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The Aspirin Regimens in Essential Thrombocythemia (ARES) phase II randomized trial design: Implementation of the serum thromboxane B 2 assay as an evaluation tool of different aspirin dosing regimens in the clinical setting

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Abstract

Once-daily (od), low-dose aspirin (75-100 mg) is recommended to reduce the thrombotic risk of patients with essential thrombocytemia (ET). This practice is based on data extrapolated from other high-risk patients and an aspirin trial in polycythemia vera, with the assumption of similar aspirin pharmacodynamics in the two settings. However, the pharmacodynamics of low-dose aspirin is impaired in ET, reflecting accelerated renewal of platelet cyclooxygenase (COX)-1. ARES is a parallel-arm, placebo-controlled, randomized, dose-finding, phase II trial enrolling 300 ET patients to address two main questions. First, whether twice or three times 100 mg aspirin daily dosing is superior to the standard od regimen in inhibiting platelet thromboxane (TX)A_2 production, without inhibiting vascular prostacyclin biosynthesis. Second, whether long-term persistence of superior biochemical efficacy can be safely maintained with multiple vs. single dosing aspirin regimen. Considering that the primary study end point is serum TXB_2, a surrogate biomarker of clinical efficacy, a preliminary exercise of reproducibility and validation of this biomarker across all the 11 participating centers was implemented. The results of this preliminary phase demonstrate the importance of controlling reproducibility of biomarkers in multicenter trials and the feasibility of using serum TXB_2 as a reliable end point for dose-finding studies of novel aspirin regimens.