Rogers Mary (Orcid ID: 0000-0001-5519-3223)

TITLE: Longitudinal Study of Short-term Corticosteroid Use by Working-Age Adults with Diabetes Mellitus: Risks and Mitigating Factors

RUNNING HEAD: Corticosteroid Use by Adults with Diabetes

AUTHORS:
Mary A. M. Rogers[1]
Paul Lin[1]
Brahmajee K. Nallamothu[1,2]
Catherine Kim[1]
Akbar K. Waljee[1,2]

1. University of Michigan Medical School, Ann Arbor, Michigan, USA
2. Veterans Administration Center for Clinical Management Research, Ann Arbor, Michigan, USA

CORRESPONDENCE:
Mary A·M. Rogers, PhD, MS
Research Associate Professor
Department of Internal Medicine
University of Michigan
Building 16, Room 422W North Campus Research Complex
2800 Plymouth Road
Ann Arbor, Michigan, USA 48109-2800
Telephone: 1-734-647-8851
FAX: 1-734-936-8944
Email: maryroge@umich·edu

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ABSTRACT

Background

We assessed the frequency of short-term oral corticosteroid use in adults with diabetes, and examined the incidence of fractures, venous thromboembolism (VTE) and hospitalization for sepsis after corticosteroid use. We also evaluated whether preventative medications mitigated adverse events.

Methods

We conducted a longitudinal study of 1,548,945 adults (ages 18-64 years) who received healthcare coverage through a large national health insurer, years 2012-2014. Incidence rate ratios (IRR) were calculated using conditional Poisson regression.

Results

Short-term oral corticosteroids were used by 23.9% of adults with type 2 diabetes, 20.8% with type 1, and 20.9% without diabetes during the 3-year period ($p<0.001$). Baseline risks of fracture, VTE, and sepsis were greater for individuals with diabetes than those without ($p<0.001$). The combined effect of having diabetes and using corticosteroids was greater than

the sum of the individual effects (synergy indices of 1.17, 1.23, 1.30 for fracture, VTE and sepsis, respectively). The IRR for venous thromboembolism was 3.62 (95% CI, 2.41-5.45) in the 5-30 days after corticosteroid use. Fractures increased in the 5-30 days after corticosteroid use (IRR=2.06, 95% CI: 1.52, 2.80), but concomitant use of ergocalciferol mitigated this risk (IRR=1.13; 95% CI: 0.12, 11.07). The risk of hospitalization for sepsis was elevated with corticosteroid use (IRR=3.79; 95% CI: 2.05, 7.01) but was mitigated by the concomitant use of statins.

Conclusions

Short-term oral corticosteroid use is common in adults with diabetes and is associated with an elevated, but low, risk of adverse events. Our findings suggest that preventative medications may mitigate risk.

KEYWORDS

Corticosteroids

Diabetes mellitus

Drug-related side effects and adverse reactions

Statins

Vitamin D

HIGHLIGHTS

Adults with diabetes mellitus have a greater risk of fracture, venous thromboembolism, and sepsis than those without diabetes. Use of corticosteroids, even for short durations, increases this risk. However, vitamin D mitigated the risk of fracture in patients with diabetes who used corticosteroids. Statins decreased the likelihood of hospitalization for sepsis in corticosteroid users with diabetes. Corticosteroids should be used with caution in patients with diabetes and mitigating factors should be considered.

INTRODUCTION

Oral corticosteroids decrease insulin secretion, promote gluconeogenesis and glycogenolysis, and diminish hepatic and skeletal muscle insulin sensitivity (1); therefore, their use in patients with diabetes mellitus requires close surveillance. Guidelines for diabetes management include recommendations for careful monitoring of blood glucose when beginning the use of oral corticosteroids and for caution when insulin dosing corrections are made to compensate for the anticipated hyperglycemia (2-4). This is notable because corticosteroid use is common (5-7); for example, approximately one-fifth of the US working-age population uses short-term corticosteroids (8).

Aside from hyperglycemia, the pleiotropic side effects of long-term oral corticosteroid use are well-recognized (9). Use for short periods has been generally considered safe, but recently has been implicated in risk, albeit at rather low frequencies (8). Because adverse events may occur infrequently, it is not always possible to evaluate such risks within the context of a randomized controlled trial due to low statistical power. Trials also impose a challenge for the evaluation of patient safety due to the dissimilarity of trial participants to the wider population of patients who may be taking the medications. Moreover, many trials do not assess all risks; for example, investigators found that venous thromboembolism was not reported in 89% of randomized

controlled trials (10). Therefore, the evaluation of patient safety is often undertaken during the post-trial period using data from a larger population of users.

We were particularly interested in the safety of medications in the young- and middle-adult populations with diabetes because of the lack of studies in adults of working age. We obtained data from a large, national sample of American adults who received private healthcare coverage. The purpose of our investigation was two-fold: (1) to assess the frequency of short-term oral corticosteroids in adults with diabetes, and (2) to examine the incidence of fractures, venous thromboembolism and hospitalization for sepsis by corticosteroid use. Secondarily, we assessed whether there were potential mitigating factors which may impact this risk.

METHODS

We conducted a longitudinal study using de-identified data collected from January 1,2012 through December 31, 2014 from adults (18-64 years of age) who received healthcare coverage through a large national health insurer (obtained through OptumInsight, Eden Prairie, Minnesota, USA). The study was reviewed by the University of Michigan Institutional Review Board for oversight regarding human subjects, designated as exempt from further review, and given a waiver for informed consent. There were 1,548,945 adults in the database, the methods of which have been described (8). Briefly, adults with three years of continuous enrollment were included

to assess corticosteroid use and the incidence of fracture, venous thromboembolism and hospitalization for sepsis. Since we were studying incident events, we excluded those individuals who experienced fractures, venous thromboembolism or sepsis in year 2011. Over the 3-year period of the study (years 2012-2014), the first occurrence for each outcome was extracted so as to not capture follow-up visits for the same event.

Oral corticosteroid use of short duration (<30 days) was extracted from pharmacy files, indicating the type of prescription(s) and the date(s) when filled. Patients who were prescribed oral corticosteroids for ≥30 days cumulatively over the study period were excluded, as were those who received any oral corticosteroids during the year prior to the start of the study (in 2011). The oral corticosteroids identified were betamethasone, dexamethasone, methylprednisolone, triamcinolone, prednisone, prednisolone, hydrocortisone, and cortisone. We focused on oral corticosteroids that were swallowed (e.g., tablets, capsules, elixirs) and excluded all other forms of corticosteroids, including aerosols, creams, drops, suspended drops, lotion, spray and vials.

Patients with type 1 diabetes mellitus were defined as individuals who had at least two ICD-9-CM codes indicating type 1 diabetes on different dates, with the use of insulin (Table 1). Patients with type 2 diabetes were identified as individuals with records of at least two ICD-9-CM codes indicating type 2 diabetes on different dates, regardless of type of antidiabetic

medication used (Table 1). Outcomes (fracture, venous thromboembolism, sepsis) were also ascertained through ICD-9-CM codes. For sepsis, hospital admissions were utilized in which the principal diagnosis was sepsis. Fractures of the torso and limbs were included from injury codes (Table 1).

There were no missing values for age or gender. There were complete data regarding diagnoses and medication prescriptions that were filled by the participants within this health insurance plan during the time period of the study.

There were several phases to the statistical analyses. In the first phase, we examined the frequency of corticosteroid use (%, 95% exact confidence intervals (CI)), stratified by type of diabetes, gender, and age category. To assess differences in the frequency of use by subgroup, Pearson's chi-squared tests were used.

In the second phase of the analyses, we assessed the frequency of the adverse events (fractures, venous thromboembolism, and hospitalization for sepsis). Both cumulative incidence (%) and rates (events/1000 person-years) were calculated with 95% exact confidence intervals, stratified by type of diabetes. Incidence rate ratios (IRR) were also calculated, comparing the event rate in corticosteroid users to that of non-steroid users, with stratification by type of diabetes. The interaction between steroid use and diabetes on adverse events was determined by using the

synergy index on an additive scale (11). A synergy index of >1.0 indicates a positive interaction; that is, the combined effect of having diabetes and using corticosteroids would be greater than the sum of the individual effects of these two factors. In addition, we examined the association between corticosteroid use and adverse events when stratified by the type of anti-diabetic medication used (i.e., ever use during the study period); odds ratios were generated from a logit model with adjustment for age, gender, and race. Heterogeneity by type of anti-diabetic medication was evaluated using Cochran's Q test and the I^2 statistic which measures the percentage of variation in the odds ratios (across the various anti-diabetic medications) that is due to heterogeneity rather than random error.

In the third phase of the analyses, the association between corticosteroid use and adverse events was evaluated. Using a self-controlled case series design, the incidence of adverse events after corticosteroid use was calculated and compared to the incidence of adverse events during the time period when the corticosteroid was not used. That is, the incidence of events was compared in different time windows within the same person. We assessed risk of adverse events in the 5-30 days, 31-90 days, and 91-180 days after the corticosteroid prescription was filled. The reference (comparator) period was 5-180 days prior to when the corticosteroid prescription was filled. Conditional (fixed) Poisson regression was used for the analyses, offset by the natural logarithm of the time under observation. Incidence rate ratios were generated with 95% CI comparing the risk of adverse events when using versus not using corticosteroids. Because this

was a within-person comparison, gender, race, genetic profile, history of past medical conditions, and past health-related behaviors remained the same. Other non-steroidal medications that were significantly associated with the outcomes were included as time-varying covariates.

In a secondary analysis of patients with diabetes, the self-controlled case series design was extended to examine whether the use of preventative medications at the same time as the corticosteroids affected the results. Specifically, concomitant use (prescription filled 0-30 days prior to the corticosteroid prescription) of Vitamin D and statin was determined. Use of corticosteroids with Vitamin D was of interest for the assessment of fractures. Use of corticosteroids with statin was of interest for venous thromboembolism and sepsis. Statistical methods were similar to those described above (i.e., fixed Poisson regression with an offset). In addition, we utilized a cohort design to further investigate the association between concomitant medications and adverse events (comparing users to non-users) in which logistic regression was used. Alpha was set at 0.05, 2-tailed. All analyses were conducted in Stata/MP 14.2 (StataCorp LP, College Station, Texas).

RESULTS

In this investigation, 8.1% (126091/1548945) of the adults had diabetes mellitus. Of those with diabetes, 87.4% had type 2 (110141/126091) and 12.6% (15950/126091) had type 1 diabetes. The mean age of those with type 2 diabetes was 53.3 years (SD, 8.2), with type 1 diabetes was

49.5 years (SD, 11.4), and without diabetes was 43.6 years (SD, 12.1). Men were more likely to have diabetes than women (60% males with type 1, 59% males with type 2, 54% males without diabetes; $p<0.001$).

Within this database, 21.1% (327452/1548945) used corticosteroids for <30 days. Individuals with type 2 diabetes were more likely to use corticosteroids than those with type 1 diabetes ($p<0.001$) and those without diabetes ($p<0.001$). The frequency of corticosteroid use is given in Table 2, by diabetes type, gender, and age categories. Women with type 2 diabetes were frequent users of short-duration corticosteroids (28.4% during the 3-year study period). Across both gender and age categories, individuals with type 2 diabetes were more frequent users of corticosteroids than either those with type 1 or those without diabetes. The mean duration of corticosteroid therapy in patients with diabetes was 6.7 days (SD, 3.0 days) and the median duration was 6 days (IQR: 5, 7 days).

Rates of fracture, venous thromboembolism and hospitalization for sepsis are given in Table 3. Adults with type 1 diabetes had greater rates of adverse events than those with type 2 diabetes ($p<0.001$) and those without diabetes ($p<0.001$). In adults with type 1 diabetes who used corticosteroids, 12.5% experienced a fracture, 4.6% experienced venous thromboembolism, and 4.4% were hospitalized for sepsis during the study period. This compares with 7.2%, 2.6%, and 1.4% (respectively) for adults with type 2 diabetes. The IRRs indicate that the risks of adverse

events were significantly elevated in patients with diabetes (both types 1 and 2) and in corticosteroid users (compared to nonusers without diabetes), although the strength of the association was greater in those with type 1 diabetes (Table 3). For example, the risk of venous thromboembolism was 7-fold greater in patients with type 1 diabetes who used corticosteroids compared to nonusers without diabetes. All outcomes exhibited positive interactions (synergy indices of 1.17, 1.23, 1.30 for fracture, venous thromboembolism, and sepsis, respectively). Therefore, the combined effect of having diabetes and using corticosteroids was greater than the sum of the individual effects.

When stratified by the type of anti-diabetic medication used, the association between corticosteroid use and adverse events remained (Figure 1). The results indicate that there was no significant heterogeneity in the odds ratios, regardless of the outcome (p=0.360 fracture, p=0.962 venous thromboembolism, p=0.465 sepsis). I^2 (measure of inconsistency) for fracture was 9.0%, for venous thromboembolism was 0%, and for sepsis was 0%. Therefore, the odds for developing the three adverse events were significantly elevated for corticosteroid users (compared to non-users), regardless of the type of anti-diabetic medication used during the time period of the study.

The results from the self-controlled case series are listed in Table 4. The risk of adverse events was greatest during the 5-30 day period after the corticosteroid prescription was filled for those

with diabetes (IRR=2.06 for fracture, IRR=3.62 for venous thromboembolism, and IRR=3.79 for sepsis). For all three outcomes, the incidence rate ratios tended to decrease over time. The results for those without diabetes are shown in Table 5, indicating that the relative risk of adverse events was similar for those with and without diabetes, although the underlying baseline risk was greater in those with diabetes (Table 3).

We also evaluated the addition of potential preventative medications on the relationship between corticosteroids and adverse events in individuals with diabetes. In this study, 11.4% (14376/126091) of individuals with diabetes used vitamin D, and 97.6% of the prescriptions were for 50,000 IU weekly of ergocalciferol (mean number of refills=5.7, SD=7.2). Results from the self-controlled case series (Table 4) indicate that adults with diabetes had a 2-fold increase in the incidence of fracture in the 5-30 day period after the corticosteroid prescription was filled. However, those patients with diabetes who were taking vitamin D with the corticosteroids did not experience an increased risk (IRR=1.13). Those taking corticosteroids without vitamin D had an elevated risk (IRR=2.09). We also examined the risk of fracture using the conventional cohort design, comparing individuals with diabetes who used versus did not use the medications (Table 6). The risk of fracture was lowest (4.4%) in adults with diabetes who used vitamin D but no corticosteroids. The highest risk of fracture was 8.1% in adults with diabetes who used corticosteroids but no vitamin D. The odds of fracture were 1.37 times

greater in those using corticosteroids without vitamin D compared to those who did not use either of these medications.

In this database, 61.4% (77419/126091) of individuals with diabetes ever used statins during the 3-year study period. The risk of venous thromboembolism was elevated (IRR=3.62) during the 5-30 day period after the corticosteroid was taken (Table 4), but this risk declined over time. Results from the self-controlled case series indicated that the addition of statins did not appreciably affect the rate ratios for venous thromboembolism; the risk remained elevated regardless of statin use. For sepsis, however, the use of corticosteroids without statin yielded a significant IRR of 4.91 (Table 4). When patients with diabetes used statins concomitantly with the corticosteroids, there was no significant elevation in sepsis risk.

We also evaluated corticosteroids with statins using the conventional cohort approach (Table 6). The greatest risk of an adverse event occurred in adults with diabetes who used corticosteroids without statins (3.3% for venous thromboembolism, 2.1% for sepsis). The odds of venous thromboembolism were 51% greater in those using corticosteroids without statins compared to those using neither (Table 6). But the odds of venous thromboembolism were not elevated when the corticosteroids were used with statins (OR=1.04). In addition, the odds of hospitalization for sepsis were lower when statins were used concomitantly with corticosteroids (OR=0.77) when compared to using neither; the (multiplicative) interaction term between corticosteroids and

statins was significant (p=0.013). The use of statins modified the association between corticosteroids and hospitalization for sepsis.

DISCUSSION

In this investigation, we found that adults with diabetes were frequent users of short-term oral corticosteroids. Use was particularly common in type 2 diabetes, affecting 1 in 4 patients, while it occurred in 1 of 5 individuals with type 1 diabetes, and 1 in 5 persons without diabetes. Short-term use was higher in middle-aged adults compared to younger adults, and was frequent in women with type 2 diabetes, affecting 28.4% during the 3-year study period.

The higher rates of fracture, venous thromboembolism, and hospitalization for sepsis in patients with diabetes confirm results from previous investigations (12-14). But our study extends the current literature with the finding of synergy between diabetes and corticosteroid use. The risks of adverse events were more elevated with these two factors together, than from each one separately. This suggests that efforts to prevent adverse outcomes with oral corticosteroids may be better targeted to individuals with diabetes than those without. Patients with type 1 diabetes may particularly benefit because of their higher baseline risk. For individuals with type 2 diabetes, the elevation in risk of adverse events after corticosteroid use remained, regardless of the type of anti-diabetic medications used.

While there was an elevated risk of adverse events after corticosteroid use, the findings suggest that certain concomitant medications could possibly mitigate risk. When individuals with diabetes used both corticosteroids and ergocalciferol (50,000 IU weekly), there was no elevated risk of fracture, but when corticosteroids were used without ergocalciferol, there was a 2-fold increased risk of fracture. Data from the National Health and Nutrition Examination Survey, a nationally representative sample, demonstrated an association between corticosteroid use and 25(OH)D deficiency (15). In a meta-analysis of 25 studies, adults receiving corticosteroid therapy were found to have low serum 25(OH)D levels which were insufficient to prevent osteoporosis (16). The US Preventive Services Task Force reviewed the data and found inconclusive evidence regarding vitamin D supplementation on the risk of fractures in older adults, but there were no trials in high risk populations of middle-aged adults (17). Our investigation found several high risk populations in adults 18-65 years of age; these include corticosteroid users and individuals with diabetes. Our findings, suggesting that the use of 50,000 IU of ergocalciferol may mitigate the effects of corticosteroid use in middle-aged adults with diabetes, should be confirmed in randomized controlled trials. Ergocalciferol is associated with minimal risk and it is significant that 42% of Americans (in general) are vitamin D deficient, as are 82% of African-Americans and 69% of Hispanics in the United States (18).

We also found that the use of statins influenced the association between corticosteroids and hospitalization for sepsis. Both the self-controlled case series (within-person approach) and the cohort study (between-person approach) suggested that statins modified this association. Previous studies have shown that statins decrease the rate of severe sepsis and intensive care admissions (19-21). Moreover, rates of hospitalization for infection have been found to be significantly elevated in patients who use corticosteroids (22) and extended corticosteroid use has long been associated with immunosuppression and higher infection rates (1). Because statin use is recommended for many adults with diabetes (based on the estimated 10-year cardiovascular disease risk) (23,24), randomized trials may be necessary to more clearly delineate potential benefits of adding statins to short-term corticosteroids for those patients with diabetes who are not currently receiving statins.

There are limitations of this study. Information was not available on levels of C-peptide and glutamic acid decarboxylase autoantibodies for all individuals with diabetes. The use of ICD-9-CM diagnosis codes and medication use to discern diabetes may have resulted in some misclassification. However, validation studies indicate that the use of 250xx diagnosis codes for diabetes (captured over a 1 year period) had a sensitivity of 97%, specificity of 97%, and positive predictive value of 98% (25). In a study to distinguish diabetes type, the use of two or more type 1 diagnosis codes yielded a sensitivity of 90% (26) and a positive predictive value of 91.3% for

the identification of type 1 diabetes (27). A prescription for insulin had a sensitivity of 95% for type 1 diabetes (26).

Another limitation is that we could not rule out confounding by indication; that is, the illness that prompted the patient's visit to the physician could be a contributing factor of the adverse event. However, infection, thromboembolism, and decreases in bone density are all listed as possible adverse events on Food and Drug Administration package inserts of corticosteroids, indicating prior evidence of association (28,29). With the use of short-term oral corticosteroids, we found that the absolute risk of such adverse effects was modest; for example, of 1000 patients with type 1 diabetes who used corticosteroids, 43 experienced a fracture over a 1-year period. This compared with 32 patients experiencing a fracture who did not use corticosteroids.

The use of a self-controlled case series is a particularly strong design for addressing other confounding factors. Our findings cannot be explained by dissimilarities in genetic profiles for different individuals because the comparison was within the same person. Likewise, other personal characteristics such as past history of venous thromboembolism, history of cancer, former smoking habits, and past personal characteristics were controlled. Because the comparator is the person him/herself, these factors (and the interactions among such factors) are held constant.

We conclude that the use of oral corticosteroids for short durations is common in patients with diabetes and is associated with an elevated (but modest) risk of fracture, venous thromboembolism and hospitalization for sepsis. The addition of ergocalciferol to prevent fractures and the addition of statins to prevent hospitalization for sepsis should be investigated in randomized trials, particularly in patients with diabetes who use corticosteroids.

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GUARANTOR:
Dr. Rogers takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

AUTHOR CONTRIBUTIONS:
Study concept and design: Rogers, Waljee, Nallamothu.
Acquisition of data: Nallamothu, Waljee.
Analysis of data: Rogers, Lin.
Interpretation of data: Rogers, Lin, Nallamothu, Kim, Waljee.
Drafting of the manuscript: Rogers.
Critical revision of the manuscript: Rogers, Lin, Nallamothu, Kim, Waljee.
Final approval: Rogers, Lin, Nallamothu, Kim, Waljee.

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CONFLICTS OF INTEREST:
The authors report no conflicts of interest.

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FIGURE LEGEND

FIGURE 1. Odds Ratios for the Association between Corticosteroid Use and Adverse Events by Type of Anti-Diabetic Medication

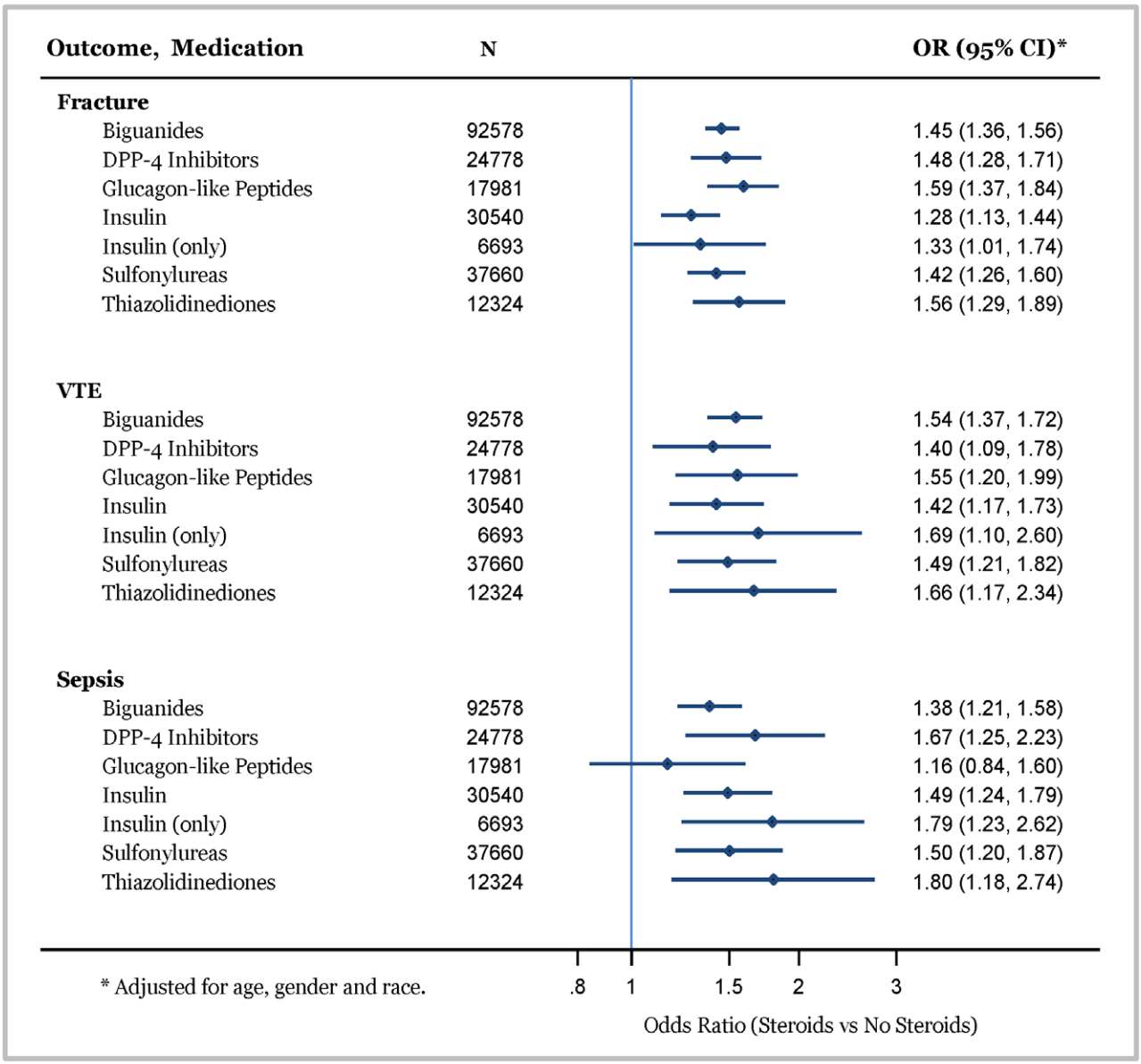

TABLE 1. Identification of Conditions in the Study

Condition	Codes
Diabetes	Minimum of two diagnoses of diabetes (ICD-9-CM code: 250xx) on different dates.
Type 1 diabetes	Minimum of two diagnoses of ICD-9-CM codes: 250x1 or 250x3 on different dates, with the use of insulin.
Type 2 diabetes	Minimum of two diagnoses of ICD-9-CM codes: 250x0, 250x2, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508 or 2509 on different dates (regardless of antidiabetic medications used).
Fractures	ICD-9-CM codes: 7331x or 805xx-829xx.
Venous thromboembolism	ICD-9-CM codes: 4151x, 4511x, 4512x, 45181, 45183, 45184, 45189, 4519x, 4532x, 4534x, 45380, 45382-45389 or 4539x.
Hospitalization for sepsis	ICD-9-CM codes: 78552, 99591 or 99592, as principal diagnosis.

TABLE 2. Short-Duration Oral Corticosteroid Use by Type of Diabetes, Age, and Gender

	Steroid Use		No Steroid Use		
	n/N	%	n/N	%	p value
Overall					
Type 1 Diabetes	3316/15950	20.8%	12634/15950	79.2%	
Type 2 Diabetes	26300/110141	23.9%	83841/110141	76.1%	
No Diabetes	297836/1422854	20.9%	1125018/1422854	79.1%	<0.001
Women					
Type 1 Diabetes	1553/6449	24.1%	4896/6449	75.9%	
Type 2 Diabetes	12699/44676	28.4%	31977/44676	71.6%	
No Diabetes	153780/653890	23.5%	500110/653890	76.5%	<0.001
Men					
Type 1 Diabetes	1763/9501	18.6%	7738/9501	81.4%	
Type 2 Diabetes	13601/65465	20.8%	51864/65465	79.2%	
No Diabetes	144056/768964	18.7%	624908/768964	81.3%	<0.001
Age <40 years					
Type 1 Diabetes	476/3106	15.3%	2630/3106	84.7%	
Type 2 Diabetes	1735/7410	23.4%	5675/7410	76.6%	
No Diabetes	97028/521916	18.6%	424888/521916	81.4%	<0.001

Age ≥40 years					
Type 1 Diabetes	2840/12844	22.1%	10004/12844	77.9%	
Type 2 Diabetes	24565/102731	23.9%	78166/102731	76.1%	
No Diabetes	200808/900938	22.3%	700130/900938	77.7%	<0.001

TABLE 3. Frequency of Adverse Events by Corticosteroid Use and Type of Diabetes

	Number of events	Number of patients	Cumulative Incidence	Incidence Rate (95% CI)*	Incidence Rate Ratio	95% CI	Synergy Index (95% CI)†
Fracture:							
No Steroids, No Diabetes	45,969	1,125,018	4.1%	13.9 (13.8, 14.0)	1.00	(reference)	
No Steroids, Type 1 Diabetes	1,161	12,634	9.2%	32.2 (30.4, 34.1)	2.31	2.18, 2.45	
No Steroids, Type 2 Diabetes	4,223	83,841	5.0%	17.2 (16.7, 17.8)	1.24	1.20, 1.28	
Steroids, No Diabetes	17,784	297,836	6.0%	20.7 (20.3, 21.1)	1.49	1.46, 1.52	
Steroids, Type 1 Diabetes	414	3,316	12.5%	43.3 (37.7, 49.6)	3.11	2.70, 3.57	
Steroids, Type 2 Diabetes	1,892	26,300	7.2%	26.3 (24.7, 27.9)	1.89	1.78, 2.01	1.17 (1.12, 1.23)
Venous Thromboembolism:							
No Steroids, No Diabetes	7,136	1,125,018	0.6%	2.1 (2.1, 2.2)	1.00	(reference)	
No Steroids, Type 1 Diabetes	341	12,634	2.7%	9.1 (8.2, 10.1)	4.30	3.85, 4.79	
No Steroids, Type 2 Diabetes	1,418	83,841	1.7%	5.7 (5.4, 6.0)	2.68	2.53, 2.84	
Steroids, No Diabetes	3,513		1.2%	4.1 (3.9, 4.3)	1.93	1.84, 2.03	

		297,836					
Steroids, Type 1 Diabetes	151	3,316	4.6%	14.8 (11.8, 18.6)	6.98	5.48, 8.76	
Steroids, Type 2 Diabetes	679	26,300	2.6%	8.8 (7.9, 9.8)	4.15	3.73, 4.61	1.23 (1.16, 1.29)
Hospitalization for Sepsis:							
No Steroids, No Diabetes	2,271	1,125,018	0.2%	0.7 (0.6, 0.7)	1.00	(reference)	
No Steroids, Type 1 Diabetes	441	12,634	3.5%	11.8 (10.8, 13.0)	17.58	15.84, 19.47	
No Steroids, Type 2 Diabetes	870	83,841	1.0%	3.5 (3.2, 3.7)	5.16	4.77, 5.58	
Steroids, No Diabetes	1,040	297,836	0.3%	1.3 (1.2, 1.4)	1.98	1.81, 2.16	
Steroids, Type 1 Diabetes	146	3,316	4.4%	16.7 (13.5, 20.7)	24.87	19.79, 30.89	
Steroids, Type 2 Diabetes	370	26,300	1.4%	5.3 (4.7, 6.1)	7.94	6.89, 9.11	1.30 (1.23, 1.37)

* per 1000 person-years at risk.

† Synergy between diabetes and steroid use on an additive scale.

TABLE 4. Incidence Rate Ratios for Adverse Events Associated with Corticosteroids and Concomitant Medications in Individuals with Diabetes

		5-30 days*			31-90 days*			91-180 days*		
Event	Medications	IRR†	95% CI	P value	IRR†	95% CI	P value	IRR†	95% CI	P value
Fracture:										
	Corticosteroids	2.06	1.52, 2.80	<0.001	1.66	1.29, 2.13	<0.001	1.46	1.16, 1.84	0.001
	Corticosteroids & Vitamin D	1.13	0.12, 11.07	0.915	0.37	0.03, 4.44	0.436	0.14	0.01, 2.82	0.197
	Corticosteroids & no Vitamin D	2.09	1.53, 2.84	<0.001	1.70	1.32, 2.19	<0.001	1.50	1.19, 1.89	0.001
Venous thromboembolism:										
	Corticosteroids	3.62	2.41, 5.45	<0.001	1.51	1.00, 2.28	0.049	0.90	0.60, 1.36	0.613
	Corticosteroids & Statin	3.86	1.74, 8.59	0.001	1.43	0.58, 3.52	0.440	1.41	0.68, 2.94	0.353
	Corticosteroids & no Statin	3.33	2.05, 5.42	<0.001	1.51	0.95, 2.42	0.083	0.73	0.44, 1.21	0.223
Sepsis:										
	Corticosteroids	3.79	2.05, 7.01	<0.001	2.64	1.44, 4.85	0.002	1.64	0.89, 3.00	0.110
	Corticosteroids & Statin	1.62	0.45, 5.85	0.458	1.91	0.68, 5.39	0.219	1.02	0.33, 3.09	0.978
	Corticosteroids & no Statin	4.91	2.31, 10.46	<0.001	2.73	1.26, 5.94	0.011	1.99	0.92, 4.30	0.078

* Reference period was 5 to 180 days prior to prescription date.

† Sepsis was adjusted for antibiotics, 5-HT3 receptor antagonists, antidepressants, anti-inflammatory agents, antimuscarinics, opiate agonists, and phenothiazine. Venous thromboembolism was adjusted for antibiotics, androgens, anxiolytics, anti-inflammatory agents, azoles, calcium channel blockers, coumarin, diuretics, opiate agonists, and platelet-aggregation inhibitors. Fractures were adjusted for anti-inflammatory agents, COX-2 inhibitors, and opiate agonists.

TABLE 5. Incidence Rate Ratios for Adverse Events Associated with Short-Term Oral Corticosteroid Use by Diabetes

		5-30 days*			31-90 days*			91-180 days*		
Adverse Event	Condition	IRR†	95% CI	P value	IRR†	95% CI	P value	IRR†	95% CI	P value
Fracture:										
	Diabetes	2.06	1.52, 2.80	<0.001	1.66	1.29, 2.13	<0.001	1.46	1.16, 1.84	0.001
	No diabetes	1.85	1.66, 2.05	<0.001	1.37	1.25, 1.51	<0.001	1.27	1.17, 1.39	<0.001
Venous thromboembolism:										
	Diabetes	3.62	2.41, 5.45	<0.001	1.51	1.00, 2.28	0.049	0.90	0.60, 1.36	0.613
	No diabetes	3.25	2.66, 3.98	<0.001	1.43	1.15, 1.76	0.001	1.21	0.99, 1.47	0.065
Sepsis:										
	Diabetes	3.79	2.05, 7.01	<0.001	2.64	1.44, 4.85	0.002	1.64	0.89, 3.00	0.110
	No diabetes	6.10	4.07, 9.15	<0.001	2.88	1.86, 4.47	<0.001	1.92	1.26, 2.93	0.003

* Reference period was 5 to 180 days prior to prescription date.

† Sepsis was adjusted for antibiotics, 5-HT3 receptor antagonists, antidepressants, anti-inflammatory agents, antimuscarinics, opiate agonists, and phenothiazine. Venous thromboembolism was adjusted for antibiotics, androgens, anxiolytics, anti-inflammatory agents, azoles, calcium channel blockers, coumarin, diuretics, opiate agonists, and platelet-aggregation inhibitors. Fractures were adjusted for anti-inflammatory agents, COX-2 inhibitors, and opiate agonists.

Table 6. Frequency of Adverse Events for Individuals with Diabetes, by Type of Medication

	Number of events	Number of patients	% with Adverse Event	Odds Ratio*	95% CI	p value
Fracture:						
no Corticosteroids, no Vitamin D	4928	86103	5.7%	1.0 (reference)		
no Corticosteroids, Vitamin D	456	10372	4.4%	0.75	0.68, 0.83	<0.001
Corticosteroids, no Vitamin D	2068	25612	8.1%	1.37	1.30, 1.45	<0.001
Corticosteroids, Vitamin D	238	4004	5.9%	0.98	0.86, 1.12	0.798
Venous thromboembolism:						
no Corticosteroids, no Statins	821	37792	2.2%	1.0 (reference)		
no Corticosteroids, Statins	938	58683	1.6%	0.66	0.60, 0.72	<0.001
Corticosteroids, no Statins	356	10880	3.3%	1.51	1.33, 1.71	<0.001
Corticosteroids, Statins	474	18736	2.5%	1.04	0.92, 1.16	0.533
Sepsis:						
no Corticosteroids, no Statins	689	37792	1.8%	1.0 (reference)		
no Corticosteroids, Statins	622	58683	1.1%	0.52	0.46, 0.58	<0.001
Corticosteroids, no Statins	224	10880	2.1%	1.14	0.98, 1.33	0.090
Corticosteroids, Statins	292	18736	1.6%	0.77	0.67, 0.88	<0.001

* Odds ratio adjusted for age, gender, and race.