

Migraine Risk Grows After Surgery for Marfan

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Denver Bureau

MUNICH — Patients with Marfan syndrome have a sharply increased prevalence of migraine, especially migraine with aura, according to Dutch investigators.

Moreover, Marfan syndrome patients who undergo aortic root surgery experience a double headache of sorts; that is, an independent further increase in the risk of migraine, Dr. Jeroen C. Vis re-

ported at the annual congress of the European Society of Cardiology.

The explanation for the association between aortic root surgery and a high rate of migraine in Marfan syndrome patients is unclear. One possibility is that the aortic graft throws off microemboli, which trigger headache attacks, according to Dr. Vis of Academic Medical Centre, Amsterdam.

He reported on 97 adults with Marfan syndrome who had a mean age of 39 years, and 80 age- and sex-matched con-

trols. All underwent a clinical interview in which diagnosis of migraine was based on International Headache Society criteria.

Migraine was diagnosed in 44% of the Marfan patients, compared with 28% of controls. Thirty-seven percent of Marfan patients had migraine with aura, as did 10% of controls.

The prevalence of migraine among controls was higher than usual. This is most likely due to the influence of familial migraine; 16 of the 80 controls

were first-degree relatives of participating Marfan syndrome patients, Dr. Vis said.

In this study, Marfan syndrome was an independent risk factor for migraine overall, and conferred an adjusted 2.4-fold increased risk, along with a 6.2-fold increased risk for migraine with aura.

Thirty-five percent of the Marfan patients underwent aortic root surgery. A history of the surgery was independently associated with a 3.9-fold increased risk of migraine and a 4.5-fold greater risk of migraine with aura. The investigators also looked at other cardiovascular features of Marfan syndrome. Neither mitral valve surgery, aortic dilatation, aortic dissection, mitral valve prolapse, nor mitral regurgitation showed an independent association with an increase in migraine. Aortic root surgery was unique in this regard.

Dr. Vis said he and his colleagues plan as a next step to look at headache patterns in patients without Marfan syndrome who have undergone aortic root surgery. The goal will be to determine whether a history of the surgery is a risk factor for migraine and migraine with aura in them, too.



Dissection flaps (arrows) are shown in a Marfan patient before aortic root surgery.

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INDICATIONS AND USAGE

PLAVIX (clopidogrel bisulfate) is indicated for the reduction of atherothrombotic events as follows:

- **Recent MI, Recent Stroke or Established Peripheral Arterial Disease**
For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, PLAVIX has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.
- **Acute Coronary Syndrome**
For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG, PLAVIX has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.
-For patients with ST-segment elevation acute myocardial infarction, PLAVIX has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke. This benefit is not known to pertain to patients who receive primary angioplasty.

CONTRAINDICATIONS

The use of PLAVIX is contraindicated in the following conditions:
Hypersensitivity to the drug substance or any component of the product.
Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

WARNINGS

Thrombotic thrombocytopenic purpura (TTP):

TTP has been reported rarely following use of PLAVIX, sometimes after a short exposure (<2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes) [fragmented RBCs seen on peripheral smear], neurological findings, renal dysfunction, and fever. (See **ADVERSE REACTIONS**.)

PRECAUTIONS

General

PLAVIX prolongs the bleeding time and therefore should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (particularly gastrointestinal and intracranial). If a patient is to undergo elective surgery and an antiplatelet effect is not desired, PLAVIX should be discontinued 5 days prior to surgery. Due to the risk of bleeding and undesirable hematological effects, blood count determination and/or other appropriate testing should be promptly considered, whenever such suspected clinical symptoms arise during the course of treatment (see **ADVERSE REACTIONS**). In patients with recent TIA or stroke who are at high risk of recurrent ischemic events, the combination of aspirin and PLAVIX has not been shown to be more effective than PLAVIX alone, but the combination has been shown to increase major bleeding.
GI Bleeding: In CAPRIE, PLAVIX was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. In CURE, the incidence of major gastrointestinal bleeding was 1.3% vs. 0.7% (PLAVIX + aspirin vs. placebo + aspirin, respectively). PLAVIX should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients taking PLAVIX. Use in Hepatically Impaired Patients: Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. PLAVIX should be used with caution in this population.
Use in Renally Impaired Patients: Experience is limited in patients with severe renal impairment. PLAVIX should be used with caution in this population.

Information for Patients

Patients should be told that it may take them longer than usual to stop bleeding, that they may bruise and/or bleed more easily when they take PLAVIX or PLAVIX combined with aspirin, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking PLAVIX and/or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken.

Drug Interactions

Study of specific drug interactions yielded the following results:
Aspirin: Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by PLAVIX. PLAVIX potentiated the effect of aspirin on collagen-induced platelet aggregation. PLAVIX and aspirin have been administered together for up to one year.
Heparin: In a study in healthy volunteers, PLAVIX did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Coadministration of heparin had no effect on inhibition of platelet aggregation induced by PLAVIX.
Nonsteroidal Anti-inflammatory Drugs (NSAIDs): In healthy volunteers receiving naproxen, concomitant administration of PLAVIX was associated with increased overall gastrointestinal blood loss. NSAIDs and PLAVIX should be coadministered with caution.
Warfarin: Because of the increased risk of bleeding, the concomitant administration of warfarin with PLAVIX should be undertaken with caution. (See **PRECAUTIONS-General**.)
Other Concomitant Therapy: No clinically significant pharmacodynamic interactions were observed when PLAVIX was coadministered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of PLAVIX was also not significantly influenced by the coadministration of phenobarbital, cimetidine or estrogen.
The pharmacokinetics of digoxin or theophylline were not modified by the coadministration of PLAVIX (clopidogrel bisulfate).
At high concentrations *in vitro*, clopidogrel inhibits P₄₅₀ (CYP2C9). Accordingly, PLAVIX may interfere with the metabolism of phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin, and many non-steroidal anti-inflammatory agents, but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadministered with PLAVIX.

In addition to the above specific interaction studies, patients entered into clinical trials with PLAVIX received a variety of concomitant medications including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), thrombolytics, heparins (unfractionated and LMWH), GPIIb/IIIa antagonists, antiepileptic agents and hormone replacement therapy without evidence of clinically significant adverse interactions.
There are no data on the concomitant use of oral anticoagulants, non study oral antiplatelet drugs and chronic NSAIDs with clopidogrel.

Drug/Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg. Clopidogrel was not genotoxic in four *in vitro* tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one *in vivo* test (micronucleus test by oral route in mice). Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m² basis).

Pregnancy

Pregnancy Category B. Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day (respectively 65 and 78 times the recommended daily human dose on a mg/m² basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, PLAVIX should be used during pregnancy only if clearly needed.

Nursing Mothers

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.
Geriatric Use
Of the total number of subjects in the CAPRIE, CURE and CLARITY controlled clinical studies, approximately 50% of patients treated with PLAVIX were 65 years of age and older, and 15% were 75 years and older. In COMMIT, approximately 58% of the patients treated with PLAVIX were 60 years and older, 26% of whom were 70 years and older.
The observed risk of thrombotic events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Figures 3 and 6 for the CURE and COMMIT trials, respectively (see **CLINICAL STUDIES**). The observed risk of bleeding events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Tables 5 and 6 for the CURE and COMMIT trials, respectively (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS

PLAVIX has been evaluated for safety in more than 42,000 patients, including over 9,000 patients treated for 1 year or more. The clinically important adverse events observed in CAPRIE, CURE, CLARITY and COMMIT are discussed below.

The overall tolerability of PLAVIX in CAPRIE was similar to that of aspirin regardless of age, gender and race, with an approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions.

Hemorrhagic: In CAPRIE patients receiving PLAVIX, gastrointestinal hemorrhage occurred at a rate of 2.0%, and required hospitalization in 0.7%. In patients receiving aspirin, the corresponding rates were 2.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for PLAVIX compared to 0.5% for aspirin.

In CURE, PLAVIX use with aspirin was associated with an increase in bleeding compared to placebo with aspirin (see Table 5). There was an excess in major bleeding in patients receiving PLAVIX plus aspirin compared with placebo plus aspirin, primarily gastrointestinal and at puncture sites. The incidence of intracranial hemorrhage (0.1%), and fatal bleeding (0.2%), were the same in both groups.

The overall incidence of bleeding is described in Table 5 for patients receiving both PLAVIX and aspirin in CURE.

Event	PLAVIX (+ aspirin) [†] (n=6259)	Placebo (+ aspirin) [‡] (n=6303)	P-value
Major bleeding †	3.7 ‡	2.7 §	0.001
Life-threatening bleeding	2.2	1.8	0.13
Fatal	0.2	0.2	
5 g/dL hemoglobin drop	0.9	0.9	
Requiring surgical intervention	0.7	0.7	
Hemorrhagic strokes	0.1	0.1	
Requiring intropies	0.5	0.5	
Requiring transfusion (≥4 units)	1.2	1.0	
Other major bleeding	1.6	1.0	0.005
Significantly disabling	0.4	0.3	
Intracranial bleeding with significant loss of vision	0.05	0.03	
Requiring 2-3 units of blood	1.3	0.9	
Minor bleeding ¶	5.1	2.4	<0.001

[†] Other standard therapies were used as appropriate.

[‡] Life threatening and other major bleeding.

[§] Major bleeding event rate for PLAVIX + aspirin was dose-dependent on aspirin:

<100 mg=2.6%; 100-200 mg=3.5%; >200 mg=4.9%

<75 years = 4.1%; ≥75 years 5.9%

[¶] Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin:

<100 mg=2.0%; 100-200 mg=2.3%; >200 mg=4.0%

Major bleeding event rates for placebo + aspirin by age were: <65 years = 2.1%; ≥65 to <75 years = 3.1%; ≥75 years 3.6%

¶ Led to interruption of study medication.

Ninety-two percent (92%) of the patients in the CURE study received heparin/LMWH, and the rate of bleeding in these patients was similar to the overall results.

There was no excess in major bleeds within seven days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (event rate 4.4% PLAVIX + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for PLAVIX + aspirin, and 6.3% for placebo + aspirin.

In CLARITY, the incidence of major bleeding (defined as intracranial bleeding or bleeding associated with a fall in hemoglobin > 5 g/dL) was similar between groups (1.3% versus 1.1% in the PLAVIX + aspirin and in the placebo + aspirin groups, respectively). This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytics or heparin therapy. The incidence of fatal bleeding (0.8% versus 0.6% in the PLAVIX + aspirin and in the placebo + aspirin groups, respectively) and intracranial hemorrhage (0.5% versus 0.7%, respectively) was low and similar in both groups.

The overall rate of noncerebral major bleeding or cerebral bleeding in COMMIT was low and similar in both groups as shown in Table 6 below.

Type of bleeding	PLAVIX (+ aspirin) [†] (N=22961)	Placebo (+ aspirin) [‡] (N=22891)	P-value
Major* noncerebral or cerebral bleeding**	134 (0.6%)	125 (0.5%)	0.59
Major noncerebral	82 (0.4%)	73 (0.3%)	0.48
Fatal	36 (0.2%)	37 (0.2%)	0.90
Hemorrhagic stroke	55 (0.2%)	56 (0.2%)	0.91
Fatal	39 (0.2%)	41 (0.2%)	0.81
Other noncerebral bleeding (non-major)	831 (3.6%)	721 (3.1%)	0.005
Any noncerebral bleeding	896 (3.9%)	777 (3.4%)	0.004

* Major bleeds are cerebral bleeds or non-cerebral bleeds thought to have caused death or that required transfusion.

** The relative rate of major noncerebral or cerebral bleeding was independent of age.

Event rates for PLAVIX + aspirin by age were: <60 years = 0.3%; ≥60 to <70 years = 0.7%; ≥70 years 0.8%. Event rates for placebo + aspirin by age were: <60 years = 0.4%; ≥60 to <70 years = 0.6%; ≥70 years 0.7%.

Adverse events occurring in ≥2.5% of patients on PLAVIX in the CAPRIE controlled clinical trial are shown below regardless of relationship to PLAVIX. The median duration of therapy was 20 months, with a maximum of 3 years.

Body System Event	PLAVIX (n=9599)	Aspirin (n=9586)
Body as a Whole - general disorders		
Chest Pain	8.3 (0.2)	8.3 (0.3)
Accidental/Inflicted Injury	7.9 (0.1)	7.3 (0.1)
Influenza-like symptoms	7.5 (<0.1)	7.0 (<0.1)
Pain	6.4 (0.1)	6.3 (0.1)
Fatigue	3.3 (0.1)	3.4 (0.1)
Cardiovascular disorders, general		
Edema	4.1 (<0.1)	4.5 (<0.1)
Hypertension	4.3 (<0.1)	5.1 (<0.1)
Central & peripheral nervous system disorders		
Headache	7.6 (0.3)	7.2 (0.2)
Dizziness	6.2 (0.2)	6.7 (0.3)
Gastrointestinal system disorders		
Any event	27.1 (3.2)	29.8 (4.0)
Abdominal pain	5.6 (0.7)	7.1 (1.0)
Dyspepsia	5.2 (0.6)	6.1 (0.7)
Diarrhea	4.5 (0.4)	3.4 (0.3)
Nausea	3.4 (0.5)	3.8 (0.4)
Metabolic & nutritional disorders		
Hypercholesterolemia	4.0 (0)	4.4 (<0.1)
Musculo-skeletal system disorders		
Arthralgia	6.3 (0.1)	6.2 (0.1)
Back Pain	5.8 (0.1)	5.3 (<0.1)
Platelet, bleeding, & clotting disorders		
Purpura/bruise	5.3 (0.3)	3.7 (0.1)
Epistaxis	2.9 (0.2)	2.5 (0.1)
Psychiatric disorders		
Depression	3.6 (0.1)	3.9 (0.2)
Respiratory system disorders		
Upper resp tract infection	8.7 (<0.1)	8.3 (<0.1)
Dyspnea	4.5 (0.1)	4.7 (0.1)
Rhinitis	4.2 (0.1)	4.2 (<0.1)
Bronchitis	3.7 (0.1)	3.7 (0)
Coughing	3.1 (<0.1)	2.7 (<0.1)
Skin & appendage disorders		
Any event	15.8 (1.5)	13.1 (0.8)
Rash	4.2 (0.5)	3.5 (0.2)
Pruritus	3.3 (0.3)	1.6 (0.1)
Urinary system disorders		
Urinary tract infection	3.1 (0)	3.5 (0.1)

No additional clinically relevant events to those observed in CAPRIE with a frequency ≥2.5%, have been reported during the CURE and CLARITY controlled studies. COMMIT collected only limited safety data.

Other adverse experiences of potential importance occurring in 1% to 2.5% of patients receiving PLAVIX (clopidogrel bisulfate) in the controlled clinical trials are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in the other clinical trials).

Autonomic Nervous System Disorders: Syncope, Palpitation. **Body as a Whole-general disorders:** Asthenia, Fever, Hernia. **Cardiovascular disorders:** Cardiac failure. **Central and peripheral nervous system disorders:** Cramps/legs, Hypoaesthesia, Neuralgia, Parosmia, Vertigo. **Gastrointestinal system disorders:** Constipation, Vomiting. **Heart rate and rhythm disorders:** Fibrillation atrial. **Liver and biliary system disorders:** Hepatic enzymes increased. **Metabolic and nutritional disorders:** Gout, hyperuricemia, non-protein nitrogen (NPN) increased. **Musculo-skeletal system disorders:** Arthritis, Arthrosis. **Platelet, bleeding & clotting disorders:** GI hemorrhage, hematoma, platelets decreased. **Psychiatric disorders:** Anxiety, Insomnia. **Red blood cell disorders:** Anemia. **Respiratory system disorders:** Pneumonia, Sinusitis. **Skin and appendage disorders:** Eczema, Skin ulceration. **Urinary system disorders:** Cystitis. **Vision disorders:** Cataract, Conjunctivitis.

Other potentially serious adverse events which may be of clinical interest but were rarely reported (<1%) in patients who received PLAVIX in the controlled clinical trials are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in the other clinical trials).

Body as a whole: Allergic reaction, necrosis ischemic. **Cardiovascular disorders:** Edema generalized. **Gastrointestinal system disorders:** Peptic, gastric or duodenal ulcer, gastritis, gastric ulcer perforated, gastritis hemorrhagic, upper GI ulcer hemorrhagic. **Liver and Biliary system disorders:** Bilirubinemia, hepatitis infectious, liver fatty. **Platelet, bleeding and clotting disorders:** hemarthrosis, hematuria, hemoptysis, hemorrhage intracranial, hemorrhage retroperitoneal, hemorrhage of operative wound, ocular hemorrhage, pulmonary hemorrhage, purpura allergic, thrombocytopenia. **Red blood cell disorders:** Anemia aplastic, anemia hypochromic. **Reproductive disorders, female:** Menorrhagia. **Respiratory system disorders:** Hemothorax. **Skin and appendage disorders:** Bullous eruption, rash erythematous, rash maculopapular, urticaria. **Urinary system disorders:** Abnormal renal function, acute renal failure. **White cell and reticuloendothelial system disorders:** Agranulocytosis, granulocytopenia, leukemia, leukopenia, neutropenia.

Postmarketing Experience

The following events have been reported spontaneously from worldwide postmarketing experience:

- **Body as a whole:**
-hypersensitivity reactions, anaphylactoid reactions, serum sickness
- **Central and Peripheral Nervous System disorders:**
-confusion, hallucinations, taste disorders
- **Hepato-biliary disorders:**
-abnormal liver function test, hepatitis (non-infectious), acute liver failure
- **Platelet, Bleeding and Clotting disorders:**
-cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal hemorrhage)
-thrombotic thrombocytopenic purpura (TTP) - some cases with fatal outcome - (see **WARNINGS**)
- **Renal and urinary disorders:**
-agranulocytosis, aplastic anemia/pancytopenia
-conjunctival, ocular and retinal bleeding
- **Respiratory, thoracic and mediastinal disorders:**
-bronchospasm, interstitial pneumonitis
- **Skin and subcutaneous tissue disorders:**
-angioedema, erythema multiforme, Stevens-johnson syndrome, toxic epidermal necrolysis, lichen planus
- **Renal and urinary disorders:**
-glomerulopathy, increased creatinine levels
- **Vascular disorders:**
-vasculitis, hypotension
- **Gastrointestinal disorders:**
-colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis
- **Musculoskeletal, connective tissue and bone disorders:**
-myalgia

OVERDOSAGE

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting (in baboons), prostration, difficult breathing, and gastrointestinal hemorrhage in all species.

Recommendations About Specific Treatment:
Based on biological plausibility, platelet transfusion may be appropriate to reverse the pharmacologic effects of PLAVIX if quick reversal is required.

DOSE AND ADMINISTRATION

Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

The recommended daily dose of PLAVIX is 75 mg once daily.

Acute Coronary Syndrome

For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave MI), PLAVIX should be initiated with a single 300-mg loading dose and then continued at 75 mg once daily. Aspirin (75 mg-325 mg once daily) should be initiated and continued in combination with PLAVIX. In CURE, most patients with Acute Coronary Syndrome also received heparin acutely (see **CLINICAL STUDIES**).

For patients with ST-segment elevation acute myocardial infarction, the recommended dose of PLAVIX is 75 mg once daily, administered in combination with aspirin, with or without thrombolytics. PLAVIX may be initiated with or without a loading dose (300 mg) was used in CLARITY; see **CLINICAL STUDIES**. PLAVIX can be administered with or without food. No dosage adjustment is necessary for elderly patients or patients with renal disease. (See **Clinical Pharmacology: Special Populations**.)

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