Validation of warfarin pharmacogenetic algorithms in real clinical practice


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Background: Warfarin is the most widely prescribed oral anticoagulant for the treatment and prevention of thromboembolic diseases. However, warfarin has a narrow therapeutic range and a certain dose has a large interindividual variation. The goal of this study was to evaluate the performance of three warfarin pharmacogenetic algorithms in a real clinical setting, namely the algorithms of Gage et al., Michaud et al., and the IWPC algorithm.

Methods: Data was obtained retrospectively for 605 patients who had initiated warfarin therapy at the Montreal Heart Institute. Stable therapeutic warfarin dose was obtained from hospital charts and CYP2C9 and VKORC1 polymorphisms were genotyped. Pearson's correlation coefficient and mean absolute error (MAE) were used to validate and compare the algorithms. Clinical accuracy of the predictions was assessed by computing the proportion of patients in which the predicted dose was underestimated, ideally estimated, or overestimated.

Results: The Gage algorithm explained most of the variation (adjusted R2=44% and MAE=1.41) and predicted 43.8% of patients within plus or minus 20% of their observed stable warfarin dose. Michaud's and the IWPC algorithms respectively had a MAE of 1.37 and 1.48 mg/day and a coefficient of determination of 45% and 43%.

Conclusions: Gage's algorithm was the most accurate for predicting stable warfarin dose in our study population. Despite the accurateness of these pharmacogenetic warfarin dosing algorithms, the routine use of genotyping for patients newly started on warfarin should not be promoted before conducting prospective clinical trials.

Keywords: Warfarin, pharmacogenetics, algorithms

When can self-controlled crossover studies of only cases be used for rapid pharmacosurveillance?

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Objectives: Mini-Sentinel aims to facilitate development of a national surveillance system to detect adverse effects of medical products by developing and piloting methods for rapid analysis of de-identified data from the Mini-Sentinel distributed database covering over 60 million Americans. Mini-Sentinel's Working Group on Case-Based Approaches addressed the title's question.

Methods: We searched PubMed for 'case-crossover' (CCO), 'self-controlled case-series' (SCCS), 'case-time-control' (CTC) or 'sequence symmetry analysis' (SSA), and reviewed papers related to medical product safety. We compared unidirectional and bidirectional designs with real and simulated data.

Results: Both CCO and SCCS have been used to study drug and vaccine safety. The original CCO was unidirectional (right-censored at outcome to avoid reverse-causation bias) and assumed prior exposure trends were negligible. The CTC is a CCO that adjusts for prior exposure trends measured in non-cases. The original SCCS, like bidirectional CCOs and SSAs, assumed reverse-causation and immortal-time bias were negligible or controllable by restriction or modeling. The designs converge when using identical person-time. Estimates from bidirectional SCCSs tended to be slightly higher than from unidirectional SCCSs, suggesting outcomes sometimes reduce subsequent exposure propensity. Simulation shows, at medication inception, when exposure trend is only upward, unidirectional CCO estimates are biased and become less biased as populations approach steady states of starting and stopping.

Conclusions: Strengths and limitations of case-based designs often complement those of cohort designs. Needing no data on time-invariant characteristics (unless for effect modification), they support privacy and efficiency. Mini-Sentinel should capture