54. Severe Malabsorption Associated with Olmesartan: A French Nation-Wide Cohort Study

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Background: Several cases of severe sprue-like enteropathy have been reported in patients treated with Olmesartan medoxomil, an angiotensin II receptor blocker (ARB) approved for the treatment of hypertension.

Objectives: To assess in a large nation-wide patient cohort the risk of severe intestinal malabsorption associated with olmesartan, compared with ARBs other than olmesartan or ACEIs.

Methods: We identified adult patients who started ARB or ACEI treatment between 2007 and 2012 from the claim database of the main insurance scheme of the French national health insurance (SNIIRAM), which covers approximately 53.1 million inhabitants of France, and the national hospital discharge database (PMSI). Patients with a history (assessed over 12 months prior to treatment initiation) of hospitalization for intestinal malabsorption or celiac disease serology testing or gluten-free dietary product prescription were excluded. Severe intestinal malabsorption was defined by hospitalization with a discharge diagnosis of intestinal malabsorption (ICD-10 code K90). Rate ratios were estimated with a Poisson regression model adjusted for age and sex.

Results: 4,546,680 patients summing up to 9,010,303 person-years were included. 218 events were observed. Compared with ACEI, the adjusted rate ratio of severe intestinal malabsorption associated with olmesartan was 2.27 (95% confidence interval 1.59-3.23, $p < 0.0001$). This adjusted rate ratio varied with treatment duration: less than 1 year RR = 0.68 (0.35-1.33, $p = 0.3$), between 1 and 2 years RR = 3.35 (1.68-6.68, $p < 0.001$), 2 years or more RR = 10.27 (4.86-21.71, $p < 0.0001$). Compared with other ARBs, the rate ratio of severe intestinal malabsorption associated with olmesartan intake was 3.04 (95% CI 2.13-4.34, $p < 0.0001$). The risk of severe intestinal malabsorption was not significantly different between patients who were prescribed ARBs other than olmesartan and ACEIs.

Conclusions: Olmesartan was associated with an increased risk of severe intestinal malabsorption. The increased risk appears after one year of treatment and reaches 10.3 after 2 years of olmesartan. ARBs other than olmesartan were not associated with an increased risk of severe intestinal malabsorption.

55. Instrumental Variable Analysis Using Multiple Databases: An Example of Antidepressant Use and Risk of Hip/Femur Fracture

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Background: Instrumental variable (IV) analysis can reduce bias due to unmeasured confounding, yet it has not been widely used in pharmacoepidemiologic studies.

Objectives: To assess the performance of several IVs across multiple databases in a study of antidepressant use and risk of hip/femur fracture (HF).

Methods: Information on adult patients with at least one prescription of a selective serotonin reuptake inhibitor (SSRI) or tricyclic antidepressant (TCA) during 2001-2009 was extracted from three European databases: THIN (UK, n = 570139), BIFAP (Spain, n = 250865), and Mondriaan (Netherlands, n = 22474). Conventional Cox model and two-stage IV analysis were applied to estimate the risk of HF associated to initiation of SSRI vs. TCA. IVs were created using the proportion of SSRI prescriptions per practice (PSP) or using the number, one (PPP1), five (PPP5) or ten (PPP10), of previous prescriptions by a physician. Quantitative methods (e.g. correlation (r), standardized difference (SDif)) were used to assess the validity of IVs. 95% confidence intervals (CI) in IV analysis were estimated using bootstrapping.

Results: Conventional analysis showed that SSRI use was associated with an increased risk of HF in BIFAP and THIN, hazard ratio (HR) 1.35 [95%CI 1.18-1.56] and 1.35 [1.26-1.44], respectively and similarly in Mondriaan (though not significant), HR 1.36 [0.86-2.15]. The IVs PSP (THIN and BIFAP) and PPP10 (THIN and

Mondriaan) were strongly associated ($r > 0.15$) with SSRI prescribing and independent of confounders (SDif < 0.10). IV analysis based on these variables showed that SSRI use was not associated with an increased risk of HF: HR 1.09 [0.75-1.60] and 2.75 [0.97-7.10] for the PSP in THIN and BIFAP, respectively; and 1.16 [0.70-1.92] and 1.67 [0.15-27.7] for the PPP10 in THIN and Mondriaan, respectively.

Conclusions: Conventional analysis showed an increased risk of HF for SSRI users, whereas IV analysis showed that SSRI did not indicate a clear association with an increased risk of HF compared to TCA. Performance of IVs varied across databases and estimates from IV analysis are imprecise, indicating that this null effect should be interpreted cautiously.

56. Using Simulation to Explore the Properties of IV Bias Amplification and Unmeasured Confounding

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Background: Recent research has explored the phenomenon of bias amplification from adjustment for instrumental variables (IV) and near instrumental variables (NIV). Analysts may encounter situations where there is a potential trade-off between avoiding error from adjustment for IV and NIV, and error from failing to adjust for a confounder.

Objectives: We used simulation to explore these two sources of error with a variety of adjustment sets.

Methods: We assumed treatment and outcome were conditionally Bernoulli distributed given covariates, with the logit of the mean given by a linear function of the simulated covariates (and exposure for the outcome). We created one true IV with a uniform distribution and three NIV, one specified using a normal distribution and two with a Bernoulli distribution. NIV were defined as having an association with the exposure and an extremely weak association with the outcome. Ten confounders were simulated using normal and Bernoulli distributions, with varying parameter values. We estimated bias, variance, and mean squared error (MSE) using eight adjustment sets. We simulated 1000 cohorts each with a sample size of 1000.

Results: Our true value for the coefficient corresponding to exposure was -0.2. The model adjusting only for confounders (leaving out the IV and NIVs) performed the best (MSE = 0.0301). MSE increased as more NIV were added to the adjustment set. The model that failed to adjust for a strong confounder ($\beta = 1.2$) performed demonstrably worse (MSE = 0.0656) than did the model including three NIV but properly adjusting for the strong confounder (MSE = 0.0346). However, the model failing to adjust for a moderate confounder ($\beta = 0.25$) performed better (MSE = 0.0307) than models that included at least one NIV.

Conclusions: Using a simulation strategy incorporating a broad range of confounders, IV, and NIV, we found that the avoidance of strong confounding was of greater importance with regards to MSE than bias amplification from adjustment. However, adjustment for the IV and NIV resulted in higher MSE than failure to adjust for a moderate confounder. Both residual confounding and bias amplification were sources of substantial systematic error.

57. Instruments and Doubly Robust Estimation: Bias and Efficiency Compared to Conventional Estimators

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Background: In conventional estimation, including instruments increases variance and may induce bias. Omitting a near instrument can also lead to bias. The doubly robust (DR) estimator is theoretically unbiased as long as one of the component models is correctly specified. Would the doubly robust property protect against bias if the instrument is only included in one of the component models?

Objectives: To evaluate the DR estimator and conventional estimators in scenarios involving instruments.

Methods: We simulated a dichotomous instrument (Z), dichotomous treatment (X), and continuous outcome (Y); some scenarios included effect measure modification (EMM) by Z or residual confounding. Z was a pure or near (weak effect on Y) instrument. We simulated 5000 iterations, each of n = 5000. We estimated the average treatment effect using DR, inverse probability of treatment weighted (IPTW), g-computation, and maximum likelihood estimators. All models were fit with and without Z. We calculated mean bias, variance, and mean squared error (MSE) across all iterations.

Results: In the base scenario (no residual confounding, no effect of Z on Y, no EMM), all estimators were unbiased (<1%); including Z in any component model