CHARISMA: The Antiplatelet Saga Continues

To the Editor:

We read with interest the Editorial by Norris and Barnett on the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. They conclude that aspirin is still the first choice in the secondary prevention of stroke, that clopidogrel is only marginally more effective than aspirin in secondary prevention of vascular end points, and that there is no convincing evidence that clopidogrel (either alone or combined with aspirin) improves the outcome in patients presenting with TIA or stroke with a cost that is 80 times that of aspirin alone.1

The Canadian Cooperative Study Group already in 1978 had observed that among men the fewest events occurred in the group receiving the combination therapy raising the possibility that a formal study might have compared aspirin with a combination of aspirin and sulfinpyrazone.2

The rationale for combining 2 antiplatelet agents with different mechanisms of action is based on the possibility of obtaining additive effects in preventing vascular recurrences in high-risk patients. However, trials designed to evaluate this hypothesis in patients considered at high risk failed to prove advantages. The CHARISMA trial showed that clopidogrel plus low-dose aspirin was not more effective than aspirin alone in reducing the rate of vascular events in patients with clinically evident cardiovascular disease or multiple risk factors.3 The Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) trial showed that adding aspirin to clopidogrel was associated with a nonsignificant difference in reducing major vascular events in patients with recent ischemic stroke or transient ischemic attack and at least one vascular risk factor.4 We wonder whether the above reported results may definitely halt any prescription of dual antiplatelet treatments.

The high number of asymptomatic patients and patients with a remote vascular event included in the CHARISMA trial might have confounded any possible benefit resulting from the association as the high number of patients with a lacunar stroke, who were less likely to benefit from antiplatelets, included in the MATCH trial.

In fact, since the late seventies we know that the high risk for stroke should be determined on the basis of symptoms, of the anatomy of cerebral arteries, and of associated medical conditions; the risk is higher during the first weeks from the index event, and when the carotid territory is involved.5 In our opinion, should patients really at high risk had been included in the trials, possible benefits of treatment with clopidogrel plus low-dose aspirin might have been shown as in patients with acute coronary syndromes and coronary stenting. So, we agree with Norris and Barnett that it is time to discard compound end points and conduct trials restricted to clearly defined types of ischemic stroke, even though this may require larger numbers of subjects.

Anyway, the conceptualization of patients to be improperly considered at high risk for a cardiovascular atherothrombotic event when under appropriate and continuously adjusted background therapy is nowadays much more intriguing than 30 years ago. In this situation we might risk to conclude that aspirin and clopidogrel roughly equal one another, irrespective of the dose, of the length of treatment, and of the patients’ characteristics. If this should be the case, we should also agree with Euclid’s two of the five Common notions stating that if equals are added to equals, then the wholes are equal and that things which coincide with one another equal one another!

Disclosures

None.

Simona Sacco, MD
Antonio Carolei, MD, FAHA
Department of Neurology
University of L’Aquila
L’Aquila, Italy

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Simona Sacco and Antonio Carolei

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