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Result of the ALCAPONE project: Identification of the best design for the assessment of drugs associated with upper gastrointestinal bleeding in the French National Healthcare System database (SNDS)

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Abstract

Validation of methods is needed to ensure the accurate detection of UGIB-associated drugs in the French National Healthcare System database (SNDS). 156 057 UGIB cases were extracted from SNDS (2009-2014). Positive and negative drug controls were used to compare 196 self-controlled case series (SCCS), case-control (CC), and case-population (CP) design variants. Each variant was evaluated in a 1/10th sample using area under the receiver operating curve (AUC) and mean square error (MSE). Parameters that had major impacts on results were identified through logistic regression. Optimal variants were replicated in the unsampled population and estimates from negative controls were used to model the distribution of the residual bias under the null. AUCs for SCCS, CC and CP, respectively, ranged from 0.64 to 0.80, 0.44 to 0.61 and 0.50 to 0.67. MSEs ranged from 0.07 to 0.39, 0.83 to 1.33 and 1.96 to 4.6, respectively. Univariate regressions showed that high AUCs were achieved using SCCS with multiple drug adjustment and a fixed 30-day risk window. The top-performing SCCS variant in the unsampled population yielded an AUC=0.84, with 10/36 negative controls presenting significant estimates. The calibration process highlighted that low systematic error was generated by the optimal SCCS, but that protopathic bias and confounding by indication remained at least partly unaddressed.

Introduction

Upper gastrointestinal bleeding (UGIB) is a serious medical emergency, related to bleeding from the esophagus, stomach, or duodenum, leading to death in about 10% of cases. France has a large nationwide longitudinal healthcare database – the Système National des données de Santé (SNDS) – which currently covers the overall French population, from birth or immigration to death or emigration, resulting in one of the largest nationwide claims and hospital databases in the world.[1] The application of an empirically-validated and calibrated case-based method to the SNDS would allow efficient generation of safety alerts regarding drugs associated with UGIB, offering an alternative to traditional pharmacovigilance spontaneous reporting.

Methods

Cases of UGIB were extracted from SNDS (2009-2014). Positive and negative drug controls were used to compare 96 self-controlled case series (SCCS),[2] 20 case-control (CC),[3] and 80 case-population (CP) design variants. In a first step, all design variants were run in a 1/10th sample of the case population to identify the best-performing approach based on area under the receiver operating characteristics curve (AUC), mean square error (MSE) and coverage probability. Only drug controls that had sufficient power to detect a relative risk ≤1.30 in this sampled population were included. MSE and coverage probability were estimated for negative controls only. Once the best performing case-based approach was identified, an univariate logistic regression analysis screened for parameters that best discriminated the performance of the different design variants. The

dependent variable was the probability that a variant had an AUC higher than the 70th percentile of the AUC distributions of the variants. The independent covariates included the parameters that were varied in SCCS analyses (*e.g.* multiple drug adjustment: yes/no). In the second step, the best-performing variant was applied to the full, unsampled case population. Considering the estimates from the negative controls, for which no association was expected, we observed how often $p < 0.05$ while the null hypothesis was true, and we fitted this distribution to the effect estimates, modeling the distribution of the residual bias under the null.[4] Estimated parameters of this "empirical null distribution" were then used to compute "calibrated" *p*-values, taking into account random and systematic error inherent to the application of a design variant to the SNDS.

Results

Over 6 years of data, 156 057 UGIB episodes were identified and included. Among the 64 drugs of interest screened in the unsampled population, 58 presented a minimum detectable relative risk ≤1.30 and were thus deemed detectable. SCCS globally showed better discrimination (**Figure 1**) and MSE than CC and CP. Univariate logistic regression analyses showed that the strongest determinant of a high AUC was multiple drug adjustment, the use of a fixed 30-day risk window, and the restriction to the first occurrence of UGIB. In the replication in the unsampled case population, the SCCS with the optimal parameters showed a better AUC (0.84 *vs.* 0.80) with slightly increased MSE and reduced coverage (respectively 0.14 *vs.* 0.07 and 75% *vs.* 86%) than in the 1/10th sampled population. For nine negative controls (i.e., miconazole, sucralfate, lactulose, sitagliptin, erythropoietin, nitrofurantoin, loratadine, methocarbamol and zopiclone) the lower bounds of their confidence intervals were above 1 whereas scopolamine had an upper bound below 1. Almost all the positive controls were significantly associated with UGIB except clindamycin, sulindac, etodolac and mefenamic acid. An empirical null distribution ($\hat{\mu}$ =0.12; $\hat{\sigma}$ = 0.17) was derived based on the negative control estimates. Calibrating *p*-values, only two negative controls were still significant (sucralfate and scopolamine), and 9 positive controls moved from significant to non-significant (potassium chloride, prednisolone, indomethacin, ibuprofen, fenoprofen, nabumetone, fluoxetine, citalopram, sertraline).

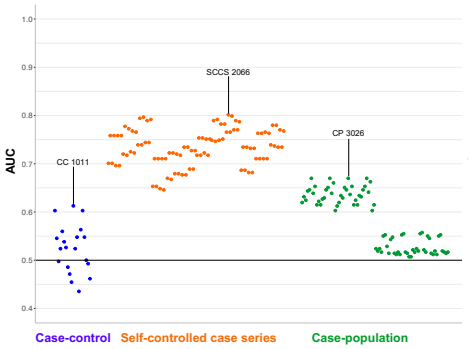

Figure 1. AUCs for SCCS, CC and CP in the 1/10th sampled population.

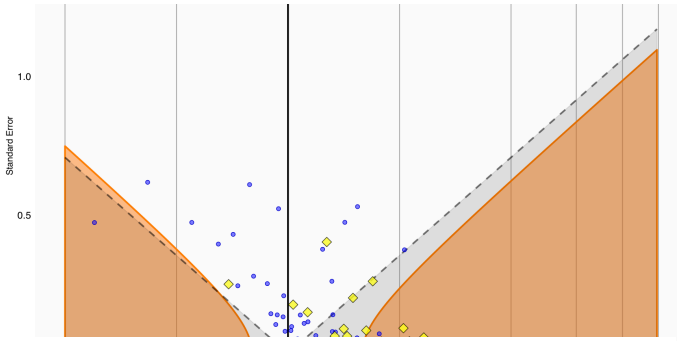

Figure 1. Estimates from optimum SCCS variant. Estimates below the dashed line have p<0.05 using traditional p-value calculation. Estimates in the orange area have p<0.05 using calibrated p-value calculation. Blue dots indicate negative controls and yellow diamonds positive ones.

Conclusion

The SCCS had the best performance for the identification of drug-related UGIB in SNDS. Adjusting for multiple drugs and considering the initial period of treatment seemed to be important features of this design. However, not all possible implementations of SCCS have been assessed here and specific design adjustment may be required in the context of particular studies. The calibration process showed that low systematic error was generated by SCCS in the SNDS. However, the analysis of negative controls indicated that some biases such as protopathic bias and confounding by indication remained unaddressed and indicate a need for a clinical expert input to ensure a correct interpretation of the results.

References

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