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ORIGINAL RESEARCH ARTICLE

Development and Application of an Active Pharmacovigilance Framework Based on Electronic Healthcare Records from Multiple Centers in Korea

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Abstract

Introduction With the availability of retrospective pharmacovigilance data, the common data model (CDM) has been identified as an efficient approach towards anonymized multicenter analysis; however, the establishment of a suitable model for individual medical systems and applications supporting their analysis is a challenge.

Objective The aim of this study was to construct a specialized Korean CDM (K-CDM) for pharmacovigilance systems based on a clinical scenario to detect adverse drug reactions (ADRs).

Methods De-identified patient records (n = 5,402,129) from 13 institutions were converted to the K-CDM. From 2005 to 2017, 37,698,535 visits, 39,910,849 conditions, 259,594,727 drug exposures, and 30,176,929 procedures were recorded. The K-CDM, which comprises three layers, is compatible with existing models and is potentially adaptable to extended clinical research. Local codes for electronic medical records (EMRs), including diagnosis, drug prescriptions, and procedures, were mapped using standard vocabulary. Distributed queries based on clinical scenarios were developed and applied to K-CDM through decentralized or distributed networks.

Results Meta-analysis of drug relative risk ratios from ten institutions revealed that non-steroidal anti-inflammatory drugs (NSAIDs) increased the risk of gastrointestinal hemorrhage by twofold compared with aspirin, and non-vitamin K anticoagulants decreased cerebrovascular bleeding risk by 0.18-fold compared with warfarin.

Conclusion These results are similar to those from previous studies and are conducive for new research, thereby demonstrating the feasibility of K-CDM for pharmacovigilance. However, the low quality of original EMR data, incomplete mapping, and heterogeneity between institutions reduced the validity of the analysis, thus necessitating continuous calibration among researchers, clinicians, and the government.

1 Introduction

The World Health Organization (WHO) defines adverse drug reactions (ADRs) as "any noxious, unintended, and undesired effects of a drug, which occur at doses prescribed for prophylaxis, diagnosis, or therapy for humans" [1, 2]. ADRs account for 2.7–15.7% of all admissions [3, 4] and are ranked between the fourth and sixth leading causes of death [5, 6]. Additionally, they incur $1.56 billion in direct hospital costs per year in the US [7, 8].

Since the establishment of the international postmarket surveillance system by WHO in the 1960s [9, 10], voluntary reporting has been limited, as <10% of total adverse events are actually reported. Given the need for the active pharmacovigilance system to use accumulated clinical data (CD) [11], the common data model (CDM) is expected to support efficient retrospective pharmacovigilance across multiple centers [12].

The CDM is a standard model for reconstructing different forms of health data from various organizations into a common structure [13, 14]. By overcoming the limitation posed by the lack of interchangeability of electronic medical record (EMR) data between institutions [15], the CDM enables the cooperation of multicenters to provide evidence of relative effectiveness between them [16]. Conversion to

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Key Points

The Korean common data model (K-CDM) achieved successful localization in Korea, with a total of 5,402,129 de-identified patient data from 13 institutions converted.

The K-CDM was perceived to be an umbrella CDM that enables multi-institution analyses for pharmacovigilance, integrating the base structure of previous CDMs and having a flexible XNet layer intended to reduce the gap between clinical practice and research.

Through distributed query analysis on the gastrointestinal bleeding risk assessment of nonsteroidal anti-inflammatory drugs and cerebrovascular bleeding risk of non-vitamin K anticoagulants, the K-CDM replicated the results of published studies and demonstrated its feasibility.

an anonymized standard model whose operation does not necessitate the sharing of raw data makes it possible to bypass ethical issues and overcome potential bias resulting from the use of a small number of samples collected within a limited environment.

However, the establishment and operation of an optimized model requires domain expertise and multiple adjustments. The mapping of local codes from various databases to standard concepts requires knowledge of the medical system in the country [17] and the internal status of each institution can lead to heterogeneity of data or incomplete mapping.

Along with the model, the applications that support analysis need to be a shared resource to allow for the achievement of a common goal [18]. Finally, the operation of a distributed health data network is necessary for collaborative research studies [14, 16], which allows for secure remote analysis of datasets from cooperative institutions, while avoiding numerous obstacles related to confidentiality, regulation, and proprietary interests [19].

Considering these challenges, the Korean CDM (K-CDM) was developed to support the secondary use of healthcare data across multiple observational databases for active surveillance of marketed medical product safety. The Medical record Observation and Assessment for drug safety (MOA) network is a nationwide pharmacovigilance network based on the K-CDM platform and was established in tandem with researchers and clinicians. In this study, we describe the development process of the K-CDM and discuss the operation of the MOA network, verifying its feasibility by multicenter analysis.

2 Methods

2.1 Data Source

To analyze and compare the ADRs detected nationwide, primary and secondary medical institutions that used EMRs were discussed to determine participants. The K-CDM was installed in 11 universities and two local hospitals evenly distributed across different regions and scales of institutions. The regional drug safety centers, which form part of the decentralized pharmacovigilance system in Korea and cover drug case monitoring, consultation, and education, were preferentially included in this study. EMR data of more than 5.4 million patients and 25 million visits were extracted in table format consisting of essential items.

2.2 Construction of the Korean Common Data Model (K-CDM)

The data extracted from the EMRs of partner institutions were automatically processed through an extraction, transformation, and loading (ETL) procedure and then converted to the common structure of the K-CDM. The items extracted from the source data were mapped to terminologies of standard vocabulary and the aggregated data were then loaded into data repositories. Anonymization and encryption technologies were applied to protect personal information, and data quality was improved through cleansing and outlier detection based on Data Quality Management (DQM) principles.

To support active surveillance of pharmaceutical safety, the K-CDM reorganized advanced cases of the Observational Medical Outcomes Partnership (OMOP) [20] and Sentinel CDM [21, 22] into three levels: Level 1 for pharmacovigilance (Sentinel CDM), Level 2 for clinical research (OMOP CDM), and Level 3 for clinical care (X-Net Hub).

Based on the 13 tables from the Sentinel CDM, the applicable elements for Korean EMR data were defined and extended by adding standardized CD and standardized derived elements (SE) from the OMOP CDM [23]. Extended tables were layered with seven tables, which are extensions of the OMOP CDM in standardized health system data (SD), standardized health economics (HE), and standardized vocabulary (SV). In this way, the role of the K-CDM can be considered analogous to that of a universal travel adaptor that allows access to various power outlets (i.e., data obtained from the previously installed CDM) and produces results in the expected form. In addition, flexible layers (X-Net layers) are connected with clinical tables including highly curated data elements designed for the X-Net hub, thereby allowing for the interlocking of multicenter clinical studies and the clinical trial system.

2.3 Vocabulary Mapping

The terminology system for expressing the clinical findings and diagnosis was mapped to the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) [Table 1]. The International Classification of Diseases (ICD) or Korean Classification of Diseases (KCD) was mapped and converted to SNOMED CT using the Unified Medical Language System (UMLS) concept ID with a Korean EMR system. The drug codes used at each hospital and the electronic data interchange (EDI) codes used in Korea were mapped to RxNorm, which provides normalized drug names as part of the UMLS terminology. SNOMED CT was used as a terminology system for expressing clinical contents related to laboratory tests. We also developed a comprehensive control-based ADR signal dictionary (CVAD) for pharmacovigilance. A detailed description of this dictionary has been reported in a previous study [23].

Drugs in the EMR were mapped to RxNorm, which has been verified and supplemented by expert consultants. RxNorm mapping was automatically processed by mapping the EDI codes for each drug to the corresponding OMOP concept code, which is assigned to the RxNorm code using the MedEx program [24].

2.4 Multicenter Distributed Analysis

The coordinating center and data partners of the K-CDM are operated as part of the MOA network, following the precedent of the Sentinel Initiative. In response to the occurrence of a safety risk for a specific drug, when the Ministry of Food and Drug Safety (MFDS) commits the problem to the K-CDM Operation Center (coordinating center), a real-time pharmacovigilance system is activated by sending queries to partner centers and multi-institution analysis is performed on the results (Fig. 1). After the queries are run at each site, the results are returned either directly to the requester or to a trusted intermediary for compilation and/or comparison.

Integrated multi-organization analysis is performed by calculating the pooled estimate through synthesis of the results of the relative risk ratios (RRs) and odds ratios (ORs) from each institution. The effect size and heterogeneity are proposed by applying a fixed-effect model or random-effects model, depending on each scenario and characteristics of the participating institutions. From the combined results, the risk factors of adverse reactions to the target drug in the Korean population can be identified, and the clinical implications and prevention measures discussed by experts.

2.5 Scenario and Distributed Query for K-CDM Evaluation

To efficiently extract cases that meet our research purposes, we devised a clinical scenario format for ADR detection. The scenario is a process for logically inferring the case of ADR induced by the target drug, based on statistical correlations identified in medical records. Under the advice of a specialist who treats the symptoms, the scenario operationally defined a health outcome of interest (HOI) [15] by retrospectively using EMRs. The signal elements suggestive of HOIs include the diagnosis name, results of laboratory tests, or history of medicine administration or procedure to treat the symptoms of ADR. The scenario can be reused and modified according to the research purpose by referring to the existing HOI library (Fig. 2).

To evaluate the potential causal relationship between a prescription and ADR, the period between the prescription and ADR onset was determined. The enrollment assessment window was identified as the period from identifying the inclusion/exclusion criteria. An index date, which is the time of first use of the drug, was created only after confirming that there was no cause for drug use in the enrollment assessment window (Fig. 3).

In the entire CDM data, a specific drug cohort was composed of patients who used the target drug. Furthermore, a control cohort was set up by propensity score matching

Table 1 Mapping of the hospital EMR codes to the controlled vocabularies in the K-CDM table

K-CDM table name	Hospital EMR code	Controlled vocabularies
Drug	Drug EDI code, local drug code	RxNorm
Condition	ICD, KCD	SNOMED-CT
Procedure	Insurance EDI code	CPT4, SNOMED-CT, ICD-9-PCS, HCPCS
Measurement	Local laboratory test code	LOINC, SNOMED- CT

EMR electronic medical record, *K-CDM* Korean common data model, *EDI* electronic data interchange, *ICD* International Classification of Diseases, *ICD-9-PCS* ICD Ninth Revision, Procedure Coding System, *KCD* Korean Classification of Diseases, *SNOMED CT* Systematized Nomenclature of Medicine Clinical Terms, *CPT-4* Current Procedural Terminology Fourth Edition, *HCPCS* Healthcare Common Procedures Coding System, *LOINC* Logical Observation Identifiers Names and Codes

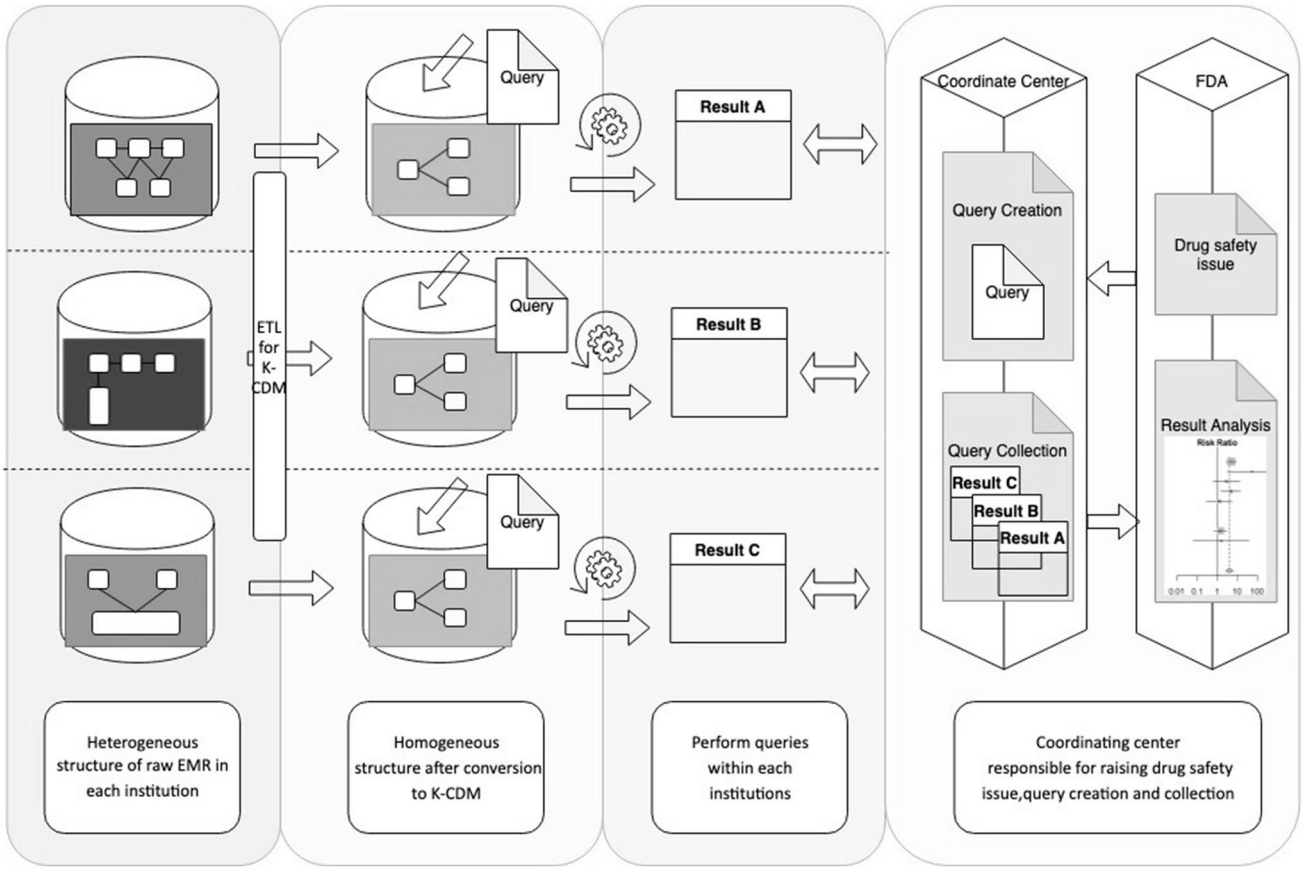


Fig. 1 Concept of a Korean active pharmacovigilance system based on the K-CDM. A decentralized or distributed network of the K-CDM. Each EMR in the individual centers is converted to a standard format, therefore a single query can be executed in parallel across multiple centers without the need for access to the entire dataset. *EMR* electronic medical record, *K-CDM* Korean common data model, *MFDS* Ministry of Food and Drug Safety, *ETL* extraction, transformation, and loading

[25] among patients who used alternative drugs or standard treatments instead of the target drug. The occurrences of HOIs according to clinical scenarios were compared in both cohorts. The complete scenario was converted to an SQL query that was applicable to the K-CDM and sent to each participating institution. The results of each institution were gathered to draw a final conclusion through meta-analysis.

2.5.1 Gastrointestinal Bleeding Risk of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Compared with Aspirin

To verify the replicability of our model with reports from previous research, we designed a scenario that was applicable to our model and system (electronic supplementary material [ESM] Fig. 1). We used the scenario to verify the severity of ADRs to non-steroidal anti-inflammatory drugs (NSAIDs), which are among the most frequently used drugs for pain control and the most common cause of ADRs in Korea [10].

In this study, 10 types of NSAIDs were evaluated as target drugs: indomethacin, diclofenac, aceclofenac, ketorolac, etodolac, ibuprofen, ketoprofen, naproxen, piroxicam, and meloxicam. The RR of the target drugs for gastrointestinal bleeding was compared with that of aspirin as a control group. Patients over 18 years of age who received the target drug for more than 90 days were included in this cohort. The washout day of the drugs was determined to be 14 days. The HOI was characterized using the diagnosis code, procedure code, or laboratory examination results, suggesting the condition and record of drug abstinence that can be inferred as causality. The HOI for suspected gastrointestinal bleeding was determined using the diagnosis code corresponding to the symptom (ICD codes: K25–K29) and treatment record (endoscopic upper digestive bleeding; EDI code: Q7620***). The detailed diagnosis and procedure codes for determining the corresponding HOI are provided in ESM Table 1.

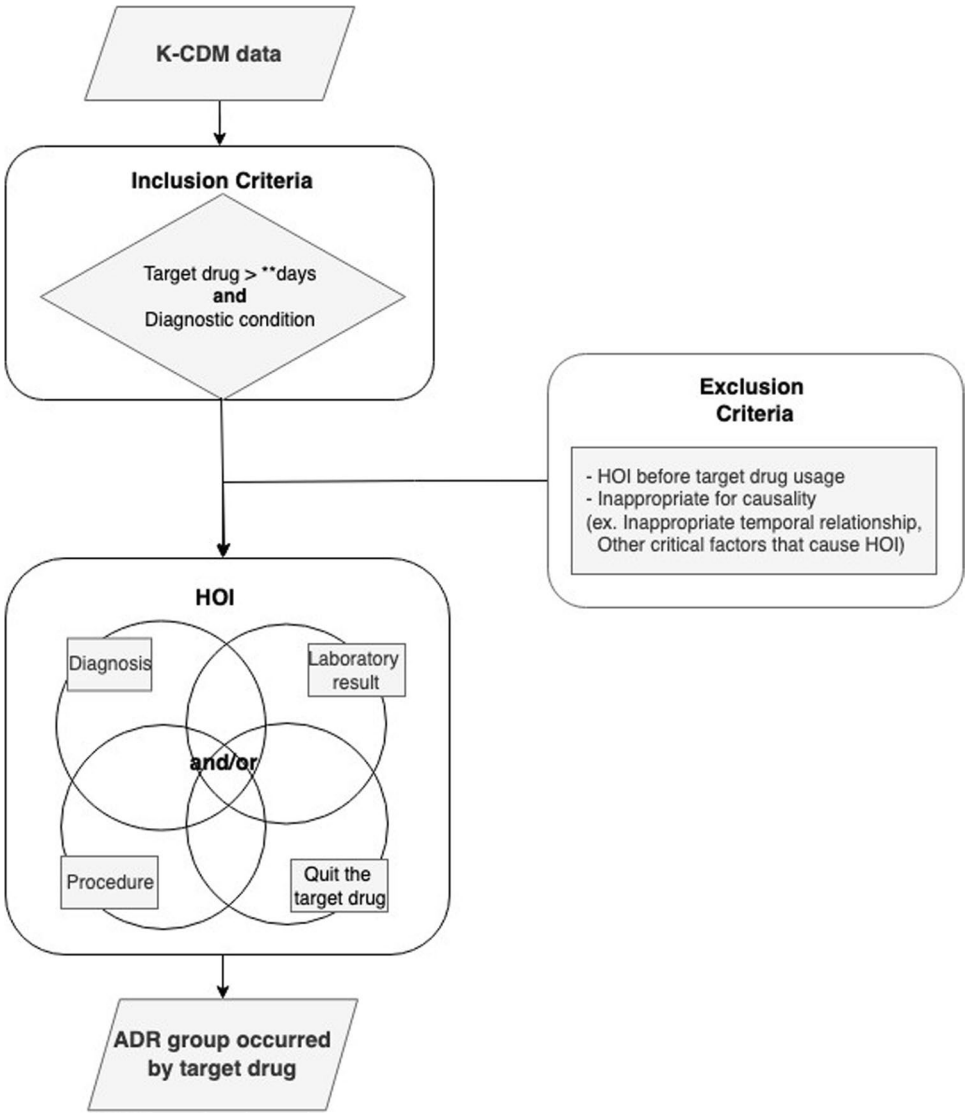


Fig. 2 Construction of a scenario to determine the occurrence of ADRs using the K-CDM database. The clinical scenario and distributed query were developed as an analysis tool applicable to the K-CDM causality assessment of ADRs. This figure is an example of a scenario structure defining an HOI. Among patients without previous symptoms related to the HOI, if a new record of diagnosis, test results, or treatment suggesting an HOI occurred after target drug administration and drug discontinuation, the symptom is inferred to have been driven by the drug. Depending on the type of drug and HOI, the structure and detailed conditions are changed. *HOI* health outcome of interest, *ADRs* adverse drug reactions, *K-CDM* Korean common data model

2.5.2 Cerebrovascular Bleeding Risk of Non-Vitamin K Anticoagulants (NOACs) Compared with Warfarin

We additionally assessed the risk of bleeding induced by non-vitamin K anticoagulants (NOACs), which are newly introduced anticoagulants acting on Factor Xa [16] or thrombin [17], compared with warfarin. Influenced by the previous research of Sentinel Initiatives to address safety concerns regarding NOACs [18] and the possible ethnic differences among the Asian population [25], we sought to verify the risk of bleeding owing to the use of NOACs and warfarin in actual clinical trials among the Korean population. The target NOACs for analysis include dabigatran, apixaban, rivaroxaban, and edoxaban. Patients aged ≥ 65 years who used the target drug and exhibited atrial fibrillation symptoms for more than 30 days were included in this cohort. The first day of target drug use was regarded as the index date, considering there are no records of previous usage in the EMR for 1 year. Considering the high medication compliance regarding these drugs, the washout period of NOACs and warfarin was regarded as the period from the last dose taken until four half-lives had passed, i.e. 2 days for NOAC and 7 for warfarin.

The structure and characteristics of the HOI are based on the records of diagnosis or treatment, which suggest the condition through consensus of an advisory panel comprising specialists.

3 Results

3.1 K-CDM Development and Data Characteristics

The K-CDM provides 80 items of information on a patient, including visit, treatment information, condition,

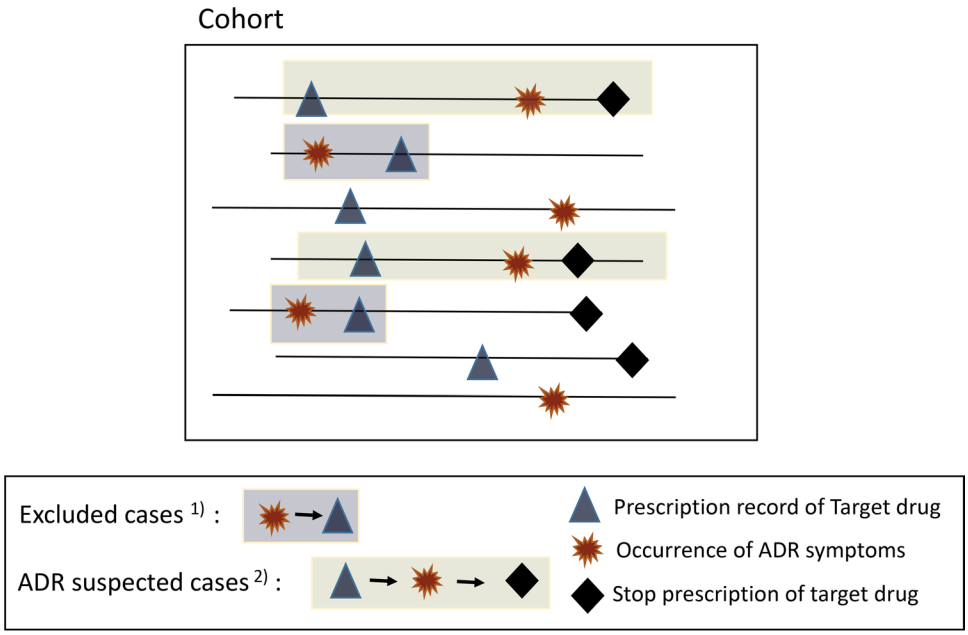


Fig. 3 ADR suspected cases corresponding to the defined scenario. Composition of scenario conditions reflecting a causal association between drugs and adverse reactions. Symptoms expressed before drug prescription were excluded. Cases with a record of symptom expression and drug discontinuation after prescription were selected. *ADR* adverse drug reaction

observation, drug exposure, measurement, and vital signs. In total, 4800 types of drugs and 139 diagnostic test items have been mapped to the international standard terminology system. Figure 4 describes the structure of the K-CDM. The three layers of the K-CDM consist of 8 tables in the Sentinel layer, 23 in the OMOP layer, and 14 in the X-Net layer.

Records of 5,402,129 patients from 13 institutions were included in the K-CDM. The duration of the included EMR data varied according to institutions, from 3–12 years, with an average of 5.46 years. On average, 1214 drugs, 3806 conditions, and 1823 procedures were included. During 37,698,535 visits at all institutions, a total of 39,910,849 conditions were observed and 30,176,929 procedures were carried out. Patients were also exposed to 259,594,727 drugs. Ten institutions met the cohort criteria and were included in the analysis. Table 2 shows the imported data size, period, and number of items included in the constructed K-CDM at each institution.

The local codes of the EMR, from diagnosis, examination, through to drug treatment, and procedures were mapped on to standard vocabulary. This was conducted and reviewed by two members of the medical team. The Korean Standard Classification of Diseases version 5 (KCD-5) or a Korean derivative of the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), i.e. the coding systems for diagnosis in Korean EMRs, were mapped to the standard vocabulary based on the SNOMED-CT. If there was no exact mapping term in the standard vocabulary, a parent term with broad meaning was mapped instead. As a result, 98.4% of the 20,721 KCD-5 codes were mapped to the CDM SVs. The local drug codes were mapped to the SVs RxNorm first, with unmatched cases converted based on the Anatomical Therapeutic Chemical (ATC) classification system.

3.2 Distributed Query Result

3.2.1 Gastrointestinal Bleeding Risk Assessment of NSAIDs Compared with Aspirin

To evaluate the model, distributed analysis was conducted on the gastrointestinal bleeding risk of NSAIDs, and 4,657,058 patients from 10 institutions were included. Table 3 shows the number of patients, their average age, and total period of drug usage in the NSAID and aspirin cohorts.

The analysis was performed using the standardized query following the procedure outlined below (ESM Table 2). For example, of the 995,272 patients in institution A, 38,099 used NSAIDs for more than 90 days. In addition to the patients with newly diagnosed bleeding within the exploration period, patients who underwent hematoma removal were added to the HOI group driven by NSAIDs. Finally, 105 patients were assigned to the NSAIDs HOI group and the same criteria were applied to patients using aspirin, resulting in 82 patients being added to the control group.

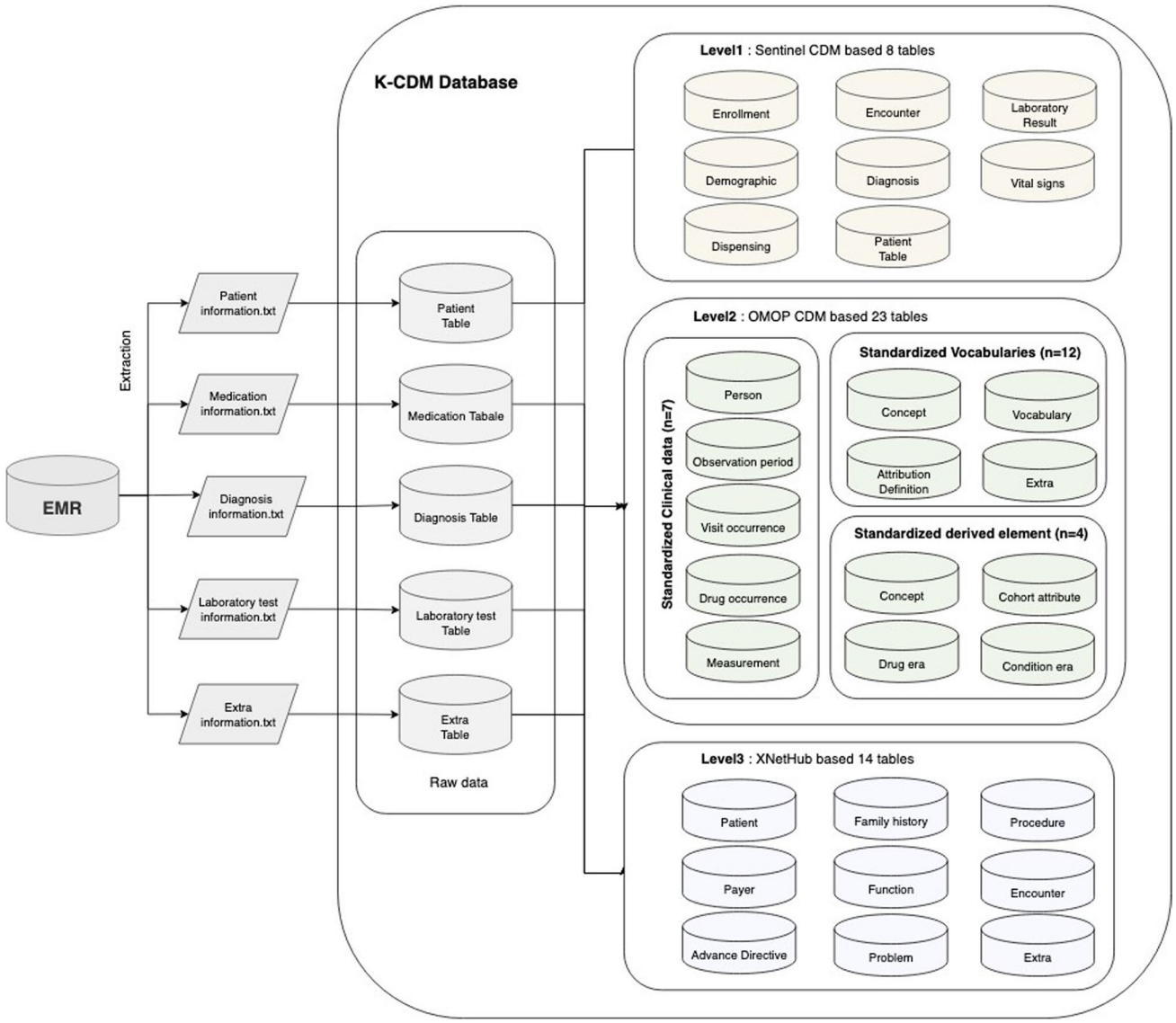


Fig. 4 Structure of the K-CDM, designed to enable drug safety monitoring, comparative effectiveness research, and multicenter clinical research. The K-CDM consists of three layers; 8 tables in the Sentinel layer, 23 in the OMOP layer, and 14 in the X-Net layer. *K-CDM* Korean common data model, *OMOP* Observational Medical Outcomes Partnership, *EMR* electronic medical record

Table 3 shows the number of patients included in the NSAID and aspirin cohorts and their demographic information. The meta-analyzed results conducted by distributed query from the institutions are shown in Fig. 5a. The risk of gastrointestinal bleeding was 1.34–fold higher (95% confidence interval [CI] 1.09–1.65; $p < 0.01$) in patients taking NSAIDs than in patients taking aspirin, and was statistically significant.

To adjust demographic similarity between the NSAID and aspirin cohorts, we extracted age, sex, duration of administration, and comorbidity (calculated as Charlson Comorbidity Index [CCI] score) as confounding factors and then established a matched cohort using a propensity score. The demographic information of the NSAIDs and aspirin groups in the original and matched cohorts are described in ESM Tables 3 and 4.

The propensity score-matched dataset showed that the RR of NSAIDs obtained via meta-analysis increased from 1.34 to 1.98 (95% CI 1.50–2.63; $p < 0.01$) (Fig. 5b). This shows the highlighted ADR risk of NSAIDs according to the adjustment for confounding variables, which might relate to the tendency of the aspirin cohort composed of older patients taking drugs for a longer period than the NSAIDs cohort.

The individual results showed that the risks of NSAIDs were higher than those of aspirin in all but three institutions, and their value increased in matched datasets. Regarding the three institutions in which the RR of NSAIDs showed

Table 2 Imported EMR data with demographic information from 13 institutions for conversion to the K-CDM

	Years of data available	Period (years)	Person	Age, years	Sex ratio[a]	Condition occurrence	Drug exposure	Measurement	Procedure occurrence	Visit occurrence
Institution 1	2005–2016	12	995,252	55.01 ± 23.4	46.49	17,984,021	114,484,036	196,773,958	13,086,620	18,698,707
Institution 2	2011–2016	6	1,711,795	55.06 ± 22.17	49.88	1,889,637	9,773,628	26,017,235	3,579,527	1,901,730
Institution 3	2011–2016	6	91,394	56.39 ± 23.91	52.26	908,367	24,195,245	10,504,202	184,078	298,962
Institution 4	2012–2016	5	217,882	50.27 ± 23.15	47.51	438,944	5,032,402	17,992,121	2,824,438	419,813
Institution 5	2014–2016	3	126,984	52.19 ± 18.37	52.23	2,650,629	786,083	6,143,889	394,312	786,083
Institution 6	2010–2016	7	118,954	58.58 ± 24.05	50.36	667,397	40,403,895	16,277,662	1,002,730	2,850,183
Institution 7	2013–2017	5	419,777	55.02 ± 24.05	49.90	1,609,988	25,625,307	47,668,683	3,934,729	4,097,113
Institution 8	2013–2017	5	379,888	47.42 ± 21.87	46.92	4,165,453	11,254,238	818,132	2,372,285	3,038,260
Institution 9	2013–2017	5	200,787	48.03 ± 23.19	50.13	2,926,992	12,414,210	12,000,013	1,241,333	1,665,500
Institution 10	2013–2017	5	391,770	40.11 ± 21.73	51.71	3,746,776	13,790,730	10,889,578	1,605,546	2,107,231
Institution 11	2013–2016	4	525,995	51.22 ± 23.58	50.97	511,253	4,283,573	6,017,092	5,357,555	798,804
Institution 12	2013–2016	4	206,551	50.35 ± 20.50	52.98	2,353,497	23,777	240,895	NA[b]	1,021,677
Institution 13	2013–2016	4	15,080	57.23 ± 16.90	47.55	57,895	2316	54,918	247	14,472

EMR electronic medical record, *ETL* extraction, transformation, and loading, *K-CDM* Korean common data model, *NA* not available

[a]The proportion of male patients to the total number of patients

[b]The ETL for procedure occurrence of institution 12 is in progress

different directions, the range of the confidence intervals was large (95% CI 0.05–3.02 in Institution 9) because of the rare number of cases, raising the need for confirmation of the prescription pattern and the characteristics of the visiting patient through in-depth analysis by the institution.

3.2.2 Cerebrovascular Bleeding Risk Assessment of NOACs Compared with Warfarin

As the anticoagulants were utilized for the prevention of thrombosis in patients with atrial fibrillation, cerebrovascular bleeding, i.e. a fatal ADR of NOACs, was assessed compared with warfarin. For the construction of this cohort, 5,183,083 patients from 11 institutions were included.

The analysis was performed using the standardized query with the following procedure (ESM Fig. 2). Of the 995,272 patients in institution A, 3962 patients used NOACs for more than 30 days and 15,937 patients used warfarin. In addition to the 17 patients newly diagnosed with bleeding within the exploration period, one person who underwent a procedure for hematoma removal was considered to represent the hemorrhage driven by NOACs. After exclusion of the age group under 18 years, 16 patients were finally assigned to the NOACs HOI group. The same criteria were applied to patients using warfarin, resulting in 90 patients in the control group.

Table 4 shows the number of patients included in the NOAC and warfarin cohorts and their demographic information. Based on the results, HOIs caused by NOACs were observed in 30 patients from seven hospitals, while HOIs possibly caused by warfarin were observed in 156 patients from nine hospitals. According to the meta-analysis results (Fig. 5c), in patients with atrial fibrillation aged ≥65 years, the risk of cerebrovascular hemorrhage was significantly reduced by 72% compared with that of warfarin.

4 Discussion

It is reported that severe ADRs are experienced by 6.7% of hospitalized patients in the US [26] and fatal reactions occur in approximately 0.3% [6]. Although there are established regional pharmaceutical safety centers in Korea, the range of coverage was insufficient and a rapid response to new safety issues was limited. With the aim to complement the existing pharmacovigilance system, the K-CDM was devised as a practical multicenter pharmacovigilance system utilizing real CD. After initially being installed in two regional pharmaceutical safety centers and two hospitals in 2016, the K-CDM was expanded to an additional nine institutions in 2017 and 2018, showing its applicability at a national level.

The K-CDM was constructed as a practical model, which maximizes its utilization while reducing the process of ETL,

Table 3 Demographic information on NSAIDs and aspirin cohorts

	NSAID group's HOI			Aspirin group's HOI		
	Patients	Average age, years	Drug usage period	Patients	Average age, years	Drug usage period
Institution 1	105	61.8	228.1 ± 229.7	82	64.7	725.1 ± 610.7
Institution 2	14	60.9	217.2 ± 105.2	83	68.5	399.8 ± 377.7
Institution 3	3	62.7	112.0 ± 1.0	197	70.2	565.5 ± 470.0
Institution 4	4	50.3	161.0 ± 59.3	26	66.4	429.8 ± 324.5
Institution 5	7	58.4	213.7 ± 137.9	26	70.0	403.7 ± 375.8
Institution 6	0	NA	NA	1	54.0	722.0
Institution 7	0	NA	NA	0	NA	NA
Institution 8	11	63.4	193.1 ± 225.0	30	69.8	281.4 ± 213.7
Institution 9	1	72.0	165.0	9	67.1	198.9 ± 125.8
Institution 10	0	NA	NA	52	69.2	666.5 ± 564.8

NSAIDs non-steroidal anti-inflammatory drugs, *HOI* health outcome of interest, *NA* not available

by selecting key items for the purpose of drug surveillance, with priority based on expert advice. The procedure of data transformation to the CDM is difficult and time-consuming. Configured as a compact model, the K-CDM has reduced the workload in the initial mapping process, achieving efficiency by reconstructing the two types of previous models.

As an initial attempt to convert EMRs into the CDM in Korea, the K-CDM was perceived to be an umbrella CDM that enables multi-institution analyses of relevance, integrating the base structure of CDM (be it OMOP or Sentinel) in a given institution.

Currently, based on widespread OMOP-CDM partnerships, a customized CDM specialized in data and target disease characteristics is recommended and has been developed. We believe each specialized CDM is meaningful for its own purpose, and in pharmacovigilance, the K-CDM could play a role analogous to that of a universal travel adaptor that allows access to various power outlets.

Furthermore, by integrating with the X-Net hub devised for clinical research, the K-CDM functions as a flexible CDM that could expand research without being disconnected from previous research, thereby reducing the gap between research and clinical practice. The flexible CDM approach that organizes information into exchangeable components has been proposed in another recent study [27], to facilitate the combined analysis of different types of secondary data from multiple, heterogeneous sources.

To verify the quality and feasibility of the K-CDM, we constructed two kinds of distributed queries, based on the clinical scenarios, to evaluate the causality of ADRs. The first cohort was designed to verify the severity of ADRs to NSAIDs. NSAIDs are the most frequently prescribed drugs for controlling a broad spectrum of pain [28], with a risk that is three times higher than that of serious gastrointestinal diseases and results in approximately 12,000 hospitalizations and 2000 deaths per year in the US [29, 30]. The second cohort was intended to verify the incidence of cerebrovascular bleeding from NOACs, which is a fatal ADR of anticoagulants. Upon introduction as a regular drug in Korea in 2013, NOACs are used to prevent thrombosis for patients with atrial fibrillation, and its safety, compared with warfarin, was confirmed in 2015 by the US FDA's sentinel program. However, the need for follow-up safety studies was raised owing to the lack of ethnic differences and the results of large-scale patients, and the safety grounds for Korean patients were lacking owing to the low amount of NOAC usage.

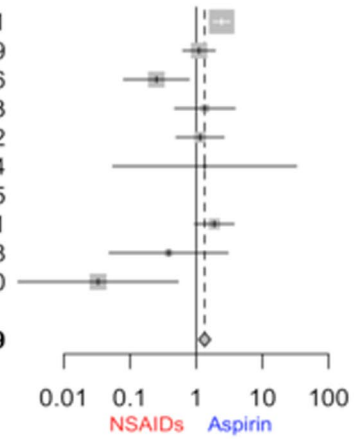
We aimed to address two cases; the risk of ADRs driven by commonly used drugs, NSAIDs, and the safety of NOACs whose usage and ADR symptoms are specific to disease. From each cohort, we obtained the duplicated results with previous studies. As the result of analysis obtained by matched K-CDM data of ten institutions, NSAIDs prescription showed an approximately 1.98-fold higher risk of gastrointestinal bleeding occurrence compared with aspirin as the control drug. In the ADR analysis results in NOACs from 11 institutions, the use of NOACs in patients with atrial fibrillation over the age of 65 years reduced the risk of cerebrovascular hemorrhage by 72% compared with warfarin, a difference that was statistically significant. The results of these studies replicated the reports of previous studies using the real-world data of each institution, and elucidated the validity of the K-CDM data. To increase the validity of ADR detection by operational definition, the clinical scenarios were modified by direct medical record reviews on sample cases.

Along with the K-CDM construction project by the Korea Institute of Drug Safety and Risk Management (KIDS) every year, the MOA network continues to expand its research partners; since 2016, when the K-CDM was first developed and piloted, five institutions have been selected annually to install the K-CDM. Proposals on drug safety topics and

a

Study	NSAIDs Events	NSAIDs Total	Aspirin Events	Aspirin Total	RR	95%-CI	Weight
institution 1	105	37977	82	71761	2.42	[1.81; 3.23]	36.7%
institution 2	14	1155	83	7549	1.10	[0.63; 1.94]	14.2%
institution 3	3	1954	197	32116	0.25	[0.08; 0.78]	14.6%
institution 4	4	589	26	5173	1.35	[0.47; 3.86]	3.4%
institution 5	7	1392	26	5912	1.14	[0.50; 2.63]	6.4%
institution 6	0	162	1	654	1.34	[0.05; 32.80]	0.4%
institution 7	0	156	0	1815			0.0%
institution 8	11	528	30	2701	1.88	[0.95; 3.72]	6.3%
institution 9	1	3401	9	11708	0.38	[0.05; 3.02]	2.6%
institution 10	0	4214	52	14550	0.03	[0.00; 0.53]	15.2%
Fixed effect model		**51528**		**153939**	**1.34**	**[1.09; 1.65]**	**100.0%**

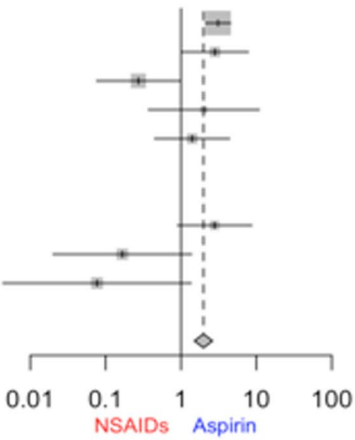
Heterogeneity: I^2 = 77%, τ^2 = 0.5198, p < 0.01
Test for overall effect: z = 2.79 (p < 0.01)



b

Study	NSAIDs Events	NSAIDs Total	Aspirin Events	Aspirin Total	RR	95%-CI	Weight
institution 1	105	37977	34	38048	3.09	[2.10; 4.55]	46.2%
institution 2	14	1155	5	1164	2.82	[1.02; 7.81]	6.8%
institution 3	3	1951	11	1943	0.27	[0.08; 0.97]	15.0%
institution 4	4	585	2	587	2.01	[0.37; 10.91]	2.7%
institution 5	7	1392	5	1394	1.40	[0.45; 4.41]	6.8%
institution 6	0	162	0	162			0.0%
institution 7	0	156	0	156			0.0%
institution 8	11	528	4	535	2.79	[0.89; 8.70]	5.4%
institution 9	1	3401	6	3396	0.17	[0.02; 1.38]	8.2%
institution 10	0	4214	6	4208	0.08	[0.00; 1.36]	8.9%
Fixed effect model		**51521**		**51593**	**1.98**	**[1.50; 2.63]**	**100.0%**

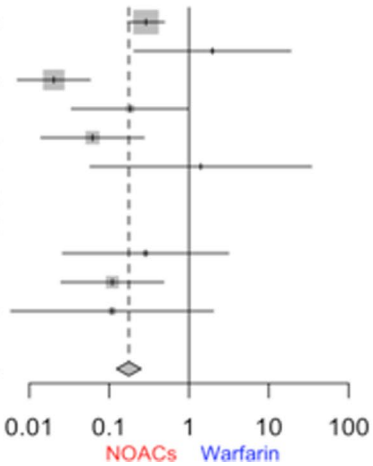
Heterogeneity: I^2 = 73%, τ^2 = 0.8163, p < 0.01
Test for overall effect: z = 4.80 (p < 0.01)



c

Study	NOACs Events	NOACs Total	Warfarin Events	Warfarin Total	RR	95%-CI	Weight
institution 1	16	4524	90	7350	0.29	[0.17; 0.49]	41.5%
institution 2	3	887	1	581	1.97	[0.20; 18.85]	0.7%
institution 3	4	6483	27	886	0.02	[0.01; 0.06]	28.8%
institution 4	2	1203	4	441	0.18	[0.03; 1.00]	3.5%
institution 5	2	2204	13	886	0.06	[0.01; 0.27]	11.2%
institution 6	0	93	1	394	1.41	[0.06; 34.25]	0.3%
institution 7	0	190	0	412			0.0%
institution 8	0	978	0	832			0.0%
institution 9	1	404	2	231	0.29	[0.03; 3.14]	1.5%
institution 10	2	1929	14	1481	0.11	[0.02; 0.48]	9.6%
institution 11	0	1871	4	1830	0.11	[0.01; 2.02]	2.8%
Fixed effect model		**20766**		**15324**	**0.18**	**[0.12; 0.25]**	**100.0%**

Heterogeneity: I^2 = 72%, τ^2 = 1.2956, p < 0.01
Test for overall effect: z = -9.58 (p < 0.01)



◂**Fig. 5** Generated analysis results through standard distributed queries based on the K-CDM. To evaluate the model, distributed analysis was conducted on the gastrointestinal bleeding risk of NSAIDs and cerebrovascular bleeding risk of NOACs, and the number of patients at risk was obtained. **a** Gastrointestinal bleeding risk of NSAIDs compared with aspirin in the original dataset. From the meta-analysis of 10 institutions, the risk of gastrointestinal bleeding was 1.34-fold higher in patients taking NSAIDs than in patients taking aspirin. **b** Gastrointestinal bleeding risk of NSAIDs compared with aspirin in the matched dataset. From the propensity score-matched dataset, the risk of gastrointestinal bleeding was 1.98-fold higher in patients taking NSAIDs than in patients taking aspirin. **c** Cerebrovascular bleeding risk of NOACs compared with warfarin. Among the 5,183,083 patients who received atrial fibrillation from 11 institutions, patients aged ≥ 65 years showed a 72% reduction in the risk of cerebrovascular hemorrhage compared with those who received warfarin. *NSAIDs* non-steroidal anti-inflammatory drugs, *NOACs* non-vitamin K anticoagulants, *OR* odds ratio, *RR* relative risk ratio, *CI* confidence interval

recruitment are discussed through the website (https://moa.drugsafe.or.kr/), where analytical queries are provided and the execution results are collected. The successful execution of government-sponsored tasks by the MOA network has shown the possibility of a surveillance system utilizing the K-CDM, thus mitigating numerous security, proprietary, and privacy concerns by allowing data holders to retain physical control of their data with no need for central data repositories [19] .

However, there were a few limitations related to the heterogeneity of data. Because the K-CDM has been installed in various hospitals in more than seven districts in Korea, the distribution of patient groups varied depending on the size, location, and history of the institution, leading to varying prescription patterns and bias in the analysis results. The potential risk of local bias in each hospital could be identified; for instance, institution 4 in the NOAC group's HOI (Table 4) showed a low 'drug usage period' compared with that in the other institutions. These differences might be a result of the small HOI cases of NOACs, various prescription patterns of institutions, different data extraction periods, and heterogeneity of internal patients.

In addition, although the institutions shared the standard terminology and medical system, the quality of the EHR data extracted from each institution was different, and the heterogeneity of the data format was high. We tried to perform institution-specific ETL considering the raw data from each institution, and performed test queries to correct incomplete mapping due to issues with individual hospitals.

Even though more than 98% of prescription information was converted in the drug mapping, the cases where mapping target did not match 1:1 were difficult to evaluate. The use of modified local codes, such as the addition of a decimal number to existing diagnostic codes, contributed to incomplete mapping. Furthermore, compared with tertiary hospitals, the mapping rate in small- and medium-sized hospitals was significantly low owing to the shortage of systematization and technicians to comprehend and extract data, confirming the current state where CDM conversion is mainly carried out in tertiary hospitals.

The following factors regarding our study design and interpretation of results should be considered.

We designed scenario queries to extract the HOI incidence, whose inference was based on the causal relationship of predefined conditions. Because it was designed for rapid safety assessments and acquisition of clue information, discrimination of several ADRs, which are affected by more complex variables than the criteria defined in our study, is challenging. For a more comprehensive risk assessment of ADRs based on the results of this study, additional corrections considering characteristics of target drugs, institutions, and symptoms are required.

The elements composing the scenario also need to be considered and improved. For example, there is a multidrug cross-prescription issue in the drug group definition. We regarded 10 different types of individual drugs included in NSAIDs as a single NSAID group, thereby defining the cross prescriptions among drugs as the prescription for a single NSAID group. Even though the cross-use of different subtypes could be included without omission in this design, comparing the risk degree of individual subtypes is difficult. In defining the NSAID and aspirin groups, those patients who had previously received both drugs within 1 month were excluded. However, the conditions for cross-administration during each drug administration process could not be separately restricted because of the small number of ADR cases whose exclusion could distort the results, disabling analysis.

Regarding the differences in clinical indications and prescription patterns depending on the drug characteristics, we attempted to compensate for these by imposing duration criteria. Because aspirin and NSAIDs have different target symptoms and prescription doses for acute and chronic pain, we set the duration criterion as 'more than 90 days', intending for chronic use to determine the prescription condition and increase the causality with HOIs. Considering the versatility of NSAIDs in multiple diseases, inclusion was not restricted by clinical indications. Instead, the effect of the patient's disease as a risk factor for gastrointestinal bleeding following long-term use of NSAIDs was analyzed. In addition to the setting of duration criterion, we established a matched cohort to adjust demographic similarity in age, sex, duration of administration, and comorbidity. Even though we verified that the ADR risk of NSAIDs increased (1.34 to 1.98) in the matched dataset, there remains a potential bias driven by differences in the distribution of important variables such as age and sex ratio, which could lead to possible residual confounding. These limitations indicate the scope for improvement and the immense potential of the K-CDM for future application and development.

Table 4 Demographic information on NOACs and warfarin cohorts

	NOAC group's HOI			Warfarin group's HOI		
	Patients	Average age, years	Drug usage period	Patients	Average age, years	Drug usage period
Institution 1	16	77.5	216.4 ± 156.2	90	74.8	441 ± 444.6
Institution 2	3	81	244.3 ± 256.7	1	70	1198
Institution 3	4	75.8	203.3 ± 114.2	27	73.8	426.9 ± 330.5
Institution 4	2	77.5	89 ± 2.8	4	76	292.3 ± 263.6
Institution 5	2	75	181.5 ± 126.6	13	72.8	383.8 ± 282.9
Institution 6	0	NA	NA	1	68	77
Institution 7	0	NA	NA	0	NA	NA
Institution 8	0	NA	NA	0	NA	NA
Institution 9	1	86	NA	2	84.5	360.5 ± 340.1
Institution 10	2	79.5	274 ± 43.8	14	75.1	329.2 ± 269.5
Institution 11	0	NA	NA	4	74.5	356.5 ± 226.3

NOACs non-vitamin K anticoagulants, *HOI* health outcome of interest, *NA* not available

The clinical scenario in this study is configured as a comprehensive format rather than detailed criteria, mainly to verify the replication of our data and methodology. If a more comprehensive cohort was designed based on the scenario template, and various analyses were performed, more specific and elaborate outcomes could be derived according to the research purpose, including survival analysis to confirm the association between timing and risk factors and the prediction model for the possible ADR cases and timing.

The K-CDM is also expected to enable international multicenter research because the scenario query can be performed locally and internationally by utilizing the concept table where domestic codes are mapped to the international standard codes.ar numerous drugs are introduced into theinternational healthcare market. In 2008 alone, a totalof 66 medicinal products received a positive opinionfrom the European Medicines Agency (EMA).

5 Conclusion

This study aimed to develop the K-CDM for drug surveillance in Korea and verify its reliability through multicenter distributed analysis. Through distributed query analysis on the gastrointestinal bleeding risk assessment of NSAIDs, the current results were found to be consistent with those of previous studies. In addition, for the first time, we assessed the cerebrovascular bleeding risk of NOACs among the Korean population, based on our methodology and using real-world data. This research demonstrated the feasibility of active surveillance methodological research utilizing the K-CDM. However, the low quality of the original EMR data, incomplete mapping, and heterogeneity between institutions reduces the validity of the analysis, thus necessitating continuous calibration among researchers, clinicians, and government.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40264-023-01296-2.

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Declarations

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Conflicts of interest Seon Choe, Suhyun Lee, Chan Hee Park, Jeong Hoon Lee, Hyo Jung Kim, Sun-ju Byeon, Jeong-Hee Choi, Hyeon-Jong Yang, Da Woon Sim, Bum-Joo Cho, Hoseok koo, Min-Gyu Kang, Ji Bong Jeong, In Young Choi, Sae-Hoon Kim, Woo Jin Kim, Jae-Woo Jung, Sang-Hoon Lhee, Young-Jin Ko, Hye-Kyung Park, Dong Yoon Kang, and Ju Han Kim declare that they have no competing interests.

Ethics approval Ethical approval for this study was granted by the Institutional Review Board of the Seoul National University (H-1707-135-871).

Consent to participate and consent for publication Consent from participants was not required as this study extracted anonymous data from an electronic health database under Korean regulations and approval from the Seoul National University.

Availability of data and material All data analyzed in this study are included in this published article.

Code availability (software application or custom code) The code generated during the current study is available from the corresponding author upon reasonable request.

Author contributions JHK designed and supervised the study, and SHL designed the K-CDM architecture and managed the mapping. DYK developed and validated the clinical scenario, and HJK constructed the query applicable to each institution. CHP and JHL proceeded with the K-CDM ETL, and SC analyzed the query results and prepared the manuscript. The remaining authors, who oversee each participating organization, extracted the EMRs for conversion to the CDM and performed queries to obtain the results. All authors read and approved the final version of the manuscript.

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