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

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Purpose: A recent large clinical trial concluded that thromboprophylaxis with aspirin was similar in efficacy to low-molecular-weight heparin (LMWH) in orthopaedic trauma patients. However, clinicians remain skeptical that the benefits of aspirin persist in certain high-risk subpopulations. In this study, we replicated the primary analysis within 11 clinically important subpopulations.

Methods: We performed a secondary analysis of PREVENT CLOT, a multicenter randomized controlled trial in which fracture patients were assigned to 81 mg of aspirin or 30 mg of LMWH, twice daily. From the 12,211-patient sample, we derived 11 subpopulations according to evidence-based thromboembolic risk factors, including (1) head injury, (2) abdominal injury, (3) spine injury, (4) thoracic injury, (5) ICU admission, (6) obesity, (7) history of venous thromboembolism, (8) isolated upper extremity fracture, (9) isolated lower extremity fracture, (10) isolated pelvic fracture, and (11) geriatric femur fracture. The primary outcome was 90-day all-cause mortality. Secondary outcomes included pulmonary embolism (PE), proximal and distal deep vein thrombosis (DVT), and bleeding events. Outcomes were assessed with treatment-specific Kaplan-Meier estimators. Our threshold for statistical significance was a Bonferroni-corrected alpha of 0.0001.

Results: Among 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 threshold for significance. Two of the 55 statistical comparisons were less than the conventional $P<0.05$ threshold. In both cases, LMWH was favored over aspirin in protecting against distal deep vein thrombosis for patients with head injuries (difference, 4.4%; 95% confidence interval [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).

Conclusion: Across 11 clinically important subpopulations, we found no evidence of differential treatment effects of aspirin versus LMWH on 90-day mortality, PE, proximal DVT, or bleeding rates. LMWH may offer better protection against clinically less important distal DVT in patients with head injuries or admitted to the ICU. However, these differences were not significant at the more conservative threshold required to account for multiple comparisons. These findings increase the likelihood that the main findings of noninferiority of aspirin apply to high-risk subpopulations as well.