



Clopidogrel and thrombotic thrombocytopenic purpura: No clear case for causality

ABSTRACT

Although the antiplatelet agent clopidogrel is associated with an increased incidence of thrombotic thrombocytopenic purpura (TTP), available evidence is not sufficient to establish or disprove a causal relationship. We review and assess the evidence and case reports linking clopidogrel use with TTP and discuss how to approach the risk of TTP in patients taking clopidogrel.

KEY POINTS

Twenty-four cases of TTP have been reported among more than 3 million users of clopidogrel. The Food and Drug Administration has estimated the incidence of TTP in patients taking clopidogrel at 1 case per 8,500 to 26,000 treated patients.

Some of the reported patients with clopidogrel-associated TTP had other potential precipitating factors for TTP or other confounding factors, making determination of a cause-and-effect relation difficult.

The index of suspicion for TTP should be high when we encounter patients taking clopidogrel who present with unexplained fever, renal failure, neurologic symptoms, bleeding, or purpura.

REPORTS OF thrombotic thrombocytopenic purpura (TTP) associated with clopidogrel (Plavix) are accumulating, despite a lack of reported cases in clinical trials of the drug. Still, current evidence appears to neither establish nor refute a causal relationship between the antiplatelet drug and this rare, potentially fatal disorder.

We review the available evidence on clopidogrel's association with TTP and discuss how to respond to the potential risk of TTP in patients taking it, given the clinical usefulness of the drug.

CLOPIDOGREL USE IS GROWING

Evidence for the clinical benefit of clopidogrel is increasing in patients undergoing arterial stenting, as well as in the initial treatment and secondary prevention of acute coronary syndromes.¹⁻⁴ Moreover, clopidogrel has replaced ticlopidine (Ticlid) as the antiplatelet agent of choice for use in addition to aspirin after coronary stenting, owing to its favorable side-effect profile, lower cost, and equivalent clinical efficacy. Whether clopidogrel is associated with the reported cases of TTP in a causal or a coincidental way becomes more important as more patients receive the drug.

PATHOGENESIS OF TTP IS UNCLEAR

TTP is a rare syndrome of intravascular platelet aggregation characterized by fever, neurologic symptoms, impaired renal function, microangiopathic hemolytic anemia, and thrombocytopenia. Its pathogenesis is largely unknown, but growing evidence suggests a role for defi-



ciency of von Willebrand factor-cleaving metalloprotease in some forms of the disorder.^{5,6} Inherited deficiency or autoantibodies against this protease permit the circulation of large von Willebrand factor multimers that bind with platelets and cause platelet aggregation. Factors implicated in the etiology of TTP include certain drugs, as well as malignancies, autoimmune disorders, and pregnancy.⁷

■ HIGH RATES OF TTP WITH TICLOPIDINE

Although intracoronary stents revolutionized coronary revascularization, high rates of acute and subacute thrombosis complicated their early use. Trials in the mid-1990s demonstrated the benefit of the antiplatelet agent ticlopidine in preventing stent thrombosis and established its role for use in addition to aspirin as antithrombotic therapy following coronary artery stenting.^{8,9}

The toxicities reported in the initial studies of ticlopidine included minor side effects such as skin rashes, gastrointestinal disturbance, and renal dysfunction in approximately 7% of patients and severe neutropenia in 0.7% to 1.2%.¹⁰ Other serious adverse effects began to be reported in postmarketing surveillance studies.

Sporadic cases of TTP associated with ticlopidine use had been reported since 1991, but reports of larger numbers of TTP cases by Bennett et al^{11,12} and Steinhubl et al¹³ in the late 1990s raised questions about the drug's safety. The incidence of ticlopidine-associated TTP has been estimated at 1 in 1,600 to 1 in 4,000 patients treated, and the condition is fatal in nearly 60% of patients who do not undergo plasmapheresis.^{13,14}

■ TTP RATES WITH CLOPIDOGREL: ESTIMATES VARY

Clopidogrel, a thienopyridine derivative, is structurally similar to ticlopidine and inhibits platelet activation through the adenosine diphosphate pathway. The clinical trials that supported its market approval reported no cases of TTP among more than 20,000 enrolled patients.

Clopidogrel's relative safety came under scrutiny, however, after Bennett et al¹⁵ report-

TABLE 1

Reported cases of clopidogrel-associated TTP*

REFERENCE	AGE (YR) AND SEX	LENGTH OF THERAPY (DAYS)
Bennett et al ¹⁵ †	66, F	14
Bennett et al ¹⁵	61, M	3
Bennett et al ¹⁵	36, F	10
Bennett et al ¹⁵	49, F	8
Bennett et al ¹⁵	49, F	8
Bennett et al ¹⁵	60, F	5
Bennett et al ¹⁵	65, M	330
Bennett et al ¹⁵	70, F	7
Carwile et al ¹⁶ ‡	55, M	7
Connors et al ¹⁷	54, M	14
Chinnakotla et al ¹⁹ §	35, M	3
Evens et al ²⁰ ¶	48, M	120
Moy et al ²¹	54, M	13
Nara et al ²² #	59, M	14
Oomen et al ²³	70, M	4

* Does not include 9 patients whose details were not reported.

† Kidney transplant recipient.

‡ Patient had TTP recurrence after administration of atorvastatin.

§ Kidney-pancreas transplant recipient on cyclosporine.

¶ Kidney-pancreas transplant recipient.

Patient was positive for human immunodeficiency virus.

Rates of TTP associated with ticlopidine: 1 case per 1,600 to 4,000 patients treated

ed 11 cases of TTP associated with clopidogrel use. This report prompted the US Food and Drug Administration (FDA) to suggest that a warning about TTP risk be included in clopidogrel's package insert.

To date, 24 cases of clopidogrel-associated TTP have been reported in the literature (TABLE 1).¹⁵⁻²³ The question that remains is whether this association is causal or coincidental.

The incidence of TTP in the community has been estimated at approximately 3.7 cases per 1,000,000 persons per year.²⁴ Worldwide postmarketing surveillance studies of clopidogrel have reported TTP at a rate of about 4

cases per 1,000,000 patients exposed to the drug, or about 11 cases per 1,000,000 patient-years.²⁵ Data from the FDA's MedWatch program suggest a higher incidence of clopidogrel-associated TTP, with an estimated rate of 1 case per 8,500 to 26,000 treated patients.¹⁸ A systematic review of the literature on drug-induced TTP revealed that 8% of reported cases were associated with clopidogrel, making clopidogrel second only to ticlopidine as the drug most commonly associated with TTP.²⁶

■ CRITERIA FOR CAUSALITY

Though the estimated rates of clopidogrel-associated TTP are higher than the rate of TTP in the general population, certain caveats must be considered before we can call the association causal. Using general guidelines suggested for the diagnosis of drug-related adverse events,²⁷ a definitive cause-and-effect relationship between a drug and TTP can be established only if all of the following criteria are met:

- Therapy with the candidate drug preceded TTP
- Recovery from TTP was complete and sustained after therapy with the candidate drug was stopped
- The candidate drug was the only drug used before the onset of TTP
- Other drugs were continued or reintroduced after therapy with the candidate drug was stopped, without recurrence of TTP
- Reexposure to the candidate drug resulted in recurrent TTP
- Other causes of TTP have been excluded.

■ LIMITATIONS IN WHAT WE KNOW

The initial problem in assessing the potential causal role of any drug in TTP is the difficulty of diagnosing TTP. The diagnostic criteria for TTP are not specific, and the combination of thrombocytopenia, microangiopathic hemolytic anemia, and other renal and extrarenal manifestations of TTP can be seen in other diseases.

The difficulty in establishing a causal relationship with a drug is compounded by the

absence of a reliable specific laboratory marker for TTP. Though severely reduced levels of von Willebrand factor-cleaving protease have been reported in ticlopidine-associated TTP,^{28,29} more evidence demonstrating deficiency of this enzyme in TTP caused by other drugs is needed before its use as a potential marker for drug-induced TTP can be considered.

A number of the reported patients with clopidogrel-associated TTP had other potential precipitating factors for TTP,³⁰ making definite determination of a cause-and-effect relationship difficult:

- Two patients had been started on a statin drug (atorvastatin or simvastatin; the latter has been associated with TTP³¹) within 3 weeks of presenting with TTP
- One patient had recurrence of TTP within 2 weeks of initiating therapy with atorvastatin
- One patient was a renal transplant recipient
- Two patients were kidney-pancreas transplant recipients
- One patient had human immunodeficiency virus infection.

Other limitations in these reports argue against a strong association of clopidogrel with TTP. One patient had been taking clopidogrel for almost a year before developing TTP, another patient developed TTP 3 weeks after discontinuing clopidogrel, and two patients had recurrent TTP while not taking clopidogrel. Decreased activity of the von Willebrand factor-cleaving protease with circulating immunoglobulin G inhibitors of the protease was described in two patients with TTP associated with clopidogrel.¹⁵ However, during clinical remission, only one of these two patients exhibited normal plasma protease activity.

On the other hand, the calculated incidence of clopidogrel-associated TTP may actually be an underestimate, owing to the inconsistencies and inaccuracies in diagnosing TTP and in ascertaining and reporting drug-related adverse events. Moreover, random error would confound calculation of an accurate estimate, given the rarity of an adverse event like TTP (only 24 cases of TTP have been reported among more than 3 million users of clopidogrel).

**Early
plasmapheresis
is critical
to improve
survival in TTP**



■ BENEFITS OF CLOPIDOGREL OUTWEIGH THE RISKS

Our review leads us to conclude that the available evidence is not sufficient to establish or disprove a cause-and-effect relationship between clopidogrel and TTP.

Despite concerns about clopidogrel's association with TTP, the evidence for the benefit of clopidogrel in patients at risk for ischemic events is convincing. In the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study, investigators estimated that clopidogrel would prevent about 24 major clinical events for every 1,000 patients treated for 1 year.¹ The CURE trial demonstrated that clopidogrel reduces the relative risk of the combined end points of cardiovascular death, nonfatal myocardial infarction, or stroke by 20% in patients presenting with acute coronary syndromes without ST-segment elevation.²

■ WHEN TO SUSPECT TTP WITH CLOPIDOGREL USE

Clopidogrel's clinical usefulness in the face of its uncertain relationship with TTP argues for vigilance among clinicians. Early detection of TTP is critical, since initiation of early plasmapheresis improves survival in drug-induced TTP. Mortality rates from 0% to 24% have been reported for patients with drug-induced TTP who received plasmapheresis, compared with rates from 50% to 67% for patients who did not.^{12,13,26}

The index of suspicion for TTP should be

high when we encounter patients taking clopidogrel who present with unexplained fever, renal failure, neurologic symptoms, bleeding, or purpura.

Notably, however, patients with drug-induced TTP may not present with this classic "pentad" of TTP.²⁶ One report of clopidogrel-associated TTP describes a patient presenting with chest pain similar to his prior angina.¹⁹ In a series of 19 patients with ticlopidine-associated TTP, two thirds presented with neurologic symptoms, and 2 patients had recurrent chest pain.¹³ These diverse clinical features underscore the need to be vigilant for TTP, especially since the presentation of this syndrome might mimic the symptoms of diseases for which clopidogrel is prescribed.

Finally, it is pertinent that most reported cases of clopidogrel-associated TTP have occurred within 2 weeks of clopidogrel initiation.

■ REPORT ADVERSE EVENTS

The only way we will clarify the relationship between clopidogrel and TTP is with more data. That is why clinicians must ensure that all serious adverse drug events in their patients are reported, especially those that are potentially fatal, like TTP. This will aid efforts to establish valid and reliable criteria for identifying causal relationships between drugs and their reported adverse events.

Physicians can report adverse drug events to the FDA's Safety Information and Adverse Event Reporting Program (MedWatch) at www.fda.gov/medwatch.

Most cases of TTP occurred within 2 weeks of starting clopidogrel

■ REFERENCES

1. **CAPRIE Steering Committee.** A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; 348:1329–1339.
2. **The CURE Investigators.** Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST segment elevation. *N Engl J Med* 2001; 345:494–502.
3. **Mehta SR, Yusuf S, Peters RJ, et al.** Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; 358:527–533.
4. **Bertrand ME, Rupprecht HJ, Urban P, et al.** Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the Clopidogrel Aspirin Stent International Cooperative Study (CLAS-SICS). *Circulation* 2000; 102:624–629.
5. **Furlan M, Lammle B.** Assays of von Willebrand factor-cleaving protease: a test for diagnosis of familial and acquired thrombotic thrombocytopenic purpura. *Semin Thromb Hemost* 2002; 28:167–172.
6. **Veyradier A, Obert B, Houllier A, Meyer D, Girma JP.** Specific von Willebrand factor-cleaving protease in thrombotic microangiopathies: a study of 111 cases. *Blood* 2001; 98:1765–1772.
7. **Gordon LI, Kwaan HC.** Cancer- and drug-associated thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. *Semin Hematol* 1997; 34:140–147.
8. **Leon MB, Baim DS, Popma J, et al.** A clinical trial comparing three antithrombotic drug regimens after coronary stenting. *N Engl J Med* 1998; 339:1665–1671.
9. **Schomig A, Neumann FJ, Kastrati A, et al.** A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary artery stents. *N Engl J Med* 1996; 334:1084–1089.
10. **Brookes CIO, Sigwart U.** Taming platelets in coronary stenting: ticlopidine out, clopidogrel in? *Heart* 1999; 82:651–652.
11. **Bennett CL, Davidson CJ, Raich DW, Weinberg PD, Bennett RH, Feldman MD.** Thrombotic thrombocytopenic purpura associated with ticlopidine in the setting of coronary artery stents and stroke prevention. *Arch Intern Med* 1999; 159:2524–2528.
12. **Bennett CL, Weinberg PD, Rozenberg-Ben-Dror K, Yarnold PR, Kwaan HC, Green D.** Thrombotic thrombocytopenic purpura associated with ticlopidine: a review of 60 cases. *Ann Intern Med* 1998; 128:541–544.



13. **Steinhubl SR, Tan WA, Foody JM, Topol EJ.** Incidence and clinical course of thrombotic thrombocytopenic purpura due to ticlopidine following coronary stenting. *JAMA* 1999; 281:806–810.
14. **Bennett CL, Kiss JE, Weinberg PD, et al.** Thrombotic thrombocytopenic purpura after stenting and ticlopidine. *Lancet* 1998; 352:1036–1037.
15. **Bennett CL, Connors JM, Carwile JM, et al.** Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med* 2000; 342:1773–1777.
16. **Carwile JM, Laber DA, Soletero ER, et al.** Thrombotic thrombocytopenic purpura occurring after exposure to clopidogrel [abstract]. *Blood* 1999; 94(Suppl 1):78b.
17. **Connors JM, Gopfert C, Robson S, Churchill WH, Benjamin RJ.** Clopidogrel-associated TTP [abstract]. *Transfusion* 1999; 39(Suppl):56S.
18. **Bennett CL, Connors JM, Moake JL.** Clopidogrel and thrombotic thrombocytopenic purpura. *N Engl J Med* 2000; 343:1193–1194.
19. **Chinnakotla S, Leone JP, Fidler ME, Hammeke MD, Tarantolo S.** Clopidogrel-associated thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in a kidney/pancreas transplant recipient. *Transplantation* 2000; 70:550–552.
20. **Evens AM, Kwaan HC, Kaufman DB, Bennett CL.** TTP/HUS occurring in a simultaneous pancreas/kidney transplant recipient after clopidogrel treatment: evidence of a nonimmunological etiology. *Transplantation* 2002; 74:885–887.
21. **Moy B, Wang JC, Raffel GD, Marcoux JR.** Hemolytic uremic syndrome associated with clopidogrel: a case report. *Arch Intern Med* 2000; 160:1370–1372.
22. **Nara W, Ashley I, Rosner F.** Thrombotic thrombocytopenic purpura associated with clopidogrel administration: case report and brief review. *Am J Med Sci* 2001; 322:170–172.
23. **Oomen PH, Tulleken JE, Zijlstra JG.** Hemolytic uremic syndrome in a patient treated with clopidogrel [letter]. *Ann Intern Med* 2000; 132:1006.
24. **Torok TJ, Holman RC, Chorba TL.** Increasing mortality from thrombotic thrombocytopenic purpura in the United States—analysis of national mortality data, 1968–1991. *Am J Hematol* 1995; 50:84–90.
25. **Plavix package insert.** New York, NY: Bristol-Myers Squibb/Sanofi-Synthelabo Pharmaceuticals Partnership; March 2002.
26. **Majhail NS, Lichtin AE.** Plasmapheresis improves survival in drug-induced thrombotic thrombocytopenic purpura: systematic review of published case reports [abstract]. *Blood* 2001; 98(Suppl 1):60b.
27. **Majhail NS, Lichtin AE.** What is the best way to determine if thrombocytopenia in a patient on multiple medications is drug-induced? *Cleve Clin J Med* 2002; 69:259–262.
28. **Tsai HM, Rice L, Sarode R, Chow TW, Moake JL.** Antibody inhibitors to von Willebrand factor metalloproteinase and increased binding of von Willebrand factor to platelets in ticlopidine-associated thrombotic thrombocytopenic purpura. *Ann Intern Med* 2000; 132:794–799.
29. **Sugio Y, Okamura T, Shimoda K, et al.** Ticlopidine-associated thrombotic thrombocytopenic purpura with an IgG-type inhibitor to von Willebrand factor—cleaving protease activity. *Int J Hematol* 2001; 74:347–351.
30. **Moake JL.** Thrombotic microangiopathies. *N Engl J Med* 2002; 347:589–600.
31. **McCarthy LJ, Porcu P, Fausel CA, Sweeney CJ, Danielson CF.** Thrombotic thrombocytopenic purpura and simvastatin. *Lancet* 1998; 352:1284–1285.

ADDRESS: Alan E. Lichtin, MD, Department of Hematology and Medical Oncology, R35, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail lichtia@ccf.org.