Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort in a Multinational Study: Study Design and Comparability of Cohorts

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CONFLICT OF INTEREST

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BACKGROUND

- Prucalopride is an oral, selective 5-HT$_4$ agonist medication licensed for chronic constipation in the European Union since 2009 for adult women and since 2015 for adult men.
- Because other 5-HT$_4$ agonists were withdrawn from the market due to cardiovascular adverse events, the Food and Drug Administration requested additional information on the cardiovascular safety of prucalopride to support the new drug application of prucalopride.

OBJECTIVE

- To describe the methods and resulting comparability of cohorts in a multi-database study of patients newly treated with prucalopride or polyethylene glycol 3350 (PEG) for chronic constipation
- To assess the performance of propensity score (PS) stratification and trimming to obtain comparable study cohorts
- To report study design decisions undertaken when comparability could not be achieved

METHODS

Key Design Aspects

- Data sources chosen based on:
  - Prucalopride reimbursed in their respective countries
  - Availability of information on exposures, outcomes, and covariates of interest
- PEG as comparator: most frequently prescribed medication for chronic constipation and unrelated to cardiovascular events
- Study endpoint:
  - Major adverse cardiovascular events: hospitalization for nonfatal acute myocardial infarction, hospitalization for nonfatal stroke, and in-hospital cardiovascular death
  - Identified by harmonized electronic algorithms using lists of diagnostic and procedural codes
  - Validation of the study endpoints in the 3 United Kingdom (UK) data sources (See poster 331.[1])

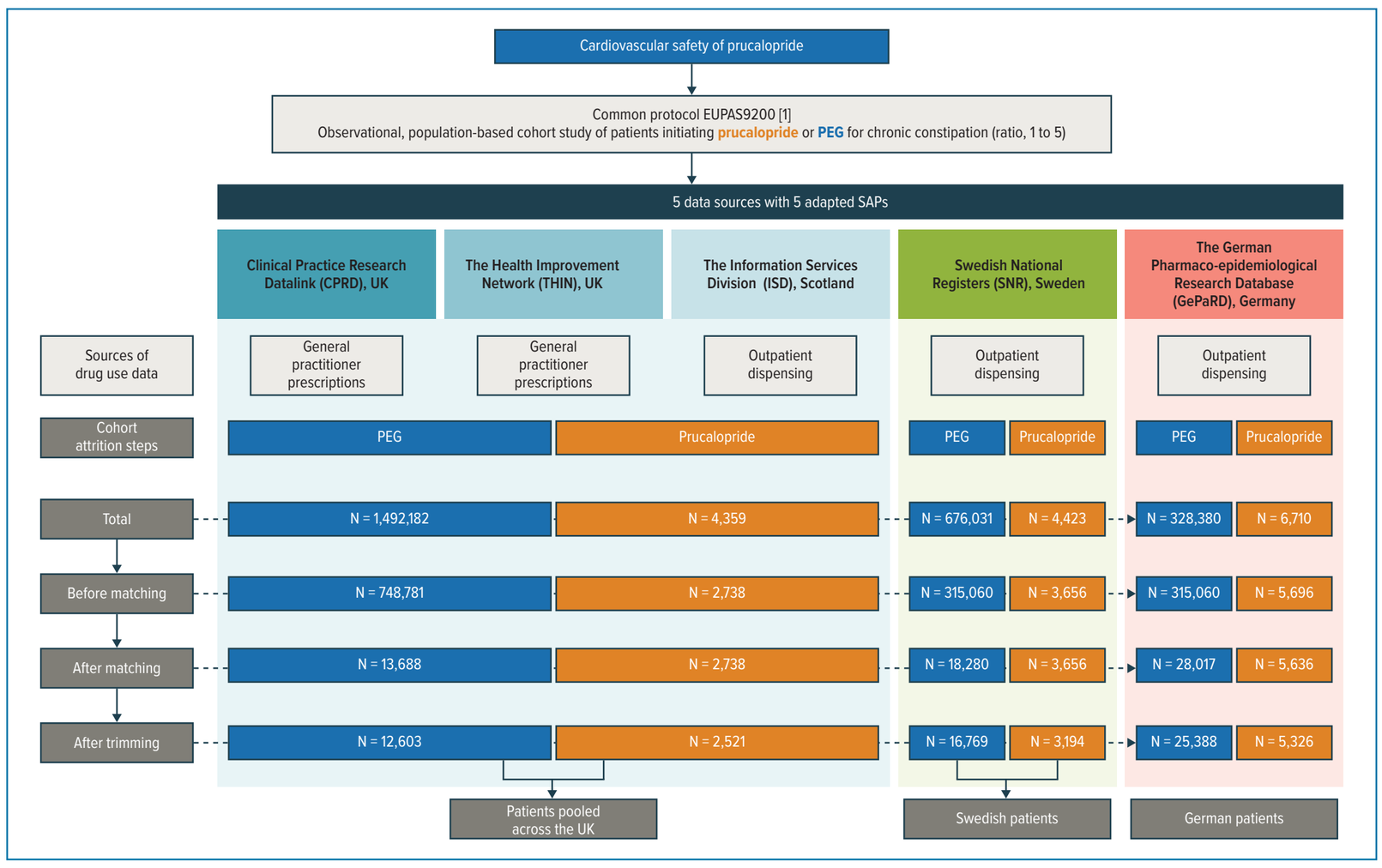
Key Statistical Methods

- From the matched cohorts, the PS was estimated for each initiator of prucalopride or PEG using the relevant covariates at the index date, and the PS distribution was used to trim both cohorts to enhance comparability.
- Figure 2 depicts the main features of the study analyses and the critical path for their implementation. Patient-level data were held at each research center, and aggregated results were pooled at the coordinating center.

RESULTS

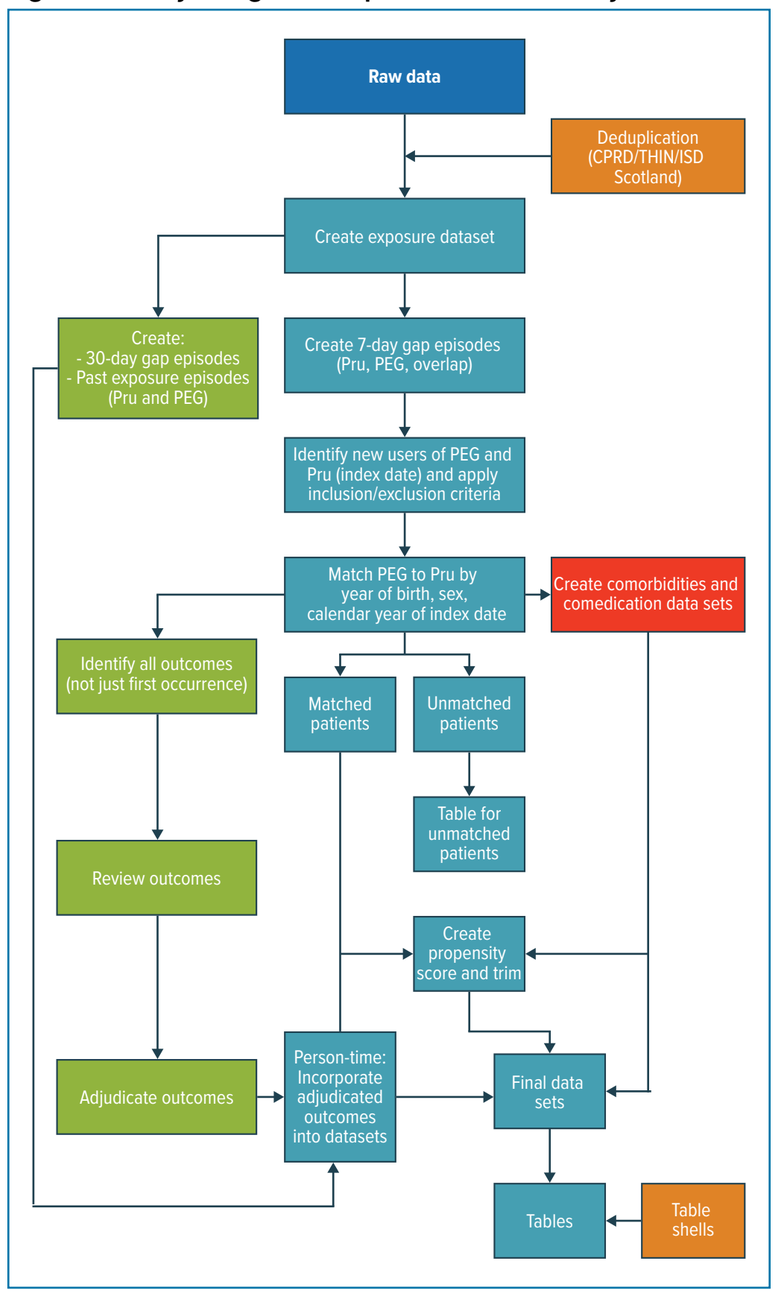
- Figure 1 shows the attrition of the cohorts included in the study.
- Figure 3 shows a description of the study population characteristics and the balance of selected covariates in the PEG and prucalopride cohorts.
- GePaRD data showed a disparate clinical profile of German patients, especially of PEG initiators, likely owing to specific drug reimbursement policies in Germany. Comparability of both cohorts could not be achieved for some important covariates, and heterogeneity with the other data sources was large. GePaRD was ultimately excluded from the pooled analysis.
- The unmatched population of the Swedish PEG initiators was similar to that of GePaRD in age and comorbidities. Further matching of prucalopride and PEG users by recent hospitalization and specialty of the prescribing physician achieved comparability of both cohorts.

Figure 1. Study Approach and Cohort Attrition



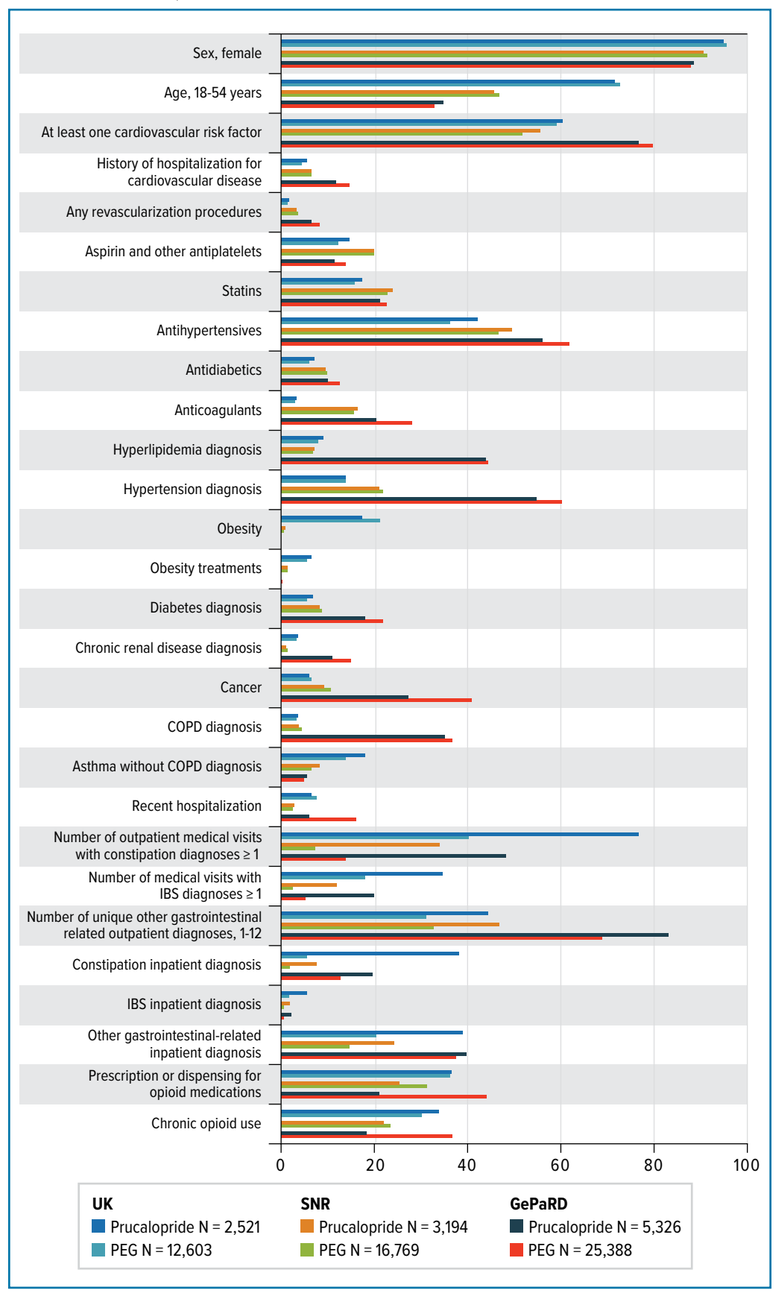
SAP = statistical analysis plan.

Figure 2. Study Design and Implementation of Analyses



Pru = prucalopride.

Figure 3. Balance of Selected Covariates in the UK (Pooled), SNR, and GePaRD Data Sources



COPD = chronic obstructive pulmonary disease; IBS = irritable bowel syndrome.

CONCLUSION

Matching, trimming, and PS stratification yielded comparable cohorts in 4 of 5 data sources. Use of these methods could not achieve balance for key covariates within the German cohort, likely due to reimbursement differences in Germany. Consequently, the pooled post-authorization safety study analyses included only data from the UK and Sweden.

REFERENCES

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Full details can be found in references 2 and 3.

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