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Letters to the Editor

Dabigatran Treatment in Embolic Stroke of Undetermined Source and Elevated Biomarkers: The RE-SPECT ESUS Trial

To the Editor:

Embolic stroke of undetermined source (ESUS) is a stroke subtype with no readily attributable cause. A significant percentage of ESUS patients develop atrial fibrillation—up to 40%[1]— making anticoagulation a possible treatment option. However, 2 trials[2,3] showed no benefit with anticoagulation in ESUS. The purpose of this study was to determine if a subgroup of ESUS patients with risk factors for both atrial fibrillation and recurrent stroke would benefit from anticoagulation. We analyzed post hoc patients with elevated levels of cardiac biomarkers, namely, high-sensitivity troponin T (Hs-TnT) and n-terminal pro brain natriuretic peptide (nt-proBNP), which have been shown to be associated with stroke as well as development of atrial fibrillation.[4]

Anonymized data were used from the **R**andomized, Double-Blind, **E**valuation in Secondary **S**troke **P**revention Comparing the **E**ffica**c**y and Safety of the Oral **T**hrombin Inhibitor Dabigatran Etexilate vs Acetylsalicylic Acid in Patients With **E**mbolic **S**troke of **U**ndetermined **S**ource (RE-SPECT ESUS) trial comparing dabigatran with aspirin. Informed, written consent was obtained from all participants. The ABC (for age, biomarkers, clinical history) score[4] was calculated for individual subjects. This established clinical risk score is used to identify patients with atrial fibrillation who benefit from anticoagulation. The score aggregates levels of the 2 biomarkers Hs-TnT and nt-proBNP, as well as age, into a single index. Treatment effects were evaluated using Cox proportional hazards regression. Adjusted Kaplan–Meier analysis adjusting for the competing risk of death was performed. All analyses were done using SAS 9.4 (SAS Institute, Cary, NC). The study was approved by the Beaumont Health institutional review board.

A total of 1134 participants from the RE-SPECT ESUS trial population underwent biomarker evaluation. A total of 1051 underwent randomization with 524 recieving aspirin and 527 recieving dabigatran. Median, baseline Hs-TnT and nt-proBNP levels were 7.23 ng/L (interquartile range [IQR] 4.98, 10.90) and 565 pg/mL (IQR 246, 1130), respectively. Average age was 64 years; 36% were female; 20.6% had diabetes; 4.9% had heart failure; and 4.9% had chronic kidney disease. The rates of recurrent stroke, systemic embolism, and transient ischemic attack were 10.8% and 9.9% in the dabigatran and aspirin arms, respectively (hazard ratio 1.13 [IQR 0.77, 1.62], $P > 0.05$). No interaction was present between treatment effect with dabigatran and biomarker levels or ABC score in unadjusted and mortality-adjusted analysis ($P > 0.05$; Fig. 1). ABC score was significantly associated with event rates (hazard ratio 1.39 [IQR 1.14, 1.70], $P = 0.001$).

Cardiac biomarker levels, combined with age into the ABC risk score, were significantly associated with cerebral ischemic event rate in this population of ESUS patients. However, no interaction occurred between score and treatment effect with dabigatran. Despite the association between risk score and events, power was limited to detect an interaction with treatment effect, owing to small sample size, as only a subgroup, accounting for 21% of the entire RE-SPECT ESUS trial population, underwent biomarker measurement. Given the significant association between levels of these cardiac biomarkers and outcomes in ESUS, future trials in this population should test baseline biomarker levels routinely and continue to explore their interaction with treatment effect.

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Ethics Statement

Informed, written consent was obtained from all participants. The study was approved by the Beaumont Health institutional review board.

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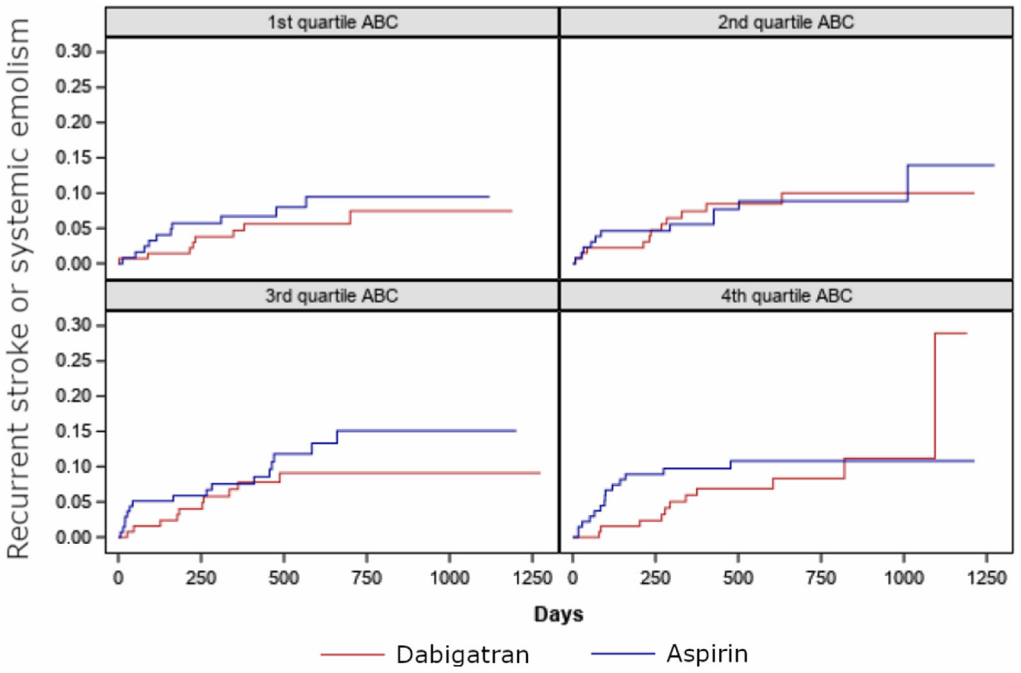

Figure 1. Survival free of stroke or systemic embolism according to quartiles of ABC (for age, biomarkers, clinical history) score. Hazard ratios for dabigatran treatment effect were similar across quartiles. No interaction was present between quartile and treatment effect ($P = 0.962$).

References

1. Kitsiou A, Rogalewski A, Kalyani M, et al. Atrial fibrillation in patients with embolic stroke of undetermined source during 3 years of prolonged monitoring with an implantable loop recorder. Thromb Haemost 2021;121:826-33.

2. Diener HC, Sacco RL, Easton JD, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. N Engl J Med 2019;380:1906-17.

3. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. N Engl J Med 2018;378:2191-201.

4. Hijazi Z, Lindbäck J, Alexander JH, et al. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. Eur Heart J 2016;37:1582-90.