Clopidogrel-Associated TTP

An Update of Pharmacovigilance Efforts Conducted by Independent Researchers, Pharmaceutical Suppliers, and the Food and Drug Administration

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Background and Purpose—Since the 1999 identification of clopidogrel-associated thrombotic thrombocytopenic purpura (TTP) through independent active surveillance, subsequent cases have been identified by pharmaceutical suppliers of clopidogrel and the Food and Drug Administration (FDA). For cases of clopidogrel-associated TTP reported between 1998 to 2002, we evaluated the quality and timeliness of data from 3 reporting systems–independent active surveillance (n=13), pharmaceutical suppliers (n=24), and the FDA (n=13)—and identified prognostic factors associated with mortality.

Methods—This study assessed the completeness of information on TTP diagnosis, treatment response, and causality from the 3 reporting systems. In addition, predictors of mortality were identified through classification tree analysis.

Results—Completeness, timeliness, and certainty of diagnosis were best for cases obtained by active surveillance, intermediate for cases reported to the pharmaceutical supplier, and poorest for cases reported directly to the FDA. Clopidogrel had been used for ≤2 weeks by 65%. The survival rate for patients with clopidogrel-associated TTP was 71.2%. Receipt of therapeutic plasma exchange within 3 days of onset of TTP increased the likelihood of survival (100% versus 27.3%, $P<0.001$).

Conclusions—Compared with reports submitted by suppliers or the FDA, reports obtained through active surveillance provided timelier and more complete information. Clopidogrel-associated TTP often occurs within 2 weeks of drug initiation, occasionally relapses, and has a high mortality if not treated promptly. **(*Stroke*. 2004;35:533-538.)**

Key Words: adverse drug reaction reporting systems ■ antiplatelet agents ■ purpura, thrombotic thrombocytopenic

Many pharmaceutical agents have serious side effects that are not discovered until several years after Food and Drug Administration (FDA) approval.[1] Identification of rare but potentially fatal adverse drug reactions is especially difficult. Active surveillance by hematologists and apheresis program directors led to identification of the first cases of thrombotic thrombocytopenic purpura (TTP) associated with the commonly used antiplatelet agent clopidogrel.[2] Since then, additional cases have been reported either directly to the pharmaceutical suppliers of clopidogrel or through MedWatch, the FDA's voluntary adverse event reporting system.

Widespread recognition of adverse drug reactions is often delayed because only 1% to 10% of cases are reported to suppliers or the FDA.[3] In a few instances, independent researchers have assisted in the identification of serious adverse drug reactions. No prior study has compared the utility of different pharmacosurveillance programs. By reviewing all reported clopidogrel-associated TTP cases, we had the unique opportunity to provide an update on the clinical and laboratory characteristics of this syndrome and to compare the quality and timeliness of case reports obtained by independent researchers, pharmaceutical suppliers, and the FDA. Analysis of these reports also provides insight into prognostic factors and mortality.

See Editorial Comment, page 537

Methods

Case Identification and Data Collection (1998–2002)

Active surveillance identified potential cases of clopidogrel-associated TTP by querying physicians providing therapeutic aphere-

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sis services and hematologists in Chicago (Ill), Pittsburgh (Penn), Raleigh-Durham (NC), Los Angeles (Calif), Baltimore (Md), Indianapolis (Ind), Boston (Mass), and Houston (Tex). These physicians had participated in a prior series of studies on ticlopidine-associated TTP and have a large caseload of TTP patients.[2,4] Of the 13 patients identified by the active surveillance group, 12 have previously been reported in the literature.[2,5] Other cases were voluntarily reported by healthcare workers directly to Sanofi-Synthelabo Inc and Bristol Myers Squibb, the suppliers of clopidogrel, or to officials at MedWatch. We obtained the verbatim reports of these cases from the FDA's Adverse Event Reporting System. From these sources, data related to sociodemographics, clinical and laboratory characteristics, and medication use were collected through the use of a case report form validated in prior ticlopidine-associated TTP studies.[2,4]

Data Completeness Assessment

For each surveillance method, assessments were made of data completeness, timeliness, usefulness of supplemental requests, and certainty of diagnosis. Data completeness was based on the reporting of the following data elements: (1) TTP diagnosis (7 items: platelet count, hemoglobin, lactate dehydrogenase (LDH), serum creatinine, schistocytes on peripheral blood smear, fever, and neurologic changes), (2) treatment evaluation (4 items: use of therapeutic plasma exchange [TPE], day of TPE initiation, duration of TPE, and outcome), and (3) association with clopidogrel (3 items: number of days of clopidogrel use before TTP onset, date of discontinuation, and names of concomitant medications). Information was scored as complete, partially complete, or incomplete on the basis of the number of elements reported for TTP diagnosis (6 to 7, 4 to 5, <4 items, respectively), treatment response (3 to 4, 2, <2 items, respectively), and association with clopidogrel (3, 2, <2 items, respectively). Data source timeliness was based on the percentage of possible or probable clopidogrel-associated TTP cases identified within the first year of marketing. Usefulness of supplemental requests was based on the percent of follow-up responses that included at least 1 of the clinical data elements associated with TTP. Diagnostic certainty, assessed by independent review of each case history by 2 study physicians (C.L.B., A.Z.), was characterized as probable (platelet count $<100\times10^9$/L, hemoglobin level <100 g/L, schistocytes on a peripheral blood smear, and absence of findings of disseminated intravascular coagulation), possible (clinical suspicion of TTP, platelet count $<100\times10^9$/L, hemoglobin <100 g/L, and lack of information on schistocytes and LDH), or incompletely reported (clinical diagnosis of TTP, no information on microangiopathic hemolytic anemia, and thrombocytopenia). Clopidogrel was considered a possible cause of TTP if at least 1 dose of clopidogrel had been prescribed before TTP onset. Clopidogrel-associated TTP diagnostic certainty was rated as probable, possible, or insufficiently reported on the basis of the certainty of the TTP diagnosis in conjunction with a history of clopidogrel use.

TTP Clinical Data: Severity, Age, Sex, Duration, Treatment, and Outcome

Clinical data were collected on the case report forms. Severity of TTP was characterized according to the staging system of Rose and Eldor.[6] The scoring system has 4 categories: platelet count, hemoglobin level, serum creatinine level, and neurological changes. The χ^2 test was used for univariate comparisons. Hierarchically optimal classification tree analysis was used to develop a multivariate nonlinear model for mortality.[7] Potential predictors included patient age and sex, duration of clopidogrel therapy, Rose and Eldor severity of TTP score, plasmapheresis, and plasmapheresis done within 3 days of admission.

Results

Case Identification

A total of 50 reports of clopidogrel-associated TTP were identified: 13 by active surveillance, 24 by the pharmaceutical suppliers, and 13 by MedWatch (Table 1). Among all probable or possible cases of clopidogrel-associated TTP in the first year of marketing, 11 cases were identified from our active surveillance effort, 6 were reported to the suppliers, and 0 were reported directly to the FDA. Supplemental information was requested and additional data elements were obtained most often with

TABLE 1. Completeness and Timeliness of Cases Reported by Independent Researchers, Pharmaceutical Suppliers of Clopidogrel, and the FDA

	Active Surveillance (n=13)	Suppliers' Reports (n=24)	FDA Reports (n=13)
Reporting timeliness*	11	6	0
Follow-up information			
Reports requested, n	13	21	0
Reports received, n	13	15	0
Requests for additional information which resulted in additional data, %	100	71	N/A
TTP diagnosis,† %			
Complete	100	8	0
Partially complete	0	79	69
Incomplete	0	12	31
Treatment,‡ %			
Complete	100	53	8
Partially complete	0	47	83
Incomplete	0	0	8
Association with clopidogrel,§ %			
Complete	100	58	23
Partially complete	0	33	54
Incomplete	0	9	23
Diagnostic certainty,‖ %			
Probable cases	92	45	23
Possible cases	8	38	23
Incompletely reported	0	17	54

*Timeliness of TTP reporting: Total possible/probable cases identified in the first year of drug marketing (November 1998–December 1999)

†TTP diagnosis (7 data elements possible: platelet count, hemoglobin, LDH, serum creatinine, schistocytes on peripheral blood smear, fever, and neurological changes)
6–7=complete
4–5=partially complete
<4=incomplete

‡TTP treatment (4 data elements possible: use of TPE, day of TPE initiation, duration of TPE, and outcome); cases without TPE were excluded (not scored)
3–4=complete
2=partially complete
<2=incomplete

§Role of clopidogrel (3 data elements possible: number of days of clopidogrel use before TTP onset, date of discontinuation, and names of concomitant medications)
3=complete
2=partially complete
<2=incomplete

‖Diagnostic certainty criteria used by study physicians
Probable: platelet count $<100\times10^9$/L, hemoglobin level <100 g/L, schistocytes on peripheral blood smear, and absence of findings of disseminated intravascular coagulation
Possible: platelet count $<100\times10^9$/L, hemoglobin level <100 g/L, clinical diagnosis of TTP, and absence of information on schistocytes and LDH
Incompletely reported: clinical diagnosis of TTP but no information on microangiopathic hemolytic anemia and thrombocytopenia

active surveillance (100% requisition response rate) compared with the suppliers' direct reporting surveillance program (70% requisition response rate) or MedWatch (no supplemental requisitions).

Completeness of Data

Data completeness varied according to the source of case report (Table 1). The completeness of information on TTP diagnosis, assessment of treatment evaluation, and evaluation of clopidogrel association was highest for cases obtained by active surveillance, intermediate for the pharmaceutical suppliers, and poorest for cases reported to the FDA ($P<0.001$). Certainty of diagnosis was determined on the basis of completeness of information provided. From these data, cases were classified as probable or possible TTP in 100% of the active surveillance cases, 83% of the suppliers' cases, and 46% of the FDA's cases ($P<0.001$).

Clinical Findings

On the basis of the diagnostic certainty of TTP, along with a history of clopidogrel use, 37 persons were characterized as probable or possible clopidogrel-associated TTP cases (Table 2). Of these, 42% were >60 years old, and 71% had received clopidogrel for coronary artery disease, primarily after coronary artery stent procedures. Clopidogrel treatment was discontinued in all patients on diagnosis of TTP. The most common concomitant drugs were aspirin and metoprolol, whereas the most common drugs initiated with clopidogrel therapy were abciximab (4 patients who underwent coronary artery stent procedures) or statins (10 patients). Clopidogrel had been prescribed for ≤2 weeks for 65% of the patients. Clinical findings included thrombocytopenia (100%), microangiopathic hemolytic anemia (100%), neurological changes (47.4%), renal dysfunction (28.8%), and fever (26.3%). TTP severity, based on Rose and Eldor scores, ranged from mild to severe; scores were <4 for 45.9%, 4 to 6 for 51.4%, and >6 for 2.7% (Table 2).

TPE was performed in 78.4% of patients. Overall, the survival rate for patients with clopidogrel-associated TTP was 73%. Persons who received TPE within 3 days of TTP onset were more likely to survive than those in whom TPE was initiated after 3 days (survival rate, 100% versus 27.3%; $P<0.0001$), although the severity of TTP was similar (mean Rose and Eldor score 4.1 for persons with TPE initiated within 3 days of TTP onset versus 3.6 for persons with later TPE; $P=0.68$). Among persons who did not receive TPE within 3 days of TTP onset, those having milder cases of TTP at diagnosis (Rose and Eldor scores <4) were more likely than persons with more severe cases (Rose and Eldor scores ≥4) to survive (60% versus 0% survival, $P<0.06$). This 2-attribute model was stable in jackknife validity analysis and explained 75% of the variation in patient mortality status that was theoretically possible to capture beyond that explained by chance alone (the Figure). Four patients required >20 TPEs before TTP resolved. Three patients had ≥1 relapses up to 1 year after resolution of the initial syndrome and after discontinuation of the drug.

Discussion

Clinical Findings

The clinical findings from our study enhance the current knowledge of clopidogrel-associated TTP and can be compared with those reported previously for ticlopidine-associated TTP.[4] The studies suggest that clopidogrel-associated TTP is 15 times more likely to occur within the first 2 weeks of drug use and more likely to require ≥20 TPEs before resolving (4 versus 0 instances). The finding that clopidogrel-associated TTP is more likely to recur (5 recurrences occurred several weeks to 1 year after clopidogrel discontinuation in 3 clopidogrel-treated patients versus 0 among 98 ticlopidine-treated patients) and the identification of ADAMTS13 activity in 2 of 4 clopidogrel-treated and 0 of 7 ticlopidine-treated patients raise concern that for some patients the link to clopidogrel as an initiator of an immunologic response may be suspect.[2,5,8] For both clopidogrel- and ticlopidine-associated TTP, TPE is the most important predictor of survival: 82% among persons who underwent TPE versus 36% among persons who did not. Moreover, plasmapheresis was initiated >3 days after disease onset for all of the clopidogrel-associated and two thirds of the ticlopidine-associated TTP fatalities. In comparison, a randomized trial of TTP patients reported mortality rates of 22% for patients who received early TPE versus 83% for patients who underwent early treatment with plasma infusion alone.[9]

Importance of Prompt Case Identification

Prompt initiation of therapy is dependent on clinician recognition of the syndrome that characterizes clopidogrel-associated TTP. The impetus for active surveillance was a prior survey of hematologists and apheresis program directors that identified TTP associated with the chemically related thienopyridine derivative ticlopidine.[4] The quality and timeliness of the first reports of clopidogrel-associated TTP were highest for cases identified by active surveillance, intermediate for cases reported to the suppliers, and poorest for cases reported directly to the FDA. The current system of voluntary reporting often misses important adverse drug reactions, and for those that are reported, the available data are frequently incomplete and not shared with the medical community in a timely manner. Although active surveillance requires an initial suspicion about a possible etiological link, it can lead to prompt and complete reporting of information necessary to appropriately inform the medical community.

Study Limitations

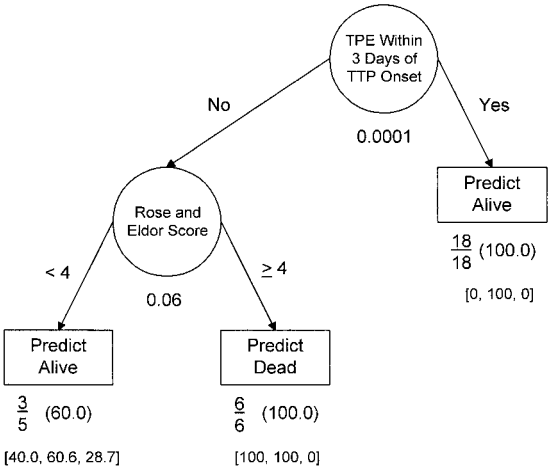
There are several limitations to our study that should be recognized. An accurate estimate of incidence rate of clopidogrel-associated TTP cannot be determined from our data. However, in postmarketing follow-up, the pharmaceutical companies have reported the estimate to be 4 cases per 1 million patients.[10] Clopidogrel has been associated with 8% of drug-induced TTP cases, the second most frequent after ticlopidine.[11] Second, the role of metalloproteinase (ADAMTS 13) activity in clopidogrel-associated TTP is not yet known. ADAMTS13 is the recently identified von Willebrand factor (vWF)–cleaving protease.[12–14] Deficiency of the protease and autoantibodies that inhibit its activity result in unusually large vWF multimers that may have a role in the pathogenesis of idiopathic TTP.[15,16] In a study of 7 patients with ticlopidine-associated TTP, Tsai et al[8] reported that during periods of active TTP, plasma samples from all 7 patients lacked the largest vWF multimers and were

TABLE 2. Clinical Characteristics and Treatment of Clopidogrel-Associated TTP

Case, n	Age, y	Sex	Duration of Clopidogrel Therapy, d	Rose and Eldor Score*	Survive	TPE	TPE Within 3 d of TTP Onset	≥20 TPEs	Relapses, n
1	40	M	2	4	No	No	No	No	0
2	44	M	1	3	No	No	No	No	0
3	60	F	5	4	No	Yes	No	No	0
4	70	F	4	4	No	Yes	No	No	0
5	74	M	395	5	No	No	No	No	0
6	74	M	4	3	No	Yes	NA	No	0
7	74	M	NA	2	No	Yes	No	Yes	0
8	76	M	14	5	No	Yes	No	No	0
9	84	F	NA	5	No	No	No	No	0
10	36	M	4	3	Yes	Yes	Yes	No	0
11	36	F	10	5	Yes	Yes	Yes	No	0
12	40	F	7	4	Yes	Yes	NA	No	0
13	42	M	30	3	Yes	Yes	NA	Yes	0
14	44	F	4	3	Yes	Yes	Yes	No	0
15	49	F	8	5	Yes	Yes	Yes	No	0
16	49	F	8	7	Yes	Yes	Yes	No	0
17	54	M	12	4	Yes	Yes	Yes	Yes	0
18	54	M	28	3	Yes	Yes	Yes	No	1
19	54	M	28	5	Yes	Yes	NA	No	0
20	55	M	8	3	Yes	Yes	No	No	1
21	59	M	14	4	Yes	Yes	Yes	No	0
22	60	F	28	3	Yes	Yes	NA	No	0
23	61	M	3	3	Yes	Yes	Yes	No	0
24	65	M	369	3	Yes	Yes	Yes	No	0
25	65	M	330	6	Yes	Yes	Yes	No	3
26	66	F	14	6	Yes	Yes	Yes	Yes	0
27	66	M	NA	3	Yes	Yes	Yes	No	0
28	68	M	7	4	Yes	NA	NA	No	0
29	70	M	3	3	Yes	No	No	No	0
30	70	F	7	3	Yes	Yes	Yes	No	0
31	71	M	NA	3	Yes	Yes	Yes	No	0
32	73	M	60	5	Yes	Yes	Yes	No	0
33	76	M	10	4	Yes	NA	NA	No	0
34	78	F	12	2	Yes	No	No	No	0
35	85	F	5	4	Yes	Yes	Yes	No	0
36	NA	M	NA	3	Yes	Yes	Yes	No	0
37	53	F	13	4	NA	Yes	No	No	0

*Rose and Eldor[4] Score: platelet: 0=>100×10^9/L, 1=20 to 100×10^9/L, and 2=<20×10^9/L; hemoglobin level score: 0=>12.0 g/dL, 1=9.0 to 12.0 g/dL, and 2=<9.0 g/dL; serum creatinine: 0=<1.5 mg/dL, 1=1.5 to 2.5 mg/dL, and 2=>2.5 mg/dL; and neurological score: 0=no deficit, 1=confusion, lethargy, and behavioral changes, and 2=focal deficit, convulsions, stupor, and coma.

severely deficient in vWF metalloproteinase, and 5 had evidence of IgG molecules that inhibited metalloproteinase activity in normal controls. In contrast, of 4 patients with clopidogrel-associated TTP, only 1 had evidence of severe deficiency of ADAMTS13 and IgG molecules in the plasma that inhibited ADAMTS13 in plasma samples of controls.[2,5] Although clopidogrel and ticlopidine have similar chemical structures and mechanisms of action, the differences in clinical presentation, response to plasmapheresis, likelihood of recurrence, and basic laboratory studies suggest that there may be differences in etiology. We are currently conducting a prospective study of 300 patients with TTP, some of whom are expected to have received clopidogrel. All patients will have plasma samples evaluated for ADAMTS13 activity and presence of IgG molecules that are inhibitory to ADAMTS13 in control plasma samples.



Classification tree analysis model for predicting mortality. Circles represent nodes; arrows, branches; and rectangles, prediction end points (As indicated, the model classifies patients having a given attribute profile as either dead or alive). Numbers or words adjacent to arrows indicate the value of the cut-point/category for the node. Fractions given under prediction end points give the number of correct classifications at the end point (numerator) and total number of observations classified at the end point (denominator). Numbers in parentheses adjacent to the fractions give the predictive value for the end point expressed as a percentage. Numbers in brackets give the percentage mortality rate at the node and mean and SD of the bootstrap (1000 iterations, 50% resample) predictive value for the model end point, respectively. Numbers underneath nodes give the generalized type I error for the node.

Conclusions

Clopidogrel-associated TTP often occurs within 2 weeks of drug initiation, occasionally relapses, and has a high survival rate if recognized and treated early with plasma exchange. Compared with reports submitted by the suppliers or the FDA, reports obtained by active surveillance provide timelier and more complete information. Therefore, to improve patient safety related to pharmaceuticals, consideration should be given to independent organizations that routinely conduct postmarketing safety evaluations of FDA-approved drugs, as suggested by Wood.[3] Finally, the quality of data reporting through the MedWatch system is quite variable. An attempt should be made to improve the completeness of these reports so that the information can be more useful in the evaluation of adverse events.

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Editorial Comment

An Approach to the Estimation of the Risk of TTP During Clopidogrel Therapy

In this issue of *Stroke*, Zakarija and 12 co-authors[1] describe 37 cases of thrombotic thrombocytopenic purpura (TTP) that occurred in the United States in the years 1998 to 2002 in association with clopidogrel (Plavix) therapy. This is of interest to those of us who (as characterized by Donnan and Davis[2]) are "strokologists," since it raises questions about our understanding of the CAPRIE study.[3] In CAPRIE there were 25 cases of platelet counts $<100\,000$ per mm^3 in 9553 patients receiving

clopidogrel 75 mg/d, and 25 cases in 9546 patients receiving aspirin 325 mg/d (2.6 cases per thousand with each treatment); no cases of TTP were reported.

We pose 2 questions: (1) Why did Zakarija et al find cases of TTP while the CAPRIE investigators did not? (2) Can we estimate the true risk of TTP during clopidogrel therapy?

With regard to the first question, a possible explanation is that TTP occurs late in clopidogrel treatment, and was not seen in CAPRIE because treatment duration was too short. This explanation fails for 2 reasons: (1) Zakarija et al found that TTP occurred within the first 30 days in 87.5% of cases, and (2) mean treatment duration in CAPRIE was fairly long (1.63 years). Alternatively, we could conclude that very large numbers of instances of thrombocytopenia must occur before even a single instance of TTP will develop (all 37 patients had thrombocytopenia), and that the CAPRIE cohort was too small to produce these numbers. This seems a more plausible explanation, and presumably underlies the pharmaceutical companies' postmarketing estimate of 4 cases per million patients, as cited by Zakarija et al.

This brings us to the second question: do we accept the pharmaceutical companies' estimate of 4 cases per million patients, or can we examine the issue ourselves? Zakarija et al did not think that they could make an independent estimate; they commented: "An accurate estimate of incidence rate of clopidogrel-associated TTP cannot be determined from our data." We, however, see a way of using their data to make estimates of TTP occurrence; we present our methods and results below.

Zakarija et al used 3 case-finding approaches. Thirteen of their cases were identified through the active querying of physicians performing plasma exchange, and of hematologists, in 8 urban areas. According to the New York Times World Almanac 2001, these 8 areas accounted for 40 million (14.8%) of the 1998 US population of 270 million. On the assumptions of completeness of ascertainment in the 8 areas, and of uniformity of distribution of cases throughout the United States, the 5-year total for the United States should have been 13/0.148=approximately 88 cases. Obviously the assumptions can be questioned; nevertheless, if the second assumption is correct then the 37−13=24 cases identified through 2 passive reporting channels represent under-ascertainment compared with the active querying method.

We have reviewed financial statements estimating the sales of Plavix by the manufacturers for the years 1998 to 2002. The approximate values for these years were $134 million, $485 million, $801 million, $1.1 billion, and $1.6 billion, respectively. On the estimate of $50 wholesale price for a month's supply, the number of "Plavix months" (PMs) of agent sold in 1998 would be $134 million/$50=approximately 2.7 million. By similar calculation the PM values in millions for the subsequent years would be approximately 9.7, 16.0, 22.0, and 32.0. The total PM for 1998 to 2002 would be 82.4 million. If each patient took 1 month of treatment and then received no more clopidogrel the total number of patients treated would have been 82.4 million and the rate of TTP would have been 88/82.4 million or approximately 1.1 per million; the order of magnitude is similar to the pharmaceutical companies' estimate of 4 per million.

The 4 per million rate from 88 TTP cases in 5 years would have required a total of 22 million patients: 88 per 22 million=4 per 1 million; in that circumstance the duration of treatment would have averaged (82.4 million/22 million)=3.745 months.

What about longer durations of treatment? The maximal treatment duration assumption would be that all patients begun on treatment at any time in the 5-year period remained on treatment as of December 31, 2002. Let us start in 1998 with the assumption that all 2.7 million PMs where consumed by first-time users whose entry into treatment was distributed uniformly across the year. Therefore these first-time users averaged 6 PMs during the year; 2.7 million/6=450 000 new patients in 1998. In 1999 these 450 000 patients would have used 450 000×12=5.4 million PMs out of the 9.7 million PMs sold that year; 9.7 million−5.4 million=4.3 million PMs, which were consumed by 4.3 million/6=approximately 717 000 patients new to treatment in 1999. Application of the algorithm to the next 3 years leads to the estimation of 333 000 new patients in 2000, 667 000 new patients in 2001, and 999 000 new patients in 2002. From this algorithm the total of new patients (and therefore of all patients treated) for 1998 through 2002 is 3.166 million; 88 TTP cases in 3.166 million patients would give a rate of approximately 27.8 per million, an order of magnitude greater than the pharmaceutical companies' estimate.

The range of our estimates—1.1 to 27.8 per million—reflects the assumptions we made. (For instance, the estimate of $65 rather than $50 per PM would result in the range of 1.4 to 36.2 per million.) It should be possible to replace some of these assumptions with data. The manufacturers can make a valuable contribution by publishing the actual net numbers of Plavix tablets sold for the years 1998 to 2002; this would obviate the need to use price estimates. Data giving ratios of new prescriptions to refills should be solicited from major retail pharmacy chains; these data would also contribute importantly to the refining of the estimation of risk of TTP during clopidogrel therapy.

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