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Epistaxis as the reason for premature discontinuation of clopidogrel after percutaneous coronary angioplasty with stent implantation

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Abstract

Background: Haemorrhagic complications, including epistaxis, are the main reason for discontinuation of antiplatelet therapy in patients after stent implantation which increases risk of in-stent thrombosis.

Aim: To evaluate the incidence of bleeding complications leading to premature discontinuation of antiplatelet therapy in patients after percutaneous coronary intervention (PCI) with stent implantation.

Methods: A total of 3250 patients (males 64%, mean age 62 ± 10 years) after PCI with stent implantation and without indications for chronic anticoagulation or the use of low molecular weight heparin participated in the survey.

Results: Antiplatelet therapy after discharge from hospital was continued by 98.5% of patients. Antiplatelet therapy, according to the current standards (clopidogrel with acetylsalicylic acid [ASA]), was used by 86.3% of the respondents and 8.4% of patients used clopidogrel without ASA. A 90.0% of patients after bare metal stent (BMS) implantation and 94.9% after drug-eluting stent (DES) implantation ($p < 0.001$) continued clopidogrel therapy for more than a month. The 12-month period of clopidogrel treatment was completed by 52.4% of patients after BMS implantation and by 68.9% after DES implantation ($p < 0.001$). Epistaxis occurred in 6.2% of patients. The incidence of epistaxis was similar in patients taking clopidogrel (4.7%) or ASA (4.6%) alone and in patients taking both drugs (5.8%). Episodes of epistaxis generally did not occur during the first month of antiplatelet therapy after DES implantation and were followed by discontinuation of clopidogrel therapy by 20.9% of patients with this bleeding complication. Factors favouring the occurrence of epistaxis included hypertension (OR = 2.22), chronic kidney disease (OR = 2.85) and liver cirrhosis (OR = 2.53). Epistaxis occurred in 12.1% of the patients who prematurely discontinued clopidogrel (OR = 2.43).

Conclusions: 1. The occurrence of epistaxis is followed by premature discontinuation of clopidogrel therapy by one fifth of patients after coronary angioplasty and DES implantation. 2. Nosebleeds are more common in subjects with hypertension, chronic kidney disease and liver cirrhosis.

Key words: antiplatelet therapy, clopidogrel, epistaxis

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INTRODUCTION

There has been a considerable increase in the usage of myocardial revascularisation in the past decade. Currently, most of these procedures are percutaneous coronary interventions (PCI) with stent implantation, which has improved the outcomes of balloon angioplasty and reduced restenosis rate [1].

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Bare metal stent (BMS) and drug-eluting stent (DES) implantation is associated with the risk of stent thrombosis, which may jeopardise the therapeutic efforts [2]. For this reason, after stent implantation, it is necessary to use combination antiplatelet therapy for at least 1 month in the case of BMS and 12 months in the case of DES [3]. It seems that patients may benefit from a longer duration of dual antiplatelet therapy. Shortening of treatment with clopidogrel or discontinuation of all antiplatelet agents increases the risk of thrombosis and restenosis [4]. However, clopidogrel formulations, which are currently much less expensive than before (as they are subject to partial reimbursement for 1 month or 12 months after PCI with stent implantation, depending on the type of stent), pose a significant financial burden on elderly patients, who often have numerous co-morbidities.

Discontinuation of clopidogrel treatment or discontinuation of all antiplatelet agents may also be caused by haemorrhagic complications. One of the most common haemorrhagic complications that make it impossible to treat the patients in accordance with the current standards are nosebleeds [5]. Most of the cases of epistaxis are mild and resolve spontaneously or after appropriate local treatment. In some cases epistaxis may be a serious therapeutic problem and can sometimes be life-threatening. About 2% of patients with epistaxis require hospitalisation due to its severity, while 0.6% of hospitalised patients die from this complication [6].

The aim of our study was to analyse haemorrhagic complications that led to discontinuation of antiplatelet therapy in patients after PCI with stent implantation.

METHODS

Study group

A total of 405 cardiologists and primary care physicians participated in this retrospective survey. A total of 3250 patients (2083 men and 1167 women) who had undergone coronary angioplasty with stent implantation at least one month earlier were invited to participate in the study. This was the only inclusion criterion with respect to consecutive patients (a maximum of 12). Exclusion criteria were as follows: a history of coronary artery bypass grafting (CABG), co-indications for long-term use of vitamin K antagonists or low-molecular-weight heparin.

The questionnaire

The questionnaire covered demographic data (gender, age, address, educational background) and historical data related to co-morbidities (hypertension, diabetes mellitus, liver cirrhosis, peptic ulcer disease, chronic kidney disease [CKD] defined as eGFR < 60 mL/min/1.73 m^2), the number of past PCI procedures with stent implantation, setting of the procedure (acute coronary syndrome, ST-elevation and non-ST-elevation myocardial infarction [MI], elective procedure without a history of MI or following MI), the type of implanted stent (BMS *vs* DES), date of procedure, questions about antiplatelet therapy based on clopidogrel, ASA and ticlopidine, a history of haemorrhagic complications during antiplatelet therapy (without specifying their severity).

Statistical analysis

Statistical analysis was performed using STATISTICA 8.0 PL and MedCalc 11.0. We analysed the age structure, where the patients lived, their educational background, co-morbidities, setting of PCI with stent implantation, type of implanted stents, antiplatelet therapy regimens and haemorrhagic complications. We compared the incidence of haemorrhagic complications relative to co-morbidities.

The results are presented as numbers and percentages or means ± SD. Qualitative variables were compared using the chi-squared test. The values of odds ratios (OR) with 95% confidence intervals (CI) were calculated using logistic regression taking into account baseline antiplatelet regimen and reported haemorrhagic complications. The following factors were included in multivariate analysis for the variable "maintenance of 12 months of treatment with clopidogrel": type of implanted stent, educational background, diabetes mellitus, hypertension, CKD, a history of peptic ulcer disease, occurrence of an episode of epistaxis, rectal bleeding, haemoptysis, haematuria and bruising. A p value < 0.05 was considered statistically significant.

RESULTS

Study group characteristics

Table 1 summarises the characteristics of the study group. A prevalence of patients inhabiting urban areas (76.5%) was slightly higher compared to the data published by the State Statistical Office in 2007 (60.1%). In 90.5% of the patients the reason for PCI with stent implantation was acute coronary syndrome, mostly without the diagnosis of MI. For the majority of the patients this was their first PCI with stent implantation. The survey was conducted 8.8 ± 5.1 (range: 1–60) months after the procedure (or the most recent procedure in the case of patients with more than one such procedure in the past). In the case of 962 (29.6%) patients at least 12 months had elapsed since their most recent angioplasty with stent implantation.

Co-morbidities were identified in 94.9% of the patients and included: hypertension, diabetes mellitus, CKD (at least stage 3), peptic ulcer disease and liver cirrhosis (Table 1).

Antiplatelet therapy

Antiplatelet therapy after discharge from hospital was continued by 98.5% of patients (Table 2). A total of 86.3% of patients were receiving antiplatelet therapy in accordance with recommendations (clopidogrel plus ASA), 8.0% of patients

Table 1. Characteristics of the study group

Age [years]	62 ± 10
Sex: male/female [%]	64.1/35.9
Area of residence [%]:	
Rural areas	23.5
Urban areas	76.5
Educational background [%]:	
Primary-level education	13.5
Vocational education	31.9
Secondary-level education	40.0
Higher-level education	14.6
Co-morbidities [%]:	
Diabetes mellitus	42.0
Hypertension	89.1
Chronic kidney disease (stage > 2)	7.7
Liver cirrhosis	1.3
Peptic ulcer disease	13.4
Indications for coronary angioplasty with stent placement [%]*:	
Acute coronary syndrome without MI	69.4
STEMI	10.4
NSTEMI	11.1
Elective procedure post MI	4.1
Elective procedure without previous MI	15.5
Number of stent implantation procedures [%]:	
1	63.2
2	31.5
3	4.0
> 3	1.3
Type of implanted stent [%]:	
BMS	56.7
DES	43.3

*The most recent one if the patient has undergone several procedures; MI — myocardial infarction; STEMI — ST segment elevation myocardial infarction; NSTEMI — non-ST segment elevation myocardial infarction; BMS — bare metal stent; DES — drug-eluting stent

were receiving clopidogrel alone, 3.8% ASA alone and 0.3% clopidogrel plus ticlopidine. A total of 3.3% of patients were receiving triple therapy.

Clopidogrel treatment was discontinued after one month by 3.9% of patients with BMS and 0.8% of patients with DES ($p < 0.001$). Therefore, clopidogrel treatment was continued beyond one month by 90.0% of patients with BMS and 94.9% of patients with DES.

A total of 962 patients (29.6% of all the patients) completed the 12-month follow-up after stent implantation. In this group, 12-month treatment with clopidogrel was completed by 52.4% of patients with BMS and 68.9% of patients with DES ($p < 0.001$), and the treatment was further continued by 13.9% of patients with BMS and 21.1% of patients with DES. Antiplatelet therapy did not depend on the area where the patient lived but on their educational background. Significantly more patients with primary-level education discontinued this treatment within the fist month and after the first month following stent implantation. Slightly more than a half of patients (51.9%) with primary-level education continued clopidogrel treatment for 12 months. Significantly more patients with higher-level education continued this treatment for 12 months (67.4%).

Haemorrhagic complications

Bruising and epistaxis were the most commonly reported complications by the patients (Table 3). When we compared the incidence of bruising during treatment with clopidogrel, ASA or ticlopidine, we found that this complication was most common in patients receiving triple therapy (clopidogrel, ticlopidine plus ASA) (42.0%), less common during treatment with clopidogrel and ASA (16.2%) and least common during monotherapy with clopidogrel or ASA (12.8% and 6.8%, respectively).

The incidence of nosebleeds was similar with the use of clopidogrel plus ASA (5.8%), clopidogrel alone (4.7%) and ASA alone (4.6%). Only when all the three agents were used concomitantly the incidence of nosebleeds was high — 22.0%.

Factors predisposing for the development of haemorrhagic complications, including epistaxis, included hypertension, CKD and liver cirrhosis. The highest risk was found in patients with CKD. After excluding patients with liver cirrhosis from the analysis the risk of bruising was 37.7% (compared to 14.3% in patients without liver cirrhosis and CKD, $p < 0.001$), OR = 3.63, and the risk of episodes of epistaxis was 14.0% (compared to 5.4% in patients without liver cirrhosis and CKD, $p < 0.001$), OR = 2.85 (1.90–4.29).

In patients with a history of liver cirrhosis (after excluding patients with CKD) the incidence of bruising was 22.5% (compared to 15.8% in patients without liver cirrhosis and CKD; $p = 0.01$; OR = 1.55 [1.09–2.20]), the incidence of epistaxis was 13.3% (compared to 5.7%; $p < 0.001$; OR = 2.53 [1.63–3.94]), the incidence of rectal bleeding was 3.1% (compared to 0.9%; $p = 0.007$; OR = 3.42 [1.39–8.41]) and the incidence of gastric bleeding was 3.1% (compared to 1.6%; $p = 0.11$; OR = 2.01 [0.85–4.78]).

In patients with hypertension, after exclusion of patients with liver cirrhosis, epistaxis was noted in 6.4% (compared to 3.07% in patients without hypertension and liver cirrhosis, $p = 0.02$; OR = 2.22 [1.16–4.25]).

In patients with a history of peptic ulcer disease (after excluding patients with liver cirrhosis and CKD) gastric bleeding occurred in 8.8% (compared to 0.3% in patients without a history of peptic ulcer disease, liver cirrhosis and CKD; $p < 0.001$; OR = 29.12 [13.30–63.72]).

Table 2. Antiplatelet therapy received

	Total	Bare metal stent			Drug-eluting stent		
		Total (n = 1846)	1 procedure (n = 1295)	Subsequent procedure (n = 551)	Total (n = 1404)	1 procedure (n = 761)	Subsequent procedure (n = 643)
Clopidogrel [%]:							
None	5.4	6.1	6.3	5.7	4.3	5.0	3.5
For 1 month	94.6	93.9	93.7	94.3	95.7	95.0	96.5
Beyond 1 month	92.0	90.0	89.4	91.2	94.9	95.0	94.8
For 12 months	58.8	52.4	53.2	50.3	68.9	67.7	70.1
Beyond 12 months	16.9	13.9	13.2	15.4	21.1	21.9	20.4
Acetylsalicylic acid [%]:							
None	9.9	9.6	10.3	7.9	10.2	12.5	7.6
Permanently since the procedure	85.4	85.6	85.7	85.5	85.2	84.6	86.0
Discontinued	4.7	4.8	4.0	6.6	4.6	2.9	6.4
Ticlopidine [%]:							
Permanently since the procedure	3.6	2.5	2.7	2.0	5.0	4.6	5.4
Later after the procedure	5.3	4.4	4.7	3.6	6.5	6.0	7.1

Table 3. Haemorrhagic complications

Total	23.3%
Bruising	16.2%
Epistaxis	6.2%
Gastric bleeding	1.6%
Macroscopic haematuria	1.2%
Rectal bleeding	1.1%
Haemoptysis	0.7%
Stroke	0.2%
Genito-urinary bleeding	0.1%
Joint bleeding	0%

More than one adverse effect occurred in 17.8% of the patients

Haemorrhagic complications and continuation of clopidogrel treatment over 12 months

Haemorrhagic complications, including bruising, occurred in 34.1% of the patients who had discontinued clopidogrel treatment within 12 months. We observed no differences here between patients with BMS and patients with DES.

Epistaxis occurred in 12.1% of the patients who had discontinued treatment. The risk of treatment discontinuation in the case of a haemorrhagic complication or bruising was OR = 2.10 (1.38–3.19), $p < 0.001$. In the case of epistaxis, the risk was OR = 2.43 (1.51–3.91), $p < 0.001$.

In patients with DES an episode of epistaxis most commonly occurred beyond the first month of treatment (93.4%) and resulted in discontinuation of clopidogrel treatment by 20.9% of patients with this haemorrhagic complication.

Table 4. Factors affecting the maintenance of 12-month clopidogrel therapy after angioplasty with stenting in 962 patients (multivariate regression analysis)

	Odss ratio	P
Diabetes mellitus	1.09 (0.81–1.47)	0.56
Liver cirrhosis	0.21 (0.06–0.69)	0.01
Hypertension	1.24 (0.81–1.91)	0.33
Chronic kidney disease	2.05 (1.10–3.84)	0.02
A history of peptic ulcer disease	0.48 (0.32–0.71)	< 0.001
Haematuria	0.74 (0.21–2.61)	0.63
Haemoptysis	0.52 (0.10–2.61)	0.43
Rectal bleeding	0.99 (0.28–3.54)	0.99
Bruising	0.49 (0.33–0.72)	< 0.001
Epistaxis	0.40 (0.23–0.69)	0.001
DES implantation	2.20 (1.62–2.99)	< 0.001
Higher-level education	1.56 (1.02–2.39)	0.04

DES — drug-eluting stent

Factors affecting the maintenance of the 12-month treatment with clopidogrel

Based on multivariate logistic regression analysis conducted on a group of 962 patients with at least 12 months of follow-up (Table 4) we showed that factors improving the chances of maintaining the 12-month treatment with clopidogrel included: implantation of a DES, higher-level education and co-existence of CKD, while the co-existence of liver cirrhosis, peptic ulcer disease and co-existence of epistaxis and bruising decreased the chances of maintaining this treatment.

DISCUSSION

Our study showed that 1.5% of patients in Poland discontinue antiplatelet therapy directly after discharge from hospital and only 86.3% receive dual antiplatelet therapy during the first month in line with the current recommendations. Clopidogrel treatment beyond the first month is continued by 94.9% of patients after DES implantation and 90.9% of patients after BMS implantation. The 12-month period of clopidogrel treatment is maintained by 68.9% of patients with DES and 52.4% of patients with BMS, although further treatment with this agent is continued by only 21.1% of patients with DES and 13.9% of patients with BMS.

Premature discontinuation of antiplatelet therapy is a worldwide problem that increases mortality and the incidence of subsequent acute coronary syndromes and revascularisation procedures due to in-stent thrombosis. The treatment is often discontinued already during the first month after stent implantation, when the risk of thrombosis is the greatest. According to Iakovou et al. [7], discontinuation of dual treatment within the first 3 months (by 0.8% of patients) increases the risk of early thrombosis by as much as 161-fold and increases the risk of DES thrombosis by 89-fold. According to Danenberg et al. [8], 60% of patients with early thrombosis after BMS implantation discontinued clopidogrel treatment during the first month after PCI. In a Danish registry [9], discontinuation of clopidogrel treatment within the first 30 days after stent implantation increases the risk of early thrombosis 36.5-fold. Beyond the first month the risk decreases to 4.6-fold (within the first 6 months) and 5.9-fold (after 6 months). In the CREDO study [10], 12-month adherence to clopidogrel treatment was 64.5%.

In light of the registry data, the incidence of discontinuation of clopidogrel treatment in the Polish population seems lower. It should, however, be assumed that the percentage of patients discontinuing antiplatelet treatment is probably higher, as many patients discontinuing therapy due to the lack of symptoms fails to complete follow-up visits and some of them die from thrombosis and acute MI.

Before the advent of DES, late (beyond 30 days) in-stent thrombosis was reported only occasionally. It was therefore initially thought that the incidence of thrombosis was higher for DES than for BMS. More recent studies, however, showed that the incidence of thrombotic episodes in both types of stents was similar [8] and the problem of late thrombosis in BMS had been overlooked [11]. There are reports indicating significant benefit from maintaining clopidogrel therapy even beyond 24 months, demonstrating lower mortality in patients continuing treatment for an average of 2.4 years (14.8% *vs* 3.5%) [12]. Hence the establishment of an optimal duration of treatment with this agent following stent implantation, particularly following DES implantation, is not currently possible. The patients' and doctors' concerns are reflected by continuation of clopidogrel treatment beyond 12 months in 21.1% of patients with DES and 13.9% of patients with BMS, despite the lack of partial reimbursement by the National Health Fund.

Most patients discontinue the treatment without an important reason and socioeconomic status is one of the significant factors affecting treatment discontinuation [8]. Our study also showed that patients with primary-level education discontinue antiplatelet therapy more often than others.

Antiplatelet therapy is limited by its adverse effects, particularly haemorrhagic complications, which in our study explain treatment discontinuation in 34.1% of patients. The occurrence of a haemorrhagic complication and bruising in the analysed group of patients increased the risk of clopidogrel treatment discontinuation within 12 months after stent implantation by more than 2-fold. The highest risk of antiplatelet therapy discontinuation was associated with the occurrence of epistaxis (2.43-fold). The occurrence of any episode of epistaxis during antiplatelet therapy resulted in discontinuation of this treatment by 20.9% of patients with this complication and probably more often in patients requiring a laryngologist's intervention. In patients receiving antiplatelet therapy, nosebleeds are often recurrent and cause haemodynamic disturbances which make continuation of the treatment impossible [13].

One of the significant factors predisposing to epistaxis in patients receiving anticoagulants is hypertension, which was present in 89.1% of our patients. Hypertension promotes mobilisation of the thrombus from the vessel, which is why epistaxis cannot be controlled without achieving a good blood pressure control [6]. Antiplatelet therapy may also reveal clinically latent haemorrhagic diathesis manifested by a massive nosebleed, which makes continuation of antiplatelet therapy impossible [14].

A particularly high incidence of nosebleeds was observed in patients with CKD (14.05; OR = 2.85) and liver cirrhosis (13.7%; OR = 2.53). This is most probably caused by the high incidence of refractory hypertension in patients with CKD and coagulation disorders in liver cirrhosis (acquired plasma coagulation factor defects and thrombocytopenia). Despite the similar incidence of nosebleeds in both of these patient groups only liver cirrhosis was a factor that dramatically decreased the chances of maintaining the 12-month therapy with clopidogrel (OR = 0.21). The reason for premature discontinuation of antiplatelet therapy in patients with liver cirrhosis is not only epistaxis, which may be more difficult to treat due to the coagulation disorders, but mainly the risk of bleeding from oesophageal varices, which is a life-threatening complication associated with a morality rate of 50% [15].

Of the other haemorrhagic complications we observed gastric bleeding in 1.6%, macroscopic haematuria in 1.2% and stroke in 0.2% of the patients. The incidence of gastric bleeding was similar to that in the literature (1.3–1.4%) [10, 16, 17]. An episode of gastrointestinal bleeding within the

first month after stent implantation is associated with a higher risk of early stent thrombosis [17]. As our study showed, a factor predisposing for discontinuation of clopidogrel therapy was a history of peptic ulcer disease (OR = 0.48 for maintaining therapy).

Limitations of the study

Limitations of our study resulting from its methodology (a retrospective assessment) include omission of patients who discontinued further treatment and outpatient follow-up visits after discharge from hospital following stent implantation and patients who suffered fatal complications during treatment. The data we collected make it impossible to differentiate between the severities of epistaxis episodes and to identify the group of patients requiring a laryngologist's intervention. We also do not know whether the decisions to prematurely discontinue clopidogrel treatment in patients following DES implantation was made by patients themselves or by their doctors.

CONCLUSIONS

1. The occurrence of epistaxis results in discontinuation of clopidogrel treatment by every fifth patient with this haemorrhagic complication following DES implantation.
2. Epistaxis is more commonly observed in patients with hypertension, CKD and liver cirrhosis.

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Krwawienie z nosa jako przyczyna przedwczesnego przerwania terapii klopidrogelem u chorych po zabiegach angioplastyki tętnic wieńcowych z implantacją stentu

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Streszczenie

Wstęp: Powikłania krwotoczne, w tym krwawienia z nosa, są jedną z głównych przyczyn przerwania terapii przeciwpłytkowej u chorych po implantacji stentu, co zwiększa ryzyko zakrzepicy stentu.

Cel. Celem badania była analiza częstości powikłań krwotocznych stanowiących przyczynę przedwczesnego przerwania leczenia przeciwpłytkowego u chorych po zabiegach przezskórnej interwencji wieńcowej (PCI) z implantacją stentu.

Metody: W badaniu o charakterze ankietowym wzięło udział 3250 chorych, 64,1% mężczyzn i 35,9% kobiet, którzy przebyli PCI z implantacją stentu i nie mieli wskazań do przewlekłego leczenia przeciwzakrzepowego czy stosowania heparyny drobnocząsteczkowej.

Wyniki: Leczenie przeciwpłytkowe po wypisaniu ze szpitala kontynuowało 98,5% pacjentów po PCI z implantacją stentu. Terapię przeciwpłytkową, zgodną z obowiązującymi standardami [klopidogrel z kwasem acetylosalicylowym (ASA)], stosowało 86,3% badanych, 8,4% osób przymowało klopidogrel bez ASA. Ponad miesiąc leczenie klopidogrelem kontynuowało 90,0% pacjentów ze stentem metalowym (BMS) i 94,9% ze stentem uwalniającym lek (DES) ($p < 0,001$). Roczną terapię klopidogrelem ukończyło 52,4% pacjentów z BMS i 68,9% chorych z DES ($p < 0,001$). Krwawienie z nosa wystąpiły u 6,2% badanych. Częstość występowania krwawień z nosa wśród chorych stosujących sam klopidogrel (4,7%), sam ASA (4,6%) i oba leki łącznie (5,8%) była podobna. Wystąpienie epizodu krwawienia z nosa miało najczęściej miejsce nie w pierwszym miesiącu leczenia przeciwpłytkowego po implantacji DES i spowodowało przerwanie stosowania klopidogrelu przez 20,9% chorych z tym powikłaniem. Czynnikami sprzyjającymi występowaniu krwawień z nosa były współistnienie nadciśnienia tętniczego (OR = 2,22), przewlekłej choroby nerek (OR = 2,85), choroby i marskości wątroby (OR = 2,53). Krwawienie z nosa wystąpiło u 12,1% pacjentów, którzy przedwcześnie przerwali przyjmowanie klopidogrelu (OR = 2,43).

Wnioski. 1. Wystąpienie krwawienia z nosa powoduje przedwczesne przerwanie stosowania klopidogrelu przez co piątego chorego po zabiegu angioplastyki z implantacją DES z tym powikłaniem krwotocznym. 2. Krwawienie z nosa częściej występuje u chorych z nadciśnieniem tętniczym, przewlekłą chorobą nerek i marskością wątroby.

Słowa kluczowe: leczenie przeciwpłytkowe, klopidogrel, krwawienie z nosa

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