Validation of Major Cardiovascular Events in a Multi-Database Post-Authorization Safety Study of Prucalopride

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CONFLICTS OF INTEREST

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BACKGROUND

- A post-authorization safety study (PASS) was conducted to assess the cardiovascular safety in initiators of prucalopride (a medication for the treatment of chronic constipation) compared with a matched comparator cohort of initiators of polyethylene glycol 3350 (PEG).[1,2]
- The primary safety outcome was major adverse cardiovascular events (MACE), a composite that included the first occurrence of any of the following components:
  - Hospitalization for acute myocardial infarction (AMI)
  - Hospitalization for stroke
  - In-hospital cardiovascular death
- The study was conducted in five data sources from the United Kingdom (UK), Germany, and Sweden.

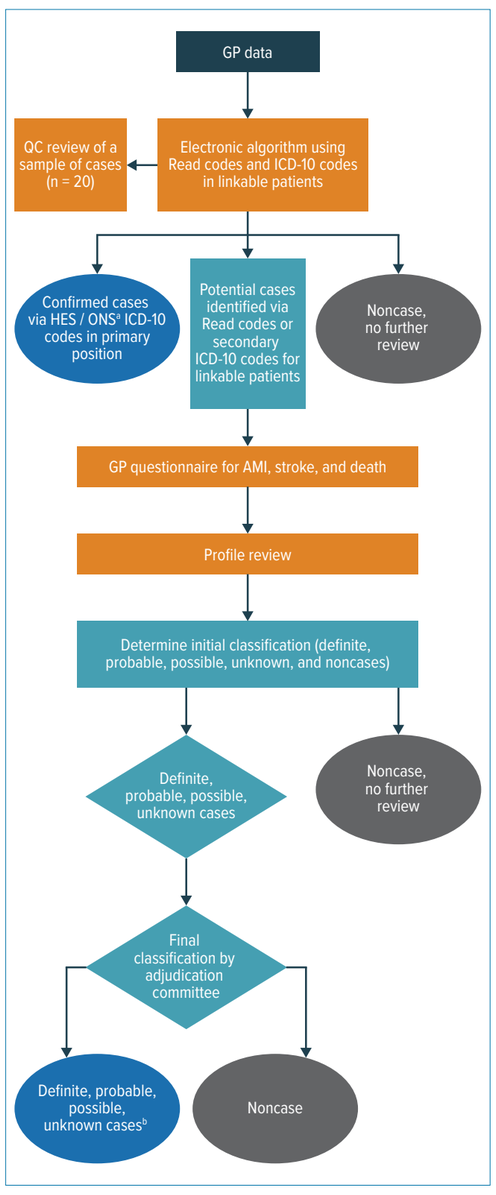
OBJECTIVE

- To report the validation process of MACE endpoints conducted for the PASS in the UK data sources: Clinical Practice Research Datalink (CPRD), The Health Improvement Network (THIN), and the Information Services Division (ISD) Scotland.[3-5]

METHODS

- Modified algorithms from prior research were used to identify potential MACE events.
- Validation was conducted per the common validation plan (as shown in Figures 1-3), which included:
  1. Direct confirmation via linkage to hospital records (CPRD only)
  2. Requests for additional clinical information through questionnaires (CPRD), free text (THIN), or original hospital case records (ISD)
  3. Patient profile review by study investigators (CPRD/THIN) to rule out noncases
  4. Event adjudication by three clinicians, all blinded to exposure, for all potential endpoints not previously confirmed or determined as noncase
- Cases were assigned final status of definite, probable, possible, or noncases.

Figure 1. Validation Process in the CPRD



GP = general practitioner; HES = hospital episodes statistics; ICD-10 = International Classification of Diseases-10; QC = quality check.

Figure 2. Validation Process in THIN

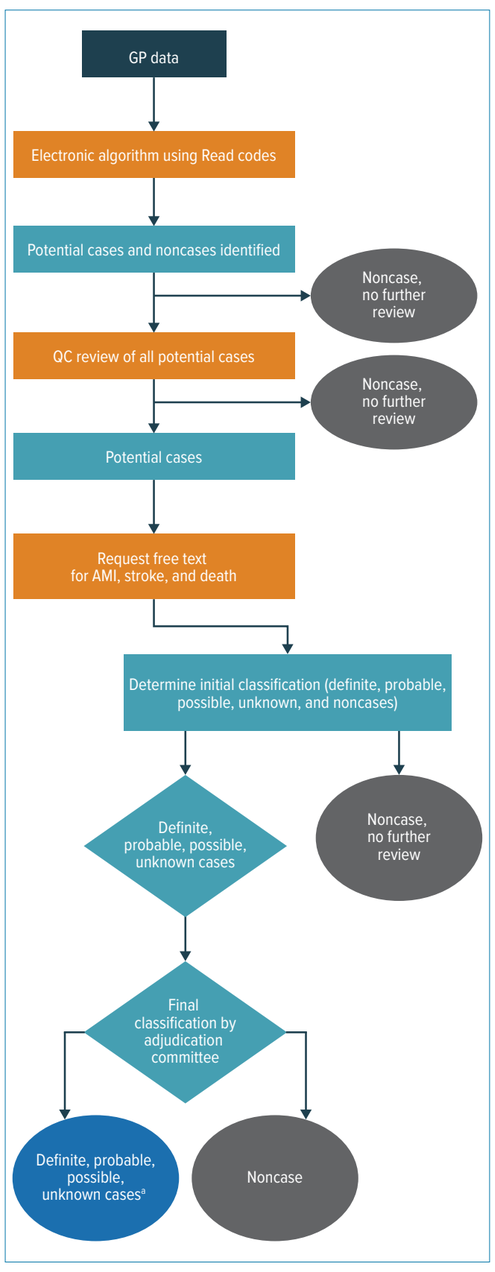
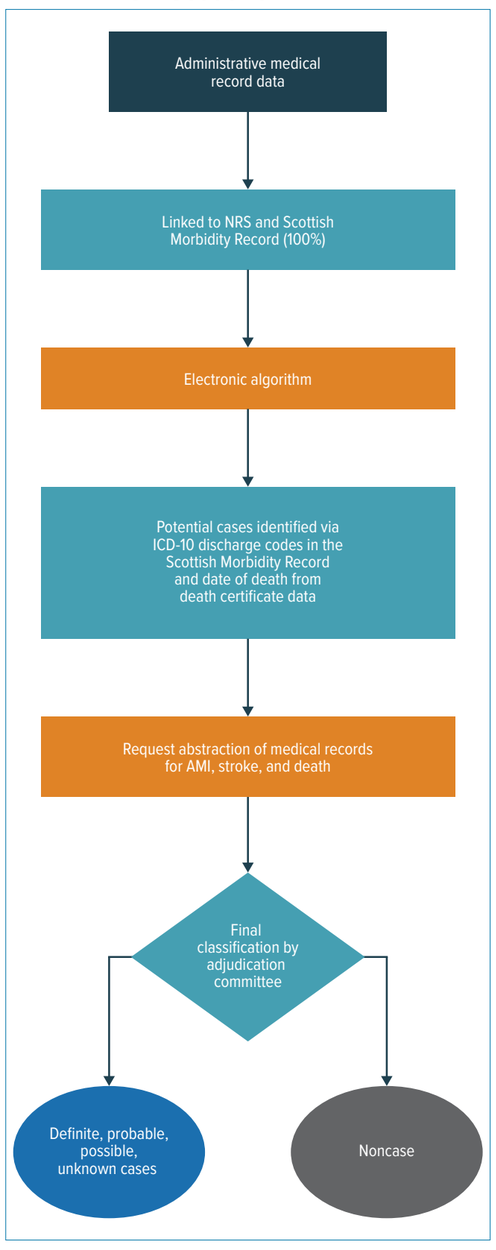


Figure 3. Validation Process in ISD Scotland



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RESULTS

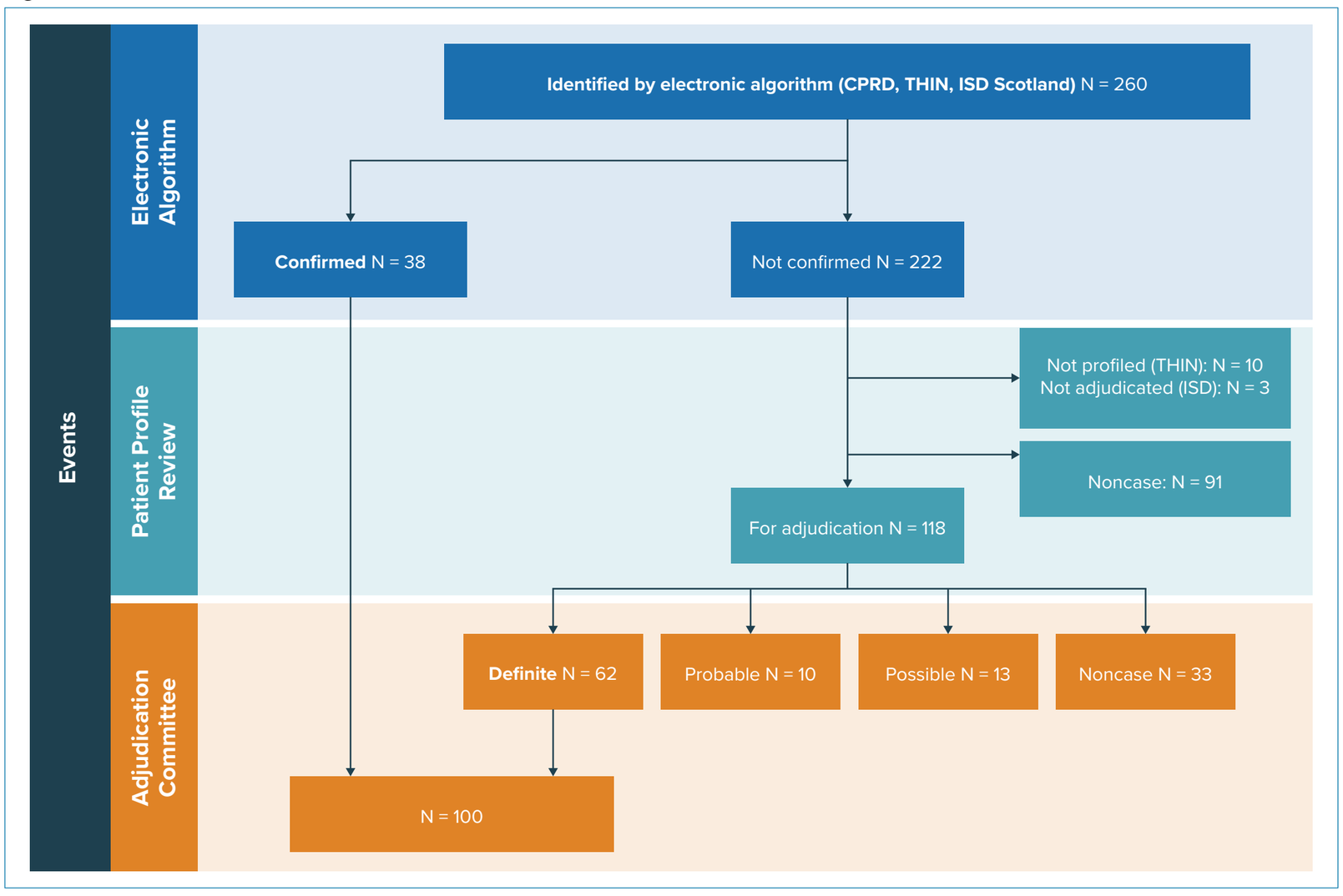
Availability of Source Validation Data

- **CPRD**: The general practitioner questionnaire response rate in CPRD was 79%.
- **THIN**: Free text was available for all potential cases from THIN.
- **ISD**: All but three requested hospital case records from ISD were retrieved. This was the first observational study in Scotland in which access to hospital case records was granted.

Adjudication Results

- The electronic algorithms identified 260 potential MACE events across all UK data sources (CPRD, THIN, and ISD Scotland):
  - 38 cases were considered confirmed via linkage to hospital records (CPRD only)
  - 91 were considered noncases after profile review (CPRD and THIN)
  - 13 were not available for adjudication (THIN and ISD)
  - Of the remaining 118 potential cases:
    - 62 were adjudicated as definite
    - 10 were adjudicated as probable
    - 13 were adjudicated as possible
    - 33 were adjudicated as noncases
  - **A total 100 cases were considered definite (38 confirmed via linkage and 62 adjudicated as definite).**
- The flow of potential study endpoints, from initial identification to final classification, is presented overall in Figure 4.

Figure 4. Validation Flowchart, All UK Data Sources



CONCLUSIONS

- Case validation in different data sources can be performed with the use of a common validation protocol that allows for modifications based on the types of clinical information available.
- Where feasible, clinical review of electronic profiles of potential cases in order to rule out obvious noncases is a means for reducing the burden of the adjudication committee.
- It is important to include clinical expert reviewers in the study validation.

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