Assessing the Impact of Site VTE Practice Variation on a Multicenter RCT Comparing Aspirin and LMWH for Mortality Prevention: A Secondary Analysis of PREVENT CLOT Study

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Purpose: PREVENT CLOT, a large, pragmatic, multicenter randomized controlled trial (RCT), evaluated non-inferiority of aspirin versus low molecular weight heparin (LMWH) for preventing all-cause mortality. A concern in pragmatic trials is whether site practice variation biases result. We assessed whether site variations observed in this trial impacted the trial's primary conclusions using three advanced statistical approaches.

Methods: We re-analyzed all-cause mortality in 12,211 patients randomized to aspirin (n = 6079) or LMWH (n = 6096). To test the robustness of results against site-level venous thromboembolism (VTE) differences, we applied three statistical approaches: a hierarchical mixed-effects model with site-specific random intercepts, inverse probability weighting (IPW) to adjust for equipoise differences, and instrumental variable (IV) analysis using site aspirin preference as an instrument for treatment assignment.

Results: Site VTE practices with substantial variance included patients being discharged without prophylaxis (0%–22%), deep vein thrombosis (DVT) imaging rates per 100 patient-days (0.00–6.40), and pulmonary embolism (PE) imaging rates (0.00–1.47) per 100 patient-days. The high range relative to the mean (range >4 × mean) and a moderately high coefficient of variation (CV = 0.88) confirm significant variability in site practices. The hierarchical model found no significant difference in mortality between aspirin and LMWH (OR: 0.96, p = 0.83) and minimal variation across sites. IPW-adjusted regression also showed no effect (OR: 0.77, p = 0.24), suggesting site practice differences did not influence outcomes. The IV approach was invalid (p = 0.46) as site aspirin preference did not predict treatment. All methods confirmed the trial's original finding of non-inferiority.

Conclusion: Site-level variation in VTE prophylaxis practices did not affect trial results, which were robust after testing with three advanced statistical approaches. These findings reinforce the validity of the trial's conclusions and suggest site level practice variation does not have to be a major impediment to the conduct of large, pragmatic, comparative effectiveness trials.