Emerging Therapies: ESPRIT

To the Editor:

It was with great anticipation and interest that I read the ESPRIT results\(^1\) and the accompanying Editorial in Stroke.\(^2\) The study reports superiority of aspirin plus dipyridamole over aspirin alone in patients with minor or transient cerebral ischemic symptoms, for the composite outcome of vascular mortality, cerebrovascular event, myocardial infarction, and major hemorrhage.\(^1\) In reviewing the outcome measure details, several concerns arose regarding the interpretation of this study by the authors and by the editorialist.

In recent cardiovascular trials, a beneficial effect of combination antiplatelet therapy for preventing myocardial ischemia greatly contributed to the benefit seen for cumulative vascular outcomes.\(^3-5\) Similarly, in ESPS-2 an overall benefit for the cumulative outcome was largely driven by the impact of aspirin plus extended-release dipyridamole in preventing cerebral ischemia.\(^5\) Unlike these studies, ESPRIT demonstrated no benefit for any primary ischemic outcome, including cardiac, cerebral, or all ischemic events.\(^1\) Being that antiplatelet therapy is primarily designed to prevent or reduce thrombosis, one must question then whether ESPRIT was truly a “positive” study.

The only end points in ESPRIT that did demonstrate superiority for combination therapy were those that allowed for the incorporation of hemorrhages into the outcome measure vis-à-vis vascular mortality, nonfatal cerebrovascular events, and nonfatal major hemorrhages.\(^1\) Given the discrepancy in major hemorrhages (which included fatal and intracranial episodes) between the combination and aspirin alone treatment groups (2.57% versus 3.85%, hazard ratio = 0.67, 95% CI = 0.44 to 1.03),\(^1\) the positive findings of ESPRIT may have been partially driven by this imbalance in hemorrhage rate, in conjunction with an overall low primary event rate. The finding of fewer hemorrhages with combination therapy is particularly perplexing when considering that similar aspirin doses were used in the 2 study arms (median dose 75 mg),\(^1\) and because it is unlikely that dipyridamole protects against hemorrhage. Thus, this spurious and clinically implausible finding may have distorted study outcome results.

Also concerning is the uniform absence of benefit for aspirin/dipyridamole in the on-treatment analysis for outcomes that showed statistical advantage in the intention-to-treat analysis.\(^1\) In the former analysis, only for major hemorrhages did combination therapy demonstrate superiority to aspirin alone (hazard ratio = 0.58, 95% CI = 0.35 to 0.97).\(^1\) Thus, the absence of benefit for aspirin/dipyridamole in any ischemic outcome measure, the contribution of hemorrhages toward statistically “positive” outcome assessments, and the absence of benefit for combination therapy in any pertinent on-treatment analysis, all prevent confident conclusions regarding the superiority of aspirin/dipyridamole based on ESPRIT.

The results of ESPRIT do not, however, detract from those of ESPS-2 which in contrast was a much larger and fully blinded study that enrolled patients earlier, and used fixed drug dosages and formulations.\(^6\) The results also do not change the fact that other combination antiplatelet treatments have consistently failed to show benefit in patients with cerebrovascular disease, and have even demonstrated detrimental increases in major hemorrhages.\(^7,8\) Therefore, at the moment, aspirin plus extended-release dipyridamole stands alone as the only antiplatelet regimen proven superior to aspirin alone.\(^9,10\) but based on the ESPS-2 results only. The methodological limitations and controversial findings from ESPRIT have added little.

Disclosures

M.M. has participated in a speaker’s opinion panel sponsored by Sanofi-BMS Pharmaceuticals and on a literary consultant’s panel sponsored by Boehringer-Ingelheim Pharmaceuticals, and has given lectures sponsored by Boehringer-Ingelheim Pharmaceuticals.

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