Is Aspirin an Effective Thromboprophylaxis in High-Risk Patients? A Comprehensive Subpopulation Analysis of the PREVENT CLOT Study

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INTRODUCTION: A recent large clinical trial concluded that thromboprophylaxis with aspirin was similar in efficacy and safety to low-molecular-heparin in orthopaedic trauma patients. However, many clinicians remain skeptical that aspirin is a safe option in certain high-risk subpopulations. Our hypothesis was that in certain high-risk subpopulations, clinical outcomes would be superior with low-molecular-weight heparin compared to aspirin.

METHODS:

We performed a secondary analysis of PREVENT CLOT, a multicenter, randomized clinical trial in which fracture patients were assigned to 81 mg of aspirin or 30 mg of low-molecular-weight heparin, twice daily. From the 12,211-patient sample, we derived 11 subpopulations according to evidence-based thromboembolic risk factors for either higher risk of VTE events or plausible differential effect of the medicines than in the overall population. The high-risk subpopulations included: 1) head injury, 2) abdominal injury, 3) spine injury, 4) thoracic injury, 5) ICU admission, 6) obesity, 7) history of VTE, 8) isolated upper extremity fracture, 9) isolated lower extremity fracture, 10) isolated pelvic fracture, 11) geriatric femur fracture. The primary outcome was 90-day all-cause mortality. Secondary outcomes included non-fatal PE, proximal and distal DVT, and bleeding events. We assessed all outcomes with treatment-specific Kaplan–Meier estimators. Due to the risk of false positive findings with multiple comparisons, our threshold for statistical significance was a Bonferroni-corrected alpha of 0.0001.

RESULTS: Among the 11 subpopulations, the 3 largest were isolated lower extremity fractures (n=6289), obesity (n=4234), and ICU admission (n=1596). None of the 55 statistical comparisons reached our corrected threshold for significance. Two of the 55 statistical comparisons were less than the conventional $p<0.05$ threshold. In both cases, low-molecular-weight heparin was favored over aspirin in protecting against distal deep vein thrombosis for patients with head injuries (difference, 4.4%; 95% CI, 0.8% to 8.1; p=0.03) and admitted to the ICU (difference, 1.7%; 95% CI, 0.2% to 3.3; p=0.03).

DISCUSSION AND CONCLUSION:

Across 11 clinically important subpopulations, we found no evidence of differential treatment effects of low-molecular-weight heparin versus aspirin on 90-day mortality, pulmonary embolism, proximal deep vein thrombosis, or bleeding rates. Low-molecular-weight heparin may offer better protection against clinically less important distal deep vein thrombosis in patients with head injuries or admitted to the ICU consistent with the original trial findings. However, these differences were not significant at the more conservative threshold required to account for multiple comparisons and are also of questionable clinical importance. These findings increase the likelihood that the main findings of noninferiority of aspirin apply to high-risk subpopulations as well.