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August 21, 2013

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Dear Dr. Woodcock, Dr. Stockbridge, and Dr. Hamburg:

Public Citizen, representing more than 300,000 members and supporters nationwide, and Neil A. Holtzman, M.D., hereby petition the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug and Cosmetic Act 21 U.S.C. Section 355(e)(3) and 21 C.F.R. 10.30, to immediately add a black-box warning on clopidogrel (brand name:

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Plavix, as well as generic equivalents). The black-box warning must address the increased risks of major and minor bleeding with use beyond 12 months following implantation of drug-eluting coronary artery stents. Such warning is made necessary both by a lack of evidence of a further reduction of thrombotic cardiovascular events, such as myocardial infarction or stroke, as well as existing evidence of continued risk of major bleeding with more prolonged use. We also urge the FDA to require the distribution of an FDA-approved, updated Medication Guide containing this information to be dispensed to all patients when their prescriptions are filled and to ask companies to send a “Dear Doctor” letter to warn physicians of these preventable adverse effects that occur with use for greater than one year.

Introduction

In 2012, more than 1 million drug-eluting stents (DES) were placed in coronary arteries in the U.S., comprising 80% of all stents implanted following angioplasty.¹ In October 2012, the last month for which data are available, 2,250,519 prescriptions for clopidogrel were written.²

The FDA has recognized that clopidogrel “can cause bleeding which can be serious and can sometimes lead to death.”³ The agency points out, however, “people who are treated with a stent, and stop taking Plavix too soon, have a higher risk of getting a blood clot on the stent, having a heart attack, or dying. If you must stop Plavix because of bleeding, your risk of a heart attack may be higher.”³

In 2008, the FDA agreed with the AHA/ACC/SCA1 practice guidelines that following implantation of a DES, clopidogrel therapy of a minimum of 3 or 6 months (depending on type of DES) should be “extended to 12 months in patients at a low risk of bleeding.”⁴ Thus, the FDA provided guidance on what it meant by stopping “too soon,” although it did not indicate how physicians were to determine whether a patient was “at low risk of bleeding.” As Kandzari et al. in an article published in 2009 noted, “this recommendation was not based on any prospective randomized trial evidence associating extended-duration DAPT [dual antiplatelet therapy with clopidogrel plus aspirin] with a reduction in late ST [stent thrombosis]; rather, the recommendation was based on consensus opinion...” From their review, primarily of observational studies, the authors concluded that “bleeding and economic costs of prolonged treatment [with DAPT in patients undergoing DES revascularization] might outweigh any potential reduction in stent thrombotic events.”⁵ Many physicians now continue clopidogrel beyond 12 months — some indefinitely.

The FDA has not revised its recommendation since 2008, despite mounting data that little benefit in terms of cardiac endpoints is to be gained by 12 or more months of clopidogrel therapy, and the risk of bleeding persists as long as patients are on the drug. Moreover, in patients who undergo percutaneous coronary intervention (PCI), increased mortality among patients who experience major bleeding is a consistent finding.⁶

In this petition, we first briefly review the pathogenesis of coronary lesions following PCI, as it provides the rationale for both initiating antiplatelet drugs such as clopidogrel and

for limiting the duration of their use. Next, we review the randomized controlled trials (RCTs) relevant to the benefit and risks of clopidogrel, followed by consideration of a number of observational studies of clopidogrel and other thienopyridines. We conclude that the evidence warrants the following black-box warning:

The continuation of clopidogrel for longer than 12 months following percutaneous insertion of a drug-eluting stent is of questionable additional benefit in preventing adverse cardiac events but continues to carry an increased risk of major and minor bleeding, even in those who have no known bleeding tendency.

The patient Medication Guide for Plavix should be revised accordingly.

Pathogenesis of Coronary Lesions Following PCI

PCI improves coronary blood flow by rupturing atherosclerotic plaque. This denudes the vascular endothelium, exposing thrombogenic substrates that stimulate the aggregation of platelets followed by mononuclear inflammatory cells. Smooth muscle proliferation, matrix deposition, and intimal growth can then lead to vascular occlusion and recurrence or worsening of coronary insufficiency.^{7,8} The risk of thrombus formation, and consequent major adverse coronary events, is greatest in the first week following PCI.^{9,10} This is not surprising, as histopathological examination of stented coronary arteries obtained primarily at autopsy of patients dying 0.5 to 390 days post-stent from myocardial infarction (n = 18), sudden unexpected cardiac death (n = 7), or noncardiac death (n = 3) revealed platelet-rich thrombi in 72%, 78%, 24%, and 0% of sections examined at ≤ 3 days post-stent, 4-11 days, 12-30 days, and > 30 days respectively ($p < 0.0001$).

Similarly, acute inflammatory cells (neutrophils) were present in 79%, 83%, 72%, and 0% respectively of sections obtained at the same time intervals ($p < 0.0001$). No mention is made of anti-thrombotic therapy.¹¹ Published in 1999, this study examined bare metal stents (BMS). A later study of autopsied patients found that thrombus formation occurred later in sirolimus or paclitaxel DES than in BMS, but usually before one year (197 ± 139 days post-stent). Five of the 14 patients with stent thrombosis 30 days or more after PCI were not receiving any antiplatelet therapy at the time of death; seven were receiving DAPT.¹² The rate of thrombus formation as measured by restenosis or major adverse cardiac events is, however, significantly lower with DES than BMS,¹³ which explains why DES has largely replaced BMS. The prevention of thrombosis with DES is the rationale for antiplatelet therapy during and following implantation.

RCTs of Clopidogrel for Differing Durations of Time

Based on the literature, low dose (75-325 mg) aspirin and clopidogrel (loading dose of 350 mg, daily dose of 75 mg) are superior to aspirin alone and/or placebo in preventing adverse cardiac effects in patients with acute coronary syndrome (due to non-ST elevation myocardial infarction, ST elevation myocardial infarction, or unstable angina) who receive PCI with the placement of a stent. Aspirin and clopidogrel inhibit platelet aggregation by different mechanisms, increasing the risk of bleeding at the PCI site or

elsewhere in the body. In most of the RCTs described below, history of a bleeding diathesis excluded the patient from the trial.

The table on the next page summarizes the results of the six RCTs examining the effect of duration of clopidogrel use on the efficacy and safety of the drug in patients in whom stents were implanted. Two of the most recent trials were specifically designed to assess the optimal time from stenting for continuing DAPT. Neither of them showed a benefit, in terms of preventing death or other cardiovascular harm from continuing DAPT after six months.^{14,15} Valgimigli et. al. found that bleeding doubled in the group treated with DAPT for greater than six months compared with those treated for only six months ($p = 0.00018$), with no difference in the rate of adverse cardiovascular endpoints.¹⁴ Gwon et al. found no difference in adverse cardiac endpoints with discontinuation of DAPT at six months compared to 12 months but an increase of any bleeding from four patients to 10 ($p = 0.12$) and major bleeding from two to four ($p = 0.42$) at 12 compared to six months.¹⁵

The third recent trial compared three months of DAPT following insertion of a zotarolimus DES (E-ZES) to 12 months of DAPT following insertion of other DES including sirolimus and everolimus DES. There was no significant difference at 12 months in any cardiac or bleeding endpoints, leading the authors to conclude that the “E-ZES+3-month DAPT is safe and noninferior for the primary composite endpoint” to other DES.¹⁶ This study has been criticized, although the author of the critique concluded, “With newer-generation DES, 6 months DAPT might be sufficient, and 3 months not completely off the wall in low-risk groups.”¹⁷

The fourth study,¹⁸ in which patients were randomized at one year to continue either DAPT or aspirin alone, found no significant benefit for clopidogrel in reducing cardiac endpoints by extending therapy and a nonsignificant increase in bleeding in those continuing on clopidogrel.

The last two RCTs in the table compared DAPT or clopidogrel alone to placebo for periods up to 12 months following stenting.^{9,10} The type of stent was not specified; at the time, BMS were most commonly used. Both found a small but significant benefit of clopidogrel in terms of cardiac endpoints. One found a borderline increase in bleeding up to 12 months, encountered primarily in major surgery.⁹ BMS are seldom implanted today.

Table: Randomized Trials

First author/year	n ^a	Dur- ation ^b	Arms of the trial ^b A v B	% with endpoint, p	
				Cardiac A v B	Bleeding A v B
Valgimigli/2012 ^{14,c}	2013	24 mo	6 v 24 mo DAPT	10.0 v 10.1 p = 0.91	3.5 v 7.4 p = 0.00018
Gwon/2012 ^{15,d}	1443	12 mo	6 v 12 mo DAPT	4.8 v 4.3 p = 0.60	0.3 v 0.6 p = 0.42
Kim/2012 ^{16,e}	2117	12 mo	E-ZES+3 mo DAPT v Other DES+ 12 mo DAPT	4.6 v 4.7 p = 0.69	0.2 v 0.6 p = 0.18
Park/2010 ^{18,f}	2701	24 mo	@ 12 mo: DAPT v aspirin	1.8 v 1.2 p = 0.17	0.2 v 0.1 p = 0.35
Steinhubl/2002 ^{9,g}	2116	12 mo	@ 29 days: DAPT v aspirin	8.5 v 11.5 p = 0.02	8.8 v 6.7 p = 0.07
Mehta/2001 ^{10,h}	2658	3-12 mo Av=8 mo	DAPT v aspirin	18.3 v 21.7 p = 0.03	2.7 v 2.5 p = 0.64

^a Generally, intention to treat

^b Measured from day of stenting unless stated otherwise by "@" followed by time of randomization

^c Cardiac endpoints: composite of death of any cause, myocardial infarction (MI), cerebrovascular accident. Bleeding endpoints: BARC types 5, 3, or 2. (See Mehran et. al. for definitions.¹⁴) Different types of DES used as well as bare metal stents.

^d Cardiac endpoints; composite of cardiac death, MI, target vessel revascularization. Bleeding endpoint: TIMI major. (See Mehran et. al. for definitions.¹⁴) DAPT=dual antiplatelet therapy with clopidogrel and aspirin.

^e Cardiac Endpoints: composite of cardiovascular death, MI, stent thrombosis, target vessel revascularization. Bleeding endpoint: TIMI major.

^f Cardiac endpoints: MI, stroke, death from cardiovascular causes. Bleeding endpoint: Borderline significant (0.09) for TIMI major. (See Mehran et. al. for definitions.¹⁴)

^g Type of stent not specified. One arm received a clopidogrel loading dose prior to PCI. Thereafter all patients received clopidogrel 75mg/d until 29 days post-stent when the clopidogrel loading group continued with DAPT. The other arm received placebo and aspirin. Cardiac endpoints: composite of death, MI, stroke. Only the composite significant. Bleeding endpoint: TIMI major.

^h Type of stent not specified. Cardiac endpoints: cardiovascular death, MI, any revascularization. (With only cardiovascular death and MI, p of difference = 0.047) Major bleeding: adjudicated as life threatening or non-life-threatening.

At least four RCTs are currently in progress. The OPTIMIZE trial is comparing three months of DAPT to twelve months of DAPT following E-ZES implantation.³⁶ Mauri et al. are comparing DAPT for twelve versus thirty months following either DES or BMS.³⁷ In addition to evaluating the effect of platelet function monitoring, Collet et al. are randomizing patients at one year post-stent to continue on clopidogrel or other thienopyridine vs no thienopyridine.³⁸ Byrne et al. are randomizing patients on clopidogrel therapy at six months post-DES implantation to discontinuation of clopidogrel versus a further six months of treatment.³⁹ A search of the clinical trials data base (Clinicaltrials.gov) using as descriptors clopidogrel, drug eluting stents, bleeding, and percutaneous coronary intervention did not reveal additional RCTs examining the effects of duration of clopidogrel therapy on outcomes (the website was accessed on Feb, 8, 2013).

In an RCT in which stents were not evaluated, 15,603 patients with multiple atherothrombotic risk factors, coronary artery disease, cerebrovascular disease, or peripheral arterial disease were randomized to clopidogrel plus aspirin or placebo plus aspirin and followed for a median of 28 months. The primary efficacy endpoints were myocardial infarction, stroke (any cause), and death from cardiovascular causes. The primary safety endpoint was severe bleeding according to the GUSTO classification (see reference¹⁹ for definition). There was no significant difference in the primary efficacy endpoint ($p = 0.22$). The rate of severe bleeding was 1.7% in the DAPT group and 1.3% in the placebo plus aspirin group (relative risk, 1.25, $p = 0.09$). Noting “a suggestion of benefit in patients with symptomatic atherothrombosis” but “a suggestion of harm in patients with multiple risk factors” the authors concluded, “Overall, clopidogrel plus aspirin was not significantly more effective than aspirin in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes.”²⁰

In another RCT in which clopidogrel for acute coronary syndrome (with or without stenting) was compared to ticagrelor, another thienopyridine, major bleeding occurred in 11.2% of patients on clopidogrel compared to 11.6% on ticagrelor ($p = 0.43$) by one year after initiation of treatment. Among patients who received a stent, the rate of stent thrombosis was 1.9% (clopidogrel) versus 1.3% (ticagrelor) ($p = 0.009$).²¹

Observational Studies

Several registry studies have compared rates of adverse cardiac events to bleeding endpoints in patients in whom thienopyridines, including clopidogrel, were discontinued either by the patients or their physicians at varying times following PCI with DES. Adjusting for confounding factors, Tada et al. found that continuing on thienopyridine (in this instance, 90% of patients were using ticlopidine) after four months post-stent did not decrease the risk of death, myocardial infarction, or stroke compared to those in whom it was discontinued by four months, whereas moderate/severe bleeding (see GUSTO criteria¹⁹) progressed linearly up to three years post-stent (Hazard Ratio = 1.51, $p = 0.049$). The Hazard Ratio at three years for continuing on thienopyridine longer than 13 months post-stent was 1.44, $p = 0.057$.²²

Using data from an HMO research network registry of DES-stented patients and pharmacy dispensing data, Tsai et al. examined hospitalizations for myocardial infarction, major bleeding,ⁱ and death in three intervals post-DES stent: 0-6 months, 7-12 months, and 13-18 months, comparing the three endpoints in patients who were on clopidogrel during the interval to those in whom clopidogrel had been discontinued. After multivariable adjustment, the relative risk of major bleeding for those on clopidogrel compared to those off clopidogrel in the three successive time periods were 2.70, 1.71, and 2.34 respectively ($p < 0.05$ for the first and third intervals). The relative risks of myocardial infarction in those on clopidogrel compared to those off that drug were 0.52, 0.46, and 0.53 (all three with $p < 0.02$) in the three successive periods. The only significant difference in deaths was in the 7-12 month interval when they were higher in those off than on clopidogrel only ($p=0.008$).²³

Sorensen et al. used the Danish nationwide register of hospitalizations and drug-dispensing data to examine whether six-month (used in 2002-2003) and 12-month (used in 2004-2005) regimens of clopidogrel post-PCI differed significantly in efficacy endpoints of all-cause mortality, recurrent myocardial infarction, or a composite of all-cause mortality and recurrent myocardial infarction; and safety endpoints of death caused by bleeding, or hospitalization (with a bleeding diagnosis) up to 18 months post-hospital discharge. There was no difference in the cardiac endpoints between the regimens. In the six-month clopidogrel regimen, 3.5% of patients had bleeding; in the 12-month regimen, 4.1% had bleeding ($p = 0.06$).²⁴ A recent report using the same Danish registries for patients undergoing PCI after a first myocardial infarction between 2004 and 2009 found no significant difference in death or recurrent myocardial infarction in those who discontinued clopidogrel between 12 and 15 months after the myocardial infarction compared to those who continued on the drug ($p = 0.33$). At least 75% of the patients received DES. Although declining steadily, the rates of death or recurrent myocardial infarction were significantly higher in clopidogrel discontinuers than continuers in every successive three-month period from one to 12 months after the first myocardial infarction. The risk of severe (not defined) or fatal bleeding was higher, but not significantly, in patients continuing on clopidogrel from six months to 15 months after the first myocardial infarction.²⁵

Faxon et al., using the Veterans Administration National Patient Care and Pharmacy databases, found that patients (more than 98% male) on clopidogrel for 12 months or longer following either BMS or DES implantation had significantly lower adjusted risk of death or myocardial infarction than patients on for a shorter duration. For outcomes measured up to four years after stenting, major bleeding did not differ significantly between the two groups. According to the authors, this study differs from others by having a much larger number of adverse cardiac events due at least in part to a greater frequency of comorbidities.²⁶

Two recent observational studies have documented the frequency of bleeding in patients

ⁱ Discharge diagnosis of intracerebral hemorrhage, gastrointestinal tract hemorrhage, hemarthrosis, hemopericardium, hematuria, vaginal bleeding, epistaxis, hemorrhage not otherwise specified, or a secondary diagnosis for bleeding with blood transfusion during hospitalization.

receiving DAPT following DES stenting. In 2,948 patients who were on DAPT at 12 months post-DES, 0.3% experienced alarming bleeding,^j 4.3% internal bleeding,^k and 28.9% “nuisance bleeding”^l within the first 12 months. At one year, the rate of major adverse cardiac event was higher in the nuisance bleeding group compared to the nonbleeding group ($p = 0.02$).²⁷ Among 1,437 consecutive patients undergoing PCI and DES implantation, major and minor bleeding (TIMI criteria) after one year of DAPT occurred in 3.0% and 5.6%, respectively. The cumulative rates of major and minor bleeding, including those who continued on DAPT beyond one year, were 3.6% and 6.9% respectively with up to four years of follow-up. The incidences of major and minor bleeding up to 4-year follow-up were 3.6 and 6.9%, respectively. In multivariate analysis, bleeding at 1 year was positively predicted by use of oral anticoagulants at hospital discharge [odds ratio (OR) $p < 0.001$ 0.001]. At one year and later, major bleeding was associated with an increased risk of major adverse cardiac events ($p < 0.001$).²⁸ The authors suggest that this increased risk might have resulted from discontinuation of DAPT as a result of bleeding; patients who had any bleeding event were more likely to prematurely discontinue antiplatelet therapy than those in whom a bleeding event was absent (50% vs. 9.6%, $P < 0.001$). No evidence to support or refute this hypothesis was presented.

Effect of Platelet Reactivity on Cardiac and Bleeding Endpoints

A number of tests have been developed to identify patients’ platelet reactivity while on clopidogrel or other thienopyridines.²⁹ DES-stented patients with high responsiveness to clopidogrel would be expected to be at greater risk of bleeding if clopidogrel was associated with bleeding but at lower risk of adverse cardiac endpoints. Two studies have reported a significant increase in major bleeds in the perioperative PCI period (up to one month) in high responders compared to low responders.^{30,31} One of these studies also showed a significantly greater rate of stent thrombosis within 30 days of PCI in low responders compared to high responders.³¹ A third study, which followed patients an average of 16 months after DES implantation, found that patients who were high responders to a thienopyridine (ticlopidine or clopidogrel) had significantly more major bleeds than low responders, with cumulative bleeding in the high responders rising from 9% at two months to 15% at 12 months. The test was not as good a predictor of cardiac events.³² Breet et al. found that low responders to clopidogrel had significantly more adverse cardiac endpoints at one year follow-up than high responders but did not differ in rates of major or minor bleeding.²⁹ In low responders, clopidogrel would not offer as much protection against thrombosis as it would in high responders. Parodi et al. made the same observation on cardiac endpoints, although they did not measure the effect of clopidogrel on bleeding.³³

Not all platelet function tests are able to discriminate endpoints and for one test that does - adenosine diphosphate-induced platelet aggregation--sensitivity, specificity, and positive predictive value for cardiac endpoints are low: 60%, 59%, 12% respectively.²⁹ For predicting early major bleeding, this test also has low sensitivity, specificity, and

^j Intracranial or life threatening bleeding or that requiring blood transfusion.

^k Hematoma, epistaxis, vaginal bleeding, melena, hematemesis, eye bleeding, hematuria.

^l Easy bruising, bleeding from small cuts, petechia, ecchymosis.

positive predictive value: 62%, 62%, 2.2% respectively.³¹ Platelet function tests of greater clinical validity would pose a dilemma in deciding whether a patient facing PCI should receive a thienopyridine or at what dosage: patients at greatest risk of bleeding because of high platelet responsiveness are also the ones most likely to have fewer adverse cardiac endpoints.

Effect of CYP2C19 Genotypes on Cardiac and Bleeding Endpoints

Clopidogrel is a pro-drug that must be activated by enzymes before it can inhibit platelet aggregation. Consequently, inheritance of genotypes that influence the activity of these enzymes could affect clopidogrel responsiveness. Common variants of the CYP2C19 gene (*2, *3, *4, *5, *6, *7, *8) are associated with reduced enzyme function, compared to *1 or *17 homo- or heterozygotes. In a systematic review and meta-analysis of 32 studies involving 42,016 patients, Holmes et al. found that patients with CYP2C19 alleles (in single or double dose) associated with reduced enzyme function had lower risk of bleeding in response to clopidogrel and higher risk of cardiovascular disease events. However, a trend to the null was observed when small studies, more likely to be biased, were removed.³⁴

Proton pump inhibitors, frequently used in conjunction with clopidogrel, are also metabolized by CYP2C19-influenced pathways and compete with clopidogrel. Patients with DES on both drugs were found to have significantly more adverse cardiac effects than those only on clopidogrel.³⁵

Conclusions

The preponderance of evidence from RCTs and observational studies indicates that prolongation of clopidogrel following the implantation of DES for longer than one year offers no benefit, in terms of death from cardiac causes, myocardial infarction, or other thrombotic events, over shorter duration of clopidogrel therapy. It does, however, increase the likelihood of major bleeding, which may be fatal.

At present there is no valid way of predicting which patients may be at increased risk of bleeding associated with clopidogrel therapy. It is possible that even a shorter duration of clopidogrel therapy than one year post-stent would provide the same protection against major adverse cardiac events and reduce the occurrence of serious, fatal bleeds. Although other antiplatelet drugs might reduce the risk of bleeding, at the present time clopidogrel dominates the market in post-DES therapy. A black-box warning, revision of the current Medication Guide, and a “Dear Doctor” letter are needed to reduce the risk of bleeding without increasing adverse cardiac outcomes.

Summary of Petition Requests

For the reasons stated above, pursuant to the Federal Food, Drug and Cosmetic Act 21 U.S.C. Section 355(e)(3) and 21 C.F.R. 10.30, we hereby petition the FDA to:

- (1) immediately add a black-box warning on clopidogrel (brand name: Plavix, as well as generic equivalents). The black-box warning must address the increased risks

of major and minor bleeding with use beyond 12 months following implantation of drug-eluting coronary artery stents. Such warning is made necessary both by a lack of evidence of a further reduction of thrombotic cardiovascular events, such as myocardial infarction or stroke, as well as existing evidence of continued risk of major bleeding with more prolonged use.

- (2) require the distribution of an FDA-approved, updated Medication Guide containing this information to be dispensed to all patients when their prescriptions are filled and to ask companies to send a "Dear Doctor" letter to warn physicians of these preventable adverse effects that occur with use for greater than one year.

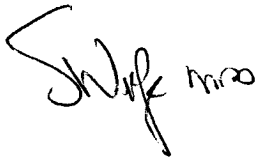
Environmental Impact Statement

Nothing requested in this petition will have an impact on the environment.

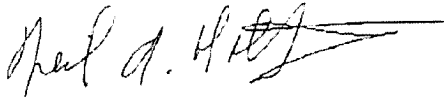
Certification

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

A handwritten signature in black ink, appearing to read "Sidney Wolfe".

Sidney Wolfe, M.D.
Founder, Senior Adviser
Public Citizen's Health Research Group

A handwritten signature in black ink, appearing to read "Neil A. Holtzman".

Neil A. Holtzman, M.D., M.P.H.
Emeritus Professor
The Johns Hopkins University School of Medicine

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