Title

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Pharmacovigilance using Clinical Text

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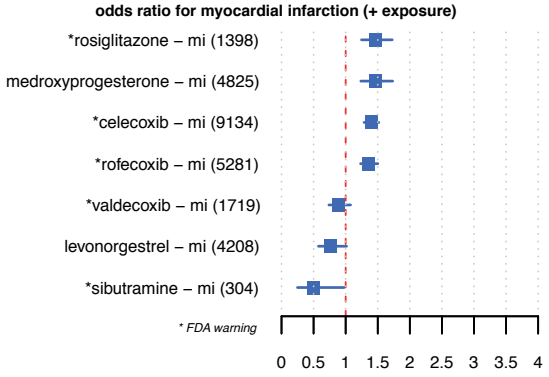
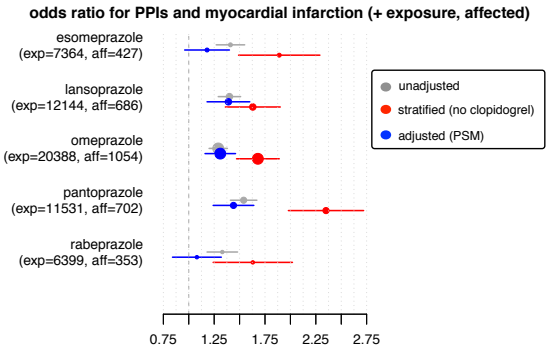
Abstract. *The current state of the art in post-marketing drug surveillance utilizes voluntarily submitted reports of suspected adverse drug reactions. We present data mining methods that transform unstructured patient notes taken by doctors, nurses and other clinicians into a de-identified, temporally ordered, patient-feature matrix using standardized medical terminologies. We demonstrate how to use the resulting high-throughput data to monitor for adverse drug events based on the clinical notes in the EHR.*

Introduction. We show that it is possible to investigate adverse drug event associations with high accuracy (46% sensitivity, 91% specificity) by analyzing textual notes in a clinical data warehouse using automated methods. We examine suspected associations for confounding via stratification and propensity score matching. We find that such an analysis of textual clinical notes could detect adverse drug events 2 years before the official alert. Using this approach we find that proton pump inhibitors (PPIs) as a class appear strongly associated with major adverse cardiovascular events, increasing the risk of myocardial infarction by 20-50% depending upon the individual PPI. The association of PPIs with such events was hypothesized based on experimental results that show that PPIs, as a class, elevate plasma levels of asymmetric dimethylarginine, a disease marker and an independent predictor of major adverse cardiovascular events.

Methods. We use an ontology-based text processing workflow to tag a corpus of 9,078,736 time-stamped textual notes from the Stanford University Medical Center with drug and disease concepts and create a concept timeline for each patient. These timelines form a patient–feature matrix. We construct 2x2 contingency tables utilizing temporal information in the matrix, e.g., to account for prior history. We calculate odds ratios, and apply propensity score adjustment on age, gender, race, length of observation, and co-morbidity and co-prescription counts.





Results. We can reproduce the rofecoxib (Vioxx) signal and other well-known drug recalls or alerts, finding two-thirds of them before the official alert. Our method performs well, with an area under the receiver operator characteristic curve of 79% on a reference standard, with a sensitivity of 46% at a specificity of 91%. Given pre-clinical evidence suggesting mechanistic effects that may cause PPIs to independently elevate the risk of MI in the general population, we also see evidence of that risk (independent of clopidogrel, a controversial explanation). The figure shows a few of the well-known positive cases as well as odds ratios for each of the common PPIs. The strata consisting of patients not taking clopidrogrel suggest that its attenuation is moot.

Conclusion. We conclude that analyzing clinical notes presents a new approach for investigating questions about drug safety using observational data. Research on the risks of PPIs is ongoing, including studies in humans.

References

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