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REVIEW

Observational studies of the association between glucose-lowering medications and cardiovascular outcomes: addressing methodological limitations

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Abstract
Background Recent years have witnessed a growing body of observational literature on the association between glucose-lowering treatments and cardiovascular disease. However, many of the studies are based on designs or analyses that inadequately address the methodological challenges involved.
Methods We reviewed recent observational literature on the association between glucose-lowering medications and cardiovascular outcomes and assessed the design and analysis methods used, with a focus on their ability to address specific methodological challenges. We describe and illustrate these methodological issues and their impact on observed associations, providing examples from the reviewed literature. We suggest approaches that may be employed to manage these methodological challenges.
Results From the evaluation of 81 publications of observational investigations assessing the association between glucose-lowering treatments and cardiovascular outcomes, we identified the following methodological challenges: 1) handling of temporality in administrative databases; 2) handling of risks that vary with time and treatment duration; 3) definitions of the exposure risk window; 4) handling of exposures that change over time; and 5) handling of confounding by indication. Most of these methodological challenges may be suitably addressed through application of appropriate methods.
Conclusions/interpretation Observational research plays an increasingly important role in the evaluation of the clinical effects of diabetes treatment. Implementation of appropriate research methods holds the promise of reducing the potential for spurious findings and the risk that the spurious findings will mislead the medical community about risks and benefits of diabetes medications.

Keywords Cardiovascular outcomes · Epidemiological methods · Glucose-lowering medications · Observational studies · Review

Abbreviations

AT	As-treated
ITT	Intention-to-treat
RCT	Randomised controlled trial

Introduction

Assessing the effects of treatment for a chronic disease and differentiating them from the consequences of the natural progression of the disease poses a range of methodological challenges for an observational researcher, and these challenges become even more pronounced when a feedback loop

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Glossary of biases and other epidemiological terms

Term	Definition
Immortal time bias	A form of bias that derives from including immortal time in the follow-up. Immortal time is a period of time, during which the event cannot occur, i.e. person-time that is event-free by definition
Exposure-defined cohort	A cohort of patients whose cohort-entry is defined by the first use of a drug of interest
Overadjustment bias	A form of bias that derives from adjusting by variables that are intermediate between exposure and outcome, i.e. outcome risk factors that have been influenced by exposure to the drug of interest
New-user design	A cohort study design that starts following patients at the time they initiate a new drug
Exposure risk window	The time period during which a drug of interest puts a patient at risk of a harmful or beneficial effect with regard to a specific outcome
Lag time after drug initiation	A time period following drug initiation during which a specific outcome cannot be attributed to the initiated drug. This time period should not be included in the follow-up time
Latency period after drug discontinuation	A time period after drug discontinuation during which a specific outcome can still be attributed to the discontinued drug. This time period should be included in the follow-up time
As-treated analysis (AT)	An analytical approach that terminates exposure to a medication when the patient discontinues that medication
Intention-to-treat analysis (ITT)	An analytical approach that carries forward the initial exposure status and disregards changes in treatment status over time
Informative censoring	A form of selection bias arising when discontinuation of a drug of interest is prognostic of (associated with) a future outcome
Confounding	A mixing of effects that arises when patients with different baseline risks are compared—the resulting effect measure is a mix of drug effects and risk factor effects

exists between disease progression and treatment progression. Studying the cardiovascular effects of glucose-lowering medications presents exactly these challenges since diabetes is a chronic disease that progresses over time with escalating cardiovascular consequences, and the medications involved in its treatment change in response to the progression of the underlying disease. Further, the very cardiovascular effects of the diabetes treatment under study may represent complications of diabetes itself so that disentangling drug from disease effects requires careful application of study design principles coupled with appropriate interpretation.

A growing body of observational literature assessing the effect of different glucose-lowering regimens on cardiovascular disease has been recently produced with inconsistent results (see Electronic supplementary material [ESM] Table 1). Increasing numbers of large databases, often based on healthcare utilisation data, have been assembled throughout the world and used to study the effect of therapeutics on health outcomes [1, 2]. These databases have attractive aspects: they reflect routine practice, which allows for the evaluation of real-world effectiveness and safety in large populations that include patients who are often under-represented in, or completely excluded from, randomised controlled trials (RCTs); are sufficiently large to allow the study of rare events or newly marketed products; and are readily available for analysis by researchers, without the time and monetary costs common to large RCTs.

However, if not rigorously conducted, studies based on observational data can encounter methodological problems that can compromise their validity and bias their results. In some instances, the medical and scientific community may be overwhelmed by the sheer numbers of people included in these studies and may overlook these methodological issues; similarly, these biases can be self serving for the custodian of the data or the sponsor of the analyses (e.g. pharmaceutical industries, private insurers, governments, etc.).

In light of these considerations, observational research can offer a valuable opportunity to evaluate the cardiovascular effects of glucose-lowering therapy, but only if adequate attention is paid to the methodological issues involved so that the risk of spurious and misleading findings is reduced.

The objectives of this review article were to assess the design and analysis methods used in studies of the

association between glucose-lowering medications and cardiovascular outcomes, with a focus on specific methodological challenges; to illustrate these methodological challenges and how they might affect a study, providing specific examples from the reviewed literature; and to suggest approaches that may be employed to manage these methodological challenges.

Identification of relevant literature, data abstraction and data review

We conducted a systematic search to identify observational studies assessing the effects of glucose-lowering medications on cardiovascular outcomes. We searched PubMed for articles published from January 2000 to December 2012, combining search terms for glucose-lowering medications, cardiovascular disease and methodological issues likely to be encountered in observational research (ESM Search strategy). We restricted the search to observational studies on glucose-lowering medications with cardiovascular disease as a primary or secondary outcome. We excluded studies in a language other than English, studies not conducted in humans, and those that focused on secondary diabetes or gestational diabetes (ESM Search strategy).

The titles and abstracts of identified articles (N= 2,875) were further screened for eligibility by three team members (E. M. Garry, V. G. Gillet, E. Patorno), and in cases where the abstract was unavailable or provided insufficient detail, the full text was evaluated. Any discordance among reviewers was resolved by consensus. This step led to the inclusion of 68 articles. We supplemented this search by reviewing bibliographies of original articles, reviews and meta-analyses to identify additional articles, and selectively searching other data sources including the Cochrane Database of Systematic Reviews, Web of Science, and relevant websites of medical societies, for the period January 2000 to December 2012. This step led to the inclusion of 13 additional articles, for a total of 81 articles (Fig. 1), including those evaluating the effect of glucose-lowering medications on cardiovascular outcomes and all-cause mortality among patients with cardiovascular disease (where mortality is a proxy for a cardiovascular outcome).

Data on type of study, exposure, outcome, effect on cardiovascular outcomes, and relevant methodological aspects were abstracted from the 81 selected articles and summarised in a table format (ESM Table 1) by three members of the team (E. M. Garry, A. R. Patrick, V. G. Gillet). Subsequently, articles were independently reviewed by three methodologically trained epidemiologists (E. Patorno, A. R. Patrick, J. D. Seeger) for the evaluation of the methodology and then discussed at meetings for consensus. At these meetings, results of the review were discussed and a list of methodological issues and their possible management, compiled up to that point in time, was reassessed and updated based on potential new elements arising from the ongoing critical review of the literature. Any difference in opinion was discussed among a broader set of authors (E. Patorno, J. D. Seeger, S. Schneeweiss, A. R. Patrick, E. M. Garry, V. G. Gillet) to achieve consensus.

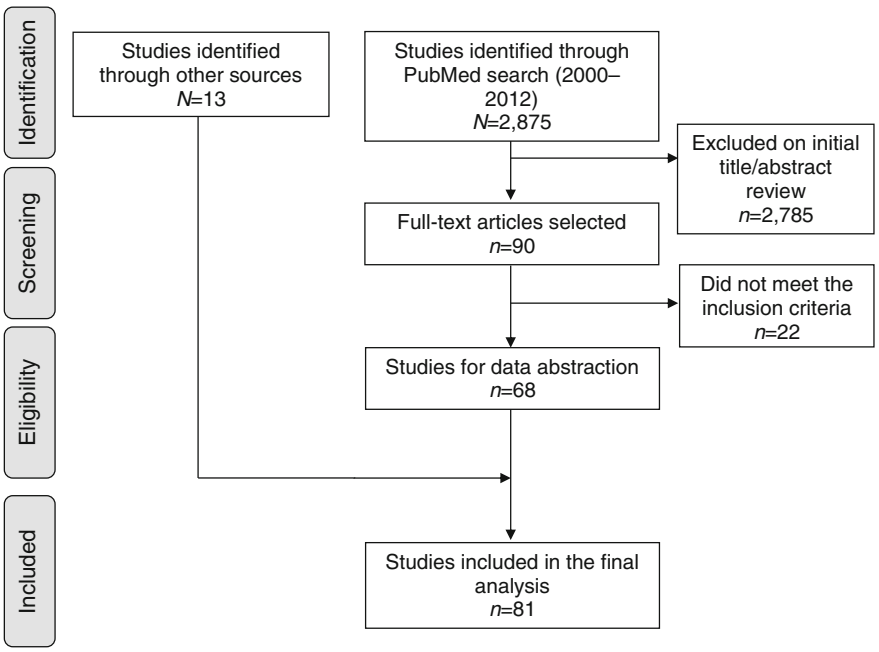

Fig. 1 Flow chart of included studies

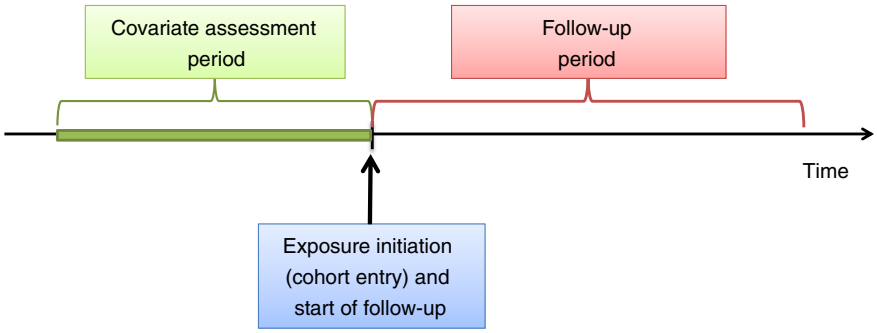

Fig. 2 Study temporality: adapted from [3] with permission. Original copyright © 2010 John Wiley & Sons, Ltd

Major methodological issues

We identified the following recurrent methodological issues among the reviewed studies: 1) handling of temporality in administrative databases; 2) handling of risks that vary with time and treatment duration; 3) unclear definitions of the exposure risk window; 4) handling of exposures that change over time; and 5) handling of confounding by indication.

Temporality considerations in administrative databases A temporal sequence that properly places exposure relative to when covariates are assessed and when outcomes occur is crucial to the assessment of exposure effects (Fig. 2) [3]. Patient characteristics (covariates) should be assessed during the time preceding the first exposure to the drug of interest, and follow-up for outcome occurrence should start after criteria for cohort entry and exposure status have been established.

Appropriate sequencing of these factors reduces opportunities for immortal time bias to become a factor in the study. Immortal time refers to a period of observation time during which the event cannot occur, i.e. person-time that is event-free by definition [4]. This happens, for example, when an exposure definition requires that everyone meeting the definition must have survived for a specified period. This event-free person-time may be incorrectly included in the denominator for the exposed group and lead to a biased reduction in the estimated incidence rate of cardiovascular events, by diluting the treated person-time with some other person-time that has no risk for study outcomes. The bias from this source can lead to a spurious finding of a protective effect of treatment. Immortal time bias can occur when exposure status depends on information that is not yet known at the time of cohort entry (i.e. it becomes known during study follow-up) (Fig. 3). In many studies, exposure status is defined on the basis of future use of a specific diabetes treatment [5–15], combination of treatments [5, 6, 16–18], or treatment dose [11, 13, 19]. This conditioning of exposure status on the basis of future information invites immortal time bias, particularly when coupled with a follow-up that begins before diabetes treatment status, i.e. exposure status, is defined. Examples from the reviewed studies used a specific calendar date [8, 9, 20] or a diagnostic definition [5, 7, 14, 18, 21–25] to identify cohort entry and follow-up initiation, but defined diabetes treatment status on the basis of future drug use 'at any time during follow-up' (Fig. 4) [16, 17, 21–23, 25]. Defining cohort entry by exposure to a drug of interest (particularly a new-user cohort, see next section) substantially reduces the opportunity for immortal time bias to affect a study, but does not remove it entirely. For example, if a study follows a cohort of drug initiators, but then compares monotherapy to combination therapy, where these subgroups are identified 'at any time during follow-up' [5, 13, 16–18, 21, 26],

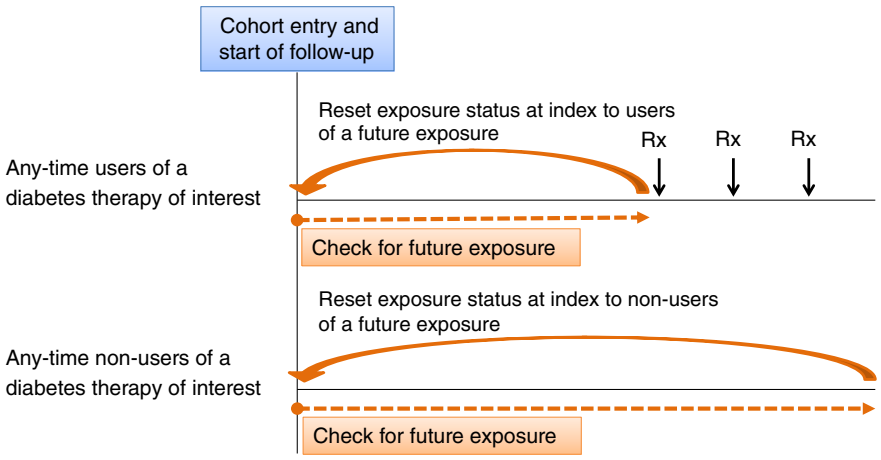

Fig. 3 Biased exposure status based on future information. Immortal time bias can occur when exposure status depends on information that is not yet known at the time of cohort entry (i.e. it becomes known during study follow-up). Rx indicates the receipt of a medication

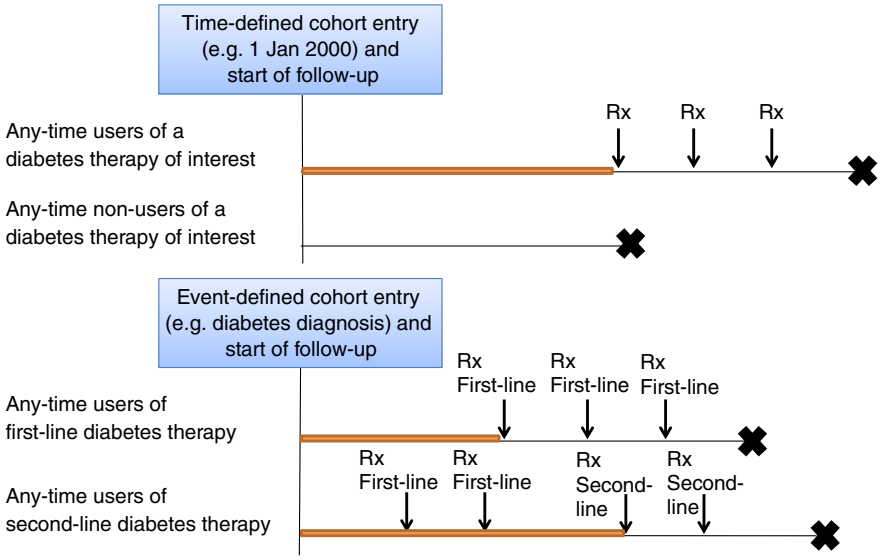

Fig. 4 Immortal time bias. Rx indicates the receipt of a medication. Orange line, immortal time; black cross, cardiovascular outcome

then immortal person-time is created by this exposure definition. Alternatively, if cohort entry is defined by more than one drug prescription/dispensing or more than a certain duration on treatment, but follow-up initiates at the first prescription/dispensing [10, 12, 17, 27–32], then immortal person-time may be a source of bias.

On a similar note, future exposures and events that occur during follow-up should not be used as criteria for cohort entry. Several studies included or excluded patients on the basis of information collected during follow-up, such as use of insulin after cohort entry [6, 10, 12, 17, 33], use of glucose-lowering combinations [29, 34–36], switching to other glucose-lowering therapy [10, 12, 20, 37] or drug adherence [6, 27, 28, 38]. By conditioning cohort entry on the basis of future information these studies have the potential for bias arising from immortal time.

Appropriate sequencing of covariate assessment, cohort entry and exposure status, and start of follow-up will also reduce the potential for bias that might arise through adjustment for covariates that have been affected by exposure to treatment. These covariates are termed 'intermediate variables' since they are intermediate between exposure and outcome, and their value has been influenced by the drug exposure so that adjustment for the covariate removes some of the drug effect, typically resulting in a bias toward the null [39] (overadjustment bias [40], Fig. 5). However, this bias is unpredictable and can lead to larger effects in particular situations [41]. Case–control studies, where patient characteristics that are used for covariate adjustment are measured during the time leading up to the case or control date, can be particularly subject to bias from this source. Many case–control investigations on the effects of diabetes therapy and cardiovascular outcomes are potentially affected by this form of bias [34, 42–49]. However, cohort studies are not exempt from this methodological concern [5, 7, 8, 12, 14, 17, 20, 22, 25, 27, 28, 30, 37, 50–53]. Examples of variables that are likely to be intermediate between glucose-lowering therapy and cardiovascular outcome include post-treatment medical conditions such as hypertension and hyperlipidaemia [34, 43, 45, 48, 49], medication use during follow-up [5, 8, 12, 14, 17, 20, 28, 37, 45, 47, 48], and metabolic information such as BMI and HbA1c ascertained after cohort entry and treatment initiation [25, 26, 34, 49–52].

A cohort study that defines entry on the basis of the first use of a drug, i.e. an exposure-defined cohort, and has a well-defined temporal sequence of covariate assessment, exposure definition and start of follow-up, improves the assessment of drug effects and reduces the potential for immortal time bias.

Time-varying hazards and treatment duration effects The risks associated with specific medical conditions tend to vary over time, mostly increasing with increases in age. Diabetes is associated with the development of cardiovascular, renal and neurological outcomes, and with an increased risk of cancer development [54, 55]. The occurrence of these disease-specific outcomes develops on different time scales, including both age and duration of diabetes.

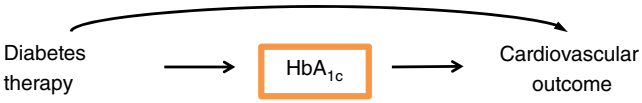

Fig. 5 Overadjustment bias. Overadjustment bias derives from adjusting for an intermediate variable between exposure and outcome, i.e. an outcome risk factor that has been influenced by exposure to the drug of interest. In the example HbA_{1c} is intermediate between diabetes therapy and cardiovascular outcome

Similarly, risks and benefits that result from use of medications may vary over time, sometimes decreasing and sometimes increasing the longer a medication is used. Early susceptibility or intolerance to drugs may lead to rapid occurrence of medication-related adverse effects and discontinuation of the medication, potentially resulting in a 'survivor cohort' of prevalent drug users that is composed of people who are less susceptible to a range of outcomes by virtue of having passed through this early high-risk period. These individuals may spuriously appear to receive more benefit from the use of a drug when compared with patients who have newly initiated its use. Further, those patients who continue to take the medication may be demonstrating adherence and this makes them more likely to do well on any therapy so that they appear to receive more benefit than new users of a drug. An existing data source contains glucose-lowering medication users at different stages of therapy, some of whom represent such a survivor cohort. A study comparing a survivor cohort of glucose-lowering medication users to new users might be expected to show that the new users experience more outcomes, including cardiovascular outcomes. Further, when a new medication is initiated in response to diabetes progression, comparing new users with prevalent drug users may lead to findings of spurious drug harm, as patients escalating therapy may have higher baseline cardiovascular risk than a survivor cohort of prevalent users with adequate glucose control.

A new-user design, which identifies cohorts of patients at the time they initiate a new drug, is particularly well suited to evaluate drug effects that vary over time [3, 56, 57]. The well-defined start of follow-up in these new-user cohorts has the effect of 'synchronising' patients on a same time scale that is relevant to the drug effect, making it possible to assess whether and by how much the risk of an outcome changes concomitantly with duration of use. Although a new-user design is better suited to detect or assess time-dependent drug effects, only a limited number of the reviewed investigations employed a new-user design [6, 12, 17, 19, 28, 30–32, 37, 58–65].

A new-user design should be applied to cohorts of both the medication being studied and that to which it is compared, with the design being enhanced by a comparison medication (or class of medications) that tends to be used for patients at a similar stage of diabetes, as this better distinguishes drug effects from disease effects. For example, if the study drug is typically used at more advanced diabetes stages, i.e. second- or third-line therapies, then a comparator medication that is similarly used is likely to be most appropriate. Conversely, a comparison with a more generally recognised first-line glucose-lowering medication such as metformin leads to extensive methodological challenges even when an incident user design is employed. A variant of the new-user design, which can address research involving patients characterised by more advanced diabetes stages, compares patients switching or augmenting from a first-line diabetes treatment to the study drug of interest with new switchers/augmenters to the comparison drug [66].

The occurrence of cardiovascular outcomes may also vary over time according to duration or cumulative dose of diabetes therapy. To account for these time-varying hazards, an investigation should include analyses that estimate the incidence of cardiovascular outcomes according to duration or cumulative exposure to glucose-lowering agents. For this purpose, the number of drug dispensings and the dispensed dose (e.g. in mg or IU) during the follow-up can be used to provide an estimate of the cumulative exposure. Specifically, the person-time with similar exposure categories can be pooled together and the observed outcomes can be assigned to categories of cumulative exposure defined by the accumulated dispensed dose or treatment duration, e.g. subjects with a 1 year exposure to a glucose-lowering medication will be compared with subjects with 1 year exposure with a comparator agent [67]. Subjects will be balanced with regard to all baseline covariates and follow-up will start after the accumulation of pre-specified levels of dispensed dose or treatment duration. Few studies included analyses assessing the effect of cumulative exposure to glucose-lowering agents [11, 12, 19, 37, 45, 47, 49, 61, 68].

In summary, a new-user design, which includes drug initiators, increases the chances of identifying more comparable patients with respect to the underlying risk of cardiovascular disease, and is particularly suited to detect and evaluate medication effects that vary over time. To account for the time-varying cardiovascular effect possibly associated with duration or cumulative dose of diabetes therapy, an investigation should include analyses assessing the occurrence of cardiovascular outcomes according to cumulative exposure to specific glucose-lowering agents.

Exposure risk window definition The exposure risk window is the time period during which any harmful or beneficial effect with regard to a specific outcome can be attributed to a drug of interest. Glucose-lowering agents may contribute to cardiovascular outcomes through different biological mechanisms, which can lead to increased or decreased risk of specific comorbidities. This mechanism should be reflected in the time window chosen for outcome identification. If a plausible biological mechanism requires some minimum time before a specific cardiovascular outcome could manifest, then it is reasonable to consider a lag time between the exposure and the start of follow-up. This approach is highly dependent on background knowledge and the specific research hypothesis, so it must be cautiously applied and carefully tailored to a particular study. A limited number of reviewed studies have considered lag periods in their study design [12, 69]. The use of a lag period reduces the chances of protopathic bias (sometimes termed reverse causation), which may occur when conditions with some preclinical phase, e.g. atherosclerosis or mild stages of heart failure, influence medication selection.

If a glucose-lowering medication is selectively chosen for a patient with early symptoms of underlying cardiovascular disease, then the medication may appear to cause cardiovascular outcomes because it was initiated closer to the occurrence of a cardiovascular event than would a comparator medication. Maru et al found that any pharmacological therapy for diabetes was associated with an increased risk of heart failure during the first year of treatment but not in the subsequent years, suggesting that some preclinical conditions that precipitated the therapy, and not the therapy itself, could explain this early increased risk in patients with diabetes [21].

Another aspect to consider is the appropriate duration of the exposure risk window, which may be quite relevant in the assessment of the effects of glucose-lowering medications on cardiovascular disease. It is plausible for example that, shortly before the occurrence of a cardiovascular event, patients may stop or change treatment. Thus, the exposure risk window is often extended for some time both to reflect an exposure latency period and to address the potential for treatment discontinuation or change close to an outcome (Fig. 6). Few studies assessing the effect of glucose-lowering medications on cardiovascular disease have considered latency periods after drug discontinuation [59–61, 63, 65, 70–72] or have conducted sensitivity analyses to test different exposure risk window definitions [46, 49, 73].

In the assessment of the clinical effects of glucose-lowering agents, it is advisable to clearly identify the biological hypothesis to test and to choose the appropriate exposure risk window in line with this, considering lag or latency periods and sensitivity analyses to address uncertainty.

Time-varying exposures Treatment for a progressive chronic condition such as diabetes tends to exhibit high levels of discontinuation, switching or augmentation.

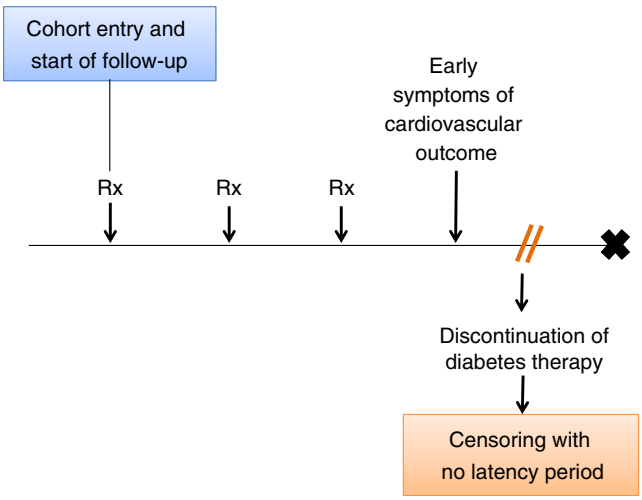

Fig. 6 Informative censoring. Rx indicates the receipt of a medication. Black cross, cardiovascular outcome

Diabetes treatment might change in response to advancing diabetes, or owing to adverse effects associated with specific agents. Both scenarios have the potential of leading to the observation of an increased risk of cardiovascular outcomes shortly after therapy change or discontinuation, and may cause bias. Although an as-treated (AT) analysis, which terminates exposure to a medication upon discontinuation, is often the approach of choice for the assessment of drug safety in observational studies, it may be prone to bias if the discontinuation predicts future cardiovascular outcomes (informative censoring, Fig. 6). In this setting, censoring upon discontinuation removes outcomes from their appropriate exposure category. The assessment of the temporal distribution of cardiovascular outcome occurrence, for example shortly after drug discontinuation, can assist in assessing the presence of informative censoring. Sensitivity analyses based on the AT approach with varying latency periods after drug discontinuation can also be used to identify potential informative censoring [58–61, 63, 65, 70–72]. An intention-to-treat (ITT) approach, which carries forward the initial exposure status and disregards changes in treatment status over time, is not affected by informative censoring bias in the same way. However, it might be biased through exposure misclassification that increases with longer follow-up periods and shorter time on treatment before discontinuation, and remains open to potential differential loss to follow-up [3, 74]. In most cases, such misclassification tends to reduce the effect of a medication and will produce conservative results [75, 76]. Although ITT analysis is the most commonly used approach in this literature review, it is worth considering results arising from both AT and ITT analyses in evaluating the clinical effects of glucose-lowering agents, in light of the strengths and limitations inherent in each approach [58, 60, 65, 70].

A few studies accounted for time-varying exposures by using Cox models analysing exposure to drugs as a time-dependent variable [19, 64, 71, 72, 77, 78]. These models make the assumption that treatment changes are independent of cardiovascular outcomes and may lead to biased results in the presence of patient characteristics that vary over time, affecting both diabetes treatment choice and cardiovascular risk [79], a likely scenario in the context of a chronic disease requiring therapy adjustments commensurate to its natural progression. Few studies have accounted for time-dependent confounders [21, 69]. Suitable strategies exist to address time-dependent confounding such as marginal structural models [80, 81] or g computation [82]. However, these methodologies require extensive programming and (as with any observational method) are based on the assumption that all important predictors for treatment change can be identified and are available in the data source, i.e. assumption of no unmeasured confounding.

In summary, both AT and ITT analyses should be considered in evaluating the effects of glucose-lowering agents on cardiovascular outcomes. Sensitivity analyses assessing when

most cardiovascular outcomes occur can assist in identifying informative censoring. When selecting the strategy to account for time-varying exposures in the analysis, the researcher may be faced with a trade-off between methodological transparency and ability to address confounding.

Confounding One of the principal challenges of observational studies is confounding, a form of bias that derives from an uneven distribution of baseline risks across comparison groups and results in confounded estimates of the differences between them [83]. In pharmacoepidemiological studies, confounding by indication [84], or drug channelling bias [85] is one of the most important threats to validity. Physicians prescribe drug treatments in light of the diagnostic and prognostic information available at the time of prescribing. If predictors of patient outcomes are unevenly distributed among treatment groups, then failing to control for such factors will lead to confounding [2].

Diabetes is an established risk factor for cardiovascular disease [86], and increasing diabetes duration or severity is associated with higher risk for cardiovascular morbidity and mortality. Thus, patients treated with medications used later in the course of diabetes, such as second- or third-line agents, might experience higher rates of cardiovascular outcomes compared with patients managed with diet alone or with first-line therapy users, and this can lead to confounding (Fig. 7), if not taken into account in the study design. Confounding can be reduced by the choice of a proper comparator group. Comparison groups that have been used in the recent literature include non-diabetic individuals [43, 87, 88], untreated diabetic patients [8, 33, 42, 48, 73, 89–92], diabetic patients receiving a comparator drug [5, 6, 9–13, 16–18, 20, 26–31, 34, 35, 37, 38, 44, 46, 47, 49, 51, 53, 58, 60–63, 65, 70–72, 77, 78, 93–95], and combinations of the above often in the form of any identifiable patient that did not use a specific agent of interest [7, 14, 15, 21–25, 45, 47, 50, 52, 64, 68, 69, 96–104].

Non-diabetic individuals are not likely to be an appropriate comparator group because unmeasured lifestyle factors such as diet, exercise, socioeconomic status and BMI, as well as unmeasured severity of underlying comorbidities, are more likely to be unbalanced between patients with and without diabetes. Untreated diabetic patients are not optimal comparators either. Patients with diet-controlled diabetes will typically have less severe disease than users of glucose-lowering drugs, and thus be at lower risk of cardiovascular outcomes, or conversely diabetic individuals not receiving medications might have differential barriers to treatment and surveillance for comorbidities compared with medication users, and thus be at higher risk for cardiovascular outcomes.

Comparisons restricted to treated patients with diabetes offer improved confounding control, particularly when both treated and comparison represent new users of medications that in clinical practice are prescribed to patients with overlapping baseline characteristics [105]. Patients initiating second- or third-line therapies or combinations of two or more glucose-lowering agents might be characterised by higher diabetes duration or severity compared with a generally recognised first-line agent such as metformin or an agent used as monotherapy [5, 10, 13, 16–18, 28, 51, 72, 89, 92]. Thus, when second- or third-line diabetes therapies or specific combinations of agents represent the treatments of interest, choosing initiators of other second- or third-line agents or other combinations as comparators [20, 29–32, 35, 46, 47, 49, 58–63, 70], considering comparisons among cohorts of new switchers/augmenters (in addition to new users), and controlling for diabetes duration and underlying diabetes-related comorbidities (e.g. cardiovascular comorbidities and diabetes complications such as neuropathy, nephropathy and retinopathy), can reduce confounding.

Once the choice of a proper comparator has been made, several strategies at the study design or analysis level can be implemented to further reduce confounding, including restrictions in the study population, matching, and stratification through regression models. Many adjustment methods are constrained by the number of covariates that can be accounted for per outcome [106]. In the setting of a large number of potential confounders such as found in large healthcare utilisation databases, propensity score methodology is an effective strategy for confounding adjustment, especially when the study outcomes are relatively uncommon [107]. A propensity score is the estimated probability of receiving one treatment exposure vs another [108], and can be used to reduce confounding via matching, stratification, regression adjustment or some combination of these strategies [109]. Propensity score matching in particular offers investigators the ability to balance treatment groups across all potential confounders and to inspect the achieved balance across covariates, by comparing these variables before and after matching in a similar manner to the comparison of randomised treatment groups in an RCT [110, 111]. Demographics, clinical characteristics and healthcare history are all likely to be

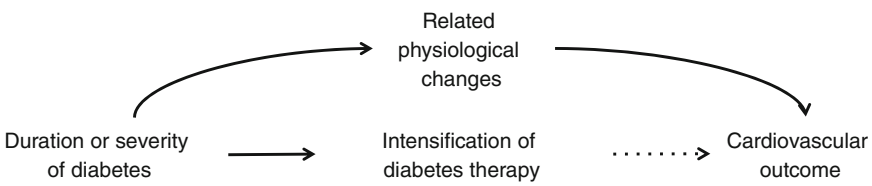

Fig. 7 Confounding by duration or severity of diabetes

associated with the choice of glucose-lowering agent, and can be considered in balancing treatment groups through propensity score matching. Similarly, cardiovascular-related indications or contra-indications that might lead to differential prescribing should be taken into account in evaluating the cardiovascular risk associated with glucose-lowering agents. For example, underlying heart failure or coronary disease may be associated with decreased likelihood of receiving a prescription for metformin and thiazolidinediones, since both are contra-indicated in patients with heart failure [112, 113] and rosiglitazone has been associated with an increased risk of myocardial infarction [114, 115]. Older patients, who are at increased risk for hypoglycaemia, which may exacerbate myocardial ischaemia and cause dysrhythmias, may be less likely to receive agents that predispose to this adverse effect, such as sulfonylureas, meglitinides or insulin [112, 113]. Likewise, overweight or obese patients might be less likely to be prescribed with agents that promote weight gain, such as thiazolidinediones and sulfonylureas, in favour of agents not influencing weight or promoting weight loss, such as metformin, DPP-4 inhibitors or GLP-1 receptor agonists [112, 113].

Finally, in the context of large administrative databases with many potential confounders, the high-dimensional propensity score algorithm, an automated extension of propensity score methodology that empirically selects covariates across thousands of diagnostic, procedural and drug treatment codes, may help the researcher in identifying proxies for confounders, which are unmeasured in healthcare claims data, and ultimately address aspects of unmeasured confounding [116–118].

In summary, the choice of a proper comparator group, i.e. one that is characterised by similar healthcare utilisation, medical conditions, and diabetes duration or severity, combined with propensity score methodology, is an effective strategy to balance important baseline risk factors across treatment groups and, therefore, reduce confounding.

Other issues

As in any observational study, there are other aspects that a researcher should consider in evaluating the clinical effects of diabetes therapies.

Misclassification of exposure, outcome, and covariates In administrative claims data, dispensed medications are recorded accurately with respect to date and quantity dispensed, and data quality is generally considered better than self-reports and physician notes [119–122]. Nonetheless, many studies used self-reported information [8, 44] and inpatient or outpatient medical records [16, 21, 23, 25, 26, 28, 31, 33, 48–50, 53, 73, 95, 97, 100] to investigate the effect of diabetes therapy on cardiovascular outcomes, which may lead to exposure misclassification. However, in claims data, chronic therapies with multiple refills, such as glucose-lowering medications, can undergo some form of misclassification depending on how the day's supply is calculated and how long a latency period is considered after drug discontinuation. These elements, combined with an understanding of the pharmacokinetics and pharmacodynamics of the drug of interest, should be considered to limit the chances of exposure misclassification.

Misclassification of the outcome is also possible when claims data are used. In this regard, high specificity of the outcome is preferable to high sensitivity, as the relative risk estimates are unbiased when specificity approaches 100% [123]. It has been shown that claims data can identify cardiovascular endpoints with very high specificity, resulting in relatively small potential for bias associated with misclassification of the outcome [124–128]. Among the evaluated literature, few explorative analyses assessed the potential effect of outcome misclassification on the study estimates [68, 70].

Finally, misclassification of confounding variables can lead to incomplete control of these variables and ultimately residual confounding. Under this scenario, prioritising sensitivity in covariate definition may minimise the chances of confounder misclassification.

Special issues in case–control studies Several observational studies have used a case–control design to assess the effects of diabetes therapy on cardiovascular outcomes [33, 34, 42–49, 73, 98, 100, 102, 104]. The time-varying nature of diabetes therapy and the long duration of follow-up required to assess cardiovascular risk are frequent arguments for the choice of this study approach [48, 49, 98]. However, in the context of administrative data, a few considerations need to be made regarding the choice of a case–control vs a cohort study design: (1) case–control studies are always nested in an underlying cohort of diabetic patients or glucose-lowering therapy users, which is always identifiable in claims data, and cannot estimate absolute incidence rates and rate differences unless the sampling fractions of cases and controls are known, i.e. the underlying cohort needs to be enumerated [3]; (2) case–control studies can be more prone to specific issues than cohort studies: as previously mentioned, the correct chronology of confounder assessment can be more challenging with a case–control design; (3) case–control studies tend to focus on the period immediately prior to an event. This period might not always be the most relevant for cardiovascular diseases and could be particularly prone to exposure misclassification if, as previously mentioned, patients are at increased risk of treatment change or discontinuation in proximity to an event, and no latency period is considered.

Thus, unless additional information such as laboratory tests, diagnostic results, or survey data are collected at additional cost and integrated into a healthcare claims dataset, case–control studies offer no advantage relative to cohort studies for the evaluation of the association between diabetes therapy and cardiovascular risk in claims data.

Identified major methodological challenges, suggested strategies to reduce bias, and specific rationale

Methodological challenge	Strategy to reduce bias	Specific rationale
Temporality considerations in administrative databases	• Use a cohort study with entry defined by the first use of the drug(s) of interest (exposure-defined cohort) and that has a well-defined temporal sequence of covariate assessment, exposure definition and start of follow-up	• To facilitate the understanding of the effects of glucose-lowering medications and reduce the potential for immortal time bias and overadjustment by intermediate variables
Time-varying hazards and treatment duration effects	• Employ a new-user design based on drug initiators	• Improves comparability of treatment groups with respect to the underlying risk of outcomes • Useful for medication effects that vary over time
	• Consider analyses that estimate cardiovascular effects according to duration or cumulative exposure to specific glucose-lowering agents	• To account for the time-varying hazards associated with duration or cumulative dose of diabetes therapy
Exposure risk window definition	• Clearly identify the biological hypothesis	• To choose an appropriate exposure risk window
	• Apply sensitivity analyses that vary the exposure risk window definition	• To address uncertainty regarding the optimal time from exposure to start of follow-up (lag time) or continuation of effects after drug discontinuation (latency period)
Time-varying exposures	• Consider both AT and ITT analyses and vary assumptions regarding duration of effect	• To address more fully potential informative censoring and exposure misclassification
	• Recognise trade-off between methodological transparency and ability to address confounding	• Improve selection of methods to account for time-varying exposures
Confounding	• Choose an appropriate comparator group (i.e. characterised by similar healthcare utilisation, medical conditions, and diabetes duration or severity)	• To reduce potential confounding by indication
	• Apply appropriate methods to account for confounding, such as propensity score methods	

Conclusions

The review of recent observational studies evaluating the association between glucose-lowering medications and cardiovascular outcomes illustrates several methodological issues that appear to be incompletely addressed. Future studies can clarify the effects of diabetes treatment by appropriately addressing recurrent methodological challenges such as temporality in healthcare databases, time-varying hazards and treatment duration effects, exposure risk window definition, time-varying exposure, and confounding (Text boxes: Identified major methodological challenges, suggested strategies to reduce bias, and specific rationale and Glossary). We provided some suggestions on strategies to minimise the impact of these methodological issues, which can be summarised as follows: (1) Use a cohort study with entry defined by the first use of the drug(s) of interest and that has a well-defined temporal sequence of covariate assessment, exposure definition and start of follow-up, to facilitate understanding of the effects of glucose-lowering medications and reduce the chances of immortal time bias. (2) Employ a new-user design based on drug initiators, which increases the chances of identifying more comparable treatment groups with respect to the underlying cardiovascular risk, and is particularly suited to detect and evaluate medication effects that vary over time; consider analyses that estimate cardiovascular effects according to cumulative exposure to specific agents. (3) In the assessment of the association between glucose-lowering agents and cardiovascular outcomes, clearly identify the biological hypothesis to test and choose the appropriate exposure risk window. Use sensitivity analyses to identify the optimal lag time before start of follow-up, and latency period after drug discontinuation. (4) Consider both AT and ITT analyses and use sensitivity analyses to assess chances of informative censoring. Remain cognisant of the implications and trade-offs in selecting the strategy for dealing with time-varying exposures.

(5) Choose an appropriate comparator group (i.e. characterised by similar healthcare utilisation, medical conditions and diabetes duration or severity) and use appropriate methods to account for confounding, such as propensity score methods.

In spite of the methodological issues identified in this review, and illustrated in this text, improper practices with regard to study design and analysis persist in observational studies that attempt to assess the effect of glucose-lowering medications on other clinical outcomes as well [129–132]. Greater attention to the principles described in this paper would serve to address certain research practices that are particularly susceptible to spurious findings and may mislead the medical community. Careful consideration by the researcher of these specific issues and of the potential strategies to address them is warranted.

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References

1. Arana A, Rivero E, Egberts TCG (2004) What do we show and who does so? An analysis of the abstracts presented at the 19th ICPE. Pharmacoepidemiol Drug Saf 13:S330–S331
2. Schneeweiss S, Avorn J (2005) A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol 58:323–337
3. Schneeweiss S (2010) A basic study design for expedited safety signal evaluation based on electronic healthcare data. Pharmacoepidemiol Drug Saf 19:858–868
4. Suissa S (2008) Immortal time bias in pharmaco-epidemiology. Am J Epidemiol 167:492–499
5. Eurich DT, Majumdar SR, McAlister FA, Tsuyuki RT, Johnson JA (2005) Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. Diabetes Care 28: 2345–2351
6. Johnson JA, Simpson SH, Toth EL, Majumdar SR (2005) Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with type 2 diabetes. Diabet Med 22:497–502
7. Aguilar D, Bozkurt B, Pritchett A, Petersen NJ, Deswal A (2007) The impact of thiazolidinedione use on outcomes in ambulatory patients with diabetes mellitus and heart failure. J Am Coll Cardiol 50:32–36
8. Anselmino M, Ohrvik J, Malmberg K, Standl E, Ryden L (2008) Glucose lowering treatment in patients with coronary artery disease is prognostically important not only in established but also in newly detected diabetes mellitus: a report from the Euro Heart Survey on Diabetes and the Heart. Eur Heart J 29:177–184
9. Khalangot M, Tronko M, Kravchenko V, Kovtun V (2009) Glibenclamide-related excess in total and cardiovascular mortality risks: data from large Ukrainian observational cohort study. Diabetes Res Clin Pract 86:247–253
10. Hsiao FY, Huang WF, Wen YW, Chen PF, Kuo KN, Tsai YW (2009) Thiazolidinediones and cardiovascular events in patients with type 2 diabetes mellitus: a retrospective cohort study of over 473,000 patients using the National Health Insurance database in Taiwan. Drug Saf 32:675–690
11. Hsiao FY, Tsai YW, Wen YW et al (2010) Relationship between cumulative dose of thiazolidinediones and clinical outcomes in type 2 diabetic patients with history of heart failure: a population-based cohort study in Taiwan. Pharmacoepidemiol Drug Saf 19:786–791
12. Corrao G, Romio SA, Zambon A, Merlino L, Bosi E, Scavini M (2011) Multiple outcomes associated with the use of metformin and sulphonylureas in type 2 diabetes: a population-based cohort study in Italy. Eur J Clin Pharmacol 67:289–299
13. Loebstein R, Dushinat M, Vesterman-Landes J et al (2011) Database evaluation of the effects of long-term rosiglitazone treatment on cardiovascular outcomes in patients with type 2 diabetes. J Clin Pharmacol 51:173–180
14. Yeh HT, Hsieh CF, Tsai YW, Huang WF (2012) Effects of thiazolidinediones on cardiovascular events in patients with type 2 diabetes mellitus after drug-eluting stent implantation: a retrospective cohort study using the national health insurance database in Taiwan. Clin Ther 34:885–893
15. Chao TF, Leu HB, Huang CC et al (2012) Thiazolidinediones can prevent new onset atrial fibrillation in patients with non-insulin dependent diabetes. Int J Cardiol 156:199–202
16. Olsson J, Lindberg G, Gottsater M et al (2000) Increased mortality in type II diabetic patients using sulphonylurea and metformin in combination: a population-based observational study. Diabetologia 43:558–560
17. Johnson JA, Majumdar SR, Simpson SH, Toth EL (2002) Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. Diabetes Care 25:2244–2248
18. Evans JM, Doney AS, AlZadjali MA et al (2010) Effect of metformin on mortality in patients with heart failure and type 2 diabetes mellitus. Am J Cardiol 106:1006–1010
19. Gamble JM, Simpson SH, Eurich DT, Majumdar SR, Johnson JA (2010) Insulin use and increased risk of mortality in type 2 diabetes: a cohort study. Diabetes Obes Metab 12:47–53
20. Chou CC, Chen WL, Kao TW, Chang YW, Loh CH, Wang CC (2011) Incidence of cardiovascular events in which 2 thiazolidinediones are used as add-on treatments for type 2 diabetes mellitus in a Taiwanese population. Clin Ther 33: 1904–1913
21. Maru S, Koch GG, Stender M et al (2005) Antidiabetic drugs and heart failure risk in patients with type 2 diabetes in the U.K. primary care setting. Diabetes Care 28:20–26

22. Engel-Nitz NM, Martin S, Sun P, Buesching D, Fonseca V (2008) Cardiovascular events and insulin therapy: a retrospective cohort analysis. Diabetes Res Clin Pract 81:97–104
23. Toprani A, Fonseca V (2011) Thiazolidinediones and congestive heart failure in veterans with type 2 diabetes. Diabetes Obes Metab 13:276–280
24. Choy-Shan A, Zinn A, Shah B et al (2012) Effect of rosiglitazone on survival in patients with diabetes mellitus treated for coronary artery disease. Coron Artery Dis 23:354–358
25. Margolis DJ, Hoffstad O, Strom BL (2008) Association between serious ischemic cardiac outcomes and medications used to treat diabetes. Pharmacoepidemiol Drug Saf 17:753–759
26. Nichols GA, Koro CE, Gullion CM, Ephross SA, Brown JB (2005) The incidence of congestive heart failure associated with antidiabetic therapies. Diabetes Metab Res Rev 21:51–57
27. Rajagopalan R, Rosenson RS, Fernandes AW, Khan M, Murray FT (2004) Association between congestive heart failure and hospitalization in patients with type 2 diabetes mellitus receiving treatment with insulin or pioglitazone: a retrospective data analysis. Clin Ther 26:1400–1410
28. Karter AJ, Ahmed AT, Liu J, Moffet HH, Parker MM (2005) Pioglitazone initiation and subsequent hospitalization for congestive heart failure. Diabet Med 22:986–993
29. Gerrits CM, Bhattacharya M, Manthena S, Baran R, Perez A, Kupfer S (2007) A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes. Pharmacoepidemiol Drug Saf 16:1065–1071
30. Rhoads GG, Kosiborod M, Nesto RW et al (2009) Comparison of incidence of acute myocardial infarction in patients with type 2 diabetes mellitus following initiation of neutral protamine Hagedorn insulin versus insulin glargine. Am J Cardiol 104: 910–916
31. Morgan CL, Poole CD, Evans M, Barnett AH, Jenkins-Jones S, Currie CJ (2012) What next after metformin? A retrospective evaluation of the outcome of second-line, glucose-lowering therapies in people with type 2 diabetes. J Clin Endocrinol Metab 97:4605–4612
32. Ziyadeh N, McAfee AT, Koro C, Landon J, Arnold Chan K (2009) The thiazolidinediones rosiglitazone and pioglitazone and the risk of coronary heart disease: a retrospective cohort study using a US health insurance database. Clin Ther 31:2665–2677
33. Koro CE, Bowlin SJ, Weiss SR (2005) Antidiabetic therapy and the risk of heart failure in type 2 diabetic patients: an independent effect or confounding by indication. Pharmacoepidemiol Drug Saf 14: 697–703
34. Horsdal HT, Sondergaard F, Johnsen SP, Rungby J (2011) Antidiabetic treatments and risk of hospitalisation with myocardial infarction: a nationwide case-control study. Pharmacoepidemiol Drug Saf 20:331–337
35. Wertz DA, Chang CL, Sarawate CA, Willey VJ, Cziraky MJ, Bohn RL (2010) Risk of cardiovascular events and all-cause mortality in patients treated with thiazolidinediones in a managed-care population. Circ Cardiovasc Qual Outcomes 3:538–545
36. Kress S, Kostev K, Dippel FW, Giani G, Rathmann W (2012) Micro- and macrovascular outcomes in type 2 diabetic patients treated with insulin glulisine or human regular insulin: a retrospective database analysis. Int J Clin Pharmacol Ther 50:821–829
37. McAlister FA, Eurich DT, Majumdar SR, Johnson JA (2008) The risk of heart failure in patients with type 2 diabetes treated with oral agent monotherapy. Eur J Heart Fail 10:703–708
38. Marceille JR, Goins JA, Soni R, Biery JC, Lee TA (2004) Chronic heart failure-related interventions after starting rosiglitazone in patients receiving insulin. Pharmacotherapy 24:1317–1322
39. Rothman KJ, Greenland S (1998) Modern epidemiology, 2nd edn. Lippincott-Raven, Philadelphia
40. Schisterman EF, Cole SR, Platt RW (2009) Overadjustment bias and unnecessary adjustment in epidemiologic studies. Epidemiology 20: 488–495
41. Greenland S (2003) Quantifying biases in causal models: classical confounding vs collider-stratification bias. Epidemiology 14:300–306
42. Hartung DM, Touchette DR, Bultemeier NC, Haxby DG (2005) Risk of hospitalization for heart failure associated with thiazolidinedione therapy: a Medicaid claims-based case-control study. Pharmacotherapy 25:1329–1336
43. Johnsen SP, Monster TB, Olsen ML et al (2006) Risk and short-term prognosis of myocardial infarction among users of antidiabetic drugs. Am J Ther 13:134–140
44. Sauer WH, Cappola AR, Berlin JA, Kimmel SE (2006) Insulin sensitizing pharmacotherapy for prevention of myocardial infarction in patients with diabetes mellitus. Am J Cardiol 97:651–654
45. Koro CE, Fu Q, Stender M (2008) An assessment of the effect of thiazolidinedione exposure on the risk of myocardial infarction in type 2 diabetic patients. Pharmacoepidemiol Drug Saf 17:989–996
46. Dore DD, Trivedi AN, Mor V, Lapane KL (2009) Association between extent of thiazolidinedione exposure and risk of acute myocardial infarction. Pharmacotherapy 29:775–783
47. Dormuth CR, Maclure M, Carney G, Schneeweiss S, Bassett K, Wright JM (2009) Rosiglitazone and myocardial infarction in patients previously prescribed metformin. PLoS One 4:e6080
48. MacDonald MR, Eurich DT, Majumdar SR et al (2010) Treatment of type 2 diabetes and outcomes in patients with heart failure: a nested case-control study from the U.K. General Practice Research Database. Diabetes Care 33:1213–1218
49. Azoulay L, Schneider-Lindner V, Dell'aniello S, Filion KB, Suissa S (2010) Thiazolidinediones and the risk of incident strokes in patients with type 2 diabetes: a nested case-control study. Pharmacoepidemiol Drug Saf 19:343–350
50. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB (2004) The incidence of congestive heart failure in type 2 diabetes: an update. Diabetes Care 27:1879–1884
51. Evans J, Ogston S, Emslie-Smith A, Morris A (2006) Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. Diabetologia 49:930–936
52. Kapinya K, Nijjar PS, Stanek M, Amanullah A (2008) Insulin-sensitizing antihyperglycaemic medications are associated with better outcome in patients with diabetes undergoing cardiac stress testing. Int Med J 38:259–264
53. Pantalone KM, Kattan MW, Yu C et al (2009) The risk of developing coronary artery disease or congestive heart failure, and overall mortality, in type 2 diabetic patients receiving rosiglitazone, pioglitazone, metformin, or sulfonylureas: a retrospective analysis. Acta Diabetol 46:145–154
54. Zendehdel K, Nyren O, Ostenson CG, Adami HO, Ekbom A, Ye W (2003) Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. J Natl Cancer Inst 95: 1797–1800
55. Adami HO, McLaughlin J, Ekbom A et al (1991) Cancer risk in patients with diabetes mellitus. Cancer Causes Control 2:307–314
56. Johnson E, Bartman B, Briesacher B et al (2013) The incident user design in comparative effectiveness research. Pharmacoepidemiol Drug Saf 22:1–6
57. Ray W (2003) Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 158:915–920
58. McAfee AT, Koro C, Landon J, Ziyadeh N, Walker AM (2007) Coronary heart disease outcomes in patients receiving antidiabetic agents. Pharmacoepidemiol Drug Saf 16:711–725
59. Walker AM, Koro CE, Landon J (2008) Coronary heart disease outcomes in patients receiving antidiabetic agents in the

PharMetrics database 2000-2007. Pharmacoepidemiol Drug Saf 17: 760–768
60. Winkelmayer WC, Setoguchi S, Levin R, Solomon DH (2008) Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy. Arch Intern Med 168:2368–2375
61. Juurlink DN, Gomes T, Lipscombe LL, Austin PC, Hux JE, Mamdani MM (2009) Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. BMJ 339:b2942
62. Juhaeri J, Gao S, Dai WS (2009) Incidence rates of heart failure, stroke, and acute myocardial infarction among type 2 diabetic patients using insulin glargine and other insulin. Pharmacoepidemiol Drug Saf 18:497–503
63. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE et al (2010) Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA 304:411–418
64. Best JH, Hoogwerf BJ, Herman WH et al (2011) Risk of cardiovascular disease events in patients with type 2 diabetes prescribed the glucagon-like peptide 1 (GLP-1) receptor agonist exenatide twice daily or other glucose-lowering therapies: a retrospective analysis of the LifeLink database. Diabetes Care 34:90–95
65. Roumie CL, Hung AM, Greevy RA et al (2012) Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. Ann Intern Med 157:601–610
66. Solomon DH, Glynn RJ, Rothman KJ et al (2008) Subgroup analyses to determine cardiovascular risk associated with nonsteroidal antiinflammatory drugs and coxibs in specific patient groups. Arthritis Rheum 59:1097–1104
67. Breslow NE, Day NE (1987) Statistical methods in cancer research. Volume II—the design and analysis of cohort studies. IARC Sci Publ 87:1–406
68. Delea TE, Edelsberg JS, Hagiwara M, Oster G, Phillips LS (2003) Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: a retrospective cohort study. Diabetes Care 26: 2983–2989
69. Habib ZA, Tzogias L, Havstad SL et al (2009) Relationship between thiazolidinedione use and cardiovascular outcomes and all-cause mortality among patients with diabetes: a time-updated propensity analysis. Pharmacoepidemiol Drug Saf 18:437–447
70. Johannes CB, Koro CE, Quinn SG, Cutone JA, Seeger JD (2007) The risk of coronary heart disease in type 2 diabetic patients exposed to thiazolidinediones compared to metformin and sulfonylurea therapy. Pharmacoepidemiol Drug Saf 16:504–512
71. Andersson C, Gislason GH, Jorgensen CH et al (2011) Comparable long-term mortality risk associated with individual sulfonylureas in diabetes patients with heart failure. Diabetes Res Clin Pract 94:119–125
72. Andersson C, Olesen JB, Hansen PR et al (2010) Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study. Diabetologia 53:2546–2553
73. Filion KB, Joseph L, Boivin JF, Suissa S, Brophy JM (2011) Thiazolidinediones and the risk of incident congestive heart failure among patients with type 2 diabetes mellitus. Pharmacoepidemiol Drug Saf 20:785–796
74. Hernan MA, Hernandez-Diaz S, Robins JM (2013) Randomized trials analyzed as observational studies. Ann Intern Med 159:560–562
75. Hernan M, Hernandez-Diaz S (2012) Beyond the intention-to-treat in comparative effectiveness research. Clin Trials 9:48–55
76. Rothman KJ, Greenland S, Lash TL (2008) Modern epidemiology, 3rd edn. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia
77. Jorgensen CH, Gislason GH, Andersson C et al (2010) Effects of oral glucose-lowering drugs on long term outcomes in patients with diabetes mellitus following myocardial infarction not treated with emergent percutaneous coronary intervention—a retrospective nationwide cohort study. Cardiovasc Diabetol 9:54
78. Schramm TK, Gislason GH, Vaag A et al (2011) Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J 32:1900–1908
79. Robins J (1992) Estimation of the time-dependent accelerated failure time model in the presence of confounding factors. Biometrika 79:321–334
80. Hernan M, Brumback B, Robins J (2000) Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology 11:561–570
81. Robins J, Hernan M, Brumback B (2000) Marginal structural models and causal inference in epidemiology. Epidemiology 11: 550–560
82. Robins J (1986) A new approach to causal inference in mortality studies with sustained exposure periods—application to control of the healthy worker survivor effect. Math Model 7:1393–1512
83. Walker AM (1991) Observation and inference: an introduction to the methods of epidemiology. Epidemiology Resources Inc., Chestnut Hill
84. Walker AM (1996) Confounding by indication. Epidemiology 7: 335–336
85. Petri H, Urquhart J (1991) Channeling bias in the interpretation of drug effects. Stat Med 10:577–581
86. Centers for Disease Control and Prevention (2011) National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. US Department of Health and Human Services, Centers for Disease Control and Prevention, Atlanta
87. Berger AK, Breall JA, Gersh BJ et al (2001) Effect of diabetes mellitus and insulin use on survival after acute myocardial infarction in the elderly (the Cooperative Cardiovascular Project). Am J Cardiol 87:272–277
88. Smooke S, Horwich TB, Fonarow GC (2005) Insulin-treated diabetes is associated with a marked increase in mortality in patients with advanced heart failure. Am Heart J 149:168–174
89. Aronow WS, Ahn C (2001) Incidence of new coronary events in older persons with diabetes mellitus and prior myocardial infarction treated with sulfonylureas, insulin, metformin, and diet alone. Am J Cardiol 88:556–557
90. Fisman EZ, Tenenbaum A, Boyko V et al (2001) Oral antidiabetic treatment in patients with coronary disease: time-related increased mortality on combined glyburide/metformin therapy over a 7.7-year follow-up. Clin Cardiol 24:151–158
91. Masoudi FA, Inzucchi SE, Wang Y, Havranek EP, Foody JM, Krumholz HM (2005) Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. Circulation 111:583–590
92. Arruda-Olson AM, Patch RK 3rd, Leibson CL et al (2009) Effect of second-generation sulfonylureas on survival in patients with diabetes mellitus after myocardial infarction. Mayo Clin Proc 84:28–33
93. Monami M, Balzi D, Lamanna C et al (2007) Are sulphonylureas all the same? A cohort study on cardiovascular and cancer-related mortality. Diabetes Metab Res Rev 23:479–484
94. Horsdal HT, Johnsen SP, Sondergaard F et al (2009) Sulfonylureas and prognosis after myocardial infarction in patients with diabetes: a population-based follow-up study. Diabetes Metab Res Rev 25: 515–522
95. Tzoulaki I, Molokhia M, Curcin V et al (2009) Risk of cardiovascular disease and all cause mortality among patients with type 2

diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ 339:b4731
96. Weih M, Amberger N, Wegener S, Dirnagl U, Reuter T, Einhaupl K (2001) Sulfonylurea drugs do not influence initial stroke severity and in-hospital outcome in stroke patients with diabetes. Stroke 32: 2029–2032
97. Inzucchi SE, Masoudi FA, Wang Y et al (2005) Insulin-sensitizing antihyperglycemic drugs and mortality after acute myocardial infarction: insights from the National Heart Care Project. Diabetes Care 28:1680–1689
98. Lipscombe LL, Gomes T, Levesque LE, Hux JE, Juurlink DN, Alter DA (2007) Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. JAMA 298:2634–2643
99. Mellbin LG, Malmberg K, Norhammar A, Wedel H, Ryden L (2008) The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. Eur Heart J 29: 166–176
100. Sadikot SM, Mogensen CE (2008) Risk of coronary artery disease associated with initial sulphonylurea treatment of patients with type 2 diabetes: a matched case-control study. Diabetes Res Clin Pract 82:391–395
101. Sillars B, Davis WA, Hirsch IB, Davis TM (2010) Sulphonylurea-metformin combination therapy, cardiovascular disease and all-cause mortality: the Fremantle Diabetes Study. Diabetes Obes Metab 12: 757–765
102. Stockl KM, Le L, Zhang S, Harada AS (2009) Risk of acute myocardial infarction in patients treated with thiazolidinediones or other antidiabetic medications. Pharmacoepidemiol Drug Saf 18: 166–174
103. Ramirez SP, Albert JM, Blayney MJ et al (2009) Rosiglitazone is associated with mortality in chronic hemodialysis patients. J Am Soc Nephrol JASN 20:1094–1101
104. Vanasse A, Carpentier AC, Courteau J, Asghari S (2009) Stroke and cardiovascular morbidity and mortality associated with rosiglitazone use in elderly diabetic patients. Diab Vasc Dis Res 6: 87–93
105. Schneeweiss S, Patrick AR, Brookhart AM et al (2007) Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. Med Care 45: S131–S142
106. Peduzzi PCJ, Kemper E, Holford TR, Feinstein AR (1996) A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 49:1373–1379
107. Cepeda MS, Boston R, Farrar JT, Strom BL (2003) Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. Am J Epidemiol 158:280–287
108. Rosenbaum PR, Rubin DB (1983) The central role of the propensity score in observational studies for causal effects. Biometrika 70:41–55
109. D'Agostino RB Jr (1998) Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 17:2265–2281
110. Rosenbaum PR, Rubin DB (1985) Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. Am Stat 39:33–38
111. Austin PC (2009) Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 28:3083–3107
112. Powers AC (2012) Diabetes mellitus. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J (eds) Harrison's principles of internal medicine, 18th edn. McGraw-Hill, New York
113. Inzucchi SE, Bergenstal RM, Buse JB et al (2012) Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 55:1577–1596
114. Singh S, Loke YK, Furberg CD (2007) Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA 298: 1189–1195
115. Nissen S, Wolski K (2007) Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 356:2457–2471
116. Rassen JA, Glynn RJ, Brookhart MA, Schneeweiss S (2011) Covariate selection in high-dimensional propensity score analyses of treatment effects in small samples. Am J Epidemiol 173:1404–1413
117. Rassen JA, Schneeweiss S (2012) Using high-dimensional propensity scores to automate confounding control in a distributed medical product safety surveillance system. Pharmacoepidemiol Drug Saf 21:41–49
118. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart AM (2009) High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology 20:512–522
119. Stergachis A (1988) Record linkage studies for postmarketing drug surveillance: data quality and validity considerations. Drug Intell Clin Pharmacol 22:157–161
120. McKenzie D, Semradek J, McFarland B, Mullooly J, McCamant L (2000) The validity of medicaid pharmacy claims for estimating drug use among elderly nursing home residents: the Oregon experience. J Clin Epidemiol 53:1248–1257
121. West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A (1995) Recall accuracy for prescription medications: self-report compared with database information. Am J Epidemiol 142:1103–1112
122. West SL, Strom BL, Freundlich B, Normand E, Koch G, Savitz DA (1994) Completeness of prescription recording in outpatient medical records from a health maintenance organization. J Clin Epidemiol 47:165–171
123. Kelsey JL, Whittemore AS, Evans AS, Thompson W (1996) Methods in observational epidemiology. Monographs in epidemiology and biostatistics vol. 26, 2nd edn. Oxford University Press, New York, pp 341–361
124. Kiyota Y, Schneeweiss S, Glynn R, Cannuscio C, Avorn J, Solomon D (2004) Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. Am Heart J 148:99–104
125. Tirschwell D, Longstreth WJ (2002) Validating administrative data in stroke research. Stroke J Cereb Circ 33:2465–2470
126. Wahl P, Rodgers K, Schneeweiss S et al (2010) Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. Pharmacoepidemiol Drug Saf 19:596–603
127. Saczynski J, Andrade S, Harrold L et al (2012) A systematic review of validated methods for identifying heart failure using administrative data. Pharmacoepidemiol Drug Saf 21:129–140
128. Birman-Deych E, Waterman AD, Yan Y, Nilasena DS, Radford MJ, Gage BF (2005) Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. Med Care 43:480–485
129. Hernandez-Diaz S, Adami HO (2010) Diabetes therapy and cancer risk: causal effects and other plausible explanations. Diabetologia 53:802–808
130. Suissa S, Azoulay L (2012) Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care 35:2665–2673
131. Johnson JA, Carstensen B, Witte D, Bowker SL, Lipscombe L, Renehan AG (2012) Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. Diabetologia 55:1607–1618
132. Renehan AG, Yeh HC, Johnson JA, Wild SH, Gale EA, Moller H (2012) Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. Diabetologia 55:1619–1632