



Title	Clopidogrel and thrombotic thrombocytopenic purpura: Letters to the editor
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Citation	New England Journal of Medicine, 2000, v. 343 n. 16, p. 1192
Issued Date	2000
URL	http://hdl.handle.net/10722/43095
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care professionals, drug withdrawals, and post-marketing drug studies and surveillance programs.

In the light of the post-marketing experience with ticlopidine, the Center for Drug Evaluation and Research was vigilant in its surveillance for thrombotic thrombocytopenic purpura and other adverse events associated with clopidogrel that may represent class effects of antiplatelet drugs. Ongoing surveillance of clopidogrel was uninformative until a cluster of reports from Bennett and others were received. When our review showed that the reported cases of thrombotic thrombocytopenic purpura were temporally associated with the use of clopidogrel and exceeded the expected numbers, the FDA promptly acted to warn practitioners by helping revise the product label so that it included a prominent warning.

We agree that strategies for active surveillance merit further development and funding. Adverse events that are frequently related to drugs, such as thrombotic thrombocytopenic purpura, may be particularly appropriate for active surveillance if there is a limited number of medical centers offering uniquely effective treatment, if patients generally survive long enough to receive treatment at such centers, and if the background rate of occurrence of the event is low. The FDA has not used independent reporting networks because of delays in reporting, difficulties in acquiring accurate drug histories, potential biases in the information obtained, and the large incremental expense associated with such strategies.

We agree with Wood that funding of safety surveillance beyond spontaneous reports is necessary, and we welcome initiatives to increase the quality and quantity of data on drug safety. We believe the FDA must have a central role in the assessment of drug safety. The FDA alone has the statutory and regulatory authority to mandate drug-safety reporting and to control the labeling and marketing of prescription drugs.

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1. Wood AJJ. Thrombotic thrombocytopenic purpura and clopidogrel — a need for new approaches to drug safety. *N Engl J Med* 2000;342:1824-6.

To the Editor: If the incidence of idiopathic thrombotic thrombocytopenic purpura is 3.7 cases per year per million persons, as Bennett et al. state, this amounts to 1 case per 270,000. Bennett et al. described 11 patients with an illness indistinguishable from thrombotic thrombocytopenic purpura, in a population of 3 million or more patients exposed to clopidogrel. Thus, the incidence of the condition among patients who took clopidogrel was virtually the same as 1 per 270,000. Although most of the clopidogrel-associated cases occurred within two weeks after the initiation of treatment, I wonder whether the authors have for the most part reported cases of naturally occurring thrombotic thrombocytopenic purpura in patients who happen also to have been given clopidogrel.

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To the Editor: Bennett and colleagues have aroused unneeded concern among the general public and clinicians. A comprehensive assessment of the safety of all new drugs requires continual post-marketing surveillance, and clopidogrel is not an exception.

The association between the use of clopidogrel and the occurrence of thrombotic thrombocytopenic purpura appears to be weak and coincidental in many of the 11 reported cases. For example, Patient 10 had been taking clopidogrel for almost one year before thrombotic thrombocytopenic purpura developed, and he had three recurrences up to seven months after the discontinuation of clopidogrel. Thrombotic thrombocytopenic purpura developed within seven days of exposure to clopidogrel in 5 of the 11 patients, including 1 of 2 patients in whom von Willebrand factor-cleaving protease activity was undetectable and in whom IgG inhibitors of the protease were present in plasma samples. Thus, in these patients, thrombotic thrombocytopenic purpura was probably caused by an antibody-mediated mechanism, but the period of exposure to clopidogrel was too short for this mechanism.

The authors also point out that most of the patients were receiving other medications concomitantly and that the results of additional laboratory studies were not available to rule out other causes of thrombotic thrombocytopenic purpura, facts that further weaken the association between the use of clopidogrel and the occurrence of thrombotic thrombocytopenic purpura. Patients 1 and 4 are good examples. Patient 1 had a recurrence of thrombotic thrombocytopenic purpura after taking atorvastatin for 14 days. Patient 4 took clopidogrel for only 3 days but was taking other medications such as atorvastatin for another 21 days or more before thrombotic thrombocytopenic purpura developed. In addition, the 9 percent mortality rate in this group of patients was lower than that among patients with idiopathic or ticlopidine-associated thrombotic thrombocytopenic purpura.

The report by Bennett et al. should not affect the routine use of clopidogrel as a safer alternative to ticlopidine in suitable patients. Regular monitoring of complete blood counts may be an appropriate cautionary measure in patients who are starting to receive clopidogrel.

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Editor's note: Dr. Cheung is conducting a prospective, multicenter study of the use of clopidogrel for prevention of secondary stroke in Chinese patients with nonvalvular atrial fibrillation, and clopidogrel is being provided by Sanofi-Synthelabo Hong Kong and Bristol-Myers Squibb (Hong Kong) in the form of free drug samples.

To the Editor: I agree with Dr. Wood that we need better post-marketing surveillance of new drugs. However, another important issue with regard to drug safety should be addressed.

Direct-to-consumer drug advertising has become increasingly prevalent.¹ Patients are bombarded by advertisements in various media and ask their physicians for specific drugs. Physicians feel pressured to prescribe these drugs.² The re-