To the Editor:

Identification of patients who benefit from statin treatment after an acute cerebrovascular event is still a matter of debate. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study was designed to address this question, and it showed that statins exert a marginally beneficial effect on stroke prevention in patients with a history of ischemic stroke, transient ischemic attack, or hemorrhagic stroke. Moreover, an increased occurrence of hemorrhagic stroke in patients on statins treatment was observed, in particular in patients with a history of hemorrhagic stroke. To confirm SPARCL data, Vergouwen and colleagues performed a systematic review focused on the effect of statin treatment on the occurrence of ischemic and hemorrhagic strokes in patients with a history of cerebrovascular disease. They meta-analyzed published results of 4 studies (Cholesterol and Recurrent Events [CARE] study; Long-Term Intervention with Pravastatin in Ischemic Diseases [LIPID]; Heart Protection Study [HPS]; and SPARCL study). As hypothesized, the results of this meta-analysis confirm the results of the SPARCL study, by showing a decreased risk of ischemic stroke in patients with a history of cerebrovascular disease, with an associated increased risk of hemorrhagic stroke. However, there are a number of methodological limitations that hamper the conclusions of this meta-analysis and that should be carefully considered.

First, a quality assessment of the included studies has not been performed. The Cochrane Collaboration Handbook, which the authors used, underlines the importance of the method of randomization. In 3 of the 4 studies—the CARE, LIPID, and HPS studies—patients were not randomized based on a history of cerebrovascular disease and, therefore, only a subgroup of patients were included in the analysis; this suboptimal selection of the participants poses the results of the study at a high risk of bias. Moreover, some baseline characteristics of this subgroup of patients are lacking. Second, data on previous cerebrovascular events, either ischemic or hemorrhagic, and on the outcome event, either ischemic or hemorrhagic, are inadequate for all but for the SPARCL study. Original data from the investigators were not requested. Third, most importantly, the use of the relative risk as a measure of treatment effect may also be an important source of bias. The use of a binary outcome measure applies when the actual time of occurrence of the event is of no special interest, or if no observations are censored. These assumptions are justified in randomized controlled trials with short-term follow-up, if the considered outcome is a short-term outcome like in-hospital mortality. If this is not the case, the authors should use statistical methods for time-to-event data. Therefore, in long-term follow-up studies, statistical methods for time-to-event data should be used in the analysis, i.e., the hazard ratio should be used as the measure of treatment effect. If the hazard ratios, and associated variances, cannot be directly extracted from the trial publications, and no additional data are available from the investigators, these data should be obtained indirectly using the methods described by Parmar and colleagues using either other available summary statistics or from data extracted from published Kaplan–Meier curves.

Overall, we believe that these methodological limitations do not allow to confirm the results of the SPARCL study and do not help physicians to identify patients who could most benefit from statin therapy. Only the randomization of patients with a different cerebrovascular history—ischemic stroke, transient ischemic attack, or hemorrhagic stroke—will definitely clarify the risk-benefit profile of statins in each subgroup.

Disclosures

None.

Alessandro Squizzato, MD
Francesco Dentali, MD
Erica Romualdi, MD
Walter Ageno, MD
Department of Clinical Medicine
University of Insubria
Varese, Italy
