Risk of lower extremity amputations in people with type 2 diabetes mellitus treated with sodium-glucose co-transporter-2 inhibitors in the USA: A retrospective cohort study

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1 | INTRODUCTION

People with type 2 diabetes mellitus (T2DM) frequently experience micro- and macrovascular complications. These complications can lead to lower extremity amputation, one of the severe consequences of advanced diabetes. Patients with diabetes account for the majority of all cases of lower extremity amputation, with the rate of lower extremity amputation for patients with diabetes reported to be ~1.5 to 5.0 per 1000 patient-years. In addition to diabetes itself, many comorbid conditions can contribute to the increased risk of
chronic lower extremity ulceration, including diabetic peripheral neuropathy, vascular insufficiency and infection, all of which can precede a traumatic lower extremity amputation.5 Additionally, cardiovascular (CV) disease is a well-documented risk factor for amputation in patients with T2DM.6,7

Optimal glycaemic control is associated with reduced risk of lower extremity amputation and other microvascular events, and is the cornerstone of diabetes therapy.8,9 Sodium glucose co-transporter 2 (SGLT2) inhibitors reduce plasma glucose by increasing the renal threshold for glucose, leading to increased urinary glucose excretion and a mild osmotic diuresis that may be associated with a reduction in intravascular volume.10,11 Canagliflozin, dapagliflozin and empagliflozin are SGLT2 inhibitors approved for the treatment of T2DM in the USA.12–14

Analysis of data from the CANVAS Program, which comprises 2 large CV outcomes trials of canagliflozin in patients with T2DM and a history or high risk of CV disease, the CANAgliflozin cardioVascular Assessment Study (CANVAS) and CANVAS-Renal (CANVAS-R), showed an increased risk of lower extremity amputation, mainly of the toe and middle of the foot, with canagliflozin. In the CANVAS Program, amputation rates were 6.3 and 3.4 per 1000 person-years with canagliflozin and placebo, respectively.15 The amputation rates were 5.9 and 2.8 per 1000 person-years with canagliflozin and placebo, respectively, in CANVAS, and 7.5 and 4.2 per 1000 person-years with canagliflozin and placebo, respectively, in CANVAS-R.16 The US Food and Drug Administration issued a Drug Safety Communication based on these findings, and the US prescribing information has been modified to reflect an increased risk of amputation in patients with high risk of CV events or a history of CV events.16,17 No imbalance in the risk of amputation in patients with high CV risk was reported in the completed EMPA-REG OUTCOME study of empagliflozin, although that trial did not systematically collect adequate data to confirm or refute this risk.18 The Dapagliflozin Effect on Cardiovascular Events (DECLARE) trial, a large-scale CV outcomes trial of dapagliflozin, is ongoing and is now required by the European Medicines Agency to collect data systematically on and report amputation events.19

Although an amputation imbalance was observed in the CANVAS Program, no such imbalance was observed across the canagliflozin phase III and IV study programme, which included more than 8100 patients with T2DM at low CV risk. In the non-CANVAS canagliflozin studies, the incidence rates of amputation were 0.5 and 2.2 per 1000 person-years with canagliflozin and placebo, respectively, and the relative risk of amputation events was 0.23 (95% confidence interval [CI] 0.06, 0.89; data on file). A total of 3 patients had amputations in the canagliflozin group and 7 in the control group among the more than 8100 patients studied; thus, the analysis lacked power to provide definitive evidence regarding amputation risk with canagliflozin. To evaluate the risk of amputation in a general population of patients with T2DM in routine clinical practice, the present retrospective study used the Truven MarketScan Commercial Claims and Encounters (CCAE) database to examine the incidence of below-knee lower extremity (BKLE) amputation among new users of any SGLT2 inhibitor (canagliflozin, dapagliflozin or empagliflozin), canagliflozin only or a non-SGLT2 inhibitor antihyperglycaemic agent (AHA).
exposure date or previous exposure to any SGLT2 inhibitors within the observation period were excluded from this study.

The incidence of BKLE amputation was described separately for patients with established CV disease and those without established CV disease (ie, based on baseline CV disease status). Because the CCAE database does not reflect a random sample of a general population, these incidence calculations are direct observations, and CIs are not provided. Established CV disease was defined as any record of a diagnosis (cerebrovascular disease, myocardial infarction or peripheral vascular disease) or a procedure (coronary artery bypass graft, percutaneous coronary intervention or peripheral revascularization) during the baseline period (Table S2).

2.4 | Cohort follow-up

Patients were followed from the index date until the end of their observation time, regardless of whether they discontinued, switched or augmented treatment (ie, intent-to-treat approach). The primary outcome was the incident case of BKLE amputation, as defined by observing an associated procedure code in the outpatient or inpatient medical service claims between the index date and the end of the observation period.

2.5 | Propensity score estimation and matching

We used EPS matching to reduce potential confounding by imbalanced baseline covariates; new users of canagliflozin were matched 1:1 to new users of non-SGLT2 inhibitor AHAs. Large-scale EPS was estimated using regularized logistic regression models, with the dependent variable being canagliflozin new user, and independent variables being the baseline confounders over the 12 months prior to the exposure index date. To avoid over-fitting models and to accommodate a large number of predictors, the regularized logistic regression model was fit using a cyclic coordinate descending method with $L_1$ penalty (ie, least absolute shrinkage and selection operator). The optimal regularization hyper-parameter was estimated using 10-fold cross-validation. A conventional greedy algorithm with nearest-neighbour matching minimizing the absolute difference between EPS was used for matching. The maximum matching caliper of the EPS (on the logit scale) was 20% of the standard deviation of the logit of the EPS. Standardized differences were tabulated across potential confounders to evaluate the matching effectiveness in achieving baseline covariate balance.

2.6 | Statistical analyses

2.6.1 | Descriptive summary

Crude incidence rates of BKLE amputation were estimated as the number of first BKLE amputation cases divided by the total at-risk follow-up time, and reported per 1000 person-years at risk, for patients treated with canagliflozin, dapagliflozin, empagliflozin, any SGLT2 inhibitor, and non-SGLT2 inhibitor AHAs, which were further stratified by CV disease status.

2.6.2 | Comparative analysis

A comparative analysis was performed using the conditional Cox proportional hazards model. While formal statistical comparisons were based on EPS-matched cohorts, residual confounding might still be present; therefore, negative controls were used to perform empirical calibration to correct P values generated by the conditional Cox proportional hazards model to further control for random and systematic errors. Both uncalibrated and calibrated P values are presented. Kaplan–Meier plots were generated for the risk of BKLE amputation over time in the EPS-matched new users of canagliflozin and non-SGLT2 inhibitor AHAs.

2.6.3 | Sensitivity analysis

A sensitivity analysis was performed that compared the risk of amputation between new users of canagliflozin who had prior metformin use and no prior DPP-4 inhibitor or GLP-1 agonist use vs new users of DPP-4 inhibitors or GLP-1 agonists who had prior metformin use and no prior SGLT2 inhibitor use.

3 | RESULTS

3.1 | Study population

Between April 1, 2013 and October 31, 2016, there were a total of 119 567 new users of SGLT2 inhibitors with 140 145 person-years at risk and 226 623 new users of non-SGLT2 inhibitor AHAs with 283 406 person-years at risk (Table 1). Of the new users of SGLT2 inhibitors, 73 024 were new users of canagliflozin with a total of 95 422 person-years at risk. A total of 22% of new users of SGLT2 inhibitors (22% of those treated with canagliflozin) and 21% of new users of non-SGLT2 inhibitor AHAs had established CV disease at baseline.

3.2 | Crude incidence of BKLE amputation

The crude incidence of BKLE amputation in the overall SGLT2 inhibitor population was relatively low (1.22 per 1000 person-years) and ranged from 0.96 per 1000 person-years with dapagliflozin to 1.26 and 1.39 per 1000 person-years with canagliflozin and empagliflozin, respectively. The incidence rate of BKLE amputation among new users of non-SGLT2 inhibitor AHAs was 1.87 per 1000 person-years.

A greater proportion of patients with established CV disease had a history of amputation before the index date compared with patients without established CV disease. The crude incidence rate of BKLE amputation in patients with established CV disease was 1.99, 1.28, 3.42, 2.03 and 3.29 per 1000 person-years with canagliflozin, dapagliflozin, empagliflozin, all SGLT2 inhibitors and non-SGLT2 inhibitor AHAs, respectively. For patients without established CV disease, the incidence rate of BKLE amputation was 1.06, 0.88, 0.80, 1.00 and 1.05 with canagliflozin, dapagliflozin, empagliflozin, all SGLT2 inhibitors and non-SGLT2 inhibitor AHAs, respectively. The distribution of BKLE amputation incident cases by procedure code is shown in Table S3.
3.3 Comparative analysis

Of the 72,797 users of canagliflozin and 225,627 users of non-SGLT2 inhibitor AHAs with no history of BKLE amputation and ≥1 day at risk who were eligible for inclusion in the comparative analysis, 63,845 pairs were formed based on matching of EPS (Figure 1). All baseline characteristics were well balanced after EPS matching (Figure 2), and patient demographics (age and sex), key comorbid conditions (including CV disease) and medications of interest (eg, commonly reported in patients with T2DM) for the treatment cohorts are presented in Table 2. The median (interquartile range [IQR]) duration of index therapy was 0.43 (0.17, 0.94) years with canagliflozin...
|                         | Before matching | After matching |
|-------------------------|-----------------|---------------|
|                         | Canagliflozin   | Non-SGLT2 inhibitor AHA | Standardized difference | Canagliflozin | Non-SGLT2 inhibitor AHA | Standardized difference |
| Number of distinct persons | 72 797          | 225 627       |                   | 63 845        | 63 845               |                   |
| Mean age, a years       | 53.3            | 52.8          | 0.06              | 53.2          | 53.3                | 0.01              |
| Standard deviation      | 8.0             | 9.0           |                   | 8.1           | 8.1                 |                   |
| Sex b                   |                 |               |                   |               |                     |                   |
| Male                    | 55.1            | 55.6          | –0.01             | 55.5          | 55.3                | 0.00              |
| Female                  | 44.9            | 44.4          | 0.01              | 44.5          | 44.7                | 0.00              |
| Index year c            |                 |               |                   |               |                     |                   |
| 2013                    | 12.6            | 25.7          | –0.34             | 13.7          | 12.6                | 0.03              |
| 2014                    | 34.9            | 32.3          | 0.06              | 35.1          | 35.2                | 0.00              |
| 2015                    | 38.2            | 23.7          | 0.32              | 36.0          | 37.0                | –0.02             |
| 2016                    | 14.2            | 18.2          | –0.11             | 15.2          | 15.2                | 0.00              |
| Comorbidities of interest b,c |             |               |                   |               |                     |                   |
| Congestive heart failure| 1.4             | 2.6           | –0.08             | 1.4           | 1.4                 | 0.00              |
| Cardiomyopathy          | 1.3             | 1.8           | –0.04             | 1.2           | 1.3                 | 0.00              |
| COPD                    | 2.4             | 3.4           | –0.06             | 2.4           | 2.4                 | 0.00              |
| Disorder due to T2DM    | 13.9            | 13.1          | 0.02              | 12.9          | 12.8                | 0.00              |
| Chronic liver disease   | 4.8             | 4.8           | 0.00              | 4.7           | 4.7                 | 0.00              |
| Hyperlipidaemia         | 75.5            | 64.6          | 0.24              | 74.1          | 74.6                | –0.01             |
| Essential hypertension  | 72.6            | 66.4          | 0.13              | 71.4          | 71.8                | –0.01             |
| Cerebrovascular disease | 1.7             | 2.4           | –0.05             | 1.6           | 1.6                 | 0.00              |
| Malignant neoplastic disease | 5.4          | 6.1           | –0.03             | 5.3           | 5.4                 | –0.01             |
| Peripheral vascular disease | 8.5           | 8.6           | 0.00              | 8.1           | 8.2                 | 0.00              |
| Rheumatoid arthritis    | 1.0             | 1.1           | –0.01             | 1.0           | 1.0                 | 0.00              |
| Renal impairment        | 3.2             | 6.4           | –0.15             | 3.2           | 3.2                 | 0.00              |
| Venous thrombosis       | 1.3             | 1.8           | –0.04             | 1.3           | 1.3                 | 0.00              |
| Pancreatitis            | 0.7             | 1.0           | –0.03             | 0.7           | 0.6                 | 0.01              |
| Obesity                 | 21.8            | 19.6          | 0.06              | 21.0          | 21.2                | 0.00              |
| Medications of interest b,d |             |               |                   |               |                     |                   |
| Agents acting on the renin-angiotensin system | 76.2          | 69.0          | 0.16              | 74.9          | 75.3                | –0.01             |
| Calcium channel blockers | 66.1            | 61.3          | 0.10              | 65.2          | 65.8                | –0.01             |
| β-blocking agents       | 51.4            | 49.4          | 0.04              | 50.6          | 51.1                | –0.01             |
| HMG-CoA reductase inhibitors | 80.0          | 74.4          | 0.13              | 79.1          | 82.1                | –0.08             |
| Diuretics               | 80.9            | 74.9          | 0.14              | 79.7          | 80.1                | –0.01             |
| Drugs for acid-related disorders | 55.3          | 53.2          | 0.04              | 54.3          | 54.6                | –0.01             |
| Digoxin                 | 0.5             | 0.7           | –0.02             | 0.5           | 0.5                 | 0.00              |
| Anti-inflammatory and anti-rheumatic products, non-steroids | 46.1          | 43.0          | 0.06              | 45.0          | 45.4                | –0.01             |
| Selective serotonin reuptake inhibitors | 14.4          | 13.0          | 0.04              | 13.9          | 14.0                | 0.00              |
| AHA therapies b,d       |                 |               |                   |               |                     |                   |
| Metformin               | 81.3            | 67.8          | 0.31              | 81.1          | 76.0                | 0.12              |
| DPP-4 inhibitors        | 35.9            | 7.7           | 0.72              | 35.9          | 8.3                 | 0.70              |
| GLP-1 agonists          | 4.9             | 0.3           | 0.29              | 4.5           | 0.3                 | 0.28              |
| Thiazolidinediones      | 10.0            | 3.2           | 0.28              | 9.8           | 3.7                 | 0.25              |

(Continues)
and 0.33 (0.12, 0.79) years with non-SGLT2 inhibitor AHAs. In comparison, the overall median (IQR) follow-up time based on the intention-to-treat analysis was 1.27 (0.62, 1.88) years with canagliflozin and 1.04 (0.48, 1.89) years with non-SGLT2 inhibitor AHAs. Prior to the index date, a greater percentage of new users of canagliflozin had prior or current treatment with various AHAs compared with new users of non-SGLT2 inhibitor AHAs. By design, use of AHAs was not included in the EPS model; therefore, it was expected that an imbalance in the use of AHAs at baseline may remain after matching (Table 2). After the index date, 99 patients treated with canagliflozin and 87 patients treated with a non-SGLT2 inhibitor AHA had a BKLE amputation event post exposure (incidence rate, 1.18 and 1.12 per 1000 person-years, respectively). The hazard of an incident BKLE amputation event was not significantly different between groups (hazard ratio [HR] 0.98 [95% CI 0.68, 1.41]; \( P = .92 \), calibrated \( P = .95 \)).

### 3.4 Sensitivity analysis

The sensitivity analysis produced results that were consistent with the primary analysis. The cohorts were sufficiently comparable and passed diagnostics after EPS matching. The matched sample had 30 380 patients in each cohort, and there were 56 patients with BKLE amputation post-exposure in the target population. The effect estimate was not significantly different between groups (HR 0.87 [95% CI 0.52, 1.46]; \( P = .60 \), calibrated \( P = .65 \)). Full results of the sensitivity analysis are available on request.

### 4 DISCUSSION

This large, observational, retrospective study was based on real-world patient data in an EPS-matched population with an average age of ~53 years, where ~8% of patients had peripheral vascular disease, 3.2% had renal impairment, and 1.4% had congestive heart failure. In the present study, we found that the overall risk of incident BKLE amputation was relatively low and found no evidence that the risk differs between patients with T2DM who were new users of canagliflozin and those who were new users of non-SGLT2 inhibitor AHAs.

The findings from this observational study should be interpreted within the context of the total available evidence. As described above, no imbalance in the risk of amputation was observed in the pooled non-CANVAS phase III and IV trials of canagliflozin, which included patients with T2DM with an average age of ~57 years and a baseline estimated glomerular filtration rate (eGFR) reflecting normal renal function (~86 mL/min/1.73 m²). In this pooled non-CANVAS population, ~22% of patients had ≥1 microvascular complication and there was also a lower proportion of patients with established CV disease (6.6%) compared with the CANVAS Program (65%); however, the analysis of the risk of lower extremity amputation in the non-CANVAS population was limited by a low number of observed events. The use of observational database studies allowed analysis of the risk of amputation with canagliflozin in a larger population. The present observational study identified a total of 186 incident BKLE amputation events in a combined cohort of 127 690 patients (~10-fold larger population than the CANVAS Program) not enriched for CV disease (22% of patients had established CV disease). Consistent with the results from the non-CANVAS population, analysis of the EPS-matched cohort also found no evidence of increased BKLE amputation with canagliflozin (HR 0.98 [95% CI 0.68, 1.41]). By contrast, in the CANVAS Program, which enrolled patients with T2DM and high CV risk, the incidence of non-traumatic BKLE amputation was increased ~2-fold.\(^1\)\(^5\) The observed difference in BKLE amputation risk in these analyses may be attributable to differences in the study populations, specifically with respect to CV risk; more studies are needed to investigate the risk of amputation in patients with high CV risk in a real-world setting. Currently, the mechanism behind the increased risk of BKLE amputation with canagliflozin in patients with T2DM and high CV risk is not well understood, although volume depletion and the potential for reduced tissue perfusion (because of the mechanism of the pharmacological action associated with this class of drug) may have played a role.

The present study was strengthened by the use of a large patient database that provided information on real-world experience and is representative of the US commercially insured population. Use of this large, detailed database allowed balancing of potential confounders by EPS matching. In addition, the use of negative control outcomes enabled us to further assess and minimize the likelihood of unmeasured confounding and systematic error.

As with all observational research, the present study is subject to several potential limitations. In spite of the more than 10,000 baseline variables that were included as potential confounders in
the calculation of EPS, there could be unmeasured and residual confounding in this study. For example, some data that may affect risk estimation were not available or mostly missing from insurance claims (eg, socio-economic status, behavioural variables, reason for BKLE amputation, body weight, changes in HbA1c, and duration of diabetes and disease state). In addition, insurance claims databases were originally constructed for financial reimbursement for services rather than research purposes. As such, some recorded and coded claims data may not be accurate and complete, and could be confounded by financial incentives. Furthermore, it was noted that the rate of amputation in the present study was lower than the rate reported in the CANVAS Program; this may be attributable, in part, to differences in patient age, duration of T2DM and prevalence of CV disease at baseline. Because the database reflects the experience of a commercially insured population, most of the study patients were aged <65 years, which may limit the study’s generalizability to older patients (eg, a Medicare population). Finally, by design, use of AHAs at baseline was not included in the exposure propensity model, and some imbalance remained after EPS matching. Although patients treated with canagliflozin may have had higher baseline HbA1c or more difficulty achieving glycaemic control (owing to more add-on AHA therapies at baseline), additional analyses based on negative controls suggest that this imbalance resulted in limited, if any, confounding or bias.

In the present study, a general population of patients with T2DM treated with canagliflozin and non-SGLT2 inhibitor AHAs did not have a different risk of lower extremity amputation. Overall, these results, based on real-world evidence, suggest that patients with T2DM and average risk of CV disease treated with canagliflozin have the same low risk of amputation as patients treated with non-SGLT2 inhibitor AHAs.

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Conflict of interest
Z. Y., F. J. D., P. B. R., M. J. S., P. E. S., M. D. and N. R. are full-time employees of Janssen Research & Development, LLC. J. A. B. is a full-time employee of Johnson & Johnson, LLC.

Author contributions
Z. Y., F. J. D., P. B. R., M. J. S., P. E. S., J. A. B., M. D. and N. R. were involved in the design of the study, collection of data, or analysis of data and preparation of the final manuscript.

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REFERENCES
1. American Diabetes Association. Standards of medical care in diabetes-2017. Diabetes Care. 2017;40(suppl 1):S1–S135.
2. Boulton AJ, Vinik AI, Arezzo JC, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 2005;28(4):956–962.
3. National Center for Chronic Disease Prevention. National diabetes statistics report, 2017. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed September 21, 2017.
4. World Health Organization. Global report on diabetes, 2016. http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf?u=1. Accessed July 5, 2017.
5. Bruun C, Siersma V, Guassora AD, Holstein P, de Fine Olivarius N. Amputations and foot ulcers in patients newly diagnosed with type 2 diabetes mellitus and observed for 19 years. The role of age, gender and co-morbidity. Diabet Med. 2013;30(8):964–972.
6. Yesil S, Akinci B, Yener S, et al. Predictors of amputation in diabetics with foot ulcer: single center experience in a large Turkish cohort. Hormones (Athens). 2009;8(4):286–295.
7. Lai YJ, Hu HY, Lin CH, Lee ST, Kuo SC, Chou P. Incidence and risk factors of lower extremity amputations in people with type 2 diabetes in Taiwan, 2001-2010. J Diabetes. 2015;7(2):260–267.
8. Zoungas S, Arima H, Gerstein HC, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol. 2017;5(6):431–437.
9. Zhou ZY, Liu YK, Chen HL, Yang HL, Liu F, HbA1c and lower extremity amputation risk in patients with diabetes: a meta-analysis. Int J Low Extrem Wounds. 2015;14(2):168–177.
10. Abdul-Ghani MA, Norton L, DeFrancesco RA. Renal sodium-glucose cotransporter inhibition in the management of type 2 diabetes mellitus. Am J Physiol Renal Physiol. 2015;309(11):F889–F900.
11. Mudaliar S, Polidori D, Zambrowicz B, Henry RR. Sodium glucose cotransporter inhibitors: effects on renal and intestinal glucose transport: from bench to bedside. Diabetes Care. 2015;38(12):2344–2353.
12. Rosenthal N, Meiningier G, Ways K, et al. Canagliflozin: a sodium glucose co-transporter 2 inhibitor for the treatment of type 2 diabetes mellitus. Ann N Y Acad Sci. 2015;1358(1):28–43.
13. Davis PN, Ndeo UA, Oliver A. Dapagliflozin: a sodium glucose cotransporter 2 inhibitor for the treatment of diabetes mellitus. J Pharm Pract. 2016;29(2):165–171.
14. Liakos A, Karagiannis T, Athanasiadou E, et al. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis, Diabetes Obes Metab. 2014;16(10):984–993.
15. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–657.
16. US Food and Drug Administration. FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR), 2017. https://www.fda.gov/downloads/Drugs/DrugSafety/UCM558427.pdf. Accessed August 9, 2017.
17. INVOKANA® (canagliflozin) tablets, for oral use [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2017.
18. European Medicines Agency. PRAC concludes that diabetes medicine canagliflozin may contribute to risk of toe amputation. Risk may also apply to other medicines in the same class. 2017. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SGLT2_inhibitors_Canagliflozin_20_Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Co... Accessed July 5, 2017.
19. European Medicines Agency. SGLT2 inhibitors: information on potential risk of toe amputation to be included in prescribing information. 2017.
20. Genkin A, Lewis DD, Madigan D. Large-scale Bayesian logistic regression for text categorization. *Dent Tech*. 2007;49(3):291–304.

21. Tibshirani R. Regression shrinkage and selection via the lasso. *J R Stat Soc Ser B Methodol*. 1996;58(1):267–288.

22. Rassen JA, Shelat AA, Myers J, Glynn RJ, Rothman KJ, Schneeweiss S. One-to-many propensity score matching in cohort studies. *Pharmacoepidemiol Drug Saf*. 2012;21(suppl 2):69–80.

23. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat*. 2011;10(2):150–161.

24. Rosenbaum P, Rubin D. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1):41–55.

25. Schuemie MJ, Ryan PB, DuMouchel W, Suchard MA, Madigan D. Interpreting observational studies: why empirical calibration is needed to correct p-values. *Stat Med*. 2014;33(2):209–218.

26. Boyce RD, Ryan PB, Noren GN, et al. Bridging islands of information to establish an integrated knowledge base of drugs and health outcomes of interest. *Drug Saf*. 2014;37(8):557–567.

27. Arnold BF, Ercumen A, Benjamin-Chung J, Colford JM Jr. Brief report: negative controls to detect selection bias and measurement bias in epidemiologic studies. *Epidemiology*. 2016;27(5):637–641.

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