**Background**

Trial results may not be generalizable to target populations treated in clinical trials with different distributions of baseline characteristics that modify the treatment effect.

**Objective**

To predict treatment effects in Medicare populations, using outcome models developed with trial data.

**Methods**

- Data sources:
  - Trial population: the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial.
  - Target population: Medicare fee-for-service claims database.
- Study population:
  - Trial population: participants with atrial fibrillation and at least one of the following characteristics: aged ≥75 years, with previous stroke or transient ischemic attack, an LVEF <40%, NYHA class II or higher heart failure symptoms; or aged 64-77 years with diabetes, hypertension, or coronary artery disease.
  - Target population: RE-LY-trial eligible Medicare beneficiaries treated with dabigatran or warfarin.
- Exposures:
  - Trial population: 1:1 random assignment of dabigatran 150mg or warfarin.
  - Target population: counterfactual assignment of dabigatran 150mg or warfarin.
- Predictors: Age, sex, race, CHADS2 score, 10 comorbidities, and 24 concomitant medications based on subject knowledge and availability in both the trial and Medicare data.

**Results**

- Baseline characteristics (Table 1): The trial and early target populations had similar mean (SD) CHADS2 scores (2.15 [1.13] vs. 2.15 [0.91]) but different mean ages (71 vs. 71 years). The early and extended time target populations had a similar distribution of baseline characteristics.
- Predicted results in the trial vs. early and extended-time target populations (Table 2): compared with RE-LY, the early target population had a similar predicted benefit of dabigatran vs. warfarin for stroke/SE (trial RR=0.63; 95% CI=0.50 to 0.76, target RR=0.73; 0.63 to 0.82) and risks for major bleeding and all-cause death. The extended-time target population showed similar results.
- Predicted vs. observed results in the extended target population (Table 3): compared with the predicted results, the observed results from the RWE study in the same population showed a similar benefit of dabigatran vs. warfarin for stroke/SE (SDa=0.67), and greater benefits for major bleeding (SDa=3.60) and all-cause death (SDa=2.21).

**Statistical Analysis**

- Missing data: No missing values for candidate outcomes considered for outcome models except for one trial participant with multiple variables missing.
- Model derivation and validation:
  - Fitted Cox proportional hazards models separately within each treatment arm for each outcome.
  - Selected variables through the relaxed LASSO, including the CHADS2 score and age, regardless of LASSO selection.
  - Measured model performance via Harrell's C-index (discrimination) and calibration slope, with correction for optimism using bootstrap resampling.
- Prediction:
  - Applied models to predict the 2-year probabilities of outcomes based on the observed distributions of baseline characteristics in the target populations.
  - Obtained risks by averaging the predicted probabilities of the outcomes for each treatment (Riskdabigatran and Riskwarfarin).
  - Calculated risk ratios (RRs = Riskdabigatran/Riskwarfarin).
  - Made inferences based on the nonparametric bootstrap resampling (percentile-based 95% confidence intervals).
- Estimation of the observed effects of dabigatran vs. warfarin in the extended time window target population:
  - Adjusted for confounding by 1:1 propensity score matching. Estimated 2-year RRs with 95% CIs in the matched population, assuming that the observed rate of events while on treatment would remain constant over two years of follow-up.

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