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Clopidogrel pre-treatment in stable angina: for all patients >6 h before elective coronary angiography or only for angiographically selected patients a few minutes before PCI? A randomized multicentre trial PRAGUE-8

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Aims To compare two different clopidogrel regimens on the outcomes of patients undergoing elective coronary angiography (CAG) ± *ad hoc* percutaneous coronary intervention (PCI).

Methods and results Open-trial randomized 1028 patients with stable angina to group A ('non-selective'—clopidogrel 600 mg >6 h before CAG; $n = 513$) or group B ('selective'—clopidogrel 600 mg in the cath-lab after CAG, only in case of PCI; $n = 515$). Combined primary endpoint was death/periprocedural myocardial infarction (MI)/stroke/re-intervention within 7 days. Secondary endpoints were troponin elevation and bleeding complications. Primary endpoint occurred in 0.8% group A patients vs. 1% group B ($P = 0.749$; 90% CI for the percentage difference −1.2–0.8). Periprocedural troponin elevation (>3× ULN) was detected in 2.6% group A vs. 3.3% group B ($P = 0.475$; 90% CI −2.5–1.0). Bleeding complications occurred in 3.5% group A patients vs. 1.4% group B ($P = 0.025$). After adjustment for covariates and factors that may influence the bleeding risk, patients in group A were shown to have more likely bleeding complications when compared with group B (OR = 3.03; 95% CI 1.14–8.10; $P = 0.027$).

Conclusion High (600 mg) loading dose of clopidogrel before elective CAG increased the risk of minor bleeding complications, while the benefit on periprocedural infarction was not significant. Clopidogrel can be given safely in the catheterization laboratory between CAG and PCI in chronic stable angina patients.

Keywords Elective percutaneous coronary intervention • Clopidogrel pre-treatment • Stable coronary artery disease • Bleeding complications • Periprocedural ischaemic complications

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Introduction

The introduction of thienopyridines to interventional cardiology 13 years ago triggered a revolutionary change—it made coronary stent implantation a safe procedure: the risk of stent thrombosis decreased from 8% (with the old complex anticoagulation regimen) to 1–2% (with thienopyridine and aspirin) and the risk of significant bleeding complications decreased from 5 to 1–2%.[1,2] Ticlopidine and later clopidogrel[3] became a routine part of every percutaneous coronary intervention (PCI). Later, the CREDO[4] and PCI-CURE[5] trials showed that the patients pretreated with clopidogrel have a lower risk of periprocedural ischaemic events. Clopidogrel became widely used for patients undergoing PCI. However, the loading dose given before PCI varies among different clinical trials and different hospitals. The approved loading dose is 300 mg. However, 600 mg loading dose was shown to be superior in a small randomized trial[6] and is used with increasing frequency with supporting data from trials in acute coronary syndromes.[7–10] These two loading doses are compared in the ongoing large randomized multicentre trial CURRENT/OASIS-7.[11] Recommended time for the loading dose is >6 h before PCI. However, nearly all PCIs are currently performed as '*ad hoc*' procedures [i.e. immediately following the diagnostic coronary angiography (CAG)], and thus the time between the decision to intervene and PCI procedure is just a few minutes. Due to this fact, some hospitals administer the loading dose of clopidogrel in advance to all patients undergoing CAG, others administer it during the procedure (i.e. after CAG) only to those undergoing PCI. It has not been established yet which of these strategies is better. Most Czech PCI centres have been using clopidogrel before PCI 'selectively' (i.e. in the cath-lab between CAG and PCI or even after PCI) in their routine practice for many years. When the new ESC guidelines for PCI were published in 2005, five study centres decided to compare their routinely used 'old selective' strategy with the ESC guidelines recommended 'new non-selective' strategy and the PRAGUE-8 trial design was born.

The hypothetical advantage of the 'non-selective' approach (clopidogrel >6 h before each elective CAG) is the full drug effect during *ad hoc* PCI resulting in a lower rate of ischaemic periprocedural complications. The disadvantage of this approach might be the increased risk of periprocedural bleeding complications, especially difficult to justify among stable angina patients, who in fact had no indication for clopidogrel (i.e. those, who underwent only CAG, but not PCI).

The hypothetical advantage of the 'selective' approach (clopidogrel on the catheterization table, just after CAG/a few minutes prior to PCI) is that clopidogrel is given only to those patients who have a clear indication (i.e. really undergo PCI) and the bleeding risk thus may be reduced. The disadvantage might be the increase of ischaemic periprocedural complications due to the fact that the full effect of clopidogrel is not yet achieved at the time of PCI.

Methods

The trial protocol, case report form, and written patient informed consent were approved by the local ethical committees of all participating institutions. The trial was registered at www.clinicaltrials.gov under registration number NCT00432120.

Patients and treatment arms

A total of 9195 patients underwent elective CAG during the study period in the participating centres. The inclusion/exclusion criteria as well as the specific numbers of patients excluded due to a given criterion are listed in *Table 1*. A total of 5055 patients fulfilled all the criteria, 4027 of them were not included merely due to logistic reasons (low study budget and staffing). In general, patients undergoing planned elective CAG for suspected or proven coronary artery disease (either chronic stable or stabilized unstable) were enrolled the day before the procedure after they signed written informed consent.

Randomization was carried out using the centralized sealed envelopes method, coordinated at the 3rd Medical Faculty, Prague. The study was conducted on an open basis: neither the patients nor the investigators were blinded to the treatment arm. The statistician (who analysed all the data and provided the results) was blinded to the treatment arms. Study enrolment began in March 2006 and ended in July 2007. A total of 1028 patients were randomized in two groups: 513 patients in group A and 515 patients in group B (*Figure 1*). All patients in group A received clopidogrel 600 mg orally more than 6 h before CAG. In group A, the mean duration between clopidogrel administration and CAG was 20.6 h (median 20 h). From these, 30% underwent PCI and 70% patients underwent only CAG. Only patients undergoing PCI ($n = 143$, i.e. 28%) in group B received clopidogrel 600 mg orally in the catheterization laboratory after CAG a few minutes prior to PCI. The remaining 72% patients in group B did

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Elective CAG for suspected or proven coronary artery disease (stable forms or fully stabilized acute coronary syndrome)	Thienopyridine treatment in previous 2 weeks (25 patients excluded due to this reason)
Signed written informed consent (48 patients excluded for signature refusal)	Contraindication for clopidogrel (0 patient excluded due to this reason)
Age ≥ 18 years (0 patient excluded)	CAG scheduled less than 6 h after potential randomization (3627 patients excluded due to this reason)
	Clinically significant bleeding (i.e. with haemoglobin fall by >50 g/L and/or requiring transfusions or surgery) in previous 3 months (85 patients excluded due to this reason)
	Participation in any project with investigational drug or device within previous 1 month (355 patients excluded due to this reason)
	Additional 4027 patients excluded due to the logistic reasons (see Methods section)

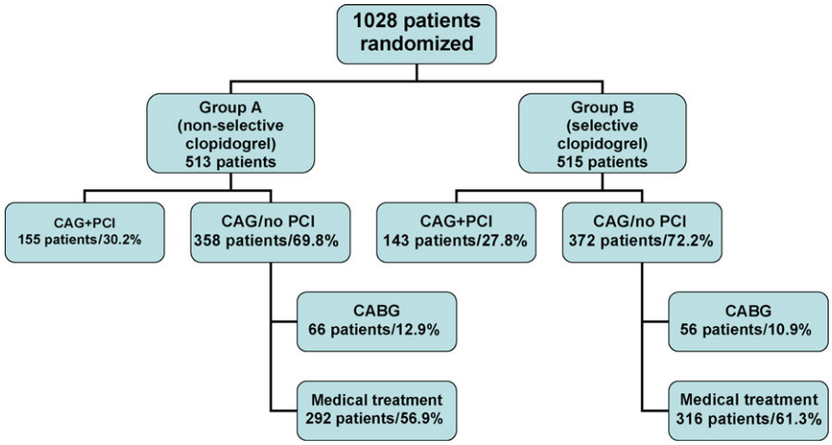

Figure 1 Study patients and the treatment used.

not receive any clopidogrel due to the fact that no PCI was indicated after CAG. Patients' baseline characteristics are shown in *Table 2*.

Invasive procedures

Cardiac catheterization procedures were performed via femoral approach using 5F or 6F sheaths and catheters. All technical aspects (including the use and dose of periprocedural heparin) of the procedure were left at the discretion of treating cardiologist as per local routine. All participating hospitals use routinely the '*ad hoc* PCI strategy': when elective CAG shows a finding suitable for PCI (mostly single-vessel or double-vessel disease), intervention follows immediately after CAG. Staged procedures (i.e. CAG and PCI in two different days) were used only for 16 patients (i.e. 5% of all PCIs) with multivessel disease, who have been discussed during the heart team meeting and were found to be poor candidates for coronary artery bypass graft (CABG) surgery.

Examinations and follow-up

The laboratory examinations at baseline were done as per local routine and included Na, K, urea, serum creatinine, AST, ALT, CK-MB, troponin I, blood count, INR, and APTT. Left ventricular ejection fraction was assessed by echocardiography or left ventriculography as per local routine in each centre. CAG was done in all patients. Electrocardiogram was recorded at baseline and after CAG/PCI. CK-MB and troponin I were analysed 8–16 h after PCI. Patients were followed until their discharge from the hospital or until day 7, whatever occurred earlier.

Endpoints

Primary endpoint was the first clinical occurrence of any of the following: death/periprocedural MI/stroke or transient ischaemic attack/re-intervention within 7 days. Secondary endpoints were periprocedural troponin elevation ($>3\times$ ULN), TIMI-flow after PCI, bleeding complications, and each individual component of the combined primary endpoint.

Death was defined as mortality from any cause (cardiovascular or non-vascular).

Periprocedural MI was defined as the post-procedural (after PCI) elevation of the serum levels of CK-MB to at least three times the upper limit of normal values in two samples collected at different sampling times. Stroke (of any cause) was defined as new focal neurological deficit occurring within 24 h after CAG and persisting more than 24 h. Transient ischaemic attack was defined similarly to stroke, but persisting less than 24 h. Re-intervention was defined as new ischaemic symptoms leading to repeat CAG and/or PCI/or CABG within 7 days.

Bleeding complications were defined as: (i) major bleeding, intracranial bleeding or clinically overt bleeding associated with a decrease in haemoglobin >50 g/L; (ii) minor bleeding, clinically visible with a decrease in haemoglobin ≤ 50 g/L according to the modified criteria of thrombolysis in myocardial infarction (TIMI).[12] Besides this internationally recognized definition, we specifically registered those bleeding complications *resulting in prolonged hospital stay* (classified as major or minor) and those *resulting in surgical intervention*. Bleeding related to CABG was defined as bleeding that met the criteria for major bleeding events according to the TIMI criteria (with a drop in haemoglobin of >50 g/L) and associated with a surgical procedure. CABG-related bleeding was evaluated separately. The diagnosis of intracranial bleeding required confirmation by computed tomography or magnetic resonance imaging. Small femoral access haematomas not requiring treatment was also registered.

Statistical methods

The initial assumption was that the endpoint will occur in 3% of group B patients. The trial was designed to have 80% power to detect a 2.5% absolute decrease (i.e. 0.5% incidence) of the primary endpoint in group A as significantly different from that in group B at a significance level of 0.05. On this basis, 508 patients were required in each group. Primary treatment comparison was based on the data from all 1028 subjects with stable angina randomized into group A or B. Patients undergoing PCI and patients with CABG, respectively, formed the two analysis sets of secondary interest. Values of continuous variables are presented as arithmetic means and Student's two-sample *t*-test was used to evaluate between-group comparisons. For dichotomous data, the percentages are given and differences in proportions between groups were analysed using Fisher's exact test and Pearson's χ^2 test in the four-fold table. Test results with *P*-value equal to or less than 0.05 were considered statistically significant. According to Hauck,[13] the equivalence of both groups may be assessed using 90% confidence

Table 2 Patients baseline clinical and laboratory characteristics

	Group A (non-selective clopidogrel before CAG)	Group B (selective clopidogrel before PCI)	*P*-value
n	513	515	
Age (year)	65.3 (9.6)	65.9 (9.6)	0.257
Females	183 (36%)	194 (39%)	0.506
Body weight (kg)	84.6 (15.8)	83.3 (14.9)	0.208
Stabilized ACS	66 (13%)	79 (15%)	0.249
Proven or suspected chronic stable CAD	446 (87%)	434 (85%)	0.249
Previous MI	137 (27%)	147 (29%)	0.497
Hypercholesterolaemia	335 (65%)	342 (67%)	0.676
Hypertension	405 (79%)	407 (79%)	0.926
Smoking (current or past)	123 (24%)	126 (25%)	0.841
Diabetes mellitus	147 (29%)	147 (29%)	0.984
Previous revascularization (PCI or CABG)	106 (21%)	117 (23%)	0.414
Known chronic renal failure	38 (7%)	35 (7%)	0.709
Treatment with ASA within 1 week before randomization	375 (73%)	403 (79%)	0.047
Anticoagulant therapy within 1 week before randomization	33 (6.5%)	33 (6.0%)	0.993
Treatment with GP IIb/IIIa inhibitors as an adjunct during PCI	1 (0.2%)	2 (0.4%)	0.608
Treatment with statins within 1 week before randomization	291 (57%)	296 (58%)	0.780
Mean platelet count	241 (74)	242 (65)	0.836
White cells count	7.7 (2.2)	7.8 (2.2)	0.688
Red cells count	4.6 (0.6)	4.6 (0.5)	0.219
INR at randomization	1.06 (0.12)	1.05 (0.12)	0.123
APTT at randomization (s)	34.5 (12.7)	33.9 (11.4)	0.496
Creatinine (μmol/L)	93.8 (26.6)	93.8 (31.4)	0.981
Ejection fraction (%)	56.8 (11.1)	57.1 (11.1)	0.654

Continuous variables are presented as means and standard deviations and categorical data are presented as absolute frequencies (counts) and percentages.

intervals (CI) for the difference in proportions found in groups A and B.

The logistic regression model was used to adjust the differences in bleeding complications for covariate effects. Following factors and covariates were entered in the model: age, gender, BMI, renal insufficiency, full anticoagulant dose of heparin (UFH or enoxaparin), treatment with GP IIb/IIIa inhibitors, indicator for INR >1.3, and indicator for platelet count $< 100 \times 10^9$ per litre. For continuous variables, the assumption of linearity in logit was checked using the Box-Tidwell approach and logit graphs constructed for a banded version of an underlying continuous variable. No violations of linearity assumption were identified.

Statistical analysis was performed by statistical software Stata, release 9 (Stata Corp. LP, College Station, TX, USA).

Results

Revascularizations

Ad hoc PCI was performed in 29% of study patients (30% in group A vs. 28% in group B) and bypass surgery (CABG) in 12% of patients (mostly after >7 days) (*Figure 1*). Medical therapy was recommended in 59% of patients (22% had at least single vessel disease, 37% had either non-significant lesions or no residual stenosis after previous revascularization or normal coronary angiogram).

Endpoints among all study patients

Primary endpoint occurred in 0.8% of group A patients vs. 1% of group B patients ($P = 0.749$; 90% CI for difference in percentages −1.2–0.8) (*Table 3*). Periprocedural troponin elevation (>3× ULN) was detected in 2.6% of patients in group A vs. 3.3% in group B ($P = 0.475$; 90% CI −2.5–1.0) (*Figure 2*). Bleeding complications (*Table 4*) occurred in 3.5% of group A patients vs. 1.4% of group B patients ($P = 0.025$) (*Figure 3*). After adjustment for specified covariates and factors that may influence the bleeding risk (see Methods section), patients in group A were shown to have more likely bleeding complications when compared with group B (OR = 3.03; 95% CI 1.14–8.10; $P = 0.027$). Statistically significant risk factors were also female gender ($P = 0.001$) and

Table 3 Periprocedural ischaemic events in both groups

	Group A (non-selective clopidogrel before CAG)	Group B (selective clopidogrel before PCI)	*P*-value
All study patients	$n = 513$	$n = 515$	
Death of any cause	1 (0.2%)	0 (0.0%)	0.498
Periprocedural MI (CK-MB $>3\times$ ULN)	0	0	1.000
Periprocedural stroke/TIA	1 (0.2%)	3 (0.6%)	0.624
Re-intervention	2 (0.4%)	2 (0.4%)	0.992
Primary endpoint	4 (0.8%)	5 (1.0%)	0.749
Periprocedural troponin increase $>3\times$ ULN	13 (2.7%)	17 (3.3%)	0.475
Death of any cause/periprocedural troponin increase $>3\times$ ULN/periprocedural stroke/TIA/re-intervention	17 (3.3%)	19 (3.7%)	0.757
Only patients, who underwent PCI	$n = 155$ (30.3%)	$n = 143$ (27.9%)	0.398
Primary endpoint	2 (1.3%)	4 (2.8%)	0.432
Periprocedural troponin elevation $>3\times$ ULN	13 (8.4%)	17 (11.9%)	0.316
Impairment of TIMI-flow to <3 after PCI	2 (1.3%)	0	0.499

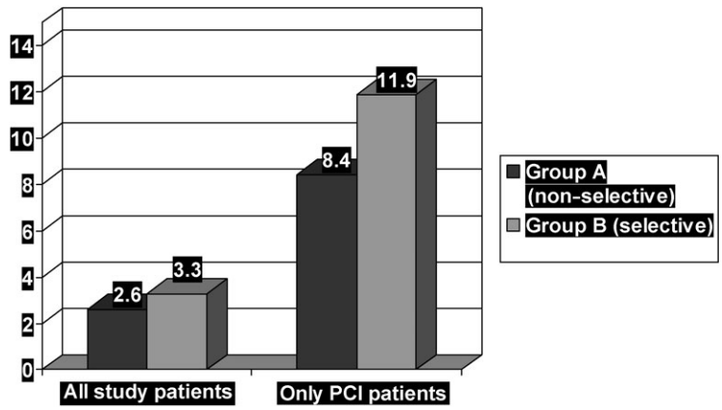

Figure 2 Periprocedural troponin elevation ($>3\times$ ULN, per cent of patients).

use of GP IIb/IIIa inhibitors ($P = 0.027$). Low thrombocyte levels showed *P*-value close to significance level ($P = 0.091$).

Endpoints among patients who underwent percutaneous coronary intervention

When only the subgroup of patients who underwent PCI was analysed, primary endpoint occurred in 1.3% group A vs. 2.8% group B ($P = 0.432$; 90% CI -4.1–1.2). Periprocedural troponin elevation ($>3\times$ ULN) was detected in 8.4% (group A) vs. 11.9% (group B, $P = 0.316$; 90% CI -2.3–9.3). TIMI-flow <3 after PCI was in 1.3% group A vs. 0% group B ($P = 0.499$). Bleeding complications occurred in 7.1% (group A) vs. 0.7% (group B, $P = 0.006$) and re-intervention within 7 days in 0.7% group A vs. 1.4% group B ($P = 0.515$).

Patients who underwent coronary artery bypass graft

CABG was performed in 122 patients. Only 17 of them (14% from those indicated for CABG and 1.7% from all CAG) underwent CABG within 1 week after CAG (7 in group A and 10 in group B). There was only one clinically overt peri-operative bleeding complication among these 17 patients and two other patients had haemoglobin decrease by >50 g/L postoperatively without any postoperative bleeding.

Discussion

Clopidogrel loading dose

The registered loading dose for clopidogrel is 300 mg and this dose was used for many years before elective PCIs. In the recent years, there has

Table 4 Bleeding complications in both groups

	Group A (non-selective clopidogrel before CAG)	Group B (selective clopidogrel before PCI)	*P*-value
All study patients (all CAGs)	*n* = 513	*n* = 515	
Major and minor bleeding complications	18 (3.5%)	7 (1.4%)	0.025
Major (intracranial or HB fall by >50 g/L)	2 (0.4%)	1 (0.2%)	0.624
Minor (clinically overt, prolonging hospital stay)	16 (3.1%)	6 (1.2%)	0.033
Breakdown of all bleeding complications (major/minor)			
Intracranial	1 (0.2%)	0 (0.0%)	0.498
Retroperitoneal	2 (0.4%)	0 (0.0%)	0.248
Gastrointestinal	1 (0.2%)	0 (0.0%)	0.498
Femoral access bleeding requiring transfusion and/or surgical repair	0 (0.0%)	0 (0.0%)	1.000
Femoral access bleeding requiring prolonged compression	8 (1.6%)	5 (1.0%)	0.419
Large superficial haematoma	5 (1.0%)	1 (0.2%)	0.122
Not included in major or minor			
Small femoral access haematomas	18 (3.5%)	9 (1.8%)	0.082
Only patients, who underwent PCI	*n* = 155	*n* = 143	0.398
Major and minor bleeding complications	11 (7.1%)	1 (0.7%)	0.006
Major (intracranial or HB fall by >50 g/L)	1 (0.6%)	1 (0.7%)	0.954
Minor (clinically overt, prolonging hospital stay)	10 (6.5%)	0 (0.0%)	0.002

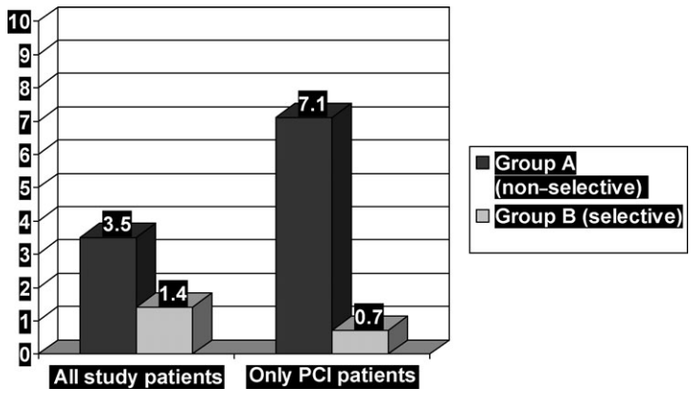

Figure 3 Bleeding complications (major+minor, in per cent) among all study patients and among PCI patients only.

been an increasing use of 600 mg loading dose, mostly triggered by the ARMYDA-2 trial.[6] Most data supporting this higher loading dose originate from acute coronary syndrome patients.[8–10] Fewer data are available on chronic stable coronary artery disease patients. Despite the fact that a recent retrospective registry showed (unlike ARMYDA-2 randomized trial) no benefit from 600 mg over 300 mg dose in PCI for chronic stable coronary artery disease,[14] many hospitals around the world (as well as most Czech PCI centres) use 600 mg routinely for pre-treatment before PCI. Thus, 600 mg loading dose was selected also for this randomized study.

Timing of the loading dose

The pre-treatment (within 3–24 h) hypothesis failed to be validated in the prospective randomized Clopidogrel for the Reduction of Events During Observation[4] trial. No treatment differences were observed in patients receiving a 600 mg loading dose 2–3 h before PCI vs. those receiving the same loading dose 12 h before PCI in the Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment (ISAR–REACT) trial.[15] The European Society of Cardiology (ESC)

guidelines on PCI[16] recommend, that 'every patient scheduled for *PCI* should be considered for pre-treatment with clopidogrel at least 6 h prior to the procedure with a dose of 300 mg ideally administered the day before a planned PCI and if this is not possible a loading dose of 600 mg should be administered at least 2 h before PCI'. However, only very few patients are actually scheduled for elective PCI, most patients are scheduled for elective coronary angiogram with immediate '*ad hoc*' PCI procedure when indicated. Thus, in the real life, only a few minutes elapse between the decision to perform PCI and the beginning of the procedure. The recommended time window 2–6 h before PCI for pre-treatment thus means that patients in many hospitals are actually pre-treated before CAG, exposing thus the majority of patients (all who undergo only CAG and not PCI) unnecessarily to aggressive antiplatelet medication and potentially causing avoidable bleeding complications. The ESC guidelines indirectly recommend this non-selective clopidogrel treatment for all CAG patients by saying 'If diagnostic angiography is negative or no stenting was performed, or if early heart surgery is indicated, clopidogrel can be stopped.' This recommendation, however, was based only on empiric position of the guidelines authors, the evidence was lacking.

Periprocedural ischaemic events

The incidence of periprocedural myocardial necrosis after PCI largely varies depending on the study populations and methods of detection. A recent study among patients with acute coronary syndromes revealed to 'biochemical' periprocedural infarctions among 43% of suboptimal responders to aspirin plus clopidogrel vs. 22% among responders.[17] Chronic stable angina patients, undergoing elective PCI were studied by Hochholzer *et al.*[18]—the 30-day incidence of clinically apparent MI was 1%. Another study on consecutive PCI patients showed the 6% combined major cardiovascular event (non-fatal MI, non-fatal ischaemic stroke, or cardiovascular death) in patients who adequately responded to clopidogrel.[19] Our study showed that among subgroup of patients undergoing *PCI*, clopidogrel pre-treatment >6 h before CAG/PCI did not significantly reduce periprocedural troponin elevation. Clinically significant 'ischaemic' periprocedural complications were few and equally distributed in both groups.

Stable coronary artery disease vs. acute coronary syndromes

The well-known difference in platelet activity and also in overall risk of ischaemic events between patients with acute coronary syndromes and those with stable coronary artery disease can explain somewhat surprising results of this study. Our results cannot be extrapolated to patients with acute coronary syndromes, in whom the benefit from early clopidogrel therapy is unequivocal.

Periprocedural bleeding complications

In general, bleeding complications are rare in the elective CAG/PCI patient population. Hochholzer *et al.*[20] found 0.5% major bleeding rate within the group of 573 patients undergoing CAG at least 2 h after administration of 600 mg clopidogrel, who did not undergo PCI.

The CLopidogrel ASpirin Stent International Cooperative Study (CLASSICS) was the first randomized trial to evaluate a loading dose of clopidogrel in coronary stenting. The 300 mg loading dose was well tolerated, notably with no increased risk of serious bleeding.[3] The incidence of major peripheral or bleeding complications was low—1.5% for clopidogrel loading dose and 1.2% for clopidogrel 75 mg QD without loading dose.[3] Pre-treatment with a higher (600 mg) dose of clopidogrel carried 1.6% risk of major bleeding in the ISAR–REACT study. However, randomized trials generally exclude patients at highest risk of bleeding and may therefore underestimate the true frequency of bleeding associated with clopidogrel use in the general population.

A subanalysis of 9478 patients with prior MI, ischaemic stroke, or symptomatic peripheral arterial disease from the CHARISMA trial[21] found no significant difference in the rate of severe bleeding: 1.7% (aspirin+clopidogrel arm) vs. 1.5% (aspirin+placebo arm), while moderate bleeding was significantly increased: 2.0 vs. 1.3%.

Despite the fact that using high dose (600 mg) of clopidogrel very early (20.6 h) before procedure in our study, we probably reached the platelet inhibition never reached before in any previous trial in chronic stable patients, the major bleedings were only few. However, a small but significant increase in minor bleeding complications was the price paid for non-selective clopidogrel use for all CAG patients in our study.

Cardiac surgeons do not like operating on patients with clopidogrel on board. A recent study[22] showed double re-operations rate among patients, who received clopidogrel 3 days prior to CABG. However, this fear of cardiac surgeons from peri-operative bleeding after clopidogrel is questioned by other studies.[23]

An interesting Czech study[24] found 0.15% incidence (9 cases) of gastrointestinal bleeding among 5955 patients hospitalized for elective CAG. However, the mortality of these patients was high (3/9, i.e. 33%).

Study limitations

This was a randomized comparison of two unapproved (but routinely used in many centres worldwide) regimens of loading dose of clopidogrel for PCI in stable angina. The approved loading dose is 300 mg. The habit of giving a 600 mg loading dose pre-PCI or at the time of PCI has spread among interventional cardiologists, but without any clear evidence of its efficacy and safety. It could be possible that a 300 or 600 mg loading dose administered long before angiography/PCI would probably not have much difference on inhibition of platelet aggregation at the time of PCI, but the impact on bleeding risk could be greater with 600 mg than with 300 mg.

This study was not designed to examine whether clopidogrel should be used before *PCI* (we believe that the answer is yes). This trial was designed to test the use of high dose clopidogrel before elective *CAG*. We believe that there is a substantial overlap in literature between the terms 'elective PCI' and 'elective CAG ± possible PCI'. We firmly believe that terminology should be unified in this field as follows: *Planned elective PCI*, scheduled PCI procedure in a patient with already known CAG result (i.e. PCI done as a separate procedure from CAG). *Ad hoc* PCI represents PCI procedure performed immediately following CAG. Planned elective CAG represents scheduled CAG procedure in a patient with clinical presentation of various forms of coronary

artery disease. In other words, the term 'planned elective PCI' should not be used for patients without known CAG result.

Conclusions

High dose clopidogrel before elective CAG increased the risk of bleeding complications while the effect on the primary ischaemic endpoint was not significant. Clopidogrel can be administered safely in the catheterization laboratory between CAG and PCI in patients with chronic stable angina. We suppose that clopidogrel should be used before 'planned elective PCI' as well as before '*ad hoc* PCI', but not before 'planned elective CAG'.

Author contributions

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Data access/responsibility

Principal Investigators of the PRAGUE 8 study—Dr Petr Widimský and Dr Zuzana Motovská—had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the analysis.

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References

1. Bertrand ME, Legrand V, Boland J, Fleck E, Bonnier J, Emmanuelson H, Vrolix M, Missault L, Chierchia S, Casaccia M, Niccoli L, Oto A, White C, Webb-Peploe M, Van Belle E, McFadden EP. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting—the full anticoagulation versus aspirin and ticlopidine (FANTASTIC) study. *Circulation* 1998;**98**:1597–1603.
2. Schömig A, Neumann FJ, Kastrati A, Schuhlen H, Blasini R, Hadamitzky M, Walter H, ZitzmannRoth EM, Richardt G, Alt E, Schmitt C, Ulm K. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996;**334**:1084–1089.
3. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, for the CLASSICS Investigators. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the CLopidogrel ASpirin Stent International Cooperative Study (CLASSICS). *Circulation* 2000;**102**:624–629.
4. Steinhubl SR, Berger PB, Mann JT, Fry ETA, DeLago A, Wilmer C, Topol EJ for the CREDO Investigators. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;**288**:2411–2420.
5. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Maimberg K, Rupprecht HJ, Zhao F, Chrolavicius S, Copland I, Fox KAA. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;**358**:527–533.
6. Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. *Circulation* 2005;**111**:2099–2106.
7. Zeymer U, Arntz HR, Darius H, Huber K, Senges J. Efficacy and safety of clopidogrel 600 mg administered pre-hospitally to improve primary percutaneous coronary intervention in patients with acute myocardial infarction (CIPAMI): Study Rationale and Design. *Cardiology* 2006;**108**:265–272.
8. Cuisset T, Frere C, Quilici J, Morange PE, Nait-Saidi L, Carvajal J, Lehmann A, Lambert M, Bonnet JL, Alessi MC. Benefit of a 600-mg loading dose of clopidogrel on platelet reactivity and

clinical outcomes in patients with non-ST-segment elevation acute coronary syndrome undergoing coronary stenting. *J Am Coll Cardiol* 2006;**48**:1339–1345.
9. Montalescot G, Sideris G, Meuleman C, Bal-Dit-Sollier C, Lellouche N, Steg PG, Slama M, Milleron O, Collet JP, Henry P, Beygui F, Drouet L. A randomized comparison of high clopidogrel loading doses in patients with non-ST-segment elevation acute coronary syndromes: the ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) trial. *J Am Coll Cardiol* 2006;**48**:931–938.
10. Kastrati A, Mehilli J, Neumann FJ, Dotzer F, ten Berg JN, Bollwein H, Graf I, Ibrahim M, Pache J, Seyfarth M, Schuhlen H, Dirschinger J, Berger PB, Schomig A. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA* 2006;**295**:1531–1538.
11. Mehta SR. Clopidogrel in non-ST-segment elevation acute coronary syndromes. *Eur Heart J Suppl* 2006;**8**:G25–G30.
12. Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, Bell WR, Knatterud G, Robertson TL, Terrin ML. Thrombolysis in Myocardial Infarction (TIMI) Trial—phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol* 1988;**11**:1–11.
13. Hauck WW. A proposal for interpreting and reporting negative studies. *Stat Med* 1986;**5**:203–209.
14. Wolfram RM, Torgusson RL, Hassani SE, Xue ZY, Gevorkian N, Pichard AD, Satler LF, Kent KM, Waksman R. Clopidogrel loading dose (300 versus 600 mg) strategies for patients with stable angina pectoris subjected to percutaneous coronary intervention. *Am J Cardiol* 2006;**97**:984–989.
15. Kandzari DE, Berger PB, Kastrati A, Steinhubl SR, Mehilli J, Dotzer F, ten Berg JM, Neumann FJ, Bollwein H, Dirschinger J, Schomig A. Influence of treatment duration with a 600-mg dose of clopidogrel before percutaneous coronary revascularization. *J Am Coll Cardiol* 2004;**44**:2133–2136.
16. Silber S, Albertsson P, Aviles FF, Camici PG, Colombo A, Hamm C, Jorgensen E, Marco J, Nordrehaug JE, Ruzyllo W, Urban P, Stone GW, Wijns W for the Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J* 2005;**26**:804–847.
17. Cuisset T, Frere C, Quilici J, Morange PE, Nait-Saidi L, Mielot C, Bali L, Lambert M, Alessi MC, Bonnet JL. High post-treatment platelet reactivity is associated with a high incidence of myonecrosis after stenting for non-ST elevation acute coronary syndromes. *Thromb Haemost* 2007;**97**:282–287.
18. Hochholzer W, Trenk D, Bestehorn HP, Fischer B, Valina CM, Ferenc M, Gick M, Caputo A, Buttner 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**:1742–1750.
19. 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**:2420–2425.
20. Hochholzer W, Trenk D, Frundi D, Blanke P, Fischer B, Andris K, Bestehorn HP, Buttner 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**:2560–2564.
21. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Fabry-Ribaudo L, Hu T, Topol EJ, Fox KAA for the CHARISMA Investigators. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA Trial. *J Am Coll Cardiol* **49**:1982–1988.
22. Kang W, Theman TE, Reed JF 3rd, Stoltzfus J, Weger N. The effect of preoperative clopidogrel on bleeding after coronary artery bypass surgery. *J Surg Educ* 2007;**64**:88–92.
23. Shim JK, Choi YS, Oh YJ, Bang SO, Yoo KJ, Kwak YL. Effects of preoperative aspirin and clopidogrel therapy on perioperative blood loss and blood transfusion requirements in patients undergoing off-pump coronary artery bypass graft surgery. *J Thorac Cardiovasc Surg* 2007;**134**:59–64.
24. Kojecky V, Coufal Z. Clinically manifest gastrointestinal bleeding in patients subject to coronary angiography. *Vnitr Lek* 2007;**53**:147–150.