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BRIEF REPORT

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Use of dipeptidyl peptidase-4 inhibitors and risk of splanchnic vein thrombosis: A Danish nationwide new-user active comparator cohort study

Anton Pottegård PhD | Lars Christian Lund MD[1] | Daniel Pilsgaard Henriksen PhD[1,2] | Lars Folkestad PhD[3,4] | Maja Hellfritzsch PhD[1,5] | Jesper Hallas PhD[1] | Kasper Bruun Kristensen MD[1]

[1]Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark

[2]Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark

[3]Department of Endocrinology and Metabolism, Odense University Hospital, Odense, Denmark

[4]Department of Clinical Research, University of Southern Denmark, Odense, Denmark

[5]Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark

Correspondence
Professor Anton Pottegård, PhD, Clinical Pharmacology and Pharmacy, University of Southern Denmark, JB Winsløwsvej 19, 2 DK-5000 Odense C, Denmark.
Email: apottegaard@health.sdu.dk

Abstract

Use of dipeptidyl peptidase-4 (DPP-4) inhibitors, on the basis of spontaneous adverse event reports, has recently been suspected of causing splanchnic vein thrombosis. Here, we report the results of a population-based new-user active comparator cohort study addressing this hypothesis, comparing DPP-4 inhibitor initiators (n = 75 042) with initiators of glucagon-like-peptide-1 receptor agonists (GLP-1RAs) or sodium-glucose co-transporter-2 (SGLT2) inhibitors (n = 38 718). We estimated the hazard ratio (HR) associating DPP-4 inhibitor use with risk of splanchnic vein thrombosis using Cox regression. In a crude analysis, the incidence rate of splanchnic vein thrombosis was 0.22/1000 person-years among DPP-4 inhibitor initiators, compared to 0.17 among GLP-1RA/SGLT2 inhibitor initiators, corresponding to an unadjusted absolute incidence rate difference of 0.05 (95% confidence interval [CI] −0.04 to 0.14) and an HR of 1.29 (95% CI 0.78 to 2.15). Adjusting for potential confounders using stabilized inverse probability of treatment weighing, we obtained an absolute incidence rate difference of 0.03/1000 person-years (95% CI −0.07 to 0.14) and an HR of 1.18 (95% CI 0.62 to 2.26). No evidence of increased risk of splanchnic vein thrombosis was found in supplementary analyses, including an absence of any dose–response patterns. As such, we found no association between DPP-4 inhibitor use and splanchnic vein thrombosis risk.

KEYWORDS

antidiabetic drug, pharmacoepidemiology

1 | INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors are commonly used second-line drugs for type 2 diabetes.[1] Recently, use of DPP-4 inhibitors was associated with an increased risk of splanchnic vein thrombosis on the basis of spontaneous adverse event reports from the World Health Organization (WHO)'s VigiBase.[2] Splanchnic vein thrombosis is often asymptomatic, but may also result in acute or subacute intestinal ischaemia, which can be difficult to diagnose, leading to delayed diagnosis and potentially worse prognosis.[3] However, studies based on spontaneous reporting systems can generally only be used in signal generation and should thus be followed up with more rigorous observational studies.[4] We therefore leveraged the population-based Danish health registries to investigate this potential association and its potential clinical impact.

2 | METHODS

We conducted a population-based, active comparator, new-user cohort study of patients aged ≥40 years initiating DPP-4 inhibitors compared to initiators of glucagon-like-peptide-1 receptor agonists (GLP-1RAs) or sodium-glucose co-transporter-2 (SGLT2) inhibitors during 2008 to 2018. GLP-1RA/SGLT2 inhibitor use was chosen as the comparator based on clinical input and previous work[5] showing users of these drugs to be most comparable with users of DPP-4 inhibitors. The choice of comparator was varied in sensitivity analyses. We excluded patients with a previous record of splanchnic vein thrombosis, patients initiating both DPP-4 inhibitors and a comparator drug on the same date (including combination products), and patients with less than 1 year of available baseline data due to recent migrations.

2.1 | Data sources

Users of antidiabetic drugs were identified using the Danish National Prescription Registry,[6] covering all prescriptions filled at community pharmacies in Denmark since 1995. Data on hospital admissions, including splanchnic vein thrombosis events, were obtained from the Danish National Patient Registry,[7] covering all hospital admissions since 1977 and outpatient contacts since 1995. Census data were obtained from the Civil Registration system[8] in order to account for death, censoring and residence within Denmark. Data were linked using the unique personal civil registration number assigned to all Danish residents.[8]

2.2 | Confounder adjustment

We used propensity score methods to reduce confounding. The propensity score is the conditional probability of receiving the treatment of interest, given a set of baseline characteristics. Propensity scores were used to calculate inverse probability of treatment weights (IPTW).[9] Use of IPTW creates a pseudopopulation, where the covariate distribution in the treated and untreated cohorts resembles the covariate distribution of the overall study population and makes estimation of the average treatment effect in the whole population possible. Weights were stabilized by using the marginal prevalence of the treatment received in the numerator when calculating IPTW.[9] Propensity score models included age, sex, markers of diabetes severity, risk factors for splanchnic vein thrombosis, and selected comorbidity and comedication (see Appendix S1). Propensity scores were calculated separately for each calendar year because the pattern of use of oral antidiabetic drugs has changed markedly during the study period'. We used stabilized weights to reduce undue influence of small strata and trimmed the propensity score distribution at the 2.5th and 97.5th percentile, to reduce potential unmeasured confounding.[10] The success of propensity score weighting was evaluated by using standardized mean differences in patient characteristics[11] and assessment of distribution of weights.[10] Patients were followed from the date of treatment initiation using an intention-to-treat approach for up to 5 years or until splanchnic vein thrombosis diagnosis, death, migration, or end of follow-up (December 31, 2018).

2.3 | Analyses

Descriptive statistics were used to describe and compare the cohorts at baseline. Categorical variables are reported as counts and percentages, while continuous variables are reported using medians and interquartile ranges. Differences between unweighted and weighted cohorts were quantified using standardized mean differences, and differences <0.1 were considered negligible. We calculated crude and adjusted (weighted) incidence rates, incidence rate differences, and "number needed to treat for one additional patient to be to harmed" (NNTH). Hazard ratios (HRs) were estimated using Cox regression. The proportional hazards assumption was evaluated based on adding a linear time-dependent effect of exposure on the log-hazard scale into the Cox regression model.

2.4 | Supplementary analyses

In supplementary analyses we did the following: (i) compared DPP-4 inhibitor initiators to initiators of GLP-1RAs, SGLT2 inhibitors and sulphonylureas individually; (ii) restricted DPP-4 inhibitor initiators to those initiating sitagliptin, the DPP-4 inhibitor that carried most of the initial safety signal;[2] (iii) restricted the outcome to portal vein thrombosis; (iv) included other thromboembolisms located in non-splanchnic abdominal veins in the outcome; (v) investigated typical venous thromboembolism (deep vein thrombosis/pulmonary embolism) as a secondary outcome; (vi) performed a per-protocol analysis (censoring at 180 days without a fill for index drug); (vii) assessed dose–response associations in a risk-set sampled case–control study nested in the DPP-4 inhibitor new-user cohort; (viii) restricted follow-up to 1 and 2 years, respectively; (ix) excluded oral anticoagulant users and patients with cancer history; (x) performed analyses without trimming of propensity score distributions; and (xi) used standardized mortality ratio weighting instead of IPTW.

3 | RESULTS

We identified 75 042 DPP-4 inhibitor initiators (median age 65 years; 40% women) and 38 718 GLP-1RA/SGLT2 inhibitor initiators (median age 60 years; 43% women [Table 1; Figure S1]). In crude analyses (Table 2), the incidence rate of splanchnic vein thrombosis was 0.22/1000 person-years among DPP-4 inhibitors initiators, compared to 0.17 among GLP-1RA/SGLT2 inhibitor initiators, corresponding to an HR of 1.29 (95% confidence interval [CI] 0.78 to 2.15) and an absolute incidence rate difference of 0.05 (95%CI −0.04 to 0.14). IPTW weighting led to well-balanced patient

TABLE 1 Baseline characteristics for new users of dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonist/sodium-glucose co-transporter-2 inhibitor initiators in the full cohort and after inverse probability of treatment weighting

	Basic cohort			IPTW-weighted population		
	DPP-4 inhibitors	GLP-1RAs/SGLT2 inhibitors	SMDs	DPP-4 inhibitors	GLP-1RAs/SGLT2 inhibitors	SMDs
	(n = 75 042)	(n = 38 718)		(n = 58 996)	(n = 28 944)	
Median (IQR) age, years	65 (56–73)	60 (52–67)	0.44	62 (54–70)	63 (55–69)	0.00
Men, n (%)	44 940 (59.9)	22 129 (57.2)	0.06	35 237 (59.7)	17 313 (59.8)	0.00
Diabetes severity						
Median (IQR) diabetes duration, years	5 (2–9)	6 (2–11)	0.16	5 (2–9)	5 (2–9)	0.00
Metformin, n (%)	64 867 (86.4)	31 589 (81.6)	0.13	51 437 (87.2)	25 456 (87.9)	0.02
Sulphonylureas, n (%)	24 240 (32.3)	9118 (23.5)	0.20	17 807 (30.2)	9067 (31.3)	0.02
Insulin, n (%)	5239 (7.0)	12 311 (31.8)	0.66	5443 (9.2)	2728 (9.4)	0.01
Diabetic nephropathy, n (%)	5336 (7.1)	2471 (6.4)	0.03	3128 (5.3)	1571 (5.4)	0.01
Diabetic retinopathy, n (%)	6548 (8.7)	5441 (14.1)	0.17	5369 (9.1)	2623 (9.1)	0.00
Diabetic neuropathy, n (%)	4199 (5.6)	3094 (8.0)	0.10	3327 (5.6)	1647 (5.7)	0.00
Prescriptions, n (%)						
Loop diuretics	13 557 (18.1)	7084 (18.3)	0.01	9587 (16.3)	4694 (16.2)	0.00
Lipid-modifying agents	53 578 (71.4)	27 477 (71.0)	0.01	42 135 (71.4)	20 672 (71.4)	0.00
NSAIDs	17 550 (23.4)	10 935 (28.2)	0.11	14 775 (25.0)	7165 (24.8)	0.01
Glucocorticoids	5579 (7.4)	2609 (6.7)	0.03	4028 (6.8)	1959 (6.8)	0.00
Low-dose aspirin	27 655 (36.9)	13 968 (36.1)	0.02	20 322 (34.4)	9952 (34.4)	0.00
Platelet aggregation inhibitors	5747 (7.7)	2837 (7.3)	0.01	4159 (7.1)	2057 (7.1)	0.00
Warfarin	4986 (6.6)	1916 (4.9)	0.07	3200 (5.4)	1574 (5.4)	0.00
Direct oral anticoagulants	1554 (2.1)	802 (2.1)	0.00	1309 (2.2)	629 (2.2)	0.00
Prior diagnoses, n (%)						
Splanchnic vein thrombosis	33 (0.0)	16 (0.0)	0.00	28 (0.0)	12 (0.0)	0.00
Deep-vein thrombosis	1044 (1.4)	475 (1.2)	0.01	749 (1.3)	358 (1.2)	0.00
Pulmonary embolism	1936 (2.6)	1196 (3.1)	0.03	1600 (2.7)	764 (2.6)	0.00
Obesity	11 740 (15.6)	11 605 (30.0)	0.35	11 682 (19.8)	5693 (19.7)	0.00
Hypertension	58 786 (78.3)	30 355 (78.4)	0.00	45 808 (77.6)	22 482 (77.7)	0.00
Myocardial infarction	6181 (8.2)	3255 (8.4)	0.01	4611 (7.8)	2240 (7.7)	0.00
Ischaemic stroke	6048 (8.1)	2461 (6.4)	0.07	3944 (6.7)	1967 (6.8)	0.00
Haemorrhagic stroke	510 (0.7)	179 (0.5)	0.03	316 (0.5)	160 (0.6)	0.00
Heart failure	6035 (8.0)	2965 (7.7)	0.01	4238 (7.2)	2070 (7.2)	0.00
Atrial fibrillation	7724 (10.3)	3080 (8.0)	0.08	5170 (8.8)	2563 (8.9)	0.00
Chronic kidney disease	3619 (4.8)	1028 (2.7)	0.11	1694 (2.9)	829 (2.9)	0.00
Alcohol-related disorders	3320 (4.4)	1713 (4.4)	0.00	2569 (4.4)	1302 (4.5)	0.01
Chronic liver disease	2189 (2.9)	1255 (3.2)	0.02	1771 (3.0)	896 (3.1)	0.01
Acute pancreatitis	1196 (1.6)	702 (1.8)	0.02	927 (1.6)	455 (1.6)	0.00
Gastrointestinal cancer	1749 (2.3)	585 (1.5)	0.06	1081 (1.8)	512 (1.8)	0.00
Non-gastrointestinal cancer	6712 (8.9)	2684 (6.9)	0.07	4726 (8.0)	2335 (8.1)	0.00
Inflammatory bowel disease	1268 (1.7)	736 (1.9)	0.02	1016 (1.7)	490 (1.7)	0.00
Diverticular disease	3580 (4.8)	1665 (4.3)	0.02	2710 (4.6)	1368 (4.7)	0.01

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like-peptide-1 receptor agonist; IPTW, inverse probability of treatment weight; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drugs; SGLT2, sodium-glucose co-transporter-2; SMD, standardized mean difference.

TABLE 2 Risk of splanchnic vein thrombosis among dipeptidyl peptidase-4 inhibitor initiators compared to GLP-1RA/SGLT2 inhibitor initiators with up to 5 years of follow-up before and after inverse probability of treatment weighting

	Crude estimates		Weighted estimates [a]	
	DPP-4 inhibitors	GLP-1RAs/SGLT2 inhibitors	DPP-4 inhibitors	GLP-1RAs/SGLT2 inhibitors
Individuals	75 042	38 718	58 996	28 944
Splanchnic vein thrombosis events	58	20	39	17
Follow-up, person-years	265 553	119 592	192 546	95 919
Incidence rate (CI) per 1000	0.22 (0.17–0.28)	0.17 (0.11–0.26)	0.20 (0.15–0.28)	0.17 (0.10–0.33)
Incidence rate difference (CI) per 1000	0.05 (−0.04–0.14)	ref.	0.03 (−0.07–0.14)	ref.
Hazard ratio (CI)	1.29 (0.78–2.15)	ref.	1.18 (0.62–2.26)	ref.
NNTH, estimate (worst case) [b]	19 540 (6967)	ref.	32 460 (7380)	ref.

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like-peptide-1 receptor agonist; NNTH, number needed to treat to harm; SGLT2, sodium-glucose co-transporter-2.

[a]Adjusted estimates obtained in an inverse probability of treatment weighted (IPTW) pseudopopulation using stabilized weights and trimming at the 2.5th and 97.5th percentile.

[b]Estimates of NNTH are based on "number of person-years" exposed, thus corresponding to the number of person-years exposed to DPP-4 inhibitors required to lead to one excess splanchnic vein thrombosis outcome. The estimate is based on the point estimate for the incidence rate difference, while the "worst case" estimate is based on the upper limit of the 95% CI for the incidence rate difference.

characteristics across age, sex and clinical characteristics (Table 1), with a mean weight of 1.0 and a maximum weight of 3.1, indicating an acceptable distribution of weights. After weighting (Table 2), we obtained an HR of 1.18 (95% CI 0.62 to 2.26) and an incidence rate difference of 0.03/1000 person-years (95% CI −0.07 to 0.14) corresponding to an $NNTH_{1\ year}$ of 32 460 (95% CI 7380 to ∞). There was no evidence of a departure from the proportional hazards assumption ($P = 0.42$).

There was no evidence of any cumulative dose–response effects (Table S1). Similar estimates were obtained in individual comparison with GLP-1RAs (HR 1.12, 95% CI 0.51–2.45; Table S2) and SGLT2 inhibitors (HR 1.01, 95% CI 0.37 to 2.76; Table S3). The per-protocol analysis yielded slightly stronger associations compared with the main analysis (HR 1.84, 95% CI 0.76 to 4.48; Table S4). An estimate similar to the main analysis was obtained when excluding users of oral anticoagulants (HR 1.31, 95% CI 0.68 to 2.54; Table S5). A slight inverse association was observed for DPP-4 inhibitor initiation and risk of typical (non-splanchnic) venous thromboembolism (HR 0.84, 95% CI 0.74–0.96; Table S6). The remaining supplementary analyses yielded results similar to those of the main analysis (Table S7–S15).

4 | DISCUSSION

In this nationwide cohort study, DPP-4 inhibitor use was not associated with risk of splanchnic vein thrombosis compared to use of SGLT2 inhibitors and GLP-1RAs. This null finding was consistent across a wide range of supplementary analyses.

The main strengths of the present analysis were the nationwide capture of all DPP-4 inhibitor users and their splanchnic vein thrombosis events over an 11-year period, and the use of relevant active comparators. Another important strength was the extensive analyses, ensuring that we did not overlook an association because of unfortunate analytical choices.

The study also has several limitations. First, the low number of splanchnic vein thrombosis events prohibited detailed subgroup analyses. Importantly, however, the low number of events is part of our finding of a null association and provides sufficient statistical power to evaluate whether there is evidence of an important risk increase with use of DPP-4 inhibitors. Second, gastrointestinal side effects from use of the comparator drug might lead to detection of subclinical portal vein thrombosis and thus surveillance bias for the comparator, leading to a spurious null result for DPP-4 inhibitors. While of particular concern for GLP-1RA users due to higher rates of gastrointestinal side-effects, direct comparison of DPP-4 inibitor users with SGLT2 inhibitor initiators did not suggest increased risks either. Third, we had no data on glycated haemoglobin (HbA1c) levels. HbA1c level, however, is not associated with venous thromboembolism,[12] and when also using active comparators, the risk of confounding from diabetes severity is likely to be limited. Finally, the validity of splanchnic vein thrombosis codes in our data is unknown.

The recent analysis based on the WHO's Vigibase[2] reported increased proportional reporting ratios for venous thromboembolic events, in particular, splanchnic vein thrombosis. However, studies based on spontaneous adverse drug event reports should generally be considered as hypothesis-generating only[4] and we failed to replicate this signal in a large comparative observational study. Importantly, there is no known biological mechanism that supports a link between DPP-4 inhibitor use and splanchnic vein thrombosis risk. Even assuming a true excess risk corresponding to the upper limit of the 95% CI obtained in the present study, the corresponding absolute risk will be negligible, as reflected in the low incidence rate differences reported. As such, we can confidently rule out a major risk at the level of the individual patient.

CONFLICTS OF INTEREST

A.P. and J.H. report participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma, all with funds paid to the institution where they are employed (no personal fees) and with no relation to the work reported in this paper. L.C.L. reports participation in research projects funded by Menarini Pharmaceutical and LEO Pharma, with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper. L.F., M.H., D.P.H. and K.B.K. report no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14253.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Danish Health Data Authority. Restrictions apply to the availability of these data, which were used under license for this study.

ORCID

Anton Pottegård https://orcid.org/0000-0001-9314-5679

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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