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Early Discontinuation of Metformin in Individuals Treated with Inhibitors of Transporters of Metformin

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Abstract: The aim of this study was to examine the risk of early discontinuation of metformin as a proxy for intolerance, associated with use of drugs known to inhibit transporters involved in metformin distribution. We analysed all incident users of metformin in Denmark between 2000 and 2012 (n = 132,221) and in a cohort of US patients (n = 296,903). Risk of early discontinuation of metformin was assessed using adjusted logistic regression for 28 drugs putatively inhibiting metformin transporters and four negative controls. Increased odds ratio of early discontinuation of metformin was only associated with codeine, an inhibitor of organic cation transporter 1 in both cohorts [adjusted odds ratio (OR) in Danish cohort (95% CI): 1.13 (1.02–1.26), adjusted OR in American cohort (95% CI): 1.32 (1.19–1.47)]. The remaining drugs were not associated with increased odds ratio of early discontinuation and, surprisingly, four drugs were associated with a decreased risk. These findings indicate that codeine use may be associated with risk of early discontinuation of metformin and could be used as a basis for further investigation.

The most widely used antidiabetic drug, metformin, is incompletely absorbed from the intestine, not metabolized in the liver and mainly excreted unchanged in the urine [1]. Thus, drug–drug interactions (DDI) have generally been considered to be of little importance for metformin pharmacokinetics. However, on a fixed daily dose of metformin, the trough steady-state concentration varies 80-fold in patients with type 2 diabetes [2] indicating large interindividual variability. The focus in recent years has thus been on genetic variation in the transporters that are involved in metformin transport and hence the pharmacokinetics (i.e. organic cation transporter (OCT) 1 and 2, multi-drug and toxin extrusion transporter (MATE) 1 and 2-K [3]) causing variation in the response to the drug. As this extensive research has only been able to explain a minor fraction of the total variation in metformin pharmacokinetics [4], the focus has recently shifted to potential DDI with drugs that affect these transporters as a source of variation [5]. Clinically relevant pharmacokinetic DDI have been described with cimetidine [6,7], vandetanib [8], trimethoprim [9] and pyrimethamine [10] while pharmacodynamic DDI have been described with rifampicin [11], St. John's wort [12] and verapamil [13].

While most DDI studies with metformin have focused on pharmacokinetic or pharmacodynamic interactions, very few describe the impact of these DDI on the side effects of metformin. Although metformin is generally well tolerated, up to 20% of patients experience gastrointestinal side effects such as nausea, loss of appetite, dyspepsia or diarrhoea [14,15], which leads to discontinuation in approximately 5% of patients [16]. Recently, Dujic *et al.* [17] described increased odds ratio of metformin intolerance among carriers of reduced-function alleles in *OCT1* as well as among patients treated with OCT1 inhibitors. OCT1 is mainly distributed in the sinusoidal membranes of the liver cells and in intestinal cells [18–20]. As metformin is a substrate for OCT1, use of drugs that inhibit OCT1 could cause accumulation of metformin in the intestines, leading to increased risk of gastrointestinal side effects with metformin. This hypothesis is supported by the finding that genetic variants in *OCT1* lead to higher risk of gastrointestinal side effects [21].

Using prescription data for more than 400,000 incident metformin users in Denmark and the USA, we sought to determine whether drugs that affect activity or function of transporters involved in metformin distribution increase the odds ratio of early discontinuation of metformin as a proxy of metformin intolerance.

Materials and Methods

In this cohort study, we identified incident users of metformin to assess whether concomitant use of drugs suspected to affect metformin transporters was associated with early metformin discontinuation. The primary analysis was conducted in a cohort of Danish patients, and we replicated the analysis in a cohort of US patients. No ethical approval was required for this study in Denmark, and it was exempted by the Brigham and Women's Hospital Institutional Review Board.

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Danish cohort.

Data sources. We used data from three sources: the Danish National Registry of Patients, the Danish National Prescription Registry and the Danish Person Registry. The Danish National Registry of Patients [22] contains data on all secondary care contacts in Denmark since 1977. From 1995, outpatient diagnoses have been included systematically. Discharge diagnoses are coded according to ICD-8 from 1977 to 1993 and ICD-10 since 1994. Virtually, all medical care in Denmark is furnished by the public health authorities, whereby this data resource allows true population-based studies, covering all inhabitants of Denmark. The Danish National Prescription Registry [23] contains data on all prescription drugs redeemed by Danish citizens since 1995. Prescription data include the Central Person Registry number, the date of dispensing, the substance, brand name and quantity. The dosing instruction and the indication for prescribing are not recorded. Drugs are categorized according to the Anatomic Therapeutic Chemical code (ATC), a hierarchical classification system developed by WHO for purposes of drug use statistics WHO [24]. The quantity for each prescription is expressed by the defined daily dose (DDD) measure, also developed by WHO [24].

The Danish Person Registry [25] contains data on vital status (date of death) and migrations in and out of Denmark, which allowed us to extract controls and to keep track of all individuals. All data sources were linked by use of the Central Person Registry number, a unique person-identifier assigned to all Danish citizens since 1968 that encodes gender and date of birth [25]. All linkage occurred within Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes. Further information on the Danish registries can be found elsewhere [26].

Study population. We included all Danish individuals filling their first-ever metformin prescription between 1 January 2000 and 31 December 2011 (n = 201,313), that is with no prior use between 1995 and 2000. The date the individual filled the first prescription was defined as the index date. We further excluded patients aged <18 years at the index date (n = 401), individuals having filled a prescription for another antidiabetic prior to their index date (n = 61,912), individuals who migrated during follow-up (n = 3510) and individuals who died within 1 year of the index date (n = 3269). This resulted in a final sample of 132,221 eligible incident metformin users.

US cohort.

Data source. We used 2004–2013 data from Optum LifeSciences Research Database, which contains longitudinal medical and pharmacy claims data on approximately 40 million beneficiaries of the commercially insured UnitedHealth population. The covered population has demographics similar to the US census for gender and age below 65 years and contains data for some Medicare beneficiaries enrolled in Medicare Advantage plans.

Study population. The cohort consisted of patients initiating metformin between 1 January 2005 and 30 June 2013 (n = 296,903) who met the following inclusion criteria: age ≥ 18 years old on the index date, continuous enrolment for 1 year before entering the cohort and no prescription for metformin or other antidiabetic during this period.

Calculations and statistics.

Outcome definition. Early discontinuation was defined as absence of a second prescription fill for metformin within 7–180 days after the index date. This definition was subjected to sensitivity analyses.

The number needed to treat for one additional patient to be harmed (NNTH) was calculated for drugs associated with increased odds ratio of early discontinuation of metformin [27]. NNTH is an absolute risk measure that indicates how many incident users of metformin need to be treated with the exposure drug to provoke an additional case of early discontinuation. It is calculated using the following formula:

$$\mathrm{NNTH} = \frac{1}{\left(\mathrm{ER}_{\mathrm{unexposed}} * \left(\mathrm{OR}_{\mathrm{adjusted}} - 1\right)\right)}$$

where $\mathrm{ER}_{\mathrm{unexposed}}$ is the risk of early discontinuation in the unexposed group and $\mathrm{OR}_{\mathrm{adjusted}}$ is the adjusted odds ratio from the main analysis. Confidence intervals were calculated using the same equation, but with $\mathrm{OR}_{\mathrm{adjusted}}$ substituted with the lower and upper limits of the confidence interval of the $\mathrm{OR}_{\mathrm{adjusted}}$.

Drug exposure. In the Danish cohort, exposure to a given drug was defined as having filled a prescription within 120 days prior to the first metformin prescription. This definition was subjected to sensitivity analyses. In the US cohort, exposure to a given drug was defined as having filled a prescription prior to the metformin index date, of which the supply overlapped with the index date.

The drugs that were assessed for an association with early discontinuation of metformin are outlined in table 1. We selected drugs that have been shown to affect SLC transporters that are relevant for metformin transport [28]. Further, these drugs had to be on the Danish market (disopyramide [29] was excluded on this basis) and had to be dispensed on prescription at pharmacies (vandetanib [8] and tyrosine kinase inhibitors [30] were excluded on this basis). These drugs can be classified into drugs that inhibit OCT1 and those that inhibit other transporters relevant for metformin (e.g. OCT2, MATE1 or MATE2-K, table 1). These putative DDI have been described in more detail in a recent literature review [5]. Finally, we included negative controls that were not expected to affect metformin transport: allopurinol (M04AA01), pravastatin (C10AA03), lithium (N05AN01) and atorvastatin (C10AA05).

Analysis. For each drug, we assessed whether its use was associated with metformin intolerance as defined by early discontinuation. We used logistic regression to estimate both crude and adjusted odds ratios (ORs). In the adjusted model, we included the following potential confounders:

1. Gender and age in 5-year intervals (while aggregating the age groups 18–29, 30–39 and 75+).
2. Charlson comorbidity index [31] in the Danish cohort and a combined comorbidity score for the US cohort [32] [in categories of none (0), low (1), medium (2) and high (3+)].
3. As markers of chronic disease, we lastly included use of low-dose aspirin and angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists as well as diagnoses (ICD-10 codes (Danish cohort) or ICD-9 codes (US cohort)) for unspecified chronic kidney disease, renal failure, heart failure and chronic inflammatory bowel diseases.

Sensitivity analyses. We performed several pre-planned sensitivity analyses in the Danish cohort:

1. We conducted subgroup analyses in strata of (a) age, (b) gender and (c) Charlson comorbidity index.
2. We applied alternative outcome definitions as proxies of 'metformin intolerance': (a) failing to fill a second prescription within the first 365 days after index date (up from 180) and (b) failing to fill a second prescription within 180 days but filling a prescription for another antidiabetic drug within the same time window.

Table 1.
All drugs examined for association with early discontinuation of metformin.

Affected transporter and drugs	References
OCT1	
Proton pump inhibitors (Mixed OCTs)	
Omeprazole	[44]
Lansoprazole	
Pantoprazole	
Esomeprazole	
Opioids	
Morphine	[29,40]
Tramadol	
Codeine	
Beta-blockers	
Metoprolol	[45,46]
Pindolol	
Propranolol	
Selective calcium antagonists	
Diltiazem	[13,29]
Verapamil	
Antidepressants	
Citalopram	[29]
Imipramine	
Amitriptyline	
Antipsychotics	
Haloperidol	[29]
Chlorprothixene	
Clozapine	
Risperidone	
Others	
Doxazosin	[29]
Spironolactone	
Quinine	
Clopidogrel	
Ondansetron	
Metoclopramide	
OCT2, MATE1 and MATE2-K	
Dipyridamol	[29]
Cimetidine	[6,7]
Trimethoprim	[9,47]
Negative controls	
Allopurinol	
Pravastatin	
Lithium	
Atorvastatin	

3 We applied alternative definitions of exposure to potentially interacting drugs: (a) changing the time window for the drug from 120 prior to index date to 90 and 180 days; (b) requiring another prescription filled within the first 120 days after the index date in addition to the prescription filled prior to the index date; and (c) at least three prescriptions redeemed of the exposure drug within the 2 years prior to the index date and one prescription within the 120 days prior to the index date to ensure chronic use of the exposure drug.

4 If metformin acts as the perpetrator in interactions with other drugs, this might lead to cessation of metformin treatment, which might be misconstrued as metformin intolerance. To assess this, we performed an analysis in which we excluded users of drugs that might be negatively affected by metformin use, namely topiramate (N03AX11) [33], vitamin K-antagonists (B01AA) [34–36], trospium (G04BD09) [37,38] and aliskiren (C09XA02) [39].

Results

An overview of all 32 drugs that were examined for association with early discontinuation of metformin is shown in table 1. Figure 1 shows the adjusted odds ratios (ORs) (adjusted for age, comorbidity, kidney disease, heart failure, chronic inflammatory bowel diseases and use of low-dose aspirin, angiotensin II antagonists or ACE inhibitors) from the individual drugs in both the Danish and the US cohort.

Danish cohort (primary cohort).
We identified 132,221 incident metformin users between 1 January 2000 and 31 December 2011. The median age of the patients was 60 years (IQR: 49–68), and 67,393 (51%) were men. A total of 16,126 individuals (12.2%) were early discontinuers of metformin. Being female increased the odds ratio of early discontinuation, while a Charlson comorbidity index >0 and age >60 years decreased the odds ratio (table 2).

The crude and adjusted odds ratios of early discontinuation of metformin associated with use of the selected drugs and the negative control drugs are shown in table 3. Among the drugs known to inhibit transporters, the proton pump inhibitors omeprazole, pantoprazole and esomeprazole, the analgesics morphine and codeine, the antiemetic metoclopramide, the antihistamine cimetidine and the antiplatelet drug clopidogrel were all associated with increased odds ratio of early discontinuation of metformin. Use of the beta-blocker metoprolol, the antipsychotics chlorprothixene, clozapine and risperidone and use of lithium and citalopram were associated with decreased odds ratio of early discontinuation of metformin.

The remaining transport inhibiting drugs (n = 15) were not associated with early discontinuation of metformin. Of the negative controls, neither allopurinol, pravastatin nor atorvastatin was associated – positively or inversely – with early discontinuation of metformin.

Pre-planned sensitivity analyses did not reveal any significant changes to the results (data available on file).

US cohort (replication cohort).
We identified 296,903 incident metformin users between 1 January 2005 and 30 June 2013 with 71,699 individuals (24.1%) being early discontinuers of metformin. The median age of the patients was 50 (IQR: 40–59) and 168,787 (57%) were men.

As in the Danish cohort, being female was associated with increased risk of early discontinuation while having age >60 years was associated with decreased odds ratio of early discontinuation of metformin. In contrast to the Danish cohort, a comorbidity score >0 was associated with increased odds ratio of early discontinuation (table 2).

The crude and adjusted odds ratios of early discontinuation of metformin associated with use of the selected drugs and the negative control drugs are shown in table 4. In this cohort, only the opioids codeine and tramadol and the antiemetic ondansetron were associated with higher odds ratio of early

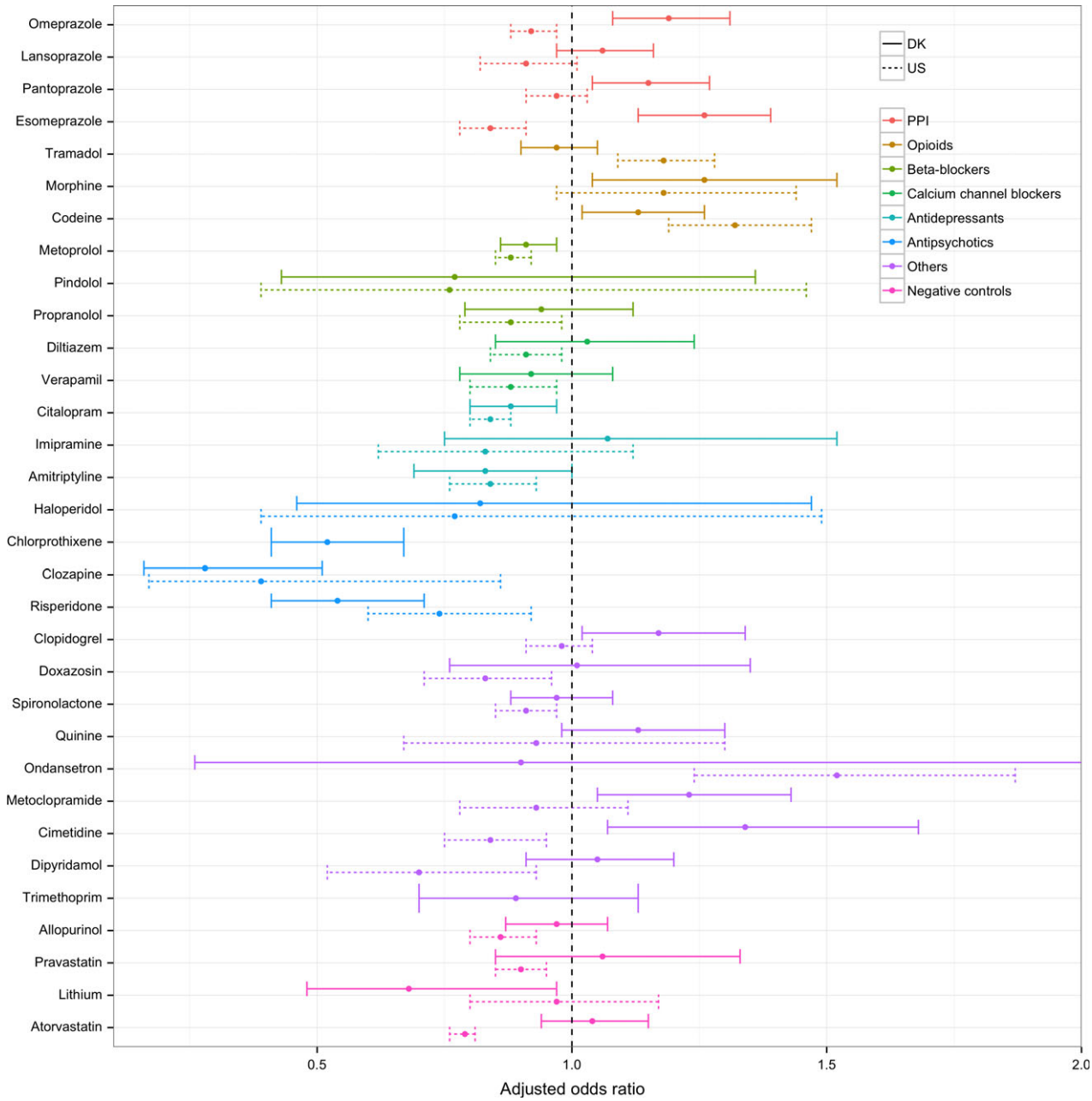

Fig. 1. The adjusted odds ratios for early discontinuation of metformin with corresponding 95% CI for all drugs in both cohorts. DK: Denmark, US: United States of America, PPI: proton pump inhibitors.

Table 2.
The effect of age, sex and comorbidity on the odds ratios of early discontinuation of metformin.

Risk factor	Danish cohort	US cohort
Age >60 years	0.68 (0.66–0.71)	0.78 (0.76–0.79)
Female	1.56 (1.50–1.61)	1.39 (1.37–1.41)
Comorbidity score* > 0	0.92 (0.89–0.95)	1.15 (1.13–1.17)

*Charlson comorbidity index was used in the Danish cohort while a combined comorbidity index was used in the US cohort.

discontinuation of metformin. However, 17 different drugs were associated with lower odds ratio of early discontinuation of metformin.

Table 5 shows the number needed to treat to harm (NNTH) for the drugs included in the analysis [27]. These ranged from 8 (for ondansetron in the US cohort) to 63 (for codeine in the Danish cohort) and can be interpreted as number of patients that are treated with a given drug to observe one additional case of early discontinuation of metformin.

Discussion

Use of the OCT1 inhibitor codeine was associated with increased odds ratio of early discontinuation of metformin in both the primary Danish cohort and the US replication cohort.

Table 3.
The effect of inhibitors of transporters related to metformin disposition and negative controls on the odds ratios of early discontinuation of metformin in the Danish cohort.

Drug	n Exposed (% ED)	n Unexposed (% ED)	Crude odds ratio (95% CI)	Adjusted odds ratio[1] (95% CI)
Proton pump inhibitors				
Omeprazole	4181 (12.7)	128,040 (12.2)	1.04 (0.95–1.15)	1.19 (1.08–1.31)
Lansoprazole	5141 (11.5)	127,080 (12.2)	0.94 (0.86–1.02)	1.06 (0.97–1.16)
Pantoprazole	3805 (12.4)	128,416 (12.2)	1.02 (0.92–1.12)	1.15 (1.04–1.27)
Esomeprazole	3373 (13.4)	128,848 (12.2)	1.12 (1.01–1.24)	1.26 (1.13–1.39)
Opioids				
Morphine	937 (14.0)	131,284 (12.2)	1.17 (0.97–1.41)	1.26 (1.04–1.52)
Tramadol	7591 (11.4)	124,630 (12.2)	0.92 (0.85–0.99)	0.97 (0.90–1.05)
Codeine	3089 (13.2)	129,132 (12.2)	1.10 (0.99–1.22)	1.13 (1.02–1.26)
Beta-blockers				
Metoprolol	17,057 (9.1)	115,164 (12.7)	0.69 (0.65–0.73)	0.91 (0.86–0.97)
Pindolol	151 (8.6)	132,070 (12.2)	0.68 (0.38–1.20)	0.77 (0.43–1.36)
Propranolol	1334 (11.1)	130,887 (12.2)	0.90 (0.76–1.07)	0.94 (0.79–1.12)
Calcium channel blockers				
Diltiazem	1156 (10.4)	131,065 (12.2)	0.83 (0.69–1.01)	1.03 (0.85–1.24)
Verapamil	1666 (9.7)	130,555 (12.2)	0.77 (0.66–0.91)	0.92 (0.78–1.08)
Antidepressants				
Citalopram	5082 (11.0)	127,139 (12.2)	0.88 (0.81–0.97)	0.88 (0.80–0.97)
Imipramine	313 (11.5)	131,908 (12.2)	0.94 (0.66–1.32)	1.07 (0.75–1.52)
Amitriptyline	1328 (9.9)	130,893 (12.2)	0.79 (0.66–0.94)	0.83 (0.69–1.00)
Antipsychotics				
Haloperidole	129 (10.1)	132,092 (12.2)	0.81 (0.45–1.43)	0.82 (0.46–1.47)
Chlorprothixene	1025 (6.8)	131,196 (12.2)	0.53 (0.41–0.67)	0.52 (0.41–0.67)
Clozapine	286 (4.2)	131,935 (12.2)	0.31 (0.18–0.56)	0.28 (0.16–0.51)
Risperidone	798 (7.3)	131,423 (12.2)	0.56 (0.43–0.74)	0.54 (0.41–0.71)
Others				
Clopidogrel	2301 (10.6)	129,920 (12.2)	0.86 (0.75–0.98)	1.17 (1.02–1.34)
Doxazosin	556 (9.2)	131,665 (12.2)	0.73 (0.54–0.97)	1.01 (0.76–1.35)
Spironolactone	4039 (11.1)	128,182 (12.2)	0.90 (0.81–0.99)	0.97 (0.88–1.08)
Quinine	1912 (12.6)	130,309 (12.2)	1.03 (0.90–1.19)	1.13 (0.98–1.30)
Ondansetron	22 (–)	132,199 (12.2)	1.14 (0.34–3.84)	0.90 (0.26–3.12)
Metoclopramide	1320 (16.0)	130,901 (12.2)	1.38 (1.19–1.59)	1.23 (1.05–1.43)
Cimetidine	603 (15.1)	131,618 (12.2)	1.28 (1.02–1.60)	1.34 (1.07–1.68)
Dipyridamol	2464 (9.4)	129,757 (12.2)	0.74 (0.65–0.85)	1.05 (0.91–1.20)
Trimethoprim	722 (10.8)	131,499 (12.2)	0.87 (0.69–1.10)	0.89 (0.70–1.13)
Negative controls				
Allopurinol	4555 (9.5)	127,666 (12.3)	0.75 (0.68–0.83)	0.97 (0.87–1.07)
Pravastatin	856 (10.0)	131,365 (12.2)	0.80 (0.64–1.00)	1.06 (0.85–1.33)
Lithium	448 (7.6)	131,773 (12.2)	0.59 (0.42–0.84)	0.68 (0.48–0.97)
Atorvastatin	4574 (9.8)	127,647 (12.3)	0.78 (0.71–0.86)	1.04 (0.94–1.15)

ED: early discontinuation of metformin.
[1]Adjusted for age, Charlson comorbidity index, ICD-10 codes for kidney disease and kidney failure, chronic inflammatory bowel diseases, heart failure and use of drugs to treat heart failure.

The remaining drugs were not associated with increased odds ratio of early discontinuation of metformin. Higher age (>60 years) was associated with decreased risk of early discontinuation while female sex was associated with increased risk of early discontinuation of metformin.

Interestingly, the majority of the investigated drugs were not associated with increased odds ratios of early discontinuation of metformin. This study was an exploratory exercise to determine whether it would be possible to use pharmacoepidemiological databases to detect complex transporter-mediated DDI causing intolerance. Thus, the results from this study should be seen as hypothesis generating. Whether specific DDIs are important for metformin intolerance should be further explored, such as by pooling of data from clinical trials, allowing large samples with registered side effects.

In general, we observed an increased odds ratio of early discontinuation associated with use of opioids. All three analysed opioids are inhibitors of OCT1 [40,41]. Morphine was associated with statistically significant increased odds ratio in the Danish cohort, but not in the US cohort, while the opposite was observed for tramadol. However, despite not being statistically significant, the odds ratio for morphine in the US cohort was similar to that of the Danish cohort.

Table 4.
The effect of inhibitors of transporters related to metformin disposition and negative controls on the odds ratios of early discontinuation of metformin in the US cohort.

Drug	n Exposed (% ED)	n Unexposed (% ED)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)[1]
Proton pump inhibitors				
Omeprazole	9157 (21.1)	287,746 (24.3)	0.84 (0.79–0.88)	0.92 (0.88–0.97)
Lansoprazole	2051 (21.2)	294,852 (24.2)	0.85 (0.76–0.94)	0.91 (0.82–1.01)
Pantoprazole	6646 (21.8)	290,257 (24.2)	0.87 (0.82–0.93)	0.97 (0.91–1.03)
Esomeprazole	4087 (19.5)	292,816 (24.2)	0.76 (0.70–0.82)	0.84 (0.78–0.91)
Opioids				
Morphine	528 (26.9)	296,375 (24.1)	1.16 (0.95–1.40)	1.18 (0.97–1.44)
Tramadol	3323 (25.9)	293,580 (24.1)	1.10 (1.02–1.19)	1.18 (1.09–1.28)
Codeine	1741 (29.5)	295,162 (24.1)	1.31 (1.19–1.46)	1.32 (1.19–1.47)
Beta-blockers				
Metoprolol	18,680 (19.1)	278,223 (24.5)	0.73 (0.70–0.75)	0.88 (0.85–0.92)
Pindolol	60 (18.3)	296,843 (24.2)	0.71 (0.37–1.36)	0.76 (0.39–1.46)
Propranolol	1766 (21.4)	295,137 (24.2)	0.86 (0.76–0.96)	0.88 (0.78–0.98)
Calcium channel blockers				
Diltiazem	4030 (19.7)	292,873 (24.2)	0.77 (0.71–0.83)	0.91 (0.84–0.98)
Verapamil	2807 (19.3)	294,096 (24.2)	0.75 (0.68–0.83)	0.88 (0.80–0.97)
Antidepressants				
Citalopram	10,859 (21.3)	286,044 (24.3)	0.84 (0.80–0.88)	0.84 (0.80–0.88)
Imipramine	287 (19.5)	296,616 (24.2)	0.76 (0.57–1.02)	0.83 (0.62–1.12)
Amitriptyline	2596 (20.2)	294,307 (24.2)	0.80 (0.72–0.88)	0.84 (0.76–0.93)
Antipsychotics				
Haloperidol	55 (20.0)	296,848 (24.2)	0.79 (0.41–1.52)	0.77 (0.39–1.49)
Chlorprothixene	–	–	–	–
Clozapine	51 (13.7)	296,852 (24.2)	0.50 (0.23–1.11)	0.39 (0.17–0.86)
Risperidone	525 (20.6)	296,378 (24.2)	0.81 (0.66–1.01)	0.74 (0.60–0.92)
Others				
Clopidogrel	6004 (18.9)	290,899 (24.3)	0.73 (0.68–0.78)	0.98 (0.91–1.04)
Doxazosin	1224 (16.6)	295,679 (24.2)	0.62 (0.54–0.73)	0.83 (0.71–0.96)
Spironolactone	4929 (26.0)	291,974 (24.1)	1.11 (1.04–1.18)	0.91 (0.85–0.97)
Quinine	219 (20.1)	296,684 (24.2)	0.79 (0.57–1.10)	0.93 (0.67–1.30)
Ondansetron	407 (35.4)	296,496 (24.1)	1.72 (1.41–2.11)	1.52 (1.24–1.87)
Metoclopramide	726 (22.5)	296,177 (24.2)	0.91 (0.76–1.08)	0.93 (0.78–1.11)
Cimetidine	1912 (18.3)	294,991 (24.2)	0.70 (0.62–0.79)	0.84 (0.75–0.95)
Dipyridamol	399 (14.8)	296,504 (24.2)	0.55 (0.41–0.72)	0.70 (0.52–0.93)
Trimethoprim	–	–	–	–
Negative controls				
Allopurinol	4533 (17.9)	292,370 (24.3)	0.68 (0.63–0.73)	0.86 (0.80–0.93)
Atorvastatin	25,324 (17.5)	271,579 (24.8)	0.64 (0.62–0.67)	0.79 (0.76–0.81)
Lithium	566 (26.0)	296,337 (24.2)	1.10 (0.91–1.33)	0.97 (0.80–1.17)
Pravastatin	7747 (19.8)	289,156 (24.3)	0.77 (0.73–0.82)	0.90 (0.85–0.95)

ED: early discontinuation of metformin.
There were no users of chlorprothixene or trimethoprim in this cohort.
[1]Adjusted for age, combined comorbidity index, ICD-9 codes for kidney disease and kidney failure, chronic inflammatory bowel diseases, heart failure and use of drugs to treat heart failure.

Generally, we observed decreased odds ratio of early discontinuation of metformin associated with use of psychotropic drugs. Lithium does not inhibit OCT1 [29] and has not been examined as a potential inhibitor of OCT2 or MATE transporters [42], while all others have been shown to inhibit OCT1 to varying degrees (see table 1 for references). As users of these drugs represent a patient group that are more closely monitored than others, they might be less likely to stop treatment due to non-compliance. Further, as many psychotropic drugs have negative effects on glucose homoeostasis [43], we expect a lower frequency of misdiagnosis of T2D in these patients, leading to a lower frequency of patients that only redeem one prescription due to misdiagnosis of T2D. Another explanation for this observation could be the pharmacodynamic inhibition of nausea caused by psychotropic drugs which, theoretically, could lead to protection against gastrointestinal side effects of metformin. All of these factors would bias the odds ratios towards zero and could explain the observed 'protective' associations.

The main strength of our study is the large sample size of more than 400,000 incident metformin users and the use of a replication cohort, which allowed us to confirm the associations observed in the primary cohort.

The main limitation of this study is the use of early discontinuation of metformin as a composite end-point as reasons for treatment discontinuation are not captured in administrative

Table 5.
Number needed to harm of the drugs associated with increased odds ratios of early discontinuation of metformin.

	Number needed to harm (95% confidence interval)	
Drug	Danish cohort	US cohort
Omeprazole	44 (27–103)	–
Pantoprazole	55 (30–203)	–
Esomeprazole	32 (21–61)	–
Morphine	32 (16–212)	–
Tramadol	–	23 (15–46)
Codeine	63 (32–545)	13 (9–22)
Clopidogrel	48 (24–444)	–
Ondansetron	–	8 (5–17)
Metoclopramide	36 (19–157)	–
Cimetidine	24 (12–119)	–

Number needed to harm is calculated using: $NNTH = 1/(ER_{unexposed} * (OR_{adjusted} - 1))$.
$ER_{unexposed}$ is the rate of early discontinuation of metformin in the individuals not exposed to the tested drug.
$OR_{adjusted}$ is the odds ratio for the association from the main analysis.

data. In addition to metformin intolerance, early discontinuation of metformin reflects factors such as poor compliance misdiagnosis of T2D or lack of response to metformin. Gastrointestinal side effects of metformin are only expected to cause discontinuation in approximately 5% of patients [16]. In the Danish cohort, 12% of patients discontinued metformin treatment, and in the US cohort, 24% discontinued. Thus, it is likely that many patients in our study who discontinued metformin did so for reasons other than gastrointestinal side effects. An effect on co-prescribed drugs on transporters would tend to overlap the multiple other reasons for early discontinuations, which might explain that there were no strong associations. Another limitation is that we restricted analyses to patients with at least 1 year of available follow-up after initiation of metformin to ensure that patients actually discontinued metformin. Such conditioning on future events can create bias in studies that seek to infer causality. However, removing this condition in the US replication cohort had no material effect on the results. Codeine can be used off label for diarrhoea. As such, a small fraction of patients might be treated with codeine for gastrointestinal symptoms that may predispose them to metformin intolerance. However, as the use of codeine for this indication is rare, we do not expect it to affect our estimates to a great extent. Other limitations include the lack of data on dose of metformin and exposure drugs in the Danish cohort and lack of genotype data from the included individuals.

Adherence behaviour may be a potential confounder in this study comparing users of a given drug to non-users. To be identified as an exposed individual, patients must have received one or more prescriptions for a drug of interest. A portion of these patients will have been performed with the drug for some time, demonstrating good adherence behaviour. Such behaviour may also manifest in the use of metformin, leading to lower odds ratio of discontinuation as compared to patients who are not required to have demonstrated use of another drug. Identifying potential confounding factors associated with such behaviour in claims databases is highly limited, and hence, adequately controlling for this confounding factor is challenging. This may explain why there are more drugs associated with lower odds ratio of early discontinuation than with higher odds ratio.

In conclusion, we reported increased odds ratio of early discontinuation of metformin, a proxy for metformin intolerance, for female sex and use of codeine while age >60 years was associated with a decreased risk of early discontinuation. It is possible that the association between exposure to codeine and metformin discontinuation could be due to gastrointestinal side effects of metformin, arising from intestinal inhibition of metformin transporters. This finding warrants additional investigation.

Disclosure

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Appendix S1. All results from both main and sensitivity analysis from the original Danish cohort.