Noncompliance in Antiplatelet Trials: The AGATE Trial Perspective

To the Editor:

Recent studies have highlighted the importance of patient compliance in clinical trials of antiplatelet therapy. The AGATE trial\(^1\) was designed as a head-to-head comparison of the antiplatelet properties of Aggrenox (a combination of aspirin and dipyridamole) versus aspirin alone in patients with a recent history of ischemic stroke (within the past 2 to 6 months) who had not been taking aspirin for at least 30 days. Of the 434 poststroke patients who were screened for the study, 46 were eligible to participate in the trial. Of these 46 patients, only 6 were excluded: aspirin allergy (n=1), history of gastrointestinal bleeding (n=2), anemia (n=1), and suspected alcohol abuse (n=2); the remainder had discontinued aspirin on their own. Thus, 40 out of 434 screened patients (9.2%) with recent ischemic stroke stopped taking aspirin. In fact, this may represent a substantial underestimation of the number of people not taking aspirin. First, patients may feel uncomfortable admitting noncompliance to their physician. Secondly, AGATE is looking at a selected population who agreed, and was paid, to participate in a clinical trial. Less motivated patients may be even less compliant.

Considering that aspirin is a less potent antiplatelet agent than thienopyridines and platelet GP IIb/IIIa inhibitors, there are further important clinical implications. While aspirin noncompliance was about 10% in the screening for AGATE, there are greater risks for noncompliance in patients treated with ticlopidine and clopidogrel due to the increased incidence of minor bleeding complications, especially due to the fact that ADP-receptor blockers are used on top of a full dose aspirin.\(^2\) Second, noncompliance may represent one of the major problems for antiplatelet trials assessment, especially for the studies that require long-term home use of medications. Moreover, the incidence of noncompliance will be higher in the arm where the most potent antiplatelet agent(s) or their combination will be used, substantially diminishing the power for the superiority of the primary vascular outcome. On the other hand, noncompliance may significantly affect the calculated risk of bleeding events, which is most likely higher than reported. Premature study drug discontinuation, as noted above, is frequently noted in the face of more “annoying” bleeding complications. Total compliance may not even be necessary. Self-directed adjustments in therapy (such as missing or skipping doses) can alter precarious pharmacokinetics of antiplatelet agents. Finally, recent disasters with the oral GP IIb/IIIa blockers,\(^3\) suggesting their association with the high incidence of secondary thrombotic vascular events may well be directly related to noncompliance. In fact, many patients receiving these potent agents complained for frequent bleedings during tooth brushing, or shaving. Obviously, certain patients just stop taking their medications without informing their physicians, representing the highest possible risk for secondary “rebound” thrombotic events.

Future antiplatelet trials should recognize noncompliance as a critical confounding factor, and every attempt should be made to minimize and strictly monitor prescribed antiplatelet regimens.

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