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Use of dipeptidyl peptidase-4 inhibitors and new-onset rheumatoid arthritis in patients with type 2 diabetes

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ABSTRACT

Background: Case reports have suggested a link between dipeptidyl peptidase-4 (DPP-4) inhibitors, antidiabetic drugs used as second- to third-line treatments, and incidence of rheumatoid arthritis. Since the DPP-4 enzyme is involved in several immunologic processes and possibly in the pathophysiology of rheumatoid arthritis, further research is warranted. This population-based study aimed to determine whether use of DPP-4 inhibitors is associated with incidence of rheumatoid arthritis.

Methods: Using the United Kingdom Clinical Practice Research Datalink, we conducted a cohort study among 144,603 patients with type 2 diabetes initiating antidiabetic drugs between 2007 and 2016. We estimated hazard ratios (HRs) with 95% confidence intervals (CIs) for incident rheumatoid arthritis using time-dependent Cox proportional hazards models, comparing use of DPP-4 inhibitors with use of other antidiabetic drugs. We imposed a 6-month exposure lag period for latency and diagnostic delays. Secondary analyses included assessment of the duration response relation and comparison with other second-line antidiabetic drugs, among others.

Results: During 567,169 person-years of follow-up, 464 patients were newly diagnosed with rheumatoid arthritis (crude incidence rate: 82 per 100,000/year). Compared with use of other antidiabetic drugs, use of DPP-4 inhibitors was not associated with an increased risk of rheumatoid arthritis (82 versus 79 per 100,000/year; HR: 1.0, 95% CI: 0.8, 1.3), with no evidence of duration–response relation. The results did not change after using second-line antidiabetic drugs as the comparator group.

Conclusions: In this large population-based study, use of DPP-4 inhibitors was not associated with an increased risk of incident rheumatoid arthritis.

Keywords: dipeptidyl peptidase-4 inhibitors; rheumatoid arthritis; type 2 diabetes; epidemiology

INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors are incretin-based drugs typically used as a second- to- third-line treatment in patients with type 2 diabetes.[1] In contrast to other second- to third line treatments such as sulfonylureas or insulin, DPP-4 inhibitors are associated with a low risk of hypoglycemia while having neutral effects on body weight.[2] Thus, their favorable safety profile has led to an increase in their use in recent years.[3]

Despite these favorable effects, DPP-4 inhibitors have been linked to certain adverse effects, including rheumatoid arthritis.[4,5] Indeed, in two case reports, patients initiating treatment with DPP-4 inhibitors developed joint swelling and arthralgia, and were subsequently diagnosed with rheumatoid arthritis.[4,5] There are some biologic data to support an association. First, the DPP-4 enzyme is expressed in various immune cells and has an important role in immunologic processes, such as T-cell activation and proliferation.[6] Second, patients with rheumatoid arthritis have been shown to have decreased DPP-4 serum levels,[7-9] as well as decreased DPP-4 activity in immune cells.[10] Still, it is unclear whether these observations are the cause or consequence of active disease. In 2015, the US Food and Drug Administration warned about the risk of DPP-4 inhibitor-related arthralgia, which can be an initial manifestation of rheumatoid arthritis, and added joint pain as a potential adverse reaction to the product labels.[11] However, arthralgia is a symptom with low specificity that can also be related to several other conditions such as osteoarthritis.

To our knowledge, only one observational study has assessed the association between the use of DPP-4 inhibitors and the incidence of rheumatoid arthritis.[12] While that study reported a decreased risk, it had some methodologic limitations, such as having a short follow-up period and not accounting for the non-acute nature of the outcome. Thus, our population-based study

aimed to determine whether there is an association between the use of DPP-4 inhibitors and the risk of incident rheumatoid arthritis in patients with type 2 diabetes.

METHODS

Data source

We conducted this study using the United Kingdom (UK) Clinical Practice Research Datalink, which contains the medical records of over 15 million people enrolled across 700 general practices.[13] Medical diagnoses and procedures are recorded using the Read code classification, and drugs prescribed by general practitioners are coded using the UK Prescription Pricing Authority dictionary. The Clinical Practice Research Datalink contains information on anthropometric variables (e.g., body mass index) and lifestyle variables (e.g., smoking), and its data have been previously validated and shown to be of high quality.[14] The study protocol was approved by the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink (protocol number 17_171R) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Study population

We first assembled a base cohort of patients newly treated for type 2 diabetes. This included all patients initiating a new non-insulin antidiabetic drug (metformin, sulfonylureas, prandial glucose regulators, thiazolidinediones, acarbose, DPP-4 inhibitors [linagliptin, saxagliptin, sitagliptin, or vildagliptin], glucagon-like peptide-1 analogs, and sodium–glucose co-transporter-2 inhibitors) between January 1, 1988 and June 30, 2016, with follow up until June 30, 2017. All patients were required to be at least 18 years of age and have at least 1 year of medical history in the Clinical Practice Research Datalink before their initial prescription. We excluded patients initially treated with insulin (as these patients likely represent those with

advanced type 2 diabetes), and women with a history of polycystic ovarian syndrome or diagnosed with gestational diabetes in the previous year (as these are other indications for metformin use).

Within this base cohort, we assembled a study cohort consisting of all patients who initiated a new class of antidiabetic drugs 1 January 2007 or later (the year the first DPP-4 inhibitor, sitagliptin, entered the UK market).[15] These patients included those newly treated with an antidiabetic drug class (i.e., first-ever antidiabetic prescription) as well as those who added on or switched to an antidiabetic drug class not previously used in their treatment history. We defined start of follow-up as the date of this new antidiabetic prescription plus 6 months. Thus, all patients meeting study inclusion criteria were followed starting six months after cohort entry until an incident diagnosis of rheumatoid arthritis (Read codes listed in **eTable 1; http://links.lww.com/EDE/B382**), or censored upon death from any cause, end of registration with the general practice, or the end of the study period (30 June 2017), whichever occurred first. We excluded patients diagnosed with rheumatoid arthritis at any time before cohort entry, as well as those with less than 6 months of follow-up after cohort entry.

Exposure definition

We used a time-dependent exposure definition to model the use of DPP-4 inhibitors, alone or in combination with other antidiabetic drugs, during the follow-up period. This exposure definition allowed patients to contribute person–time to two mutually exclusive exposure categories: person–time exposed to DPP-4 inhibitors, and person–time exposed to other (non-DPP-4 inhibitor) antidiabetic drugs. Specifically, patients were considered exposed to other antidiabetic drugs until 6 months after the first prescription for a DPP-4 inhibitor and considered exposed to DPP-4 inhibitors thereafter for the remainder of follow-up. The comparator group

consisted of use of other antidiabetic drugs, which was considered appropriate as no individual antidiabetic drug class has been previously associated with the incidence of rheumatoid arthritis. The 6-month exposure lag period was necessary for latency considerations, given that short duration exposures are unlikely to be associated with the incidence of rheumatoid arthritis. The lag period also accounts for possible diagnostic delays associated with rheumatoid arthritis,[16] and reduces detection bias and bias from reverse causality. This was considered the primary exposure definition (**eFigure 1; http://links.lww.com/EDE/B382**).

We also considered two secondary exposure definitions. First, we assessed the risk of incident rheumatoid arthritis based on DPP-4 inhibitor cumulative duration of use. This time-dependent variable was defined as the sum of the durations associated with each prescription for a DPP-4 inhibitor from cohort entry to the time of the event. Second, we assessed the risk of incident rheumatoid arthritis based on the time since initiation of DPP-4 inhibitors. This time-dependent variable was defined as the time between the first ever DPP-4 inhibitor prescription and the time of the event.

Statistical analysis

We used descriptive statistics to summarize the characteristics of the cohort at baseline. We calculated crude incidence rates, with 95% confidence intervals (CIs) based on the Poisson distribution, of rheumatoid arthritis overall and for each exposure category. Cox proportional hazards regression models using the time-varying exposure definition were used to estimate adjusted hazard ratio (HRs) with 95% CIs of incident rheumatoid arthritis associated with use of DPP-4 inhibitors compared with use of other antidiabetic drugs.

All models were adjusted for known risk factors associated with rheumatoid arthritis incidence that might also influence the choice of antidiabetic treatment.[17] These included the

following variables measured at cohort entry: year of cohort entry (2007 to 2016), age, sex, alcohol-related disorders (including alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and hepatic failure), smoking status (current, former, never, unknown), and body mass index category (<25 kg/m^2, 25-29 kg/m^2, ≥30 kg/m^2, unknown). We also adjusted for hemoglobin A1c (last measurement before cohort entry), duration of treated diabetes, presence of microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (myocardial infarction, ischemic stroke, peripheral arteriopathy) complications of diabetes (measured at any time before cohort entry), and number of antidiabetic drugs used at any time before cohort entry, all as proxies for disease severity. Moreover, the models were adjusted for the presence of autoimmune conditions (e.g., large-, medium-, and small-vessel vasculitides, lupus erythematosus, Sjögren syndrome, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease) measured at any time before cohort entry, and for the use of statins in the year before cohort entry, because statins have been associated with a decreased risk of rheumatoid arthritis.[18] Finally, the models were adjusted for the total number of unique non-diabetic drugs in the year before cohort entry as a general measure of comorbidity.[19] We modeled age and duration of treated diabetes using cubic splines to account for possible non-linear associations with the outcome.

Secondary analyses

We performed four secondary analyses using the same comparator group as in the primary analysis. First, we assessed whether there is a duration–response relation for DPP-4 inhibitor cumulative duration of use on the incidence of rheumatoid arthritis. For this time-dependent analysis, we estimated HRs for three predefined duration categories: ≤1 year, >1 to 2 years, and >2 years. Second, we investigated associations between time since initiation of DPP-4 inhibitors and risk of rheumatoid arthritis, estimating HRs for three predefined categories: ≤2

years, >2 to 4 years, and >4 years. Third, to investigate whether there is a drug-specific effect, we repeated the primary analysis by stratifying on type of DPP-4 inhibitor (sitagliptin, saxagliptin, and linagliptin). Finally, since female sex has been associated with an increased risk of rheumatoid arthritis,[20] we repeated the primary analysis after stratifying by sex.

Sensitivity analyses

We conducted 12 sensitivity analyses to assess the robustness of our findings. First, given uncertainties related to the length of the latency time window, we repeated the analysis by using alternate exposure lag periods of three months and one year. Second, to assess the validity of our outcome definition, we used an algorithm whereby rheumatoid arthritis events had to be accompanied by at least one clinically-relevant supporting event in the six months before or after the diagnosis (a prescription for a disease-modifying antirheumatic drug [methotrexate, leflunomide, sulfasalazine, anti-malarial drugs, gold compounds, penicillamine, azathioprine, ciclosporin, tumor necrosis factor-alpha inhibitors, tocilizumab, abatacept, anakinra, rituximab[21]], or a referral to/feedback from a rheumatologist). Third, to account for possible informative censoring, we conducted a competing risk analysis by death from any cause, using the subdistribution Cox proportional hazards model proposed by Fine and Gray.[22] Fourth, to address potential misclassification of exposure from the irregular use of DPP-4 inhibitors, the exposure definition was redefined by requiring at least four prescriptions during a 12-month moving window. As with the primary exposure definition, we imposed a 6-month lag period, and thus patients were considered exposed only 6 months after the fourth qualifying prescription. Fifth, to assess the possibility of anti-inflammatory effects of thiazolidinediones,[23] we repeated the analysis after excluding users of thiazolidinediones at baseline and censoring on their use during follow-up. Sixth, to account for a possible incretin effect from glucagon-like peptide-1

analogs, we reclassified the exposure according to the following four mutually exclusive categories: DPP-4 inhibitors (alone or in combination with other antidiabetic drugs, excluding glucagon-like peptide-1 analogs), glucagon-like peptide-1 analogs (alone or in combination with other antidiabetic drugs, excluding DPP-4 inhibitors), switch from DPP-4 inhibitors to glucagon-like peptide-1 analogs and vice versa, and use of all other antidiabetic drugs. Seventh, we conducted a marginal structural Cox proportional hazards model to investigate the impact of time-varying confounding during the follow-up period using inverse-probability-of-treatment and -censoring weighting (described in **eMethods 1**). Eighth, we conducted a disease risk score analysis and multiple imputation for variables with missing data to investigate the impact of residual confounding (described in **eMethods 2-3**). Ninth, we conducted a post-hoc sensitivity analysis including an interaction term between year of cohort entry and use of statins. Finally, we conducted a post-hoc sensitivity analysis further assessing the potential impact of residual confounding on our point estimates using the approach proposed by Ding and VanderWeele (described in **eMethods 4**).[24] All analyses were conducted with SAS, version 9.4 (SAS Institute, Cary, NC).

Ancillary analyses

We conducted two post-hoc ancillary analyses to further assess the robustness of our findings. First, we repeated the primary analysis by comparing the use of DPP-4 inhibitors with an alternate comparator consisting of the use of at least two different non-insulin antidiabetic drug classes at the time of the risk set (i.e., second-to -third line treatment). This was achieved by using the following time-dependent hierarchical exposure definition: use of DPP-4 inhibitors (alone or in combination with other antidiabetic drugs), use of at least two non-insulin antidiabetic drug classes (new comparator group), and use of other antidiabetic drugs (mainly

drugs used as first-line treatments or insulin). Second, we identified within our study cohort (in which all the study exclusion criteria had already been applied) a subcohort of all patients initiating a DPP-4 inhibitor or other second- to third-line non-insulin antidiabetic drugs at cohort entry. Thus, we excluded all patients who have never used any antidiabetic drug before cohort entry (i.e., patients initiating a first-line treatment) as well as patients who have previously used insulin (i.e., a last-line treatment). As with our primary analysis, we required all patients to have at least six months of follow-up after cohort entry (with follow-up starting six months after cohort entry). We then estimated propensity scores of being prescribed a DPP-4 inhibitor versus another second- to third-line non-insulin antidiabetic drug, conditional on the covariates listed in the manuscript. Patients in non-overlapping propensity score distributions were trimmed from the analysis. The remaining patients were followed until an incident diagnosis of rheumatoid arthritis, or censored patients in the comparator group at the time of a switch to a DPP-4 inhibitor, death from any cause, end of registration with the general practice, or end of the study period. Finally, we assessed the risk of rheumatoid arthritis associated with use of DPP-4 inhibitors compared to use of other second- to third line non-insulin antidiabetic drugs after stratifying on propensity score quintiles.

RESULTS

The cohort included 144,603 new users of antidiabetic drugs (**Figure 1**). The median follow-up was 3.7 years beyond the 6-month post-cohort entry lag period, generating a total of 567,169 person-years (users of DPP-4 inhibitors, median follow-up: 2.7 years; users of other antidiabetic drugs, median follow-up: 3.0 years). During follow-up, 31,355 patients received DPP-4 inhibitors, with the median and maximum durations of use being 1.6 and 9.7 years, respectively. Overall, 464 patients were newly diagnosed with rheumatoid arthritis during

follow-up, corresponding to an incidence rate of 82 (95% CI, 75-90) per 100,000/year. The majority of these events (n = 408/464, 88.0%) had at least one clinically relevant supporting event (**eTable 2; http://links.lww.com/EDE/B382**).

Table 1 presents the characteristics of the entire cohort (mean age [standard deviation] 62 [14] years) and stratified by antidiabetic drug use at cohort entry. Compared with users of other antidiabetic drugs (mean age [standard deviation] 62 [14] years), users of DPP-4 inhibitors (mean age [standard deviation] 66 [12] years) were more likely to have elevated hemoglobin A1c levels (>8% or >64 mmol/mol), had a longer duration of treated diabetes, were more likely to have a history of nephropathy, neuropathy, or retinopathy, and to have used statins or other antidiabetic drugs. Users of other, non-DPP-4- inhibitor antidiabetic drugs entered the study cohort mostly upon initiation of metformin in monotherapy (76%), sulfonylureas in monotherapy (12%), and a combination of metformin plus sulfonylureas (4%).

Table 2 presents the results of the primary and secondary analyses. Compared with use of other antidiabetic drugs, use of DPP-4 inhibitors was not associated with an increased risk of rheumatoid arthritis (crude incidence rates, 82 versus 79 per 100,000/year, respectively; adjusted HR: 1.0, 95% CI: 0.8, 1.3). In the duration–response analyses, the HRs for the different time intervals ranged from 0.6 to 1.2 (cumulative duration of use; p for heterogeneity 0.07) and from 0.8 to 1.2 (time since initiation; p for heterogeneity 0.38). In addition, there was no evidence of a drug-specific effect, with the HRs and the accompanying 95% CIs for the individual DPP-4 inhibitors being 1.0 (0.8, 1.4) for sitagliptin, 0.8 (0.4, 1.8) for saxagliptin, and 1.1 (0.5, 2.7) for linagliptin (no separate analysis was conducted for vildagliptin due to the low number of exposed patients) (**eTable 3; http://links.lww.com/EDE/B382**). Finally, there was no evidence of effect modification by sex (**eTable 4; http://links.lww.com/EDE/B382**).

The results of the sensitivity analyses are summarized in **Figure 2** and presented in detail in **eTables 5-16; http://links.lww.com/EDE/B382**. Overall, these analyses produced results that remained consistent with those of the primary analysis. In particular, extending or shortening the lag period, restricting the outcome definition, reclassifying the exposure, conducting a competing risk analysis, and using methods dealing with residual confounding did not materially change the HRs, all of which ranged between 0.9 to 1.1. Based on a post-hoc analysis, these findings are unlikely to be driven by an unmeasured confounder under most plausible exposure–confounder and confounder–outcome associations (**eTable 17; http://links.lww.com/EDE/B382**).

Table 3 presents the results of the comparisons between DPP-4 inhibitors and other second- to third-line non-insulin antidiabetic drugs. In the first of these analyses (main model), DPP-4 inhibitors compared with other second- to third-line non-insulin antidiabetic drugs was not associated with an increased risk of rheumatoid arthritis (HR: 1.0, 95% CI: 0.7, 1.3). We observed similar findings in the second analysis conducted within the subcohort of new users of second- to third-line non-insulin antidiabetic drugs (HR: 0.8, 95% CI: 0.4, 1.5; see **eFigure 2; http://links.lww.com/EDE/B382** for subcohort formation, **eTable 18; http://links.lww.com/EDE/B382** for subcohort description, and **eFigure 3; http://links.lww.com/EDE/B382** for cumulative incidence curves.

DISCUSSION

The results of our large, population-based study indicate that use of DPP-4 inhibitors was not associated with an increased risk of incident rheumatoid arthritis in patients with type 2 diabetes. Moreover, while we cannot exclude the possibility of depletion of susceptibles with longer durations, there was no strong evidence of a duration–response relationship and no

evidence of a drug-specific effect with respect to sitagliptin, saxagliptin, and linagliptin. Overall, these findings remained consistent in several sensitivity analyses.

Preclinical studies have suggested an important role of the DPP-4 enzyme in the immune system.[6] DPP-4 is expressed in various immune cells including T cells, activated B cells, and activated natural killer cells; it is also involved in immune processes such as T-cell activation, T-cell proliferation, and chemotaxis.[6] With respect to rheumatoid arthritis, DPP-4 deficient mice were shown to exhibit increased disease severity.[8] In humans, it was shown that patients with rheumatoid arthritis have decreased DPP-4 serum levels compared with healthy controls.[7,9] Moreover, it was shown that they also had decreased DPP-4 serum levels as well as decreased DPP-4 activity in immune cells compared with patients with osteoarthritis.[8,10]

Our observation of no association between the use of DPP-4 inhibitors and the incidence of rheumatoid arthritis does not necessarily contradict the aforementioned studies. With respect to the human studies, it is important to note that these measured DPP-4 levels and activity in patients already diagnosed with rheumatoid arthritis. It is unclear from these studies whether these DPP-4 alterations are the consequence or the cause of active disease. In contrast, our study assessed the risk of new-onset rheumatoid arthritis in patients with type 2 diabetes. Thus, while our findings suggest that DPP-4 inhibitors do not influence the risk of developing rheumatoid arthritis, it remains possible that these drugs may aggravate pre-existing disease. Finally, our findings do not necessarily contradict the link between the use of DPP-4 inhibitors and arthralgia as suggested by case reports,[25] pharmacovigilance analyses,[26] and a meta-analysis of randomized controlled trials.[27] While arthralgia can be one of the initial symptoms of rheumatoid arthritis, its specificity is low, since it can also be related to other diseases such as osteoarthritis. Moreover, cases of drug-induced arthralgia not associated with rheumatoid arthritis have been previously

reported for a wide range of drugs, including antimicrobial agents, vaccines, chemotherapeutics, and antidepressants.[28]

To our knowledge, only one observational study has assessed the association between the use of DPP-4 inhibitors and incident rheumatoid arthritis.[12] Using US health claims data from 2005 to 2012, the use of DPP-4 inhibitors was associated with a 34% decreased risk of rheumatoid arthritis (HR: 0.66, 95% CI: 0.44, 0.99), when compared with the use of second-line oral antidiabetic drugs (mostly sulfonylureas and thiazolidinediones).[12] While these surprising results contrast with our findings, it is important to note that the previous study had a short duration of follow-up of approximately nine months.[12] Furthermore, the decreased risk was apparent as soon as 50 days after treatment initiation,[12] which is biologically questionable given the insidious nature of rheumatoid arthritis and its associated diagnostic delays.[16,29]

Our study has several strengths. First, the use of a base cohort eliminated left truncation, thus allowing us to precisely assess important clinical characteristics such as duration of treated diabetes. Second, this method excluded prevalent users,[30] since all patients entering the base and study cohorts were required to be newly treated with antidiabetic drugs not previously used. Third, our analysis considered the insidious nature of the study outcome and the associated diagnostic delays by using a 6-month lag period, as well as shorter and longer exposure lag periods in sensitivity analyses.

This study also has some limitations. First, due to its observational nature, it is susceptible to potential residual confounding. However, to mitigate this potential bias, we were able to adjust for important variables, including smoking and body mass index.[17] Moreover, despite the fact that the association between type 2 diabetes and rheumatoid arthritis remains inconclusive,[31,32] we went to great lengths to adjust the models for proxies of disease severity,

including hemoglobin A1c levels, duration of treated diabetes, and presence of diabetic macro- and microvascular complications. Furthermore, we conducted several sensitivity analyses, such as a marginal structural model and disease risk score analysis which yielded consistent findings. Second, prescriptions in the Clinical Practice Research Datalink represent those issued by primary care physicians, which could lead to misclassification of exposure in case of low patient adherence or treatment by specialists. However, UK primary care physicians are permitted to prescribe DPP-4 inhibitors[33] and are generally responsible for the long-term care of patients with type 2 diabetes. Finally, diagnostic codes of rheumatoid arthritis have rarely been validated in the Clinical Practice Research Datalink albeit with >80% sensitivity and specificity.[34] However, a sensitivity analysis using what ought to be a more specific outcome definition requiring rheumatoid arthritis diagnoses to be accompanied by either a prescription of a disease-modifying antirheumatic drug or a referral to/feedback from a rheumatologist led to similar results. Furthermore, our overall incidence rate of rheumatoid arthritis (82 per 100,000/year) is comparable with previously reported rates in populations of similar age groups (87-92 per 100,000/year for females and 42-58 per 100,000/year for males between 55 and 74 years of age).[35]

In summary, the results of this large, population-based study indicate that the use of DPP-4 inhibitors is not associated with an increased risk of incident rheumatoid arthritis compared with the use of other antidiabetic drugs either overall, according to measures of duration or by specific DPP-4 inhibitor.

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FIGURE LEGENDS

Figure 1

Flowchart describing the construction of base and study cohorts.

Abbreviations: DPP-4, dipeptidyl peptidase-4

Figure 2

Forest plot summarizing the results of the primary analysis and sensitivity analyses, showing adjusted hazard ratios and 95% confidence intervals for the association between the use of dipeptidyl peptidase-4 inhibitors and rheumatoid arthritis. CI indicates confidence interval, HR hazard ratio.

Table 1. Baseline demographics and clinical characteristics of the cohort and stratified by drug use at cohort entry

Characteristic		Use at cohort entry	
	Entire cohort	**DPP-4 inhibitors**	**Other antidiabetic drugs**
Total, N (%)	144,603	7462	137,141
Males, n (%)	82,839 (57)	4268 (57)	78,571 (57)
Alcohol-related disorders, n (%)	21,293 (15)	1478 (20)	19,815 (15)
Smoking status, n (%)			
Current	23,140 (16)	971 (13)	22,169 (16)
Past	53,010 (37)	2905 (39)	50,105 (375)
Never	67,927 (47)	3579 (48)	64,348 (47)
Unknown	526 (0.4)	7 (0.1)	519 (0.4)
Body mass index, n (%)			
<25 kg/m^2	15,102 (10)	760 (10)	14,342 (11)
25-30 kg/m^2	42,525 (29)	2217 (30)	40,308 (29)
≥30 kg/m^2	83,938 (58)	4454 (60)	79,484 (58)
Unknown	3038 (2.1)	31 (0.4)	3007 (2.2)
Hemoglobin A1c, n (%)			
≤7.0% (≤53 mmol/mol)	26,336 (18)	1380 (19)	24,956 (18)
7.1%-8.0% (54-64 mmol/mol)	31,553 (22)	2483 (33)	29,070 (21)
>8.0% (>64 mmol/mol)	44,161 (31)	3267 (44)	40,894 (30)
Unknown	42,553 (29)	332 (4.5)	42,221 (31)
Duration of treated diabetes in years, mean (SD)	1.3 (3.0)	7.7 (4.2)	1.0 (2.5)
Diabetic complications			
Nephropathy, n (%)	35,782 (25)	2957 (40)	32,825 (24)
Neuropathy, n (%)	15,076 (10)	1921 (26)	13,155 (9.6)
Retinopathy, n (%)	15,675 (11)	2409 (32)	13,266 (9.7)
Myocardial infarction, n (%)	9902 (6.9)	619 (8.3)	9283 (6.8)
Ischemic stroke, n (%)	7109 (4.9)	469 (6.3)	6640 (4.8)
Peripheral arteriopathy, n (%)	5199 (3.6)	436 (5.8)	4763 (3.5)
Class of unique antidiabetic drugs, n (%)[a]			
Metformin	27,952 (19)	6643 (89)	21,309 (16)
Sulfonylureas	13,972 (9.7)	4155 (56)	9817 (7.2)
Thiazolidinediones	7373 (5.1)	2534 (34)	4839 (3.5)
Insulin	1254 (0.9)	382 (5.1)	872 (0.6)
Other	963 (0.7)	285 (3.8)	678 (0.5)
Other autoimmune conditions, n (%)	4237 (2.9)	238 (3.2)	3999 (2.9)
Statins, n (%)	92,158 (64)	6168 (83)	85,990 (63)

Characteristic	Use at cohort entry		
	Entire cohort	**DPP-4 inhibitors**	**Other antidiabetic drugs**
Number of non-antidiabetic drugs			
0	6240 (4.3)	60 (0.8)	6180 (4.5)
1	7302 (5.1)	105 (1.4)	7197 (5.3)
2	8933 (6.2)	175 (2.4)	8758 (6.4)
3	10,145 (7.0)	266 (3.6)	9879 (7.2)
≥4	111,983 (77)	6856 (92)	105,127 (77)

Abbreviations: DPP-4, dipeptidyl peptidase-4

[a] Non-mutually exclusive groups measured any time before (not including) cohort entry

Table 2. Crude and adjusted HRs for the association between the use of DPP-4 inhibitors and the risk of rheumatoid arthritis

Exposure	Events	Person-years	Incidence rate [a] (95% CI)	Crude HR	Adjusted HR [b] (95% CI)
Other antidiabetic drugs	389	472,623	82 (74, 91)	1.0 [Reference]	1.0 [Reference]
DPP-4 inhibitors	75	94,546	79 (62, 99)	1.0	1.0 (0.8, 1.3)
Duration of DPP-4 inhibitor use					
≤1 year	35	37,213	94 (66, 131)	1.2	1.1 (0.8, 1.6)
>1 to 2 years	25	26,172	96 (62, 141)	1.2	1.2 (0.8, 1.8)
>2 years	15	31,161	48 (27, 79)	0.6	0.6 (0.4, 1.0)
					P for heterogeneity = 0.07
Time since first DPP-4 inhibitor use					
≤2 years	38	39,712	96 (68, 131)	1.2	1.2 (0.8, 1.6)
>2 to 4 years	22	33,359	66 (41, 100)	0.9	0.9 (0.6, 1.3)
>4 years	15	21,475	70 (39, 115)	0.8	0.8 (0.5, 1.4)
					P for heterogeneity = 0.38

Abbreviations: HR, hazard ratio; CI, confidence interval; DPP-4, dipeptidyl peptidase-4

[a] Per 100,000 person-years.
[b] Adjusted for year of cohort entry, age, sex, alcohol-related disorders (including alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic failure), smoking status, body mass index category, hemoglobin A1c level, duration of treated diabetes, presence of microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (myocardial infarction, ischemic stroke, peripheral arteriopathy) complications of diabetes, use of antidiabetic drugs at baseline, presence of other autoimmune conditions, use of statins, and total number of non-antidiabetic drugs in the year before cohort entry

Table 3. Head-to-head comparisons of DPP-4 inhibitors versus other second-to-third line non-insulin antidiabetic drugs on the risk of rheumatoid arthritis

Exposure	Patients [c]	Events	Person-years	Incidence rate [d] (95% CI)	Crude HR	Adjusted HR [e, f] (95% CI)
Main model [a]						
Other second-to-third line non-insulin antidiabetic drugs	-	130	160,379	81 (68, 96)	1.0 [Reference]	1.0 [Reference]
DPP-4 inhibitors	-	75	94,546	79 (62, 99)	1.0	1.0 (0.7, 1.3)
Subcohort analysis [b]						
Other second- to third-line non-insulin antidiabetic drugs	19,204	60	77,577	77 (59, 100)	1.0 [Reference]	1.0 [Reference]
DPP-4 inhibitors	6381	18	24,583	73 (43, 116)	0.9	0.8 (0.4, 1.5)

Abbreviations: HR, hazard ratio; CI, confidence interval; DPP-4, dipeptidyl peptidase-4

[a] Repeat of the primary analysis using non-DPP-4 inhibitor second-to-third line non-insulin antidiabetic drugs as the reference category.
[b] Based on the subcohort of new users of second-to-third line non-insulin antidiabetic drugs (DPP-4 inhibitors or others).
[c] Number of patients in main analysis is not displayed as exposure was defined in a time dependent fashion.
[d] Per 100,000 person-years.
[e] Adjusted for year of cohort entry, age, sex, alcohol-related disorders (including alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic failure), smoking status, body mass index category, hemoglobin A1c level, duration of treated diabetes, presence of microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (myocardial infarction, ischemic stroke, peripheral arteriopathy) complications of diabetes, use of antidiabetic drugs at baseline, presence of other autoimmune conditions, use of statins, and total number of non-antidiabetic drugs in the year before cohort entry
[f] Stratified on propensity score quintiles.

Figure 1

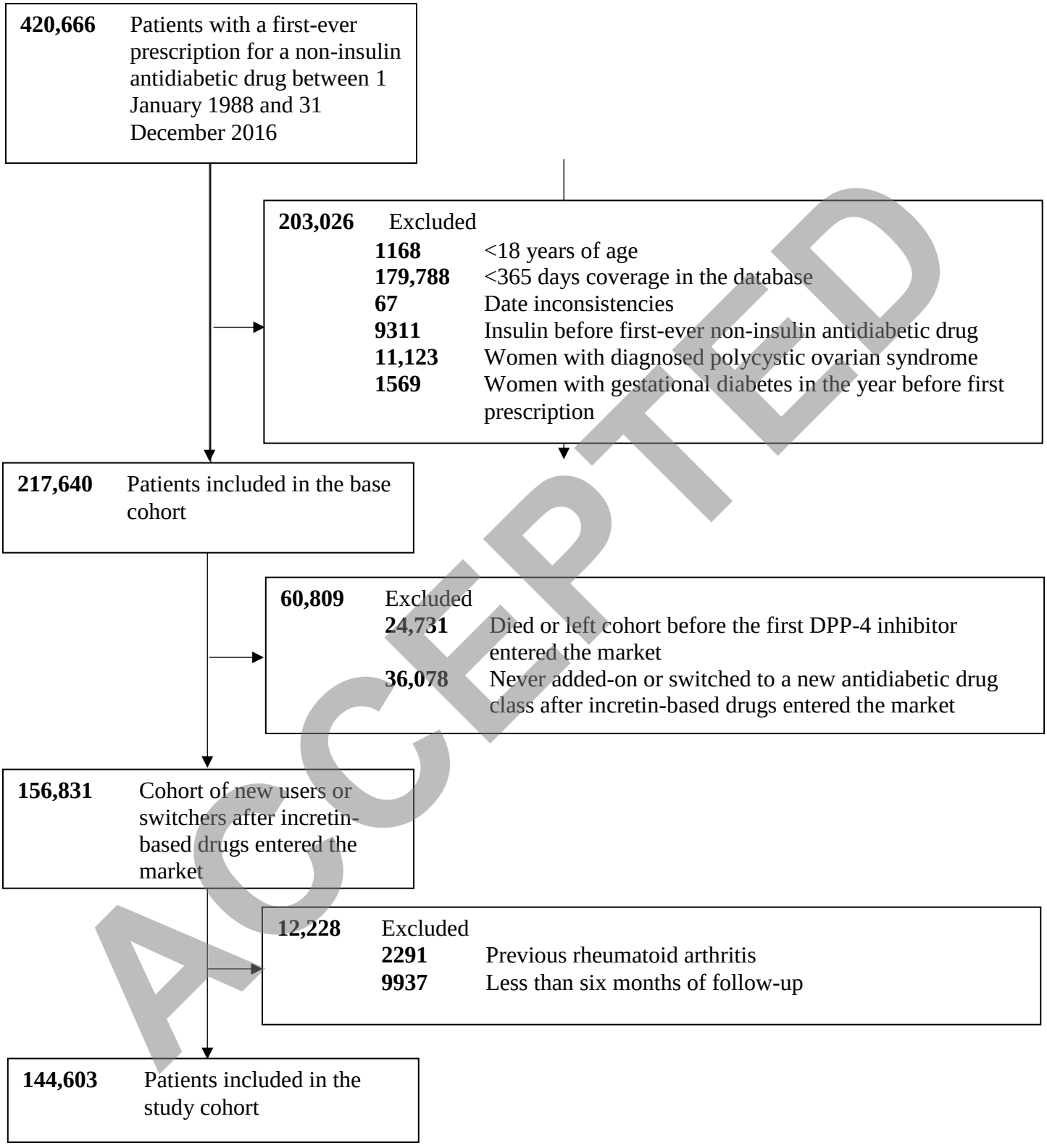

Figure 2