platelet reactivity[10,17]. The ISAR-CHOICE 2 study[18] as well as the OPTIMUS study[19] randomised patients to daily doses of either 75 or 150 mg clopidogrel and demonstrated an increase in antiplatelet effect by the higher maintenance dose. In contrast to the aforementioned studies we aimed to investigate, if and to what extent an inadequate antiplatelet response to clopidogrel can be corrected by increased dosing specifically in patients with inadequate initial antiplatelet response during maintenance therapy.

To address this question, we conducted the EXCELSIOR-Adjusted Clopidogrel Treatment (ACT) study. This prospective observational cohort study tested whether residual platelet aggregation in patients with inadequate response to clopidogrel after the first 75-mg maintenance dose can be substantially improved by an increase in maintenance dose to 150 mg.

Furthermore, we compared residual platelet aggregation in the EXCELSIOR-ACT cohort with selective dose adjustment in addition to platelet aggregation in a historic subgroup from the EXCELSIOR study without any dose adjustment. This historic control group consisted of 57 patients of the EXCELSIOR trial with platelet function testing at 14 and 28 days. The entry criteria of EXCELSIOR were identical to those of EXCELSIOR-ACT, but all patients continued on the 75-mg maintenance dose, irrespective of the results of platelet function testing performed two to four hours after administration of the first maintenance dose of 75 mg clopidogrel at day one after PCI.

Methods

Study population

Patients undergoing elective coronary stent placement after pre-treatment with 600 mg of clopidogrel and aspirin (≥ 100 mg per day for at least five days) were eligible for the study. Major exclusion criteria were acute myocardial infarction according to the American Heart Association/American College of Cardiology (AHA/ACC) criteria, chronic oral anticoagulation, thienopyridine treatment within the last 2 weeks before admission, use of a glycoprotein IIb/IIIa inhibitor within the last seven days or during study period, contraindications to aspirin, clopidogrel or heparin, cancer, haemodialysis and haemodynamic instability. Concomitant treatment with strong inhibitors (such as macrolide antibiotics, azole antifungals) or inducers (such as rifampicin) of cytochrome P450 3A4 was not permitted. All patients gave written informed consent. The study complies with the Declaration of Helsinki and was approved by the ethics committee of the medical faculty of the University of Freiburg, Germany.

Before the intervention, all patients were on aspirin and received a loading dose of clopidogrel 600 mg. Catheterisation and stent placement was performed according to current standard guidelines. All patients received an intra-arterial dose of 100-140 U/kg heparin. The choice of stent type was left to the operator's discretion. After PCI, the vast majority of patients were treated with aspirin 100 mg per day for at least the duration of the study. Only one patient received 300 mg aspirin daily. We administered the first 75-mg maintenance dose of clopidogrel in the morning of the day following PCI, i.e., one day after loading. The blood sample for platelet function testing was obtained between two to four hours after intake of the first maintenance dose. Patients with a residual platelet aggregation >14% in response to 5 µmol/l ADP received a further bolus dose of clopidogrel 300 mg followed by an increased daily dose of 150 mg (75 mg bid). No further dose adjustments were performed. If residual platelet aggregation at baseline was ≤ 14%, patients continued on the 75-mg maintenance dose. The threshold of 14% for the 5 µmol/l ADP-induced RPA at 24 hours after PCI was identified by EXCELSIOR as predictive for subsequent adverse cardiac events[7]. We scheduled all patients for follow-up visits at 14 and 28 days after PCI for re-evaluation of platelet function. Concomitant medication was not altered during the study. To check compliance to antiplatelet treatment, we interviewed the patients and performed pill counting.

Platelet function assays

Blood was drawn for platelet function assays using tubes containing 3.8% sodium-citrate (S-Monovetten, Sarstedt AG, Nuembrecht, Germany). Platelet aggregation was assessed by turbidimetric aggregometry using a four-channel Bio/Data PAP4 aggregometer (Moelab, Langenfeld, Germany), as described previously[7]. We prepared platelet-rich plasma by centrifugation of blood samples (750 g/2 minutes) and adjusted to $275\text{-}325 \times 10^9$ thrombocytes/l by dilution with platelet poor plasma from the same patient. Results were expressed as percentage of maximal light transmission determined five minutes after stimulation with ADP 5 µmol/l using platelet poor plasma as reference (=100% aggregation). We elaborated on late or residual platelet aggregation (RPA) because previous experiments found a lower rate of variability at stabilisation of aggregation, measured by disaggregation and late aggregation, which is mainly driven by the activity of $P2Y_{12}$ receptor[20]. Peak aggregation used in some of the previous studies[4,21,22] is influenced

by the activity of both the $P2Y_1$ and $P2Y_{12}$ purinergic receptors, whereas clopidogrel blocks only the latter. The coefficient of variation of our optical aggregometry assay is 6.1%[3]. Laboratory personnel were blinded to treatment assignments.

Statistics

The primary endpoint of EXCELSIOR-ACT was the decrease in residual platelet aggregation after adjustment of the maintenance dose of clopidogrel to 150 mg. We designed the study to have a power of 80% to detect a 20% decrease in residual platelet aggregation with a level of significance of $P < 0.05$. Based on the EXCELSIOR-substudy we assumed an initial residual ADP-induced platelet aggregation of 35±15% for the group with platelet aggregation >14%. With these assumptions we obtained a sample size of 39 patients with dose adjustment (nQuery Advisor, Statistical Solutions, Cork, Ireland; version 5.0).

In general, we report discrete variables as counts (percentages) and continuous variables as mean ± standard deviation. Unless stated otherwise, we tested differences between groups with the χ^2-test or Fisher's exact test (for estimated cell sizes ≤ 5) for discrete variables and with one-way ANOVA for continuous variables. Because of the non-normal distribution of residual platelet aggregation (Kolmogorov-Smirnov test) we report platelet data as median (interquartile range). We used the Wilcoxon signed rank test to assess the changes in platelet aggregation between two time points and the Mann-Whitney-U test to compare the EXCELSIOR-ACT and the EXCELSIOR-substudy cohorts with respect to platelet function. To corroborate our non-parametric tests, we analysed paired platelet function data by the t-test for paired samples. We also compared the change in ADP-induced residual platelet aggregation between the study group and the control group with and without adjustment for differences in baseline characteristics at $P \leq 0.1$ (Table 1) by calculating univariable and multivariable general linear models. For all statistical analyses, we used the SPSS software package (SPSS, Chicago, IL, USA; version 14). In the two-tailed test, a P-value < 0.05 was regarded as significant.

Results

The study flow-chart is provided in Figure 1. The EXCELSIOR-ACT cohort comprised 117 consecutive patients. Baseline characteristics of these patients are shown in Table 1. As shown in Table 1 and in Figure 2, 39 patients (33%) exhibited a residual

Table 1. Base-line demographic, clinical and angiographic characteristics of the patients according to study cohorts.

	EXCELSIOR-ACT Cohort			EXCELSIOR Cohort		
	Entire cohort (n=117)	Patients with RPA ≤14% (n=78)	Patients with RPA >14% (n=39)	Entire cohort (n=57)	P#	P##
Age (years)	64.8±9.0	63.2±9.8	67.8±6.2	66.5±8.7	0.24	0.009
Women	16 (13.7)	13 (16.7)	3 (7.7)	12 (21.1)	0.21	0.26
Active smoker	23 (19.7)	19 (24.4)	4 (10.3)	10 (17.5)	0.74	0.09
Arterial hypertension	95 (81.2)	63 (80.8)	32 (82.1)	48 (84.2	0.63	1.00
Diabetes mellitus	26 (22.2)	13 (16.7)	13 (33.3)	15 (26.3)	0.55	0.06
Hypercholesterolaemia	92 (78.6)	61 (78.2)	31 (79.5)	46 (80.7)	0.75	1.00
Body mass index (kg/m²)	27.2±3.9	27.6±4.1	26.6±3.3	26.7±2.7	0.40	0.20
Creatinine (µmol/l)	88.5 (22.1)	79.6 (26.5)	88.5 (26.5)	79.6 (26.5)	0.49	0.16
Impaired LV function	28 (23.9)	19 (24.4)	9 (23.1)	16 (28.1)	0.56	1.00
Previous myocardial infarction	24 (20.5)	16 (20.5)	8 (20.5)	10 (17.5)	0.64	1.00
CCS Angina class III or IV	36 (30.8)	24 (30.8)	12 (30.8)	12 (21.1)	0.18	1.00
Acetylsalicylic acid	117 (100.0)	78 (100.0)	39 (100.0)	57 (100.0)	1.00	1.00
β-blockers	100 (85.5)	69 (88.5)	31 (79.5)	50 (87.7)	0.69	0.27
ACE inhibitors	75 (64.1)	49 (62.8)	26 (66.7)	29 (50.9)	0.10	0.84
AT1-Blockers	8 (6.8)	3 (3.8)	5 (12.8)	9 (15.8)	0.06	0.12
Diuretics	42 (35.9)	26 (33.3)	16 (41.0)	13 (22.8)	0.08	0.54
Nitrates	3 (2.6)	3 (3.8)	0 (0.0)	6 (10.5)	0.07	0.55
Statins	107 (91.5)	70 (89.7)	37 (94.9)	50 (87.7)	0.44	0.49
Multivessel PCI	34 (29.1)	22 (28.2)	12 (30.8)	15 (26.3)	0.71	0.83
DES used	86 (73.5)	56 (71.8)	30 (76.9)	15 (26.3)	<0.001	0.66
Stented segment						
Left main coronary artery	6 (5.1)	3 (3.8)	3 (7.7)	0 (0)	0.08	0.40
Left anterior descending artery	57 (48.7)	42 (53.8)	15 (38.5)	25 (43.9)	0.55	0.17
Circumflex artery	41 (35.0)	26 (33.3)	15 (38.5)	24 (42.1)	0.37	0.68
Right coronary artery	46 (39.3)	30 (38.5)	16 (41.0)	20 (35.1)	0.59	0.84
Bypass graft	5 (4.3)	2 (2.6)	3 (7.7)	3 (5.3)	0.77	0.33

Creatinine level expressed as median (interquartile range) with P by Mann-Whitney-U test. All other data are expressed as mean value +SD or number of patients (percentage). P#, p-value for comparison between EXCELSIOR-ACT and EXCELSIOR cohorts. P##, p-value for comparison between EXCELSIOR-ACT subcohorts with RPA ≤14% and RPA >14%. P values by one-way ANOVA, or χ^2-test between study cohorts. CABG, coronary artery bypass grafting. CCS, Canadian Cardiovascular Society. DES, drug eluting stent. LV function, Left ventricular function. PCI, percutaneous coronary intervention.
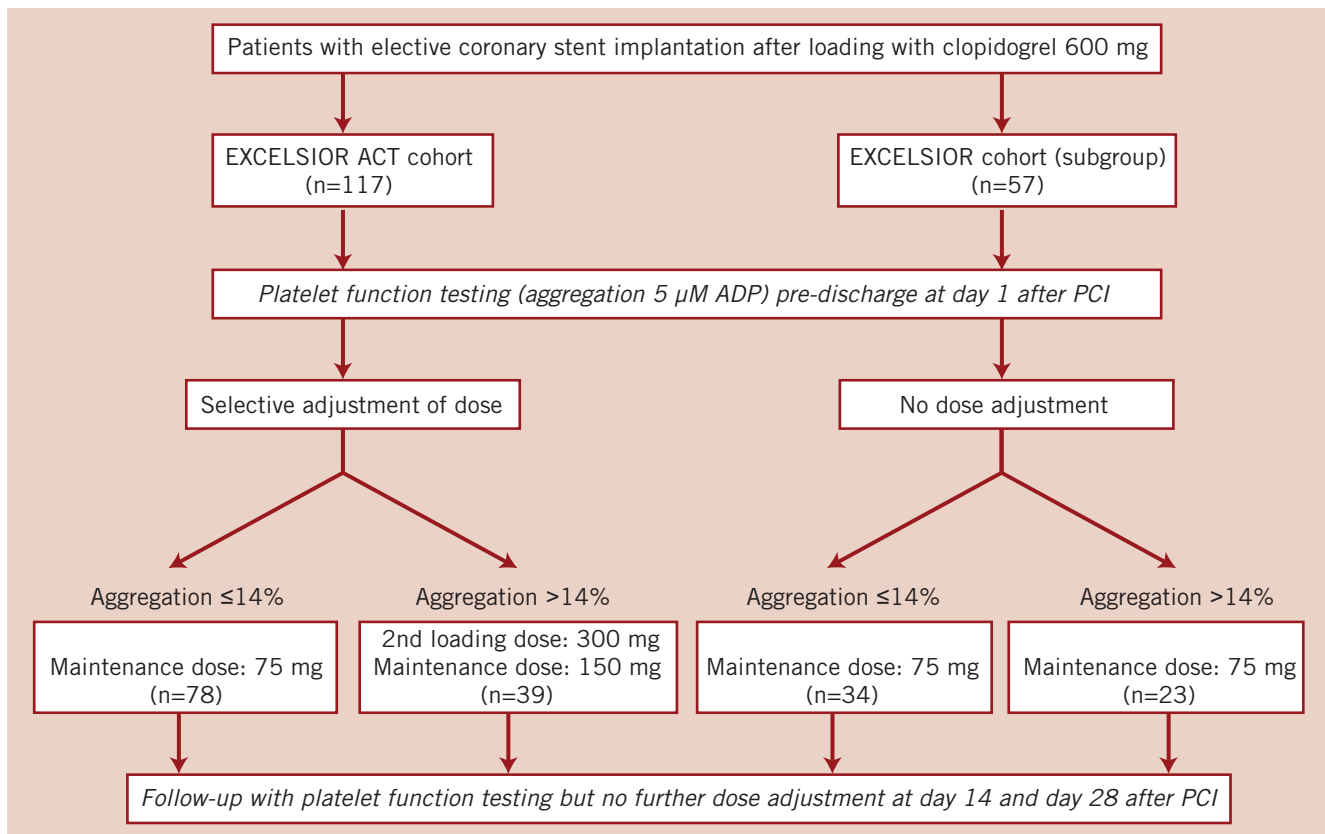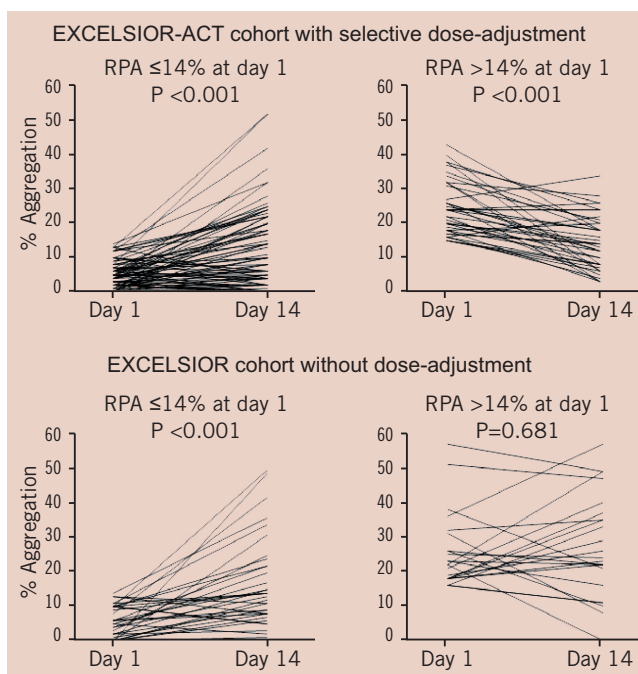
Figure 1. Study flow-chart

Figure 2. Graphs showing individual RPA from day one to day 14 in patients from the EXCELSIOR-ACT and the EXCELSIOR cohort. Patients were stratified according to RPA at day one. Patients with RPA >14% at day one (upper right panel) were treated thereafter with clopidogrel 150 mg daily, while all remaining patients received clopidogrel 75 mg per day throughout. P-value by Wilcoxon signed rank test.

ADP-induced platelet aggregation >14% after the first 75-mg maintenance dose of clopidogrel. Increasing the maintenance dose to 150 mg in these patients significantly reduced ADP-induced RPA by 9.0% (5.0 to 15.0%; median and interquartile range) from a median of 24.0% (interquartile range: 18.0-32.0%) after the first maintenance dose to a median of 14.0% (interquartile range: 8.0-20.0%) at 14 days (P < 0.001; Figures 2 and 3). At day 28, platelet aggregation was not significantly different from that at day 14 (Figure 3).

Patients with an initial ADP-induced RPA ≤ 14%, who continued on the 75-mg maintenance dose, showed a slight, but statistically significant increase in RPA during the first 14 days without any further significant changes from day 14 to day 28 (Figures 2 and 3). At day 14, ADP-induced RPA in patients with a blunted response to clopidogrel, but maintenance-dose adjustment, still had a significantly higher level of RPA than those with an adequate response to clopidogrel and no maintenance dose adjustment (P=0.040, Figure 3).

The baseline characteristics of the 57 patients of the historic control group from the EXCELSIOR-substudy are shown in Table 1. Compared with the EXCELSIOR-ACT cohort, the EXCELSIOR-substudy cohort received fewer drug eluting stents. Regarding concomitant medication, trends for a more frequent use of nitrates and angiotensin 1 receptor blockers and a lower prescription rate of diuretics and ACE-inhibitors were observed in the EXCELSIOR-substudy cohort. In the entire EXCELSIOR-substudy cohort there was a statistically significant (P < 0.001) increase in ADP-induced

Error bars represent interquartile range. P-values for the difference between the two time points by Wilcoxon signed rank test are shown above (patients with dose adjustment) and below (patients without dose adjustment) the line. # P=0.04 for the difference between the groups with and without dose-adjustment by Mann-Whitney-U test.
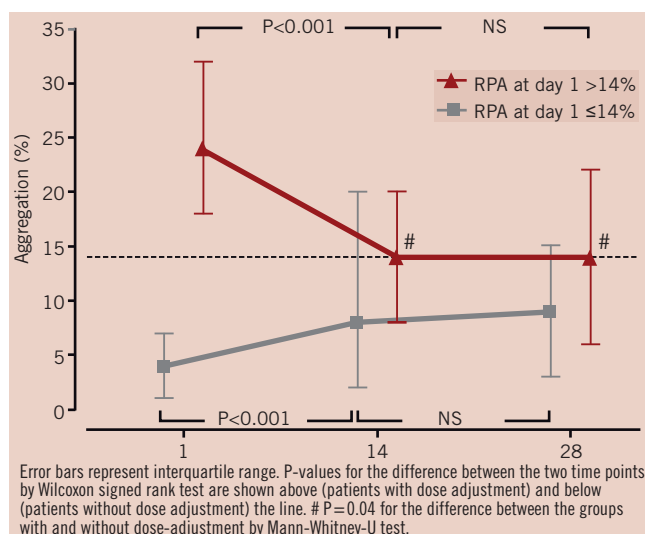
Figure 3. Time courses of median residual RPA in the EXCELSIOR-ACT cohort for patient groups stratified according to RPA at day one. Patients with RPA >14% at day one were treated subsequently with maintenance doses of clopidogrel 150 mg per day.

RPA from a median of 10.0% (interquartile range: 4.0-20.0%) after the first maintenance dose to a median of 17.0% (interquartile range: 9.0-32.0%) at 14 days (Table 2). Comparing the EXCELSIOR-substudy cohort with the recent EXCELSIOR-ACT cohort, we found a significant effect of the increase in maintenance dose in patients with an ADP-induced RPA >14% at study entry with regard to RPA at day 14: Among patients with a blunted response to clopidogrel, the change in ADP-induced RPA differed significantly between the two patients subsets with (EXCELSIOR-ACT) and without increase in maintenance dose (EXCELSIOR), by –12.1% (95%-confidence interval: –18.1 to –6.1%, P < 0.001) without adjustment and by –11.0% (95%-confidence interval: –18.8 to –3.1%, P=0.007) with adjustment for the difference in the use of drug-eluting stents and use of angiotensin 1 receptor blockers, nitrates, diuretics and ACE-inhibitors. At 14 and 28 days, the cohort with selective increase of the maintenance dose to 150 mg (EXCELSIOR-ACT) showed a significantly lower overall level of ADP-induced RPA than the cohort with the fixed 75-mg maintenance dose. The proportion of patients of the EXCELSIOR-

ACT cohort reaching the target of RPA≤ 14% was by 17.6% (day 14) and by 23.7% (day 28) higher than that in patients of the control group without selective dose adjustment (Table 2).

Discussion

As the main message of our study we demonstrate that doubling of the conventional maintenance dose of clopidogrel is an option to improve platelet inhibition in patients with an initially poor response to clopidogrel. In patients with a residual ADP-induced platelet aggregation >14% after the first 75-mg maintenance dose preceded by a 600-mg loading dose the day before, the increase in maintenance dose to 150 mg substantially reduced the steady-state level of RPA compared with continuation of the 75-mg maintenance dose. After doubling the maintenance dose of clopidogrel, ADP-induced RPA at 14 days in patients with a poor initial response was significantly lower than at pre-discharge, whereas RPA at 14 days in patients with an adequate initial response and no increase in maintenance dose was slightly but significantly higher than at pre-discharge. Thereby, the level of RPA in patients with a poor response and increase in dose improved markedly but was still significantly worse than that of patients with a good response but no dose adjustment. Similar findings were obtained in a small cohort of diabetics using a point-of-care assay for the assessment of antiplatelet effect[23]. In the overall cohort, monitoring of antiplatelet effect with selective dose adjustment of clopidogrel induced a more consistent and lower RPA than the routine administration of the approved 75-mg maintenance dose. Thus, more than 60% of our cohort displays an adequate response to clopidogrel during maintenance dosing of clopidogrel. The proportion of patients with optimal RPA (≤ 14%) in EXCELSIOR-ACT is substantially higher than in the OPTIMUS study (40%) which investigated patients with type 2 diabetes mellitus[19]. Although different definitions of adequate response were used it seems more likely that the lower responder rate in OPTIMUS can be attributed to the known enhanced platelet reactivity and the reduced *in vitro* responsiveness to antiplatelet agents in diabetics[24,25].

Clinically, it is desirable to obtain an estimate of platelet function during maintenance treatment before discharge from hospital. The clopidogrel effect, however, has not yet reached a steady-state level at this time point. We found that the level of RPA determined between two and four hours after administration of the first

Table 2. Residual platelet aggregation and frequency of patients with inadequate antiplatelet effect of clopidogrel according to study cohorts.

	EXCELSIOR-ACT Cohort (n=117)		EXCELSIOR Cohort (n=57)		P Value
RPA ADP 5 µmol/L					
Baseline	7.0	(2.5–18.0)	10.0	(4.0–20.0)	0.229
Day 14 after PCI	10.0	(4.0–20.0)	17.0	(9.0–32.0)	<0.001
Day 28 after PCI	10.0	(4.0–18.0)	20.0	(9.0–22.0)	<0.001
Proportion of patients with RPA >14%					
Baseline	39	(33.3)	23	(40.4)	0.404
Day 14 after PCI	45	(38.5)	32	(56.1)	0.035
Day 28 after PCI	40	(34.2)	33	(57.9)	<0.001

RPA: residual platelet aggregation; ADP: adenosine diphosphate; Data are expressed as median (interquartile range) or number of patients (percentage).
P: Mann-Whitney-U test or χ^2 between study cohorts.

maintenance dose of clopidogrel 75 mg at day one after PCI overestimates residual platelet aggregation during maintenance treatment by about 7.5%. This finding may be explained by a residual effect of the 600 mg loading dose administered before PCI, and presents additional circumstantial evidence that the antiplatelet effect of the 75-mg maintenance dose of clopidogrel is sub-maximal. Despite the overestimation of the chronic antiplatelet effect, the level of RPA measured between two to four hours after the patients received the first maintenance dose of clopidogrel at day one post-PCI is predictive of cardiac complications during the first year after PCI[10]. Therefore, pre-discharge assessment of platelet function may be clinically useful for tailoring subsequent maintenance therapy, as also suggested by two recently published studies[26,27].

The threshold of 14% for the 5 μmol/l ADP-induced RPA assessed at that time after PCI was validated by EXCELSIOR as predictive for subsequent adverse cardiac events[7,10]. The level of RPA (14%) used in our study represented the 72nd percentile of the distribution of platelet aggregation of the EXCELSIOR cohort and the 67th percentile of EXCELSIOR-ACT. Hence, the level of RPA must be considered hazardous if it exceeds the upper tertile of the cohort. In the EXCELSIOR substudy, the upper tertile of RPA at 14 days was 24%. After the increase in maintenance dose in EXCELSIOR-ACT, 90% (35 of 39) of the patients with blunted response to clopidogrel at 24 hours reached a platelet aggregation below this threshold (Figure 3). Thus, in the majority of patients with dose adjustment platelet aggregation may be considered sufficiently suppressed. Nevertheless, doubling the maintenance dose of clopidogrel could not fully correct the low response to clopidogrel and a small number of patients did not respond to the increase in dose at all.

The first circumstantial piece of evidence which shed doubts on the adequacy of the approved maintenance dose of clopidogrel was the finding that re-administration of a loading dose of clopidogrel in patients already on maintenance treatment evokes further platelet inhibition[28]. Later on the same group presented data that doubling the maintenance dose to 150 mg early after PCI and loading with 600 mg clopidogrel improves the antiplatelet effect[18]. These results were confirmed most recently in a study using a similar design[27]. A previous randomised pilot study by Angiolillo and co-workers comprised 40 diabetic patients with a low response to clopidogrel in which antiplatelet effects were assessed during chronic treatment[19]. Consistent with our current findings, the increase in maintenance dose to 150 mg enhanced the antiplatelet effect. Apart from expanding the data base for the 150-mg maintenance dose, our study adds two important new aspects: (1) Pre-discharge assessment of platelet function after PCI is a sensitive tool to identify patients with a poor response to clopidogrel who benefit from an increase in maintenance dose. (2) Selective dose adjustment in one third of the patients suffices to suppress the level of RPA in the entire cohort substantially.

Clinical implications

The current study demonstrates that in many patients doubling the maintenance dose represents an option to correct an inadequate response to the 75-mg dose of clopidogrel. Moreover, our study suggests that monitoring the antiplatelet efficacy with selective dose

adjustment of clopidogrel is a cost-effective means of achieving optimal suppression of platelet aggregation in the majority of patients. Although dedicated clinical studies are needed to confirm this concept, it is elusive that individualised dosing of clopidogrel with doubling of maintenance dose will improve the clinical outcome after PCI, particularly when drug-eluting stents have been used.

Increasing the maintenance dose of clopidogrel, however, does not always correct inadequate platelet inhibition. In those patients who do not reach a sufficiently low level of residual platelet aggregation despite increased maintenance doses, an alternative pharmacological approach to the inhibition of the $P2Y_{12}$-receptor is warranted. Newer $P2Y_{12}$-receptor antagonists that are currently investigated in phase III trials such as prasugrel and AZD-6140 appear promising[29,30].

Limitations

The non-randomised design of the study represents a limitation for the comparison between the study group and the control group. Except for the use of drug-eluting stents which increased over time and the use of nitrates, there were, however, no major baseline differences between the EXCELSIOR-ACT cohort and the historical EXCELSIOR sub-study cohort. In EXCELSIOR we did not find any interaction between the placement of a drug-eluting stent and the effect of clopidogrel or treatment with nitrates. Moreover, to adjust for the placement of a drug-eluting stent and for differences in concomitant medication, we performed a multivariable analysis which confirmed the result of the non-adjusted comparison.

Our study did not address the question whether selective dose adjustment of clopidogrel improves the outcome after PCI with stent placement. EXCELSIOR demonstrated that an ADP-induced RPA above 14% is associated with a more than 3-fold increase in risk of death and myocardial infarction during 1-year follow-up[10]. Although EXCELSIOR-ACT showed that an inadequate response to clopidogrel can be corrected in a large proportion of patients by increasing the dose, the study did not have the power to assess the effect on clinical outcome. EXCELSIOR-ACT breaks the ground for larger studies that address the clinical efficiency of selective dose adjustment which will also have adequate statistical power to assess the bleeding risk associated with an increased maintenance dosing regimen of clopidogrel.

Some patients did not respond to the increase in the dose of clopidogrel to 150 mg. We did not test maintenance doses higher than 150 mg. Therefore, we cannot clarify whether non-response to 150 mg clopidogrel was caused by a principle resistance to clopidogrel or by a still insufficient dose.

Conclusions

The current study demonstrates that in a large proportion of patients treated with the approved maintenance dose of clopidogrel platelet activity is poorly suppressed. Early laboratory assessment of the antiplatelet effect of clopidogrel is a useful tool for identification of patients with an attenuated therapeutic response. Increasing the maintenance dose of clopidogrel to 150 mg only in patients with an inadequate initial antiplatelet response to clopidogrel may be a cost-effective approach to improve antiplatelet

effects of clopidogrel during maintenance dosing. However, the clinical efficacy and safety of this approach remains to be investigated in the context of a large scale trial.

References

1. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramirez C, Sabate M, Banuelos C, Hernandez-Antolin R, Escaned J, Moreno R, Alfonso F, Macaya C. High clopidogrel loading dose during coronary stenting: effects on drug response and interindividual variability. *Eur Heart J.* 2004; 25 (21):1903-10.

2. Gurbel PA, Bliden KP, Hayes KM, Yoho JA, Herzog WR, Tantry US. The relation of dosing to clopidogrel responsiveness and the incidence of high post-treatment platelet aggregation in patients undergoing coronary stenting. *J Am Coll Cardiol.* 2005; 45 (9):1392-6.

3. Hochholzer W, Trenk D, Frundi D, Blanke P, Fischer B, Andris K, Bestehorn HP, Büttner HJ, Neumann FJ. Time dependence of platelet inhibition after a 600-mg loading dose of clopidogrel in a large, unselected cohort of candidates for percutaneous coronary intervention. *Circulation.* 2005; 111 (20):2560-4.

4. Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Bhatt DL, Topol EJ. Variability in platelet responsiveness to clopidogrel among 544 individuals. *J Am Coll Cardiol.* 2005; 45 (2):246-51.

5. Matetzky S, Shenkman B, Guetta V, Shechter M, Bienart R, Goldenberg I, Novikov I, Pres H, Savion N, Varon D, Hod H. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. *Circulation.* 2004; 109(25):3171-5.

6. Geisler T, Langer H, Wydymus M, Gohring K, Zurn C, Bigalke B, Stellos K, May AE, Gawaz M. Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. *Eur Heart J.* 2006; 27 (20):2420-5.

7. Hochholzer W, Trenk D, Bestehorn HP, Fischer B, Valina CM, Ferenc M, Gick M, Caputo A, Büttner HJ, Neumann FJ. Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. *J Am Coll Cardiol.* 2006; 48 (9):1742-50.

8. Buonamici P, Marcucci R, Migliorini A, Gensini GF, Santini A, Paniccia R, Moschi G, Gori AM, Abbate R, Antoniucci D. Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. *J Am Coll Cardiol.* 2007; 49 (24):2312-7.

9. Price MJ, Endemann S, Gollapudi RR, Valencia R, Stinis CT, Levisay JP, Ernst A, Sawhney NS, Schatz RA, Teirstein PS. Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. *Eur Heart J.* 2008; 29 (8):992-1000.

10. Trenk D, Hochholzer W, Fromm MF, Chialda L-C, Pahl A, Valina CM, Stratz C, Schmiebusch P, Bestehorn H-P, Büttner HJ, Neumann F-J. Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. *J Am Coll Cardiol.* 2008; 51 (20):1925-34.

11. Thebault JJ, Kieffer G, Cariou R. Single-dose pharmacodynamics of clopidogrel. *Sem Thrombos Hemost.* 1999; 25 Suppl 2:3-8.

12. Thebault JJ, Kieffer G, Lowe GD, Nimmo WS, Cariou R. Repeated-dose pharmacodynamics of clopidogrel in healthy subjects. *Sem Thrombos Hemost.* 1999; 25 Suppl 2:9-14.

13. Mills DC, Puri R, Hu CJ, Minniti C, Grana G, Freedman MD, Colman RF, Colman RW. Clopidogrel inhibits the binding of ADP analogues to the receptor mediating inhibition of platelet adenylate cyclase. *Arterioscler Thromb.* 1992; 12 (4):430-6.

14. Savi P, Laplace MC, Maffrand JP, Herbert JM. Binding of [3H]-2-methylthio-ADP to rat platelets - effect of clopidogrel and ticlopidine. *J Pharmacol Exp Ther.* 1994; 269 (2):772-7.

15. Gachet C, Cattaneo M, Ohlmann P, Hechler B, Lecchi A, Chevalier J, Cassel D, Mannucci PM, Cazenave JP. Purinoceptors on blood platelets: further pharmacological and clinical evidence to suggest the presence of two ADP receptors. *Brit J Haematol.* 1995; 91 (2):434-44.

16. von Beckerath N, Taubert D, Pogatsa-Murray G, Wieczorek A, Schömig E, Schömig A, Kastrati A. A patient with stent thrombosis, clopidogrel-resistance and failure to metabolize clopidogrel to its active metabolite. *Thromb Haemost.* 2005; 93 (4):789-91.

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

18. von Beckerath N, Kastrati A, Wieczorek A, Pogatsa-Murray G, Sibbing D, Graf I, Schömig A. A double-blind, randomized study on platelet aggregation in patients treated with a daily dose of 150 or 75 mg of clopidogrel for 30 days. *Eur Heart J.* 2007; 28 (15):1814-9.

19. Angiolillo DJ, Shoemaker SB, Desai B, Yuan H, Charlton RK, Bernardo E, Zenni MM, Guzman LA, Bass TA, Costa MA. Randomized comparison of a high clopidogrel maintenance dose in patients with diabetes mellitus and coronary artery disease: results of the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) study. *Circulation.* 2007; 115 (6):708-16.

20. Labarthe B, Theroux P, Angioi M, Ghitescu M. Matching the evaluation of the clinical efficacy of clopidogrel to platelet function tests relevant to the biological properties of the drug. *J Am Coll Cardiol.* 2005; 46 (4):638-45.

21. Taubert D, Kastrati A, Harlfinger S, Gorchakova O, Lazar A, von Beckerath N, Schömig A, Schömig E. Pharmacokinetics of clopidogrel after administration of a high loading dose. *Thromb Haemost.* 2004; 92 (2):311-6.

22. Gurbel PA, Bliden KP, Samara W, Yoho JA, Hayes K, Fissha MZ, Tantry US. Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST Study. *J Am Coll Cardiol.* 2005; 46 (10):1827-32.

23. Angiolillo DJ, Costa MA, Shoemaker SB, Desai B, Bernardo E, Suzuki Y, Charlton RK, Zenni MM, Guzman LA, Bass TA. Functional effects of high clopidogrel maintenance dosing in patients with inadequate platelet inhibition on standard dose treatment. *Am J Cardiol.* 2008; 101 (4):440-5.

24. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramirez C, Sabate M, Jimenez-Quevedo P, Hernandez R, Moreno R, Escaned J, Alfonso F, Banuelos C, Costa MA, Bass TA, Macaya C. Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. *Diabetes.* 2005; 54 (8):2430-5.

25. Angiolillo DJ, Bernardo E, Ramirez C, Costa MA, Sabate M, Jimenez-Quevedo P, Hernandez R, Moreno R, Escaned J, Alfonso F, Banuelos C, Bass TA, Macaya C, Fernandez-Ortiz A. Insulin therapy is

associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment. *J Am Coll Cardiol*. 2006; 48 (2):298-304.

26. Fontana P, Senouf D, Mach F. Biological effect of increased maintenance dose of clopidogrel in cardiovascular outpatients and influence of the cytochrome P450 2C19*2 allele on clopidogrel responsiveness. *Thromb Res*. 2007; 121 (4):463-8.

27. Angiolillo DJ, Bernardo E, Palazuelos J, Desai B, Weisberg I, Alfonso F, Guzman LA, Hernandez-Antolin R, Zenni MM, Macaya C, Fernandez-Ortiz A, Bass TA. Functional impact of high clopidogrel maintenance dosing in patients undergoing elective percutaneous coronary interventions - Results of a randomized study. *Thromb Haemost*. 2008; 99 (1):161-8.

28. Kastrati A, von Beckerath N, Joost A, Pogatsa-Murray G, Gorchakova O, Schömig A. Loading with 600 mg clopidogrel in patients with coronary artery disease with and without chronic clopidogrel therapy. *Circulation*. 2004; 110 (14):1916-9.

29. Angiolillo DJ. ADP receptor antagonism: what's in the pipeline? Am *J Cardiovasc Drugs*. 2007; 7 (6):423-32.

30. Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, Neumann FJ, Michelson AD, Angiolillo DJ, Hod H, Montalescot G, Miller DL, Jakubowski JA, Cairns R, Murphy SA, McCabe CH, Antman EM, Braunwald E. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation*. 2007; 116 (25):2923-32.