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Aspirin versus clopidogrel after surgical off-pump coronary revascularization – a prospective, randomized, head-to-head pilot trial

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Abstract

Background: Postoperative clopidogrel use after surgical coronary revascularization may provide short- and long-term reduction of risk of negative cardiovascular events. However, there are not enough data from prospective randomized trials comparing head-to-head monotherapy with either aspirin or clopidogrel.

Aim of the study: The aim of the study was to evaluate the safety and effectiveness of aspirin or clopidogrel use in patients after elective coronary artery bypass grafting.

Material and methods: The study involved 50 patients who were referred for elective off-pump coronary artery bypass grafting (OPCAB). Preoperatively patients were randomized to postoperative antiplatelet treatment with either aspirin (150 mg per day) or clopidogrel for 6 months (75 mg per day). After 6 months all patients were turned to aspirin. In all patients platelet function on aspirin was checked before surgery. After 1, 6 and 12 months in all cases follow-up was collected in terms of any adverse events.

Results: During follow-up 26 negative events occurred, including repeated revascularization, stroke and bleeding. In the clopidogrel arm cumulative risk of negative events was significantly lower (14%) in comparison to the aspirin group (25%, $p < 0.05$). In patients with preoperative persistent platelet function on aspirin the highest cumulative event risk was observed (35%). The lowest cumulative event risk was observed in aspirin responders randomized to the clopidogrel arm (2%).

Conclusions: Clopidogrel therapy provided for 6 months after OPCAB instead of the standard aspirin protocol may reduce the risk of negative adverse cardiovascular events. Occurrence of preoperative persistent platelet function on aspirin is related to worse 1-year outcome after off-pump coronary revascularization.

Key words: coronary artery bypass grafting, antiplatelet therapy.

Streszczenie

Wstęp: Zastosowanie klopidogrelu u pacjentów po chirurgicznej rewaskularyzacji serca może przynieść wczesną i odległą redukcję ryzyka wystąpienia niepożądanych zdarzeń sercowo-naczyniowych. Opublikowano niewiele prospektywnych badań z randomizacją porównujących terapię przeciwpłytkową jedynie kwasem acetylosalicylowym lub jedynie klopidogrelem w tej populacji.

Cel pracy: Celem badania była ocena skuteczności i bezpieczeństwa prowadzenia terapii przeciwpłytkowej kwasem acetylosalicylowym lub klopidogrelem u pacjentów po planowej chirurgicznej rewaskularyzacji serca.

Materiał i metody: Do badania zrandomizowano prospektywnie 50 pacjentów, u których po wykonanej operacji pomostowania tętnic wieńcowych bez zastosowania krążenia pozaustrojowego przez 6 miesięcy prowadzono terapię jedynie kwasem acetylosalicylowym (150 mg) lub jedynie klopidogrelem (75 mg), a następnie u wszystkich tylko kwasem acetylosalicylowym. W całej populacji chorych oznaczono stopień zablokowania płytek krwi przez kwas acetylosalicylowy. Po 1, 6 i 12 miesięcach przeprowadzono kontrolę wystąpienia zdarzeń niepożądanych.

Wyniki: W czasie obserwacji odnotowano 26 zdarzeń niepożądanych, włączając w to powtórną rewaskularyzację, udar i krwawienia. W ramieniu klopidogrelu skumulowane ryzyko wystąpienia zdarzeń niepożądanych było istotnie niższe (14%) w porównaniu z grupą, w której stosowano kwas acetylosalicylowy (25%, $p < 0,05$). U pacjentów z funkcją płytek niepoddającą się zablokowaniu kwasem acetylosalicylowym obserwowano najwyższe skumulowane ryzyko (35%). Z kolei najniższe ryzyko wystąpienia zdarzeń niepożądanych obserwowano u osób z przedoperacyjnie zablokowaną funkcją płytek przez kwas acetylosalicylowy i zrandomizowanych do ramienia klopidogrelu (2%).

Wnioski: Zastosowanie klopidogrelu zamiast kwasu acetylosalicylowego w ciągu 6 miesięcy po chirurgicznej rewaskularyzacji serca jest bezpieczne i wydaje się poprawiać rokowanie w porównaniu z leczeniem jedynie kwasem acetylosalicylo-

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wym. Brak blokowania funkcji płytek krwi kwasem acetylosalicylowym jest związany ze zwiększeniem ryzyka wystąpienia zdarzeń negatywnych w ciągu roku po operacji.
Słowa kluczowe: pomostowanie tętnic wieńcowych, leczenie przeciwpłytkowe.

Introduction

Coronary artery bypass grafting (CABG) is standard treatment of stable ischemic heart disease in the general population. Long-term results of the SYNTAX trial show that CABG remains the best option for patients with more complex coronary atherosclerosis [1]. However, the long-term result of CABG is determined by numerous factors, such as: factors related to the surgical procedure (i.e. completeness of revascularization, type of grafts used, atherosclerosis complexity), risk factors of atherosclerosis progression (i.e. diabetes, dyslipidemia, arterial hypertension, age, genetic factors) and secondary pharmacological and non-pharmacological prevention [2]. The positive impact on short- and long-term prognosis of antiplatelet treatment with aspirin is scientifically proven after CABG and remains a class I recommendation [3]. Other antiplatelet drugs (i.e. clopidogrel, ticagrelor, prasugrel) in combination with aspirin are under numerous studies conducted in patients after percutaneous coronary intervention (PCI) and those treated medically. The results of those trials show improvement in early and long-term results, but not enough data are available in terms of the CABG population [4]. Effectiveness of dual antiplatelet therapy (aspirin and clopidogrel) may be a result of more effective platelet inhibition in comparison to aspirin in patients with persistent platelet activation on aspirin monotherapy. Some studies have reported higher risk of major cardiovascular adverse events in patients with persistent platelet activation also in the early period after CABG [5]. Persistent platelet activation on aspirin therapy should not be recognized as aspirin resistance. Hovens *et al.* revealed that diagnosis of aspirin resistance strongly depends on the diagnostic technology used since few of them are available in clinical practice [6]. This is why it is proposed to use the term laboratory-defined aspirin resistance (LAR). Moreover, the working group of the Cardiovascular Intervention Association of the Polish Society of Cardiology recommends similar terms, i.e. partially effective antiplatelet treatment or increased platelet reactivity despite aspirin treatment instead of using the term aspirin resistance [7].

Aim of the study

The aim of the study was to compare effectiveness of aspirin monotherapy and clopidogrel monotherapy in prevention of adverse cardiac and vascular events in midterm follow-up after an elective CABG procedure.

Material and methods

Study protocol

The study was designed with a prospective randomized protocol. Preoperatively patients were randomized to postoperative antiplatelet monotherapy with aspirin (150 mg per day) or 6 months long clopidogrel monotherapy (75 mg per day) with subsequent turn to aspirin (150 mg per day). After randomization in all patients double check of platelet inhibition with aspirin was assessed with the Platelet Function Analyzer (PFA-100). In all cases there were cartridge tests used with membranes coated with collagen and epinephrine as an agonist. Laboratory methodology was described by Golański *et al*. In all measurements 3.2% buffered sodium citrate was used as an anticoagulant (Vacutainer, BD-Plymouth) [8]. Increased platelet reactivity despite aspirin treatment was diagnosed according to the manufacturer's guidelines if capillary closure time (CT) was less than 163 seconds. It should be mentioned that to date there is no strict cut-off CT value widely accepted for LAR diagnosis. Golański *et al*. adopted a CT value less than 160 seconds [8]. In another study conducted by Żytkiewicz *et al.* a cut-off CT value less than 165 seconds was accepted for LAR diagnosis [9]. The International Society on Thrombosis and Haemostasis recommends standardization to be performed by each local laboratory [10].

After randomization and platelet inhibition with aspirin assessment the whole study population was divided into 4 subgroups: patients with inhibited platelet function randomized to the aspirin arm, the group with increased platelet reactivity despite aspirin treatment randomized to the aspirin arm, patients with inhibited platelet function randomized to the clopidogrel arm, and the group with increased platelet reactivity despite aspirin treatment randomized to the clopidogrel arm.

Patients were included according to the following criteria: age 40-80 years, qualification to elective CABG, preoperative treatment with aspirin (75-150 mg per day), beta adrenolytic, angiotensin convertase inhibitor or sartan and statin, operative risk evaluated with the Euroscore logistic system between 0.1 and 6%. On purpose to preserve homogeneity of early and late risk of adverse events exclusion criteria were adopted as follows: history of hematologic disorders, malignancy, transfusion less than 4 months prior to procedure, thrombolytic or GP IIb/IIIa platelet receptor inhibitor treatment less than 4 weeks prior to procedure, vitamin K antagonist therapy, history of acute coronary syndrome or PCI less than 4 weeks prior to surgery, end-stage coronary atherosclerosis. Patients referred to CABG non-electively were excluded from the study due to increased risk of operative mortality according to Euroscore II risk stratification.

During in-hospital stay intraoperative and postoperative parameters were collected. After discharge in all patients after 1, 6 and 12 months follow-up data were collected in terms of safety and efficacy of provided therapy. Composite end-point was structured with two major sec-

tions: safety profile (number of large and small bleeding events, antiplatelet therapy cessation) and effectiveness profile (mortality, myocardial infarction, stroke or transient ischemic attack, acute coronary syndrome, need for coronary revascularization, hospitalization due to cardiovascular reasons). The study protocol was accepted by the local Bioethical Committee of the Military Institute of Medicine. The trial was funded by a Ministry of Science and Higher Education grant (no. NN403165437).

Study population characteristics

There were 50 patients at mean age of 62.5 ±6.9 years who underwent elective CABG in stable coronary ischemic disease included in the study during a 12-month period. In all cases an elective off-pump coronary artery bypass grafting procedure was performed. The study population consisted of a low and medium risk cohort. Study population characteristics are presented in Table I.

Results

In-hospital observation

Randomization was successful since there were no statistically significant difference found between groups in terms of operative risk and long-term prognostic risk factors (Tables II and III). There were 30 patients randomized to the aspirin arm and 20 patients to the clopidogrel arm. Preoperative platelet inhibition measured with CT did not differ significantly between the aspirin group (mean CT 223 ±91 seconds) and clopidogrel group (mean CT 216 ±91 seconds; $p = 0.7$). There was no difference in increased platelet reactivity despite aspirin treatment occurrence rate between the aspirin arm (34%) and clopidogrel arm (36%). In all cases planned off-pump coronary revascularization was performed using internal thoracic artery and saphenous vein grafts. The average number of distal anastomoses performed in the aspirin group was 2.4 ±0.9 and was not significantly different to that in the clopidogrel arm (2.6 ±1; $p = 0.4$).

In the postoperative period no adverse events were recorded. Average mechanical ventilation time was 7.2 ±6 hours in the aspirin arm and 7 ±5 hours in the clopidogrel arm ($p = 0.9$). Mean in-hospital stay did not differ significantly between groups: 8.5 ±0.4 days in the aspirin group and 8.1 ±1 days in the clopidogrel arm ($p = 0.1$). There were no significant differences between patients with inhibited and persistent platelet function in postoperative chest drainage and transfusion rate (Table IV).

Composite end-point analysis

There were in total 26 adverse events noted at the following observation points: after 1, 6 and 12 months from

Tab. I. Preoperative population characteristics

Parameter	Number of patients or mean parameter value	Percentage or SD
number of patients	50	–
age (years)	62.5	±6.9
females	12	24%
males	38	76%
CCS class	2.8	±0.7
NYHA class	0.8	±0.3
diabetes	11	22%
arterial hypertension	38	76%
history of myocardial infarction	20	40%
left ventricle ejection fraction (%)	54	±9
extracardiac atherosclerosis	6	12%
renal failure	2	4%
chronic obstructive pulmonary disease (COPD)	3	6%
BMI (kg/m^2)	28.5	±3.3
SYNTAX score	24.9	±8.2
EUROscore logistic (%)	2.5	±1.7

CCS – Canadian Coronary Score symptoms; NYHA – New York Heart Association; BMI – body mass index; SD – standard deviation

Tab. II. Preoperative comparison of randomized study arms in terms of operative risk

Parameter	Aspirin arm	Clopidogrel arm	*p* value
age (years)	61.4 ±7.4	63.2 ±6.5	0.3
females	20%	26%	0.5
EUROscore (%)	2.3 ±1.3	2.7 ±2.1	0.6
SYNTAX Score	25.7 ±9	24.3 ±7.1	0.5
history of PCI	31%	23%	0.6
history of MI	31%	52%	0.2
LVEF (%)	53 ±9	54 ±9	0.8
extracardiac atherosclerosis	13%	9%	0.7
renal failure	3%	4%	0.9
GFR (ml/min/1.72 m^2)	85 ±17	88 ±24	0.5
COPD	3%	9%	0.7
BMI (kg/m^2)	27.5 ±2	29.5 ±3	0.09

PCI – percutaneous coronary intervention; MI – myocardial infarction; LVEF – left ventricular ejection fraction; GFR – glomerular filtration rate; COPD – chronic obstructive pulmonary disease; BMI – body mass index

Tab. III. Preoperative comparison of randomized study arms in terms of atherosclerosis progression risk

Parameter	Aspirin arm	Clopidogrel arm	*P* value
diabetes	17%	28%	0.4
arterial hypertension	79%	71%	0.6
smoking	34%	33%	0.9
LDL-C (mg/dl)	105 ±34	122 ±54	0.3
HDL-C (mg/dl)	44 ±12	46 ± 9	0.5
TC (mg/dl)	178 ±44	187 ±58	0.6

LDL-C – low density lipoprotein cholesterol; HDL-C – high density lipoprotein cholesterol; TC – total cholesterol

Tab. IV. Comparison of groups in terms of postoperative blood lost and need for transfusion

Parameter	Patients with preoperatively inhibited platelet function	Patients with increased platelet reactivity despite aspirin treatment	*P* value
total chest drainage (ml)	920 ±421	836 ±478	0.5
need for blood transfusion	25% (8)	39% (7)	0.4
need for plasma transfusion	50% (16)	66.7% (12)	0.3
average amount of blood units transfused	0.5 ±1.1	0.6 ±0.9	0.5
average amount of plasma units transfused	1.1 ±1.6	1.3 ±1.0	0.7

hospital discharge. No death, acute coronary syndrome or myocardial infarction occurrence was recorded. In two patients percutaneous coronary angioplasty was performed. There were 7 incidents of hospitalization, 6 incidents of heart failure progression and 1 transient cerebral ischemic attack collected in follow-up. Four patients required medical intervention due to gastro-intestinal bleeding (major bleeding). Minor bleeding events (oral cavity, nasal cavity, gingiva) occurred six times. In order to compare the safety profile and effectiveness of antiplatelet therapy accumulation of adverse events risk from 3 observation time points was performed. Six months clopidogrel therapy independently from preoperative platelet reactivity resulted in significantly lower risk of any adverse event (14%; including safety profile) in comparison to aspirin therapy (25%; $p < 0.05$). In patients with preoperative increased platelet reactivity despite aspirin treatment significantly more adverse events were recorded (19 events; risk level – 0.35) in comparison to the population with fully inhibited platelet function (7 events; risk level – 0.07; $p < 0.05$). In patients with increased platelet reactivity despite aspirin treatment and randomized to the aspirin arm the highest risk of adverse event was recorded (11 events; risk level – 0.36). However, in the group with increased platelet reactivity despite aspirin treatment and randomized to clopidogrel there were 8 adverse events collected (risk level – 0.33). In patients with preoperatively inhibited platelet function and randomized to aspirin therapy there were 6 adverse events recorded with a low risk level – 0.1. Moreover, in patients with inhibited platelet function and randomized to clopidogrel therapy the lowest risk of any adverse event was calculated – 0.02 (1 event collected).

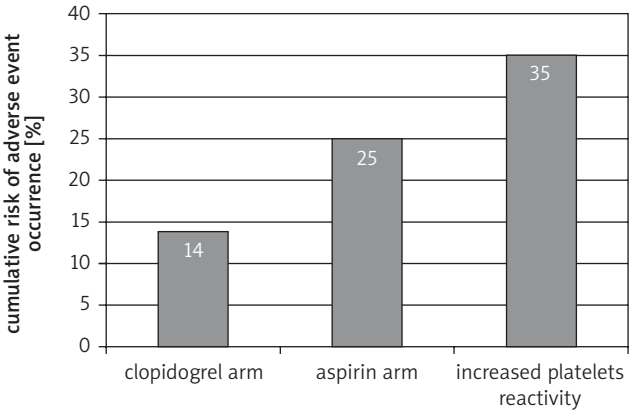

Fig. 1. Cumulated risk of any adverse event occurrence in 12 months follow-up

Discussion

Aspirin therapy in secondary prevention in patients after the CABG procedure is a class I recommendation of American scientific societies (American College of Cardiology, American Heart Association with cooperation of the American Association for Thoracic Surgery and Society of Thoracic Surgeons) published in 2004 [3]. The latest guidelines published in 2010 by the European Society of Cardiology and the European Association for Cardiothoracic Surgery do not recommend alternative antiplatelet therapy in that population of patients [11]. There are not enough data supporting the need for secondary prevention after CABG other than aspirin, which is opposite to widely studied strategies after PCI. Clopidogrel addition to aspirin after PCI is a class I recommendation with evidence A level. It is reasonable to recapitulate scientific data in order to optimize secondary antiplatelet therapy in patients after surgical coronary revascularization. In 2006 there were two prospective trials published supporting the thesis of safety of early dual antiplatelet therapy (aspirin and clopidogrel) after off-pump CABG. Moreover, those studies revealed some benefit of such a strategy in reduction of cardiac and vascular adverse events risk in a period of 30 days and 2 years [12, 13]. Early administration of clopidogrel seems to play a key role as over-reactivity of platelets due to surgical trauma which occurs shortly after surgery and its suppression with a high dose of aspirin (300 mg 48 hours after chest closure) is not effective. Those results were published by authors elsewhere [14]. The hypercoagulation phenomenon is strongly expressed in patients who were operated with off-pump technique [15]. In 2010 two important randomized studies were published which proved the benefits of dual antiplatelet therapy after CABG in reduction of early (30 days and 3 months long observation) risk of venous and arterial bypass graft thrombosis [16, 17]. However, such a positive effect was not proved in the CASCADE trial [18].

The studies mentioned above focused on comparison of dual antiplatelet therapy (aspirin and clopidogrel) versus monotherapy with aspirin, which does not determine whether the benefit is reached by aspirin resistance breakdown with clopidogrel or an additive antiplatelet effect of two agents. This thesis should be studied since it is known from the CURE trial that long-term (12 months) dual antiplatelet therapy increases the risk of major bleeding. This

was the reason for the six-month long clopidogrel therapy protocol in our study. It is also fundamental that ESC/EACTS guidelines on coronary revascularization published in 2010 do not strictly recommend use of any certain technology of platelet function monitoring in secondary prevention [5].

The present study obtained results similar to other trials showing potential benefit of clopidogrel use directly after surgical coronary revascularization. However, our study did not confirm usefulness of the PFA-100 analyzer in prediction of postoperative blood loss in patients electively referred for CABG and receiving aspirin. Six-month long monotherapy with clopidogrel was safe and irrespectively of preoperatively increased platelet reactivity despite aspirin treatment existence did not increase risk of minor or major bleeding. Moreover, use of clopidogrel seemed to significantly reduce risk composite end-point in a 12-month observational period. However, preoperative diagnosis of increased platelet reactivity despite aspirin treatment constituted a risk factor of any adverse event in both the aspirin and the clopidogrel arm.

In view of the obtained results it seems reasonable to accept the phenomenon of increased platelet reactivity despite aspirin treatment as an undesirable marker of a coagulative state which correlates with less favorable prognosis. However, that risk may be suppressed by the use of antiplatelet monotherapy other than aspirin.

The present study has limitations that should be mentioned. We included an initial pilot cohort of 50 patients to firstly evaluate the value of the protocol in the safety part. The first results of clopidogrel effectiveness gave a rationale to continue the trial. Moreover, assessment of increased platelet reactivity despite aspirin treatment with solely use of PFA-100 is not satisfactory and all patients will undergo secondary evaluation with another system. At last we see the necessity of coronary artery bypass patency studies in the whole population to differentiate etiology of adverse cardiac events.

Conclusions

Data gathered in this pilot study support the thesis that aspirin monotherapy substitution with clopidogrel monotherapy for six months after elective off-pump CABG is safe and may reduce the risk of any cardiac and vascular adverse events. The phenomenon of increased platelet reactivity despite aspirin treatment may be recognized as a marker of an undesirable hypercoagulative state worsening prognosis regardless of antiplatelet therapy.

The study was presented at the 6th Congress of the Polish Society of Cardio-Thoracic Surgeons in Cracow, May 24–26, 2012.

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