Clinical Kidney Journal

Clinical Kidney Journal, 2021, vol. 14, no. 5, 1307–1316

doi: 10.1093/ckj/sfaa244
Advance Access Publication Date: 14 December 2020
CKJ Review

CKJ REVIEW

# Pharmacoepidemiology for nephrologists (part 1): concept, applications and considerations for study design

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## ABSTRACT

Randomized controlled trials on drug safety and effectiveness are the foundation of medical evidence, but they may have limited generalizability and be unpowered to detect rare and long-term kidney outcomes. Observational studies in routine care data can complement and expand trial evidence on the use, safety and effectiveness of medications and aid with clinical decisions in areas where evidence is lacking. Access to routinely collected large healthcare data has resulted in the proliferation of studies addressing the effect of medications in patients with kidney diseases and this review provides an introduction to the science of pharmacoepidemiology to critically appraise them. In this first review we discuss the concept and applications of pharmacoepidemiology, describing methods for drug-utilization research and discussing the strengths and caveats of the most commonly used study designs to evaluate comparative drug safety and effectiveness.

**Keywords:** adverse effects, biostatistics, drugs, epidemiology, nephrotoxicity

## INTRODUCTION

Drug prescription epitomizes modern medicine. The safety and effectiveness of drugs are tested in adequately designed Phase III randomized controlled trials (RCTs) to gain regulatory approval and enter into the market. However, the results of such trials may not generalize to the general population that will receive the drugs, due to strict inclusion and exclusion criteria, strict treatment strategies and monitoring protocols. A historical sad example of the unintended effects of drugs dates back to the 1960s, with the withdrawal of thalidomide after serious teratogenic effects [1]. This is not an isolated example; ~10% of all drugs introduced in the market during the last 70 years have been withdrawn because of the discovery of adverse drug reactions (ADRs) [2–4]. Consequently, testing of the long-term safety of newly introduced drugs in the community (i.e. post-marketing studies) is mandated by regulatory agencies. Because routine care is 'complex and diverse' (Table 1), a discipline within epidemiology, i.e. pharmacoepidemiology,

*Received: 13.8.2020; Editorial decision: 12.10.2020*

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focuses on complementing trial evidence with the evaluation of drug use, safety and effectiveness at the bedside.

With this review we initiate a series of three articles to introduce the rationale, methods, applications and biases that are commonly applied in pharmacoepidemiology research, with a focus on studies in the field of nephrology. We herein describe basic concepts, applications of pharmacoepidemiology and the most commonly used study designs.

## WHAT IS PHARMACOEPIDEMIOLOGY AND WHY IS NEPHROLOGY IN NEED OF IT?

The loss of kidney function alters drug metabolism and clearance [5, 6]: low kidney function prolongs the half-life of drugs and metabolites, which may limit the efficacy of the drugs and increase the risk of ADRs; the kidneys are vulnerable to injury due to their high filtration capacity and high metabolic activity, and drug-induced nephrotoxicity accounts for 18–27% of episodes of acute kidney injury (AKI) [7]; and persons with chronic kidney disease (CKD) have multiple comorbidities and use multiple drugs, which means a higher potential risk of ADRs and drug–drug interactions. Perhaps due to these and other reasons, there are traditionally fewer RCTs conducted in the field of nephrology as compared with other disciplines in medicine, and CKD patients have been largely excluded or underrepresented in RCTs in cardiovascular and cancer research [8–12]. Even when trials have been carefully conducted, included patients are not representative of the general population of patients consuming those drugs [13]. In addition, the size or duration of the trials may not be enough to explore AKI or end-stage kidney disease (ESKD) risks [14].

Pharmacoepidemiology is commonly defined as the study of the therapeutic effect(s), risk(s) and use of drugs in large populations using epidemiological methods and/or reasoning [15]. It is a powerful but complex discipline that can provide guidance in areas with limited evidence. However, wrong conclusions can be drawn if inadequate methods are utilized and when biases are not accounted for.

Pharmacoepidemiology can fill this void of evidence in nephrology and address medical dilemmas where trials are unlikely to happen, such as:

i. a trial that would not be ethical. Randomizing malnourished patients on dialysis to oral nutritional support would not be ethical, yet we lack proof that treating malnutrition is effective. Lacson *et al.* [16]. compared outcomes of hypoalbuminaemic patients who received (or not) oral nutritional supplements.
ii. a trial unlikely to be financed, such as the evaluation of the safety profile of off-patent drugs like warfarin in patients with advanced CKD [17].
iii. a trial that excluded certain populations, such as pivotal trials on the safety and effectiveness of fondaparinux that included patients with ST-segment elevation myocardial infarction (STEMI) but excluded patients with CKD [18].

## WHAT DATA ARE NEEDED?—THE DEVIL IS IN THE DETAILS

The choice of the study design and analysis, as well as the conclusiveness of the results all depend on the quality of the data at hand. For pharmacoepidemiological studies, we ideally need rich longitudinal data and awareness of the medication use process (Figure 1). In Table 2 we compare some potential advantages and disadvantages of classical data sources for pharmacoepidemiological research. It should be noted, however, that each data source is unique and may not necessarily fit into the categories described. The objective of Table 2 is simply to make

**Table 1. Selected differences between RCTs and observational analyses from routinely collected healthcare data**

| Characteristic | RCTs | Routine care data |
|---|---|---|
| Data collection | Prospective | Prospective/retrospective |
| Population | Population with strict inclusion and exclusion criteria | Wider and more inclusive segment of the population |
| Adherence | Facilitated by planned visits during follow-up | Reflect the drug usage in clinical practice; cannot be guaranteed |
| Outcomes | Allows one to demonstrate efficacy and safety needed for drug approval but may miss the power to detect adverse effects | Investigate the effectiveness and safety of the drug in routine clinical practice |
| Health economics | Often not possible to evaluate costs | Can provide cost–benefit evaluations |

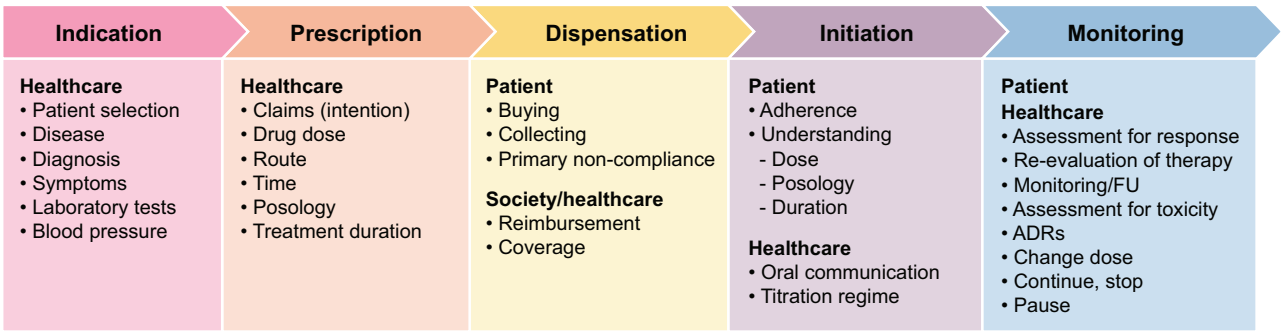


**FIGURE 1:** Steps in the process of drug use and interplay between different players (i.e. healthcare, society and patients).

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**Table 2. Most common administrative data sources for pharmacoepidemiological research**

| Type of source | Description | Advantages | Disadvantages |
|---|---|---|---|
| Disease-specific cohorts or registers | Data are collected for a specific disease | Availability of disease-specific data<br>Potentially data-rich (including laboratory measurements), collected on planned visits<br>Low degree of missing data | Less generalizable<br>Information available from pre defined visits but not between visits (e.g. medication may have been started between visits) |
| Healthcare utilization cohorts | Data obtained from healthcare sources (e.g. hospital visits) | Availability of frequent longitudinal data<br>Population coverage<br>Wide coverage of medications | Data availability depends on the frequency of healthcare use<br>Missing information on drugs dispensed in pharmacies |
| Reimbursement or insurance data sources | Data obtained on reimbursed procedures or prescriptions | Wide coverage of medications<br>Population coverage<br>Potentially complete longitudinal data | Data availability depends on the frequency of healthcare use<br>Missing in-hospital drugs<br>Missing over-the-counter medications |

the reader reflect on the importance of data richness for drug-related analyses.

'Disease-specific cohorts' or registers are created around a certain disease or characteristic (e.g. incident CKD Stage 4). Patients are often followed during per-protocol planned visits (e.g. annually) that are scheduled depending on the nature of the disease and the availability of resources. These data sources can be rich if adequately designed, collecting information on patient characteristics, medical history and medications use at each visit. However, it may be less accurate for events occurring between visits. 'Healthcare utilization cohorts' have become more accessible with the increased availability of data from electronic clinical records. They may have large sample sizes and the duration of follow-up can be longer, but the information available tends to be less rich. Information on when a drug is initiated may be available. Since information during follow-up depends on healthcare use (as opposed to the planned visits of a cohort study), sicker individuals will have more detailed information than healthy ones and the indications for starting a drug may be multiple. Finally, 'reimbursement/insurance databases' can provide other complementary aspects of healthcare, such as the dispensing of prescribed drugs at pharmacies. This is a rich source of longitudinal information on prescriptions and/or the dispensing of drugs with potentially complete population coverage (if the country provides universal healthcare). In some cases the databases are linked to a specific healthcare provider or insurance system, so only insurers of that company or accesses of the particular healthcare provider will be recorded.

Data on prescribed drug dosages and laboratory measurements during follow-up are particularly important for pharmacoepidemiology: information on prescribed drug dosages at each dispensation may help to identify dose adequacy, under/overdosing or drug titrations after relevant events [e.g. reduction of renin–angiotensin system inhibitor (RASi) dose after hyperkalaemia]. While some ADRs are severe and result in clinical diagnoses (e.g. rhabdomyolysis due to statin use), laboratory measurements can help to quantify many ADRs that often are not coded with diagnoses (e.g. most hyperkalaemia events associated to RASi need to be identified from potassium measurements as they may not be severe enough to result in a diagnostic code).

'Prospective data collection' has many strengths. However, it requires that we identify early on all the information that we might need, since it will not be possible to obtain that information in the future. In prospective data collection, it is possible to schedule the same number of visits for all included patients, which is important for data homogeneity (e.g. all patients will have the same number of laboratory tests). This data collection approach, however, comes with elevated costs in terms of resources and funding. In addition, prospective cohorts may not contain a sufficient number of new users of a medication and be underpowered to evaluate safety and effectiveness [19]. Conversely, 'historical cohorts' (such as electronic healthcare extractions) are less expensive and more time efficient since the data have already been collected (often from administrative and registry data). However, the quality and frequency of the data rely completely on the type of data source available, with an increased risk of missing information or data sparsity and healthcare utilization bias (e.g. the sicker come to visit the doctor more often and will have, for example, more laboratory measurements taken).

## APPLICATIONS OF PHARMACOEPIDEMIOLOGY I: DRUG UTILIZATION RESEARCH

Drug utilization research integrates descriptive and analytical methods for the quantification, understanding and evaluation of the processes of prescribing, dispensing and consumption of medicines and for the testing of interventions to enhance the quality of these processes. The discipline is also closely related to health outcomes research, pharmacovigilance and health economics. Drug utilization studies can be performed to evaluate the extent of drug use, rate of introduction of novel therapies, differences in patterns of use across health systems, inappropriate use (off-label or no dose adjustments) and inadequate therapy monitoring and surveillance. Through the next sections we will describe common methods for this and provide examples of its application.

### Measuring medication use and treatment initiation/monitoring

Treatment initiation is defined as the moment 'when the patient takes the first dose' [20]. Identifying the moment of a

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drug initiation may not be easy in administrative data, especially when the time window is limited. New users can be identified by defining a time period prior to the drug prescription in which we assess that there are no other prescriptions of the same class of medication. How long this period should be depends on the study objective, available administrative data and pattern of use of the drug being investigated [21–23]. The expected duration and long-lasting effects of a single dispensation can be used to determine the length of the time period.

Pharmacoepidemiology can be used to identify healthcare gaps in drug monitoring practices, which sets a basis for educational campaigns targeting physicians. Nilsson *et al.* [24] explored the adherence to the guideline recommendation of monitoring potassium and kidney function in patients with heart failure (HF) during the initial weeks of mineralocorticoid receptor agonists (MRAs) treatment. They evaluated the presence of potassium and creatinine laboratory testing before MRA initiation and in the early (Days 1–10) and extended (Days 11–90) post-initiation periods. Although potassium and creatinine monitoring before MRA initiation was frequent, rates of post-initiation monitoring were largely inferior to the recommendation in clinical guidelines, especially among primary care centres.

Pharmacoepidemiology can also be used to learn how clinicians treat the same condition differently and identify best therapeutic approaches. Alencar de Pinho *et al.* [25] evaluated the prevalence of uncontrolled blood pressure and blood pressure management across 17 geographically diverse cohort studies of CKD patients. The authors observed large differences in the prevalence of uncontrolled hypertension across cohorts (between 38% and 61%), but more interestingly, there was considerable heterogeneity in both the type and number of antihypertensive drug classes prescribed in these patients.

It should be remembered that no perfect assessment of drug use exists. For example, the presence of a prescription claim does not necessarily mean that the patient collected it at the pharmacy, a drug dispensation does not necessarily mean that the patient took the medicine dispensed and self-reported drug use may suffer from recall bias.

## Measuring medication persistence and discontinuation

Once the medication has been prescribed and dispensed, information on subsequent dispensations provides longitudinal information on the length of treatment and allows us to evaluate changes in treatment patterns, dose or cessation/interruptions. Medication persistence refers to the 'duration of time from initiation to discontinuation of therapy' [26]. Persistence and discontinuation can be investigated using administrative data, provided that there is information from subsequent prescription or dispensation claims as well as of the amount of drug dispensed (e.g. number of pills). There are two main methods to assess medication persistence: the refill-gap method and the treatment anniversary method.

The refill-gap method is based on the concept that patients are persistent in their therapy as long as they keep refilling the drug within a pre-specified period of time (Figure 2). This period can be specified using the information on the dispensed number of days of supply. It is recommended to allow for a time gap that has to be added to the expected date of refill [27–33]. This gap is used to account for medications stockpiling or non-registered changes in the treatment regime (the drug dose might be reduced for a short period or temporarily discontinued). Moreover, periods in which the patient was hospitalized should also be excluded when there is no available information on in-hospital treatments in the administrative data, assuming that the treatment is provided in the hospital. Whenever patients do not meet the aforementioned requirements, there is a discontinuation in the treatment. Usually the date of discontinuation is set as the date on which the patient was expected to refill the prescription, but other approaches, such as defining the discontinuation date in the middle of the last prescription period [31], have been applied. As an example, Qiao *et al.* [29] evaluated the risk of discontinuation of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) in patients with an estimated glomerular filtration rate (eGFR) $\geq$15 mL/min/1.73 m$^2$ and without ESKD [29]. Discontinuation was defined by the lack of a prescription of ACEis/ARBs within 60 days from the end of the previous prescription, including also a sensitivity analysis with a gap of 90 days.

This method is useful to describe drug utilization patterns. The length of drug use can be estimated as the difference in time from initiation to discontinuation [27, 34]. However, the refill-gap method also has a number of limitations. First, the definition of persistence periods is sensitive to the definition of the permissible gaps. The shorter the gap, the greater the chance of identifying discontinuations during follow-up. Sensitivity analyses using different time windows can help to assess the robustness of the results [27, 29]. Second, some medications can be stocked over time and the patient may be late to refill because they are using their accumulated supplies, causing an overestimation of the discontinuation rate [35]. Third, administrative data do not always provide reliable information on the days of supply, e.g. due to non-specific or missing physician's prescriptions.

The treatment anniversary method defines persistence based on whether or not patients are still taking treatment at a pre-specified period of time after treatment initiation (Figure 3). It can be applied for as long as a patient remains under follow-up, using different anniversary dates (e.g. the 6-, 12- or 24-month anniversary) [36–38]. As an example, Tonelli *et al.* [37] evaluated the risk of AKI among elderly patients and statin use.

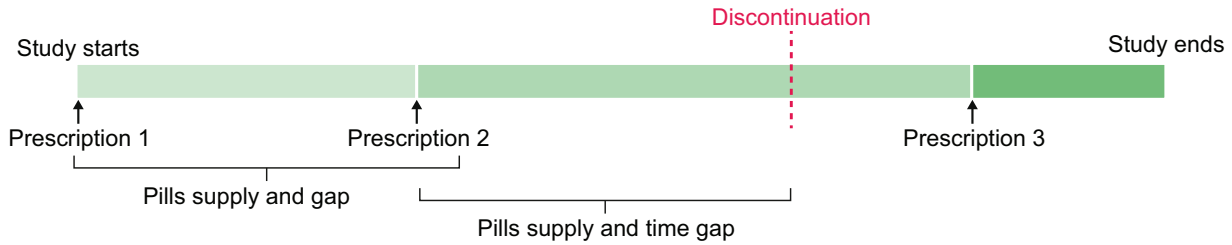


**FIGURE 2:** Assessment of drug persistence/discontinuation based on the refill-gap method. In this example there is a treatment discontinuation during follow-up because the third prescription of the treatment occurred after the pill supply + time gap period from the second prescription.

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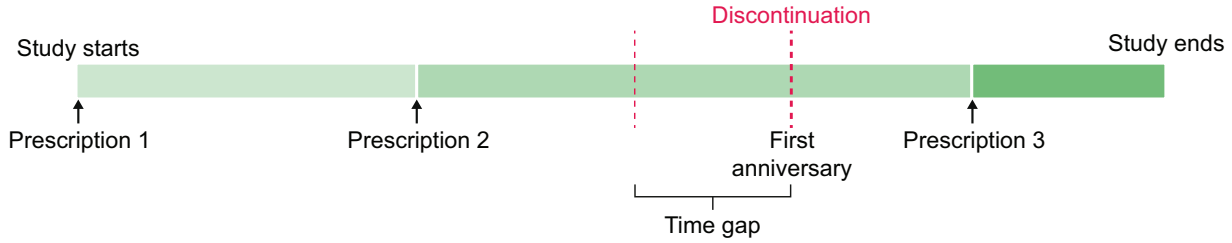


**FIGURE 3:** Assessment of persistence/discontinuation based on the treatment anniversary method. In this example there is a treatment discontinuation during follow-up because the third prescription of the treatment occurred after the predefined 'anniversary' (including also a time gap).

Treatment was reassessed every 30 days, allowing for switching between treated and untreated periods. Applying these methods the authors showed a small but significant increase in the risk of AKI among statin users. The challenging part is to define an appropriate anniversary period, which should be based on clinical practice and previous research. As for the refill-gap method, it may be appropriate to add a permissible gap when defining the anniversary refill period.

The treatment anniversary method has certain advantages. First, it can be applied in situations where administrative data are only collected in specific periods of time (e.g. yearly). Second, it is easier to apply compared with the refill-gap method. Third, it can be used together with a compliance measure (see next section). Limitations are similar to those of the refill-gap method in terms of the definition of the gap and drug stockpiling. Moreover, if the anniversary date is not correctly specified (too far in time), then discontinuation events that occur between anniversaries will not be captured.

### Measuring medication compliance

Medication compliance (i.e. adherence) refers to the degree of conformity to the recommendations given by the provider about day-to-day treatment, including timing, dosage and frequency of the medication [26]. In order to measure compliance with administrative data, we rely on the same data and assumptions required for measuring persistence and discontinuation. The most commonly used method to assess compliance is the proportion of days covered (PDC) [28, 39–41], calculated as the total number of days with medication in a certain period divided by the length of the period (e.g. in days). The challenging aspect of this method is to define a reasonable time window in which to calculate compliance, which will depend on the research question and the expected persistence. As an example, Khedri *et al.* [42] evaluated the risk of non-compliance with guideline-recommended medications by patients with CKD developing acute coronary syndrome (ACS). Treatment compliance was defined in the year after ACS using the PDC metrics, defining adherent patients as those with a PDC >80%.

This method presents some limitations. It can only be applied to patients that are persistent at the end of the period, limiting its use in settings where patients tend to discontinue and not reinitiate or have a high short-term mortality. Furthermore, it may be challenging to calculate compliance in treatment regimes that allow for possible switches to treatments in the same therapeutic class. In such situations, two treatment periods may overlap, which makes it difficult to reliably calculate compliance. Alternatively, data on compliance can be obtained through patient questionnaires or collection of empty packages in prospective data collections [43–47]. In studies that use questionnaires to assess compliance, patients' answers are summarized in a score based on predefined compliance scales (see the example in Cukor *et al.* [45]). Due to the potential risk of recall bias, these methods are only recommended when no other administrative data are available.

## APPLICATIONS OF PHARMACOEPIDEMIOLOGY II: DRUG SAFETY AND EFFECTIVENESS

Pharmacoepidemiological studies offer the opportunity to address questions regarding the safety and effectiveness of medications. This is probably the most widely used application of this discipline. Several study designs can be applied to investigate the effectiveness and safety of drugs. Their advantages and limitations are summarized in Table 3.

### Case–control study design

The case–control design identifies individuals that develop the outcome of interest (cases) and compares their prior medication use with that of a group of controls that have not experienced the outcome (Figure 4). Data for a case–control study can either come from a fixed cohort (often then referred to as a nested case–control study) or a dynamic population (individuals can enter and exit at any time) [48].

For example, Lapi *et al.* [49] analysed the risk of AKI associated with a triple-therapy combination consisting of diuretics with ACEis or ARBs and non-steroidal anti-inflammatory drugs (NSAIDs). Across 0.5 million users of antihypertensive drugs, the authors defined those cases with an AKI hospitalization and selected random patients as controls matched for age, sex, year of cohort entry and duration of follow-up. The outcome was the rate ratios of AKI associated with the use of double- and triple-therapy combinations of antihypertensive drugs with NSAIDs in the 90 days prior to the event. The selection of AKI cases improved the efficiency and allowed the detection of these potentially adverse events that may not give a strong signal in other study designs and may not have allowed the detection of drug–drug interactions.

Potential limitations of a case–control design are the risk of misclassification bias (e.g. whether patients were on/off drug), inability to identify cumulative versus single exposures and the timing at which confounders are assessed. For example, the definition of comorbidities and concurrent medications is often made at the time of the event instead of the time of exposure initiation. In this situation, one will adjust for characteristics that actually happened after the exposure started, opening the possibility of adjustment for intermediaries instead of confounders [50]. However, with careful planning, some of these caveats can be addressed, as in the example above, improving the efficiency of case–control designs.

Carefully designed case–control designs performed in a well-defined population can provide good estimates of the relative

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**Table 3. Characteristics, advantages and disadvantages of classic study designs used in pharmacoepidemiology**

| Study design | Study population | Advantages | Limitations |
|---|---|---|---|
| Case–control | Cases are those that experience the event and their exposure history is compared with the exposure history of controls who did not experienced the event | Suitable to investigate rare outcomes and multiple exposures<br>Less expensive<br>Easier to assess effects of compliance to the treatment on outcomes | Investigate only one outcome<br>Recall bias[a]<br>Selection bias |
| Case-crossover | Only cases are included. Within the same individual, the exposure in the period prior to the event is compared with the exposure in a different period | Suitable to study acute effects of transient exposures<br>No confounding from time-fixed characteristics | Only focusses on cases (not very efficient)<br>Bias due to time-varying characteristics that affect exposure and outcome<br>Difficult to identify comparable periods of exposure |
| Self-controlled case series | Only cases are included and periods of exposure are compared within individuals with all the other periods in the observation time window | Suitable to investigate acute effects of transient treatments<br>Possible to investigate recurrent events in multiple exposure periods<br>No confounding from time-fixed characteristics | Assumption of no association between outcome and future exposure<br>Recurrent events need to be independent from each other<br>Bias due to high risk of mortality after the outcome |
| Cohort | Treated and untreated subjects are selected at a specific point in time (e.g. disease diagnosis) and followed until outcome, censoring or end of follow-up | Suitable to assess absolute risk and investigate multiple outcomes<br>Increased generalizability compared with other study designs | Potentially costly and time consuming<br>Difficult to study rare outcomes and effect of treatment compliance<br>Selection bias |

[a]Depending on the source of the data. Not applicable when obtained from electronic healthcare data.

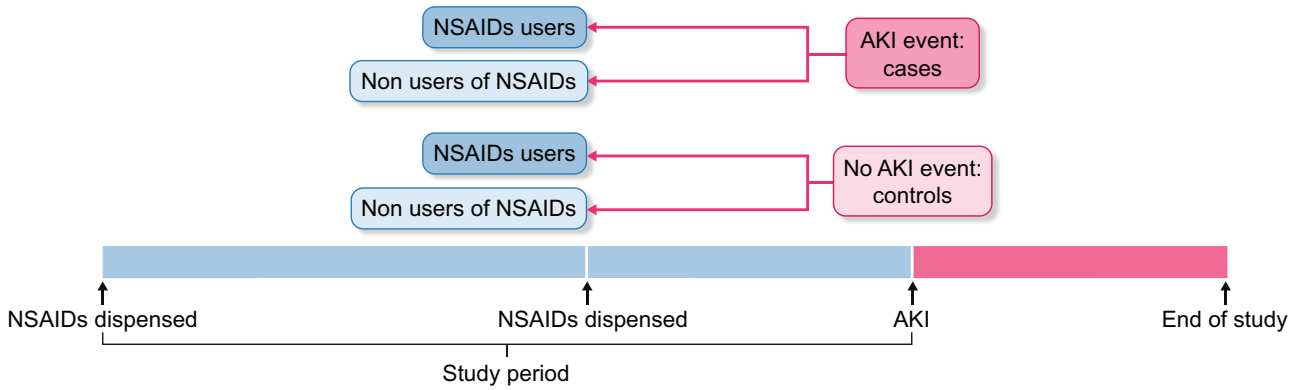


**FIGURE 4:** Schematic representation of a hypothetical case–control design investigating the association between NSAIDs and AKI. Cases are selected at the time of AKI. Controls are selected from the remaining population of individuals who did not experience AKI at the same point in time. Exposure to NSAIDs is compared between cases and controls.

risk of the event associated with the treatment and are more efficient (i.e. require less patients) than cohort studies in the case of rare outcomes. However, there is debate about the usefulness of this design in scenarios where complete information is available and including only a subgroup of controls will reduce the precision of the estimates compared with a cohort design [51]. A case–control design might be useful when a confounder is not available in the dataset and needs to be collected; the cost and time needed to collect such information is reduced because only a sample of controls is selected. This design also allows one to consider multiple exposures at the same time, which makes this design suited for polypharmacy studies. Finally, it allows one to study acute events associated with short-term exposures through a flexible definition of the exposure time window prior to the event [50].

## Case-crossover design

When a medication is used intermittently, it might be of interest to compare these periods within a subject. In a case-

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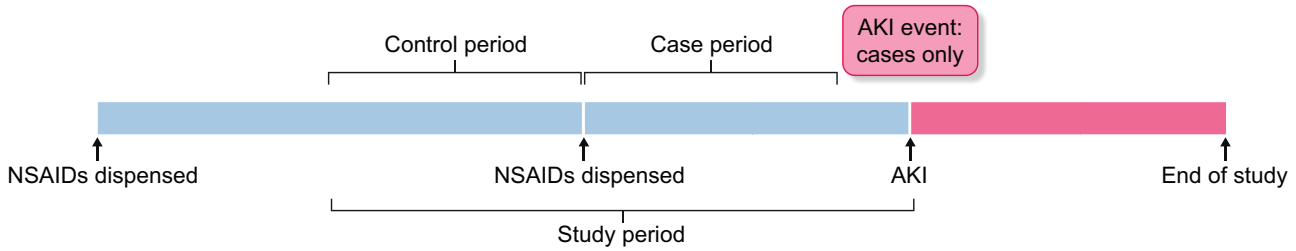


**FIGURE 5:** Schematic representation of a hypothetical case-crossover design investigating the association between NSAIDs and AKI. Cases are selected at the time of AKI. The exposure to NSAIDs in the period right before the AKI is compared with a similar period earlier in time.

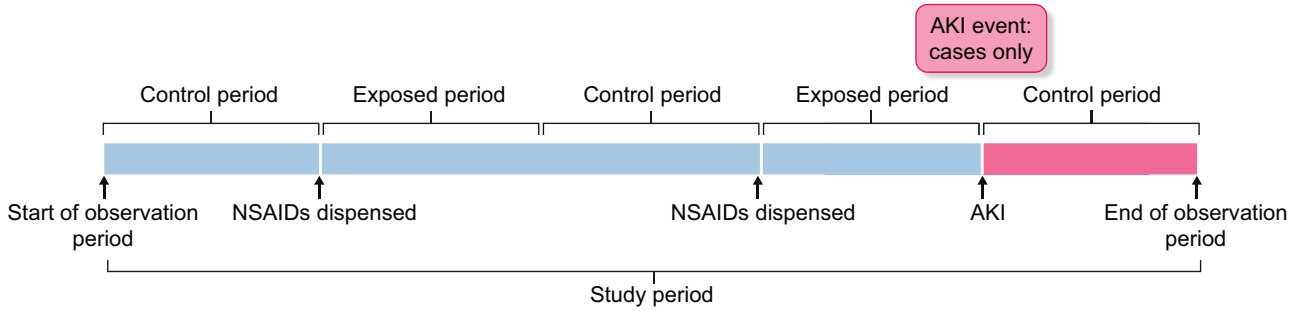


**FIGURE 6:** Schematic representation of a hypothetical self-controlled case-series design investigating the association between NSAIDs and AKI. The self-controlled case-series design consists of three steps: (i) cases are selected at the time of AKI, (ii) a particular observation period is selected (in this case the study period from NSAIDs dispensed to end of study) and (iii) the entire exposure history inside this observation period is classified as exposed or unexposed periods. The periods of exposure to NSAIDs are compared with all available control periods within the observation period.

crossover design, the focus is only on the cases (those who experienced the event), which act as their own controls: a comparison is made regarding the exposure between the period immediately prior to the event and a similar period earlier in time prior to the event (when we assume that the treatment was different) (Figure 5). This 'control' time period has the same length as the case period and needs to be carefully chosen (e.g. immediately before the exposure period). The dataset is then analysed as an individually matched case–control study. This method can also account for situations in which patients switch between two similar drugs without stopping the treatment. When the causes of switching are unrelated to health events (although often not plausible), within-person effect estimates from crossover designs will be unbiased. The case-crossover design is thought to be appropriate for studying acute effects of transient exposures [52]. Kilpatrick *et al.* [53] applied this method to investigate the association between the use of vitamin D and the risk of hypercalcaemia and hyperphosphataemia in haemodialysis patients. The study included individuals who survived at least 5 months after haemodialysis and experienced hypercalcaemia or hyperphosphataemia after this period. The treatment–outcome association was investigated by comparing the average monthly dose of vitamin D administered in the 2 months prior to the event with the average monthly dose in the period of 3–4 months prior to the event. This design allows for control of within-patient confounding but may suffer from time-dependent confounding (i.e. complications may have resulted in increased vitamin D dose and complications may be a cause of the event).

This design has several advantages. First, there is no need to select controls, which can be difficult in certain settings or may not be available in the data. Second, matching within individuals allows for control of unmeasured factors, e.g. genetic factors. Third, the possibility to investigate short-term reversible effects in those treated allows for assessment of the effects of adherence/persistence on the outcomes in those who have initiated treatment [54]. However, because only cases with discrepant exposure histories contribute information to the analysis, the case-crossover design may not be very efficient. Despite avoiding confounding by measured and unmeasured factors that are stable over time, it can still be confounded by factors that vary over time. Therefore the possibility of time-varying conditions leading to changes in treatment and increasing the risk for the outcome (i.e. confounding by indication) need to be carefully considered.

## Self-controlled case-series design

The self-controlled case-series design (SCCS) incorporates some of the concepts of the case-crossover and cohort designs [55]. This design is based on three steps: (i) all individuals that experienced the event(s) of interest are included (i.e. cases only), (ii) a certain observation period is defined [which can include periods before and after the event(s)] and (iii) exposed and unexposed period(s) are defined within the observation period

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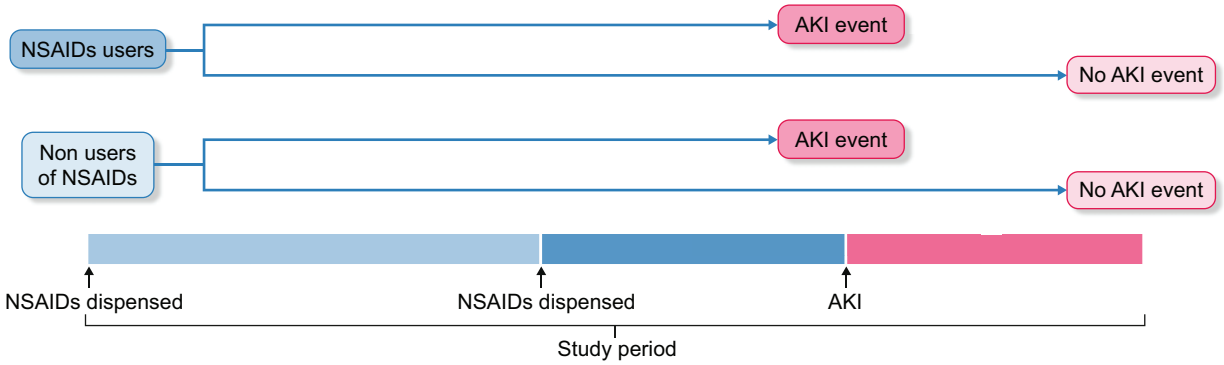


**FIGURE 7:** Schematic representation of a hypothetical cohort design investigating the association between NSAIDs and AKI. NSAID users are selected when they start therapy. A group of controls is selected at the same point in time among those who were not using the drug or were using another drug (active comparator). Both users and non-users are followed until the AKI event or end of follow-up.

(Figure 6). As with the case-crossover design, only cases are considered, but in the SCCS the entire exposure history is investigated. At the same time, the SCCS design allows one to account for recurrent events and multiple exposure periods.

The SCCS design presents several advantages. First, it allows one to control for within-person confounders that do not vary significantly over time. Second, by using all the available person-time information, it has the potential to increase efficiency compared with the case-crossover design. It is especially suited for drugs of intermittent use and for acute outcomes, which explains why this design was mostly applied in nephrology to evaluate the risk of AKI [56–58]. For example, Rennie *et al.* [58] applied this design to investigate the association between antibiotic use and AKI events. The authors identified all individuals who experienced AKI and defined the exposed period as the days from the prescription of antibiotics until 14 days after the end of the prescription. This design allows one to identify multiple exposure periods in the follow-up and account for recurrent events. Comparisons within individuals ensured controlling for patient characteristics that do not vary significantly over time.

Some assumptions in this design might limit its applicability and efficiency. First, the occurrence of the outcome should not affect the likelihood of being prescribed the drug, which is often unrealistic. Second, recurrent events need to be independent from each other, which is an assumption that might not be biologically plausible or only applicable to longer observation periods. Finally, when the event increases the probability of death, the observation period will be cut short soon after the event, which can bias the results in either direction.

## COHORT STUDY DESIGN

A cohort design is defined by selecting individuals with a common characteristic at a certain point in time (baseline date) and then following them until the occurrence of the outcome of interest or the end of the study (Figure 7). The cohort entry point should be carefully selected and preferably it should correspond with the occurrence of a meaningful event (e.g. developing HF) or the time at which a certain medication is initiated. Biases exist as to the indications for which the drug is given (confounding by indication), as well as when the drug is given (immortal time bias), and these are discussed in more detail in the second article of this series. One of the main advantages of the cohort design is the clear temporality of the exposure, outcome and potential confounders that allows, under certain assumptions, for investigation of causality. Other advantages of the cohort design are the possibility of estimating the incidence rate (or absolute risk) of an outcome and to investigate the association between an exposure and multiple outcomes. Moreover, because of similarities with how RCTs are conducted, cohort designs are easier to understand and interpret. However, the cohort study design also has limitations: if the data need to be prospectively collected, recruiting and following the individuals over time can become costly and inefficient if the outcome is rare. It is also very difficult to investigate the effect of certain utilization patterns (i.e. compliance) on the incidence of the outcome, because not all individuals have the same follow-up.

The availability of large health systems data may help mitigate some of these limitations. A recent study used a cohort design to investigate the association between the use of RASis in patients who experienced AKI and the risk of death or rehospitalization in routinely collected data from Canada [59]. The cohort entry point consisted of patients who experienced AKI and were discharged alive. The exposure was defined as the use of RASis in the 6 months following the hospital discharge. The design allowed the study of multiple outcomes using the same study population and to control for a good number of baseline comorbidities and medications. However, the study could not fully account for the specific reason (be it patient- or physician-related) patients were maintained on RASis or not, and this was assumed to be at random.

## CONCLUSION

In this review we provide an overview of methods that can be applied in nephrology research to assess patterns of drug use and study designs employed to investigate drug effectiveness and safety. Pharmacoepidemiological studies are an important contribution to drug-related research and a complement to RCT evidence. When using adequate study design and methods, it is possible to assess drug utilization and benefit/

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harm of the medications outside the strictly controlled environment of RCTs.

## FUNDING

This study was supported by the Swedish Research Council (grant 2019-01059) and the Swedish Heart and Lung Foundation.

## CONFLICT OF INTEREST STATEMENT

None declared.

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