Review

Clinical epidemiology and pharmacoepidemiology studies with real-world databases

By Satomi YOSHIDA,[*1] Masato TAKEUCHI,[*1] Sachiko TANAKA-MIZUNO,[*1] Kayoko MIZUNO,[*1] Masayuki NAKASHIMA,[*1] Toshiki FUKASAWA[*1] and Koji KAWAKAMI[*1,†]

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Abstract: Hospital-based registry data, including patients' information collected by academic societies or government based research groups, were previously used for clinical research in Japan. Now, real-world data routinely obtained in healthcare settings are being used in clinical epidemiology and pharmacoepidemiology. Real-world data include a database of claims originating from health insurance associations for reimbursement of medical fees, diagnosis procedure combinations databases for acute inpatient care in hospitals, a drug prescription database, and electronic medical records, including patients' medical information obtained by doctors, derived from electronic records of hospitals. In the past ten years, much evidence of clinical epidemiology and pharmacoepidemiology studies using real-world data has been accumulated. The purpose of this review was to introduce clinical epidemiology and pharmacoepidemiology approaches and studies using real-world data in Japan.

Keywords: clinical epidemiology, pharmacoepidemiology, real-world databases, claims database, diagnosis procedure combinations database, electronic medical records

1. Introduction

Clinical epidemiology, which has made remarkable progress since the 1980s, is an academic field in which researchers conduct clinical studies on various questions derived from clinical practice, with appropriate epidemiological study designs. Pharmacoepidemiology was established in the U.S. in the 1980s to cover clinical epidemiology and clinical pharmacology.[1),2)] The research fields have expanded to include the effects of pharmaceuticals and biologics, economic research to evaluate the cost-effectiveness of medical treatment, and regulatory science to evaluate the safety of pharmaceuticals, medical devices, and diagnoses. Many types of registry databases are available for clinical and pharmacoepidemiology studies, including product (drug) and disease registries, which were previously used for clinical research, including patients' information collected by academic societies or research groups funded by the Ministry of Health, Labour and Welfare. With the digitizing of patient records owing to advances in information technology, real-world data (RWD) routinely obtained in healthcare settings are now being used.[3),4)] The types available of RWD vary depending on each country's medical system. In Japan, RWD include a database of claims originating from health insurance associations for reimbursement of medical fee, diagnosis procedure combinations (DPCs) database for comprehensive payment for acute inpatient care in hospitals, and a drug prescription database.[5)–7)] More recently, electronic medical records (EMRs), including patients' medical information entered by doctors, derived from electronic records of hospitals, have also come to be used as RWD. Thus, clinical epidemiology and pharmacoepidemiology research have drastically advanced with increase in the data accessibility. Owing to the evolution of computers

[*1] Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan

[†] Correspondence should be addressed to: K. Kawakami, Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshidakonoe-cho, Sakyo-ku, Kyoto 606-8501, Japan (e-mai: kawakami.koji.4e@kyoto-u.ac.jp).

Abbreviations: RWD: real-world data; DPCs: diagnosis procedure combinations; EMRs: electronic medical records; NDB: National Database of Health Insurance Claims and Specific Health Checkups of Japan.

and the enhancement of RWD, especially in pharmacoepidemiological studies, various analytical approaches to the study of epidemiology, such as propensity score methods, and self-controlled/case-only designs, in addition to the traditional regression model analyses have been introduced.[8]–[10] This paper is a review of our published studies, to introduce clinical epidemiology and pharmacoepidemiology approaches using real-world databases.

2. Real-world databases

Claims databases. Japan has been providing universal health coverage to its citizens since 1961. Almost all citizens are enrolled in one of the following types of health insurance: (i) national health insurance, which covers self-employed and unemployed individuals; (ii) employees' health insurance, which covers civil servants and salaried employees; and (iii) the medical care system for the elderly in the latter stage of life (age $\geq$75 years).[11] Patients have free access to any hospital or clinic in the Japanese healthcare system. All medical institutions issue claims for each patient monthly and send them to the corresponding insurers. Claims include information on demographics, medical institutions, inpatient and outpatient diagnoses, procedures, and pharmacy dispensing. Public and private sectors have collected claims from insurers and created claims databases.

In Japan, two types of claims databases are commonly used for epidemiological studies: (i) the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) constructed by the Ministry of Health, Labour and Welfare (MHLW); and (ii) commercial claims databases constructed by private companies. The NDB is largely composed of health insurance claims data and specific health checkup/guidance data, and comprises medical treatment information of virtually the entire Japanese population of over 100 million.[12] Hence, the NDB provides not only a domestic resource for collecting evidence in the fields of healthcare and medicine but it also provides insights for other countries, especially with growing aged populations. Since 2011, the NDB has been made available for research and other purposes upon the request of researchers and through reviews by the expert panel of the MHLW. However, to use NDB, the users are subject to several strict conditions for protecting patient privacy. First, for data management and analysis, the users must use an on-site research center or a facility with advanced security measures. Second, the users must access only the minimum

number of data items necessary for the study. Finally, when users publish their results of analyses, they must ensure that individual patients are not identified. Although smaller in scale than the NDB, the commercial claims database can be used not only by academia and regulatory authorities but also by private companies. Some of these databases contain the registry of insured persons, making it possible to estimate the prevalence and incidence of diseases among the general population with using the accurate enrollment data in insurance registry. However, most of the data sources in commercial databases are claims from corporate health insurance associations, in which case the databases contain little data for people aged $\geq$65 years and no data for people aged $\geq$75 years.

Claims databases and other databases discussed below use a relational database model because they need to manage large amounts of structured data. As a result, a single patient's data are distributed across multiple relations. On the other hand, when analyzing data in epidemiological studies, it is necessary to create a patient-level analysis dataset with one record per patient, as in clinical trials. Thus, researchers need to extract and integrate each patient's data from multiple relations. Building the dataset requires advanced data handling skills, but there are several attempts to make it accessible to non-specialists.[13]

The strength of claims databases is that individuals can be tracked longitudinally across medical institutions by a unique, anonymized identifier unless they discontinue their health insurance. These databases are therefore suitable for studies evaluating outcomes that require long-term tracking. Further, claims databases allow for population-based studies because the population can be clearly identified. On the other hand, claims databases have several weaknesses. First, diagnoses may be inaccurate for some diseases because they are recorded for insurance claims rather than for research purposes. Therefore, when diagnostic records alone cannot identify a particular disease with the expected accuracy, an algorithm combined with medication and procedure records may be used to identify the disease.[14] Algorithms for identifying a disease can be as simple as one for acute myocardial infarction, defined by a single diagnostic code during hospitalization,[15] or as complex as one for the Stevens-Johnson syndrome or toxic epidermal necrolysis, defined by a combination of diagnoses, hospitalization, medications, and multiple procedures.[16]

Second, records of prescriptions and dispensing do not necessarily mean that a patient has taken their medications. If the record is of an injection, it likely means that the medication was used. However, for oral or topical medications, the use of the medication is influenced by the patient's adherence. Finally, claims databases do not contain laboratory test results. However, these results at the time of the specific health checkups for individuals aged 40–74 years can be used by linking them with the claims database.[17),18)]

DPC databases. DPC is the Japanese payment system based on the combinations of diagnoses and procedures for inpatients of acute care hospitals. It is a case-mix payment system according to diagnosis and procedures launched in 2002, which consists of two elements: flat-free per day payment and free-for-service payment.[5)] DPC hospitals account for approximately 20% of all hospitals in Japan. In large hospitals, the proportion is greater (about 55% in the case of 500 beds or more). The advantage of DPC databases is that they capture data of a large number of patients with serious illnesses that require hospitalization. In addition to medical information that can be obtained from the claims databases, DPC databases store information that is useful for understanding the patient's condition at the time of admission, such as weight, height, smoking history, and various clinical scores.[19)] On the other hand, DPC databases have several weaknesses. First, patient tracking in the DPC databases is incomplete. Within the database, one identifier is assigned to each patient for each DPC hospital. Consequently, records of medical care that patients received at the same DPC hospital can be captured, but those received at other medical institutions cannot. DPC databases are therefore suited for research on diseases that are continuously treated at the same hospital, such as hepatitis[20)] and autoimmune diseases,[21)] as well as for research to evaluate patient outcomes during hospitalization. Second, the generalizability of the study results is limited. Results from studies using DPC databases may accurately reflect the reality of acute care, but may not be generalizable to clinics and chronic care settings. Finally, most test results (blood test, biochemical test, pathology, imaging findings, *etc.*) cannot be obtained.

Pharmacy dispensing databases. Pharmacy dispensing datasets are constructed by companies that manage pharmacy dispensing chains.[22),23)] Major pharmacy dispensing companies collect prescription information from pharmacy chains and generate real-world data on dispensing nationwide. The strength of pharmacy dispensing databases is that they store not only data on drugs dispensed under insurance coverage but also information on drugs used off-label or dispensed at their own expense.[24)] On the other hand, a weakness of the pharmacy dispensing databases is that they do not contain data other than dispensing-related information, such as data on diagnoses, procedures, and laboratory test results. These databases are therefore suitable for research assessing utilization patterns of drugs with few indications, but not for outcomes research. Another weakness is that patient tracking is incomplete, as it is only possible within the same pharmacy chain.

EMR databases. Electronic medical records (EMRs), also interchangeably referred to as electronic health records, contain large quantities of health care data that are captured during routine care.[25)] EMRs have been recognized as important resources for observational health research because they encompass data derived from the large volume of real-world practice that may include a diverse patient population. Although the common set of parameters for the minimal data variables necessary to constitute EMRs may not yet exist, they typically involve structured data such as diagnosis (coded by the disease classification system), prescription records, procedures, and laboratory values. Some EMRs contain unstructured data such as physician's notes, however, currently there are challenges to using such data when they are contaminated by redundant and erroneous information resulting from copying and pasting of older information.[26)]

The strength of EMR databases is that they store a wide variety of laboratory test results. This makes it possible to observe changes over time in laboratory values, such as renal function, liver function, and inflammation markers, which generally cannot be evaluated based on claims data alone.[27)] In addition, it is possible to evaluate the effectiveness and safety of drugs for each subgroup classified based on laboratory values. Another strength is that diagnoses are recorded more accurately than in claims databases. This is because EMRs are recorded by physicians for patient management, not for claims reimbursement. It should be noted, however, that the accuracy of diagnoses depends on the physician's expertise, and thus the accuracy may vary depending on the disease. The weakness of EMR databases is that, as with the aforementioned DPC databases, medical information cannot be ascertained if a

patient is transferred or receives treatment at another medical institution.

3. Epidemiological studies using the administrative claims database of health insurance

To date, various epidemiological studies have been conducted using claims databases.[28)–66)] Four such examples are described below.

The first is a descriptive study on pharmacological treatment patterns of patients with young-onset Parkinson's disease (YOPD).[45)] YOPD has been reported to account for only 5–10% of all PD cases, and their treatment patterns remain unclear. This study included 131 patients aged 21–50 years newly diagnosed with PD between January 2005 and March 2016. Of this total, 93.1% were prescribed antiparkinson drugs. Dopamine agonists (77.1%) were the most frequently prescribed medications, followed by levodopa (44.3%), and anticholinergics (27.5%). Dopamine agonists (49.2%) were the most commonly prescribed first antiparkinson drugs, followed by anticholinergics (23.8%), levodopa (19.7%), and others (4.1%). The equivalent daily dose of levodopa increased steadily with disease duration. These findings should be helpful to physicians who rarely encounter YOPD patients.

The second is a cohort study comparing adherence, persistence, and major adverse cardiac and cerebrovascular events (MACCE) between generic and branded statin users during one-year follow-ups.[32)] Generic drugs are less expensive than branded drugs and may improve adherence and persistence. However, some patients suspected that generic drugs are inferior to branded ones. This study's population included 32,130 patients initiating the use of generic statin and 15,640 patients initiating consumption of branded statin between 2014 and 2016. After a 1:1 propensity score matching, 14,313 patients in each group were included for analysis. Adherence to statin treatment was higher in the generic group than in the branded group (median proportion of days covered, 90.2% *vs.* 87.9%; p < 0.001). Fewer patients discontinued statins in the generic group (24.2% *vs.* 27.7%; hazard ratio [HR], 0.91; 95% confidence interval [CI], 0.87–0.95). Differences in MACCE occurrence were not significant between the two groups (4.3% *vs.* 4.2%; HR, 1.04; 95% CI, 0.93–1.17). These findings suggested that generic statin did not impair the therapeutic benefits and might improve medication adherence and persistence.

The third is a cohort study comparing outcomes of laparoscopic surgery (LS) with those of open surgery (OS) for pediatric inguinal hernia.[47)] The study included 5,554 patients, with 2,057 patients in LS and 3,497 patients in OS. The incidence of recurrence was not significantly different between OS and LS (unilateral: OS 0.2% *vs.* LS 0.3%, p = 0.44, bilateral: OS 0.6% *vs.* LS 0.6%, p = 1.00). The incidence of metachronous hernias was significantly higher in OS than in LS (4.8% *vs.* 1.0%, p < 0.001). The surgical site infection rate was significantly lower after OS than after LS for unilateral surgeries (0.9% *vs.* 2.2%, p = 0.002). There was no difference between OS and LS in the length of hospital stay. Both methods have advantages and disadvantages; therefore, the choice of operative technique depends on the patient, their family, and the doctor's preference.

The fourth is a case–control study of the association between diabetes and the risk of early-onset Alzheimer's disease (AD).[57)] Previous studies have reported that diabetes is a risk factor for all-cause and vascular dementia. However, diabetes as a risk factor for AD remains controversial. This study included 371 AD cases and 1,484 non-AD controls aged 40–64 years and took place between 2005 and 2016. Conditional logistic regression was used to estimate odds ratios (ORs) of early-onset AD associated with diabetes. There was no significant association between diabetes and risk of early-onset AD (adjusted OR, 1.31; 95% CI, 0.90–1.92). In the subgroup analysis of gender, a weak association was observed among male patients (adjusted OR, 1.68; 95% CI, 1.06–2.67) but not female patients (adjusted OR, 0.73; 95% CI, 0.38–1.39).

Other than these studies, we conducted claims database studies for mothers and children because each health insurance package was applicable for the entire family and some claims data allow identification of family members. We examined the association between antidepressant use and autism spectrum disorders (ASDs) using claims data collected in Japan because there are concerns that treating pregnant women with antidepressants may increase the risk of ASDs in their offspring.[46)] For 26,925 mother-child pairs, a crude analysis showed that the ASD prevalence in children was significantly higher with any antidepressant use than with non-use (odds ratio [OR], 2.32; 95% confidence interval [CI], 1.08, 4.95). However, when the analysis was adjusted for the confounding effect of maternal depression during pregnancy, statistical significance was lost (OR, 0.76; CI, 0.27, 2.18). After adjustment for confounders, we

found no significant association between antidepressant use during pregnancy and ASD in children in Japan. Furthermore, we also evaluated the association between maternal antidepressant use during pregnancy and the children's congenital anomalies using the same claims data.[39] However, we found no increased risk of congenital anomalies in children whose mothers used antidepressants during the first trimester of pregnancy compared to that of non-users.

For further studies using the claims database for mothers and children, we tested the effects of antibiotic exposure during pregnancy on the patients' offspring. The first study examined the effects of prenatal exposure to antibiotics and asthma development in children.[53] The results showed that antibiotic exposure during the fetal period was associated with early asthma development (until age 3; HR: 1.18, 95% CI: 1.08–1.30) but this association was absent after 3 years. That is, though exposure to antibiotics during the first year of life was associated with childhood asthma even after adjusting for familial factors, the association was weak. Furthermore, we also examined the association between prescribing antibiotics for infants and subsequent atopic dermatitis (AD).[66] The exposed group was more likely to develop AD than the non-exposed group, but this association was absent when we carried out the secondary, sibling-matched analysis of the two groups. Though antibiotic use in infancy was associated with a subsequent increase in the incidence of AD, antibiotic use may not be a critical factor in the development of AD.

4. Epidemiological studies using NDB

A variety of clinical research using NDB has also been conducted.[67]–[69] Two such examples are described below. Ono et al.,[67] evaluated a risk-based antithrombotic strategy for Japanese patients with atrial fibrillation (AF) who undergo percutaneous coronary intervention (PCI) based on CHA_2DS_2-VASc and HAS-BLED scores using NDB. They identified 10,862 AF patients who underwent PCI from April 2014 to March 2015 and 87.5% had high risk scores. There were no significant differences in antithrombotic therapies across the risk strata. More than 30% of patients at high risk of thrombosis did not receive oral anticoagulant prescriptions at discharge. The hazard ratio of incidence of stroke in patients with prior stroke compared with patients without prior stroke was 9.09 (95% CI, 7.86–10.50, p < 0.01). Among Japanese AF patients who under-

went PCI, prescriptions for antiplatelet agents were more common than those for anticoagulant agents. The majority of study participants were classified as high risk, suggesting a need for a new risk classification that reflects the risk profiles of Japanese patients.

The NDB database is also useful for research on rare diseases since epidemiological data on them are often difficult to evaluate when not collected nationwide. Matsubayashi et al.[68] examined 12,713 people aged ≥20 years, newly diagnosed with acromegaly, and their treatment patterns between January 2014 and December 2017. The annual prevalence in 2015–2017 was 9.2 cases per 100,000 in the prevalence cohort, and the annual incidence in 2013–2017 was 0.49 cases per 100,000. Regarding the treatment patterns, 54% and 45% of patients received surgery and medical treatment as the primary treatment, respectively. These researchers were able to show real-world evidence on rare diseases like acromegaly using the NDB database.

5. Epidemiological studies using the diagnosis procedure combinations (DPCs) database

This section describes the DPC and reviews several studies using DPC databases.[65],[70]–[97] There are two pathways to access the DPC databases, one is upon a request to the Ministry of Health, Labour and Welfare and the other is purchasing from private companies. Here, several research studies using private databases are reviewed below.

The first one is a self-matched, case-crossover study.[75] This study investigated the association between potentially inappropriate medication (PIM) use and unplanned hospitalization among elderly patients. Records from 247,897 patients aged ≥65 years with unscheduled admissions between January 2009 and December 2015 were analyzed. PIMs were defined based on the Japanese Guidelines for Medical Treatment and Its Safety in the Elderly. Conditional logistic regression analysis to fit self-matched case-crossover models was used and each patient's PIM use over five case periods (1, 2, 4, 8, and 12 weeks) prior to each unplanned hospitalization was compared. The highest odds ratios (ORs) of unscheduled admission related to PIM use was in the 1-week case period [OR 4.15; 95% confidence interval (CI) 4.05–4.25], followed by the 2-week (OR 3.01; 95% CI 2.95–3.07), 4-week (OR 3.91; 95% CI 3.83–4.00), 8-week (OR 2.00; 95% CI 1.96–2.05), and 12-week case periods (OR 1.48; 95% CI 1.44–1.51). Elderly patients commonly used PIMs, especially

antidiabetics and diuretics. PIM use was associated with a 1.5- to 4-fold increase in the ORs of unplanned hospitalization among them.

The second example is a retrospective cohort study on chemotherapy.[76] A survival benefit of using regorafenib and trifluridine/tipiracil (TFTD) in patients with colorectal cancer has been shown in previous randomized controlled trials (RCTs). However, there is no RCT or large-scale observational study directly comparing regorafenib and TFTD. Therefore, this study compared the effectiveness of regorafenib, TFTD, and sequential combination therapy with both these drugs. The study included 7,279 patients (regorafenib: 1,501, regorafenib/ TFTD: 973, TFTD: 3,777, and TFTD/regorafenib: 1,028). The corresponding median overall survival (OS) was 6.4, 16.4, 10.2, and 16.9 months, respectively. A log-rank test showed significant intergroup differences (p < 0.001). In the subgroup analysis, the group in which TFTD was administered first showed significantly longer OS. The incidences of adverse events were the lowest in the TFTD group. The TFTD group showed longer OS than the regorafenib group, and sequential drug use resulted in the most prolonged OS. This study is the first in which TFTD resulted in significantly longer survival than did regorafenib when used singly. Compared with single-agent use, the concomitant use of both regorafenib and TFTD resulted in prolonged survival, regardless of order.

The third is a retrospective cohort study evaluating the effectiveness and safety of early enteral nutrition (EN) for patients who received targeted temperature management (TTM) after out-of-hospital cardiac arrest (OHCA).[77] OHCA patients who received TTM from April 2008 to March 2017 were included. Those who received EN within 2 days from the start of TTM were defined as the 'early EN group', and the remaining patients comprised the control group. Of these, 266 propensity-score matched pairs were created. Cox regression analyses revealed no significant difference in 30-day mortality between the groups (hazard ratio [HR]: 0.90; 95% confidence interval [95% CI]: 0.65–1.25). Subgroup analyses of patients with a low body mass index ($< 18.5\,\mathrm{kg/m^2}$) revealed a significant decrease of 30-day mortality in the early EN group (HR: 0.30; 95% CI: 0.092–0.97). This study suggested that early EN could be beneficial for patients with a low BMI.

The fourth one is a retrospective cohort study of the risk of developing venous thromboembolism (VTE) in patients with nephrotic syndrome.[78] Nephrotic syndrome is associated with a higher risk of developing VTE. However, the risk factors of VTE in nephrotic syndrome are not well established. Data derived from patients aged ≥18 years hospitalized with nephrotic syndrome were extracted from the database. Of the 7,473 hospitalized patients with nephrotic syndrome without VTE, 221 (3.0%) developed VTE. The risk factors of VTE in patients with nephrotic syndrome during hospitalization were determined through multivariable logistic regression. Being female (odds ratio [OR] 1.39, 95% confidence interval [CI] 1.05–1.85), body mass index (BMI) ≥30 (OR 2.01, 95% CI 1.35–2.99), acute kidney injury (OR 1.67, 95% CI 1.07–2.62), sepsis (OR 2.85, 95% CI 1.37–5.93), lupus nephritis (OR 3.64, 95% CI 1.58–8.37) and intravenous corticosteroids use (OR 2.40, 95% CI 1.52–3.80) were associated with an increased risk of VTE.

The fifth one is a retrospective cohort study of the prognoses of patients with tongue cancer.[79] Whether the prognosis of tongue cancer differs between young patients and elderly patients remains controversial. This study aimed to compare prognoses of patients with young-onset and old-onset tongue cancer. Patients ≥ 20 years of age diagnosed with tongue cancer between April 2008 and January 2019 were included. Patients were divided into two groups based on age at tongue cancer diagnosis, a < 45 years group, and a ≥ 45 years group. A total of 2,315 patients diagnosed with tongue cancer were included in the study, of whom 1,412 patients were diagnosed based on the seventh edition of the Union for International Cancer Control in the multivariable Cox proportional hazards modeling. The adjusted hazard ratio for overall survival was 1.22 (95% CI 0.66–2.24, p = 0.54) and that for disease-free survival was 1.14 (95% CI 0.80–1.61, p = 0.47), and neither differed significantly between the two age groups.

6. Epidemiological studies using pharmacy dispensing datasets

This section describes studies using datasets constructed by companies that manage pharmacy dispensing chains.[22),98)–102] Kochi *et al.*[100] integrated pharmacy datasets from three major companies of dispensing pharmacies in Japan to investigate the prescription of antipsychotics. The 152,592 outpatients included 101,133 (66%) adults (18–64 years of age) and 51,459 (34%) elderly individuals (≥65 years of age). Among the adults, second-generation antipsychotics (SGA) monotherapy prescriptions increased from 49% in 2006 to 71% in 2012, first-

generation antipsychotics (FGA) monotherapy pre- scriptions decreased from 29% to 14%, and anti- psychotic polypharmacy decreased from 23% to 15%, respectively. Among the elderly individuals, SGA monotherapy prescriptions increased from 64% to 82%, FGA monotherapy prescriptions decreased from 29% to 12%, and antipsychotic polypharmacy decreased from 7% to 6%, respectively. They concluded that high-dose prescriptions and antipsy- chotic polypharmacy among Japanese outpatients were not as prevalent as has been previously thought. Dispensing databases also contain prescriptions for self-funded treatments and treatments not reim- bursed by the medical insurance system. Kinoshita et al.,[102] using pharmacy dispensing datasets, inves- tigated the use of combined oral contraceptives (COCs) among women who were prescribed COCs during 2006–2014. They found that a very small proportion of women use oral contraceptives, although the proportion is increasing.

7. Epidemiological studies using the electronic medical records (EMR) database

There have been few studies conducted by utilizing EMRs in Japan, to date.[27),103)] We introduce here, our study using EMRs to illustrate how laboratory test results added value to observational research in two aspects: enhanced comparability between groups, and sound outcome definition. Sodium–glucose cotransporter-2 (SGLT2) inhibitors are the latest class of antidiabetic medication.[27)] In placebo-controlled trials, renoprotective effects of SGLT2 inhibitors have been demonstrated. We aimed to establish that this renal benefit would also be expected among patients with type 2 diabetes, via a comparison of SGLT2 inhibitors with an active drug (i.e., a non-placebo). From EMRs, we extracted data of new users of SGLT2 inhibitor class, and compared them with the new users of other types of antidiabetic drugs (e.g., dipeptidyl peptidase-4 in- hibitor class). The new user design includes a cohort of patients initiating treatment with a drug of interest, who are followed up from treatment initiation, similar to randomized trials. This may also minimize the indication bias by comparing cohorts with a similar drug indication.[104)] In the case of diabetic medication, the patient introduced to a new anti-diabetic drug may be a native medication user who was originally diagnosed with diabetes, or may be a prevalent user whose glycemic control was not optimized. It was expected that the effects of the new class of drug was similar among different

antidiabetic drugs. However, the initiators of SGLT2 inhibitor had different characteristics as compared with the initiators of other class drugs; they differed in age, glycemic control, baseline renal function, and history of medication use. To account for these imbalances, we created a matched cohort with a propensity score. The propensity score represented the probability of being treated with the new prescription of SGLT2 inhibitors, calculated with patient characteristics using laboratory values (e.g., hemoglobin A_{1c} or the baseline estimated glomerular filtration rate [eGFR]). Finally, cohorts were com- parable in that they shared similar baseline charac- teristics. In our study, the endpoint was the trajectory of eGFR after the initiation of either SGLT2 inhibitor or other class of diabetic medica- tion. The new onset of end-stage renal disease or the initiation of chronic dialysis is the "true" or patient- centered endpoint of renal diseases, but it may take a decade or longer to experience such outcomes in patients with diabetes who had less advanced kidney disease. The slope of eGFR is instead considered as the surrogate of the advanced kidney endpoint (e.g., dialysis) in the short term; as SGLT2 inhibitors were introduced into the market in 2014, only the short-term data were thus far available for SGLT2 inhibitor users. The value of eGFR at each time-point was estimated with serum creatine measures. Finally, we compared a matched cohort of 1,433 SGLT2 inhibitor initiators and 2,739 initiators of other classes of diabetic medication (mean age: 61 years).
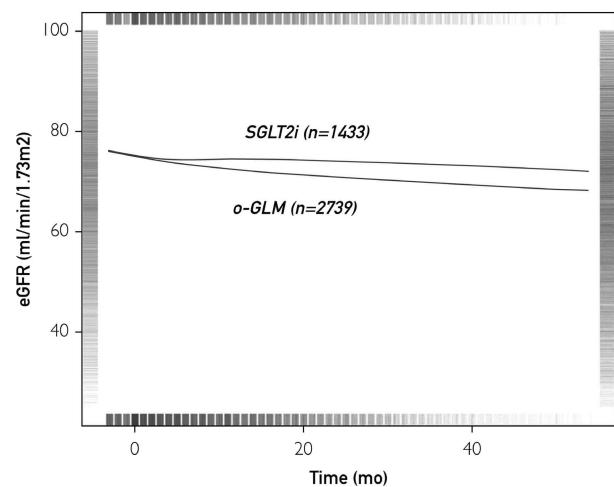

Fig. 1.   (Color online) SGLT2i: sodium–glucose cotransporter-2 inhibitor, o-GLM: other glucose lowering medication, eGFR: baseline estimated glomerular filtration rate. This figure is distributed under CC BY 4.0 license, with the permission of the Journal Office of Ref. 27.

They were followed for median: 17 months (maximum: 54 months). Although the eGFR declined over time in both groups, the slower declining eGFR was graphically observed in SGLT2 inhibitor users (Fig. 1).

In summary, we overviewed the latest clinical epidemiology and pharmacoepidemiology using real-world databases through reviewing our published studies. Since our study is not a systematic review that includes entire previous studies, there is a limitation in our review because of introducing publications from a single laboratory. For further enhancements in this field, both the development of RWD and evolving the analytical approaches are necessary.

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Profile

After graduating from Tsukuba University, Japan, in 1997, Dr. Koji Kawakami underwent residency training in head and neck surgery and otorhinolaryngology. During his PhD program, Dr. Kawakami moved to the Center of Biologics Evaluation and Research (CBER) at the United States Food and Drug Administration (FDA) as a postdoctoral fellow, and he was subsequently promoted to an IND reviewer of clinical trials in the US. His specialty was the evaluation of cancer vaccines, gene therapy, and cellular therapy products. After 6 years with the FDA-CBER, Dr. Kawakami moved back to Japan as an Associate Professor of the University of Tokyo Hospital to perform cutting-edge research on applied biotechnology to develop new therapeutics and medical devices against cancer and inflammatory diseases. In 2006, Dr. Kawakami moved to Kyoto University Graduate School of Medicine as a Professor and Chair of Pharmacoepidemiology, where he is conducting research programs focusing on clinical- and pharmaco-epidemiology utilizing large medical databases, cost-effectiveness research on drugs, and the development of novel anticancer drugs and devices. Dr. Kawakami has also served as a Director of Science for the Innovation Policy Unit, Center for Promotion of Interdisciplinary Education and Research of Kyoto University since 2012.