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Effect of Glucagon-like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors on Colorectal Cancer Incidence and Its Precursors

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Abstract

Aims—Incretin-based antihyperglycemic therapies increase intestinal mucosal expansion and polyp growth in mouse models. We aimed to evaluate the effect of dipeptidyl peptidase-4 inhibitors (DPP-4i) or glucagon-like peptide-1 receptor agonists (GLP-1ra) initiation on colorectal cancer incidence.

Methods—We conducted a cohort study on *US* Medicare beneficiaries over age 66 from 2007-2013 without prevalent cancer. We identified three active-comparator and new-user cohorts: DPP-4i versus thiazolidinediones (TZD), DPP-4i versus sulphonylureas (SU), and GLP-1ra versus long acting insulin (LAI). Follow-up started from six months post second prescription and ended six months after stopping (primary as-treated analysis). We estimated hazard ratios (HR) and 95%

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Authors' contributions

P.T.H. participated in the study conception and design, the acquisition, analysis and interpretation of the data and wrote the first draft of the manuscript. P.T.H. is the guarantor of this work, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

J.B. participated in study conception and design, and the acquisition, analysis and interpretation of the data. J.B. also participated in writing the first draft of the manuscript, reviewed and provided comments on the manuscript.

M.G. participated in study conception and design, and the acquisition, analysis and interpretation of the data. M.G. reviewed and provided comments on the manuscript.

M.M. participated in study conception and design, and the acquisition, analysis and interpretation of the data. M.G. reviewed and provided comments on the manuscript.

V.P. participated in the acquisition, analysis and interpretation of the data. V.P. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

T.S. participated in study conception and design, and the acquisition, analysis and interpretation of the data. T.S. also participated in writing the first draft of the manuscript, reviewed and provided comments on the manuscript.

Compliance with Ethical Standards

This retrospective large database study was approved by the University of North Carolina at Chapel Hill Institutional Review Board. For this type of study formal consent is not required.

This research has not been previously presented nor posted

confidence intervals (CI) for incident colorectal cancer adjusting for measured confounders using propensity score weighting.

Results—The median duration of treatment ranged 0.7-0.9 years among DPP-4i cohorts. Based on 104 events among 39,334 DPP-4i and 63 events among 25,786 TZD initiators, there was no association between DPP-4i initiation and colorectal cancer (adjusted HR=1.17 (CI: 0.88, 1.71)). There were 73 events among 27,047 DPP-4i and 266 events among 76,012 SU initiators with the adjusted HR: 0.98 (CI: 0.74, 1.30). We identified 5,600 GLP-1ra and 54,767 LAI initiators and the median duration of treatment was 0.8 and 1.2 years, respectively. The adjusted HR was 0.82 (CI: 0.42, 1.58) based on <11 events among GLP-1ra versus 276 events among LAI initiators.

Conclusion—Although limited by the short duration of treatment, our analyses based on real world drug utilization patterns provide evidence of no short-term effect of incretin-based agents on colorectal cancer.

Keywords

comparative effectiveness research; Dipeptidyl peptidase-4 inhibitors; glucagon-like peptide-1 receptor agonists; colorectal cancer; pharmacoepidemiology; cohort study

Introduction

Incretin-based therapies, glucagon-like peptide-1 receptor agonists (GLP-1ra) and dipeptidyl peptidase-4 inhibitors (DPP-4i), are commonly used second line therapies in the management of type 2 diabetes mellitus (DM) [1]. GLP-1ra are injected peptides, analogues or natural mimetics of human GLP-1, which enhance glycemic control by promoting glucose-dependent insulin secretion, suppressing fasting glucagon secretion, regulating gastric emptying and reducing appetite [2]. DPP-4 is the enzyme which degrades GLP-1 and as well as other biologically active peptides. Thus, DPP-4i exert their antihyperglycemic action by inhibiting this enzyme increasing endogenous incretin hormones levels [3].

GLP-1ra were first introduced in the United States in 2005. Exenatide was the first in class followed by liraglutide in 2010 and albiglutide and dulaglutide in 2015 [4]. They have been recommended because of their powerful efficacy, lack of intrinsic hypoglycemia as an adverse effect and associated weight loss; however, market penetration has been limited related to nausea, the need for injection, high cost and concerns about safety, particularly with regards to cancer and pancreatitis [1]. DPP-4i were approved in 2006. Sitagliptin was the first in class, followed by saxagliptin (2008), linagliptin (2011) and alogliptin (2012) [5]. The DPP-4i have been recommended related to reasonable efficacy, but excellent tolerability without nausea, weight-gain or hypoglycemia. Furthermore, large-scale cardiovascular outcome trials have been completed demonstrating no substantial safety concerns, particularly with market-leading sitagliptin [6-8].

GLP-1 receptor signaling has been found in genetically predisposed mice to stimulate intestinal mucosal expansion, increased polyp number and growth. In mouse studies exenatide was observed to increase small intestinal growth over 14-16 weeks after treatment and stimulated growth factor expression in colon polyps [9]. Currently there are no

population-based studies, which report the effect of incretin-based agents on the colorectal cancer incidence.

Methods

We registered the study protocol in the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) electronic register of studies. (http://www.encepp.eu/encepp/viewResource.htm?id=3411). Our study was approved by the University of North Carolina at Chapel Hill Institutional Review Board.

Study design

We conducted an active comparator, new user cohort study in a 20% random sample of U.S. Medicare beneficiaries 2007-2013 [10,11]. We identified three pairs of second line antihyperglycemic treatment initiators, who are likely to have similar stages of diabetes mellitus progression: DPP-4i versus TZD, DPP-4i versus SU, and GLP-1ra versus LAI [12]. These antihyperglycemic initiators were identified after requiring a twelve-month "drug free" period (six months for GLP-1ra versus LAI cohorts due to sample size) during which they could be treated with antihyperglycemic drugs other than the ones being compared (except for short-acting insulin for GLP-1ra versus LAI). All participants were required to have continuous enrollment in Medicare parts A, B, and D for twelve months (six months part D for GLP-1ra versus LAI) before the first prescription.

To increase the probability that patients actually took the dispensed medications, study participants were required to refill their prescription within the 30-day grace period (90 for injections) of the days' supply of the first prescription. The date of the second prescription was defined as the baseline. Patients with any prevalent cancer related diagnosis or procedure codes (except for non-melanoma skin cancer: see Online Resource Appendix Table S1) during the 12-month period prior to the first prescription and between the first and the second prescriptions were excluded. [13].

Outcome

The primary outcome of interest was colorectal cancer defined as at least two ICD-9 CM diagnosis codes of 153.X or 154.0 or 154.1 within two months. We required a second diagnosis code within two months after the first code to minimize the problem of rule-out diagnosis codes submitted as a part of surveillance and to maximize specificity [14]. We also included carcinoma-in-situ (230.3 and 230.4) and colorectal polyps or adenomas (45.42 and 48.36) in our outcome definition as secondary analyses.

Follow up and analyses

For our primary analysis we assumed a six-month lag period following second prescription to allow for an induction and latent period (delayed effect of the drug on cancer and preclinical phase) and excluded patients with incident colorectal cancer during this period [15]. We followed the remaining patients until switching, stopping or augmenting the drug (plus six-month lag time to allow for a latent period), the incidence of the outcome, any cancer (except non-melanoma skin cancer), all-cause mortality, end of enrollment in

Medicare Parts A and B, or December 31, 2013, whichever came first. We also performed an analysis in which patients were not censored when they stopped/switched/augmented therapy (first treatment carried forward).

Confounding control

Our first line of confounding control was by design comparing pairs of initiators of treatments recommended for similar stages of progression of type 2 diabetes [12,16]. Potential remaining confounders were assessed before the first drug prescription date. We estimated separate propensity scores (PS) for each treatment pair predicting the probability of initiating incretins versus the comparator based on potential confounders using multivariable logistic regression [17,18]. To implement confounding control, we then assigned a weight of 1 to patients in the incretin cohorts and a weight of the propensity odds (PS/(1-PS)) to active comparators (TZD, SU or LAI) [19]. This weighting allows us to estimate the unconfounded treatment effect in a population defined by the covariate distribution of patients initiating incretin drugs (assuming no unmeasured confounding). We then fitted PS weighted Cox proportional hazards models with a robust variance estimator and weighted Kaplan-Meier survival curves to estimate the effect of initiation of incretins on the time to colorectal cancer. We ran separate Cox models stratified by the duration of treatment to assess the estimates over time.

Assessment of potential bias

It is possible that patients initiating incretins are more likely to undergo diagnostic or screening procedures leading to earlier diagnosis of preclinical cancer, which could bias our results [20-22]. We checked for this potential differential detection by comparing the probability of having a colonoscopy in a year prior to and six months after the *baseline* prescription between our cohort pairs. We also excluded varying small proportions of patients in both tails of the PS including patients treated contrary to prediction (i.e., patients initiated on incretin drugs with the lowest PSs and patients treated with the comparator with the highest PSs) since it is plausible that some unmeasured characteristic made their physicians “override” the predicted treatment decision, which can lead to unmeasured confounding [23]. We varied the lag period prior to the start of follow up from six (primary analysis) to zero, twelve and twenty-four months to check the robustness of our assumptions. Other sensitivity analyses varying the censoring patterns are presented in Online Resource Appendix Tables S10 and S11.

Results

We present baseline characteristics of the patients initiating DPP-4i, TZDs, and SUs in Table 1. Compared with TZD initiators, DPP-4i initiators were slightly older, less likely to be men and more likely to be white. DPP-4i initiators were more likely to have major comorbidities and use statins, diuretics, angiotensin receptor blockers and beta blockers than TZD initiators. Among the DPP-4i (different from the above DPP-4i initiators) and SU initiators, DPP-4i initiators were less likely to be men, and had a higher prevalence of diabetic neuropathy, retinopathy, nephropathy, hypertension, and connective tissue disorders than SU initiators.

We present baseline characteristics of the patients initiating GLP-1ra and LAI in Table 2. GLP-1ra initiators were younger and generally healthier than LAI initiators with fewer major comorbidities. Both incretins (DPP-4i in both cohort pairs and GLP-1ra) were more likely to be on metformin, use preventive services such as lipid testing and flu vaccination, less likely to have hospital admissions and more likely to have outpatient visits. The magnitude and direction of the association of each covariate with the treatment choice between GLP-1ra and LAI as estimated in the PS model is presented in PS model parameters column in Table 2. Covariate differences between our cohort pairs were removed after the propensity score weighting. One thing of note is that both incretins were more likely to be prescribed after 2010 than comparators, and this trend was most pronounced for DPP-4i versus TZD.

In Table 3, we present the number of events, the duration of treatment, the crude and adjusted (weighted) hazard ratios with their 95% confidence intervals for the various cohorts and comparisons. For the primary as treated analyses, there were 104 colorectal cancer events among 39,334 DPP-4i initiators and 63 among 25,786 TZD initiators and the fully adjusted HR was 1.17 (95% CI: 0.88, 1.71). For the DPP4i and SU comparison, there were 73 colorectal cancer events among 27,047 DPP-4i initiators and 266 events among 76,012 SU initiators. The fully adjusted HR was 0.98 (95% CI: 0.74, 1.30). The number of colorectal cancer events in 5,600 GLP-1ra initiators was less than 11, the minimum cell size that our data use agreement with CMS allows us to publish. The fully adjusted HR for GLP-1ra initiators versus LAI initiators was 0.82 (95% CI: 0.42, 1.58). We present weighted Kaplan-Meier plots for all treatment comparisons in Figure 1. The median duration of treatment ranges from 0.7-1.2 years for as treated analyses and 2.0-3.3 years for first treatment carried forward analyses (where treatment changes were uncensored), both of which revealed similar results (Table 3).

Our secondary analyses examined the composite outcome of invasive and in-situ colorectal cancer and cancer precursors (polyps/adenomas) (Online Resource Appendix Table S4). The fully adjusted HR was 0.95 (95% CI: 0.74, 1.23) for DPP-4i versus TZD and 1.08 (95% CI: 0.90, 1.31) for DPP-4i versus SU. The fully adjusted HR for GLP-1ra versus LAI was 0.76 (95% CI: 0.48, 1.23).

Changing our assumption about induction and latent periods (to allow for a delayed effect of antihyperglycemic drugs on colorectal cancer and a preclinical phase) to 0, 12 and 24 months and stratifying the duration of treatment to assess the effects over time reveal consistent hazard ratios similar to our primary results (Online Resource Appendix Tables S5, S6, and Appendix Figures S1-S3). Assessment of potential detection bias also reveals similar proportions of colonoscopy between our cohorts. Other sensitivity analyses also suggested the robustness of our primary analyses (Online Resource Appendix Tables S7-S12).

Discussion

In this first population-based cohort study addressing the real world effects of incretins on colorectal cancer risk, we observed no short-term effect of DPP-4i and GLP-1a initiation on

the risk for colorectal cancer compared with initiation of alternative treatments indicated for similar stages of diabetes duration and severity. Like previous studies on antihyperglycemic treatments and cancer risk, our study was restricted to short-term use of incretins due to the real-world dynamics of antihyperglycemic treatments where only a small proportion of patients stay on the same drug class for prolonged periods of time [22]. This dynamic in treatments makes it very difficult to study long-term effects of treatments on cancer risk but also limits any potential public health impact on cancer risk.

To allow for some delay in the effect of the drug on late stage carcinogenesis [15], we allowed a six-month lag period before follow up and after censoring for treatment changes. Varying this lag period did not substantially change our results. Findings from first treatment carried forward analyses, which do not suffer from potential selection bias and provide a longer follow up time, also revealed similar estimates to our primary as treated analyses, suggesting that censoring of study participants due to drug changes is not informative with respect to colorectal cancer incidence.

A randomized controlled trial with three year follow up data on the sitagliptin versus placebo revealed similar finding to ours with the 0.3% colon cancer risk among sitagliptin initiators (21 cases among 7332 initiators) versus 0.5% risk among placebo (34 cases among 7339 initiators), which though numerically slightly protective, *was not statistically or clinically significant* over a similar period of duration of treatment [6].

The major strength of our study is the utilization of the active comparator new user cohort study design, which restricts the study population to initiators of therapies with similar indication [12,24]. By selecting guideline recommended active comparator drugs we tried to minimize unmeasured confounding by indication and frailty [12]. While we cannot precisely measure neither the indication nor frailty, we implicitly control for these by selecting an active comparator drug class that is a clinical alternative for the same degree of disease progression as the treatment of interest. This implicit control by study design is very different from the “usual” control for a covariate during the analysis phase because it does not rely on a good measure of the indication or frailty.

As a result of our study design, the distribution of most measured risk factors for colorectal cancer was similar between DPP-4i initiators and TZD/SU cohorts even before adjustment using propensity scores. GLP-1ra initiators on the other hand represented a generally healthier and younger group of new users more likely to undergo preventive health services compared to LAI initiators [25]. While LAI is not a perfect active comparator, it has the advantage of being an injectable drug, similar to GLP-1ra. After propensity score weighting these differences were removed and the HR for the GLP-1ra versus LAI increased substantially. Most of this confounding was due to the health care utilization, which was strongly related to the risk of colorectal cancer diagnosis in our data.

Our study has limitations. Since drug utilization was assessed from pharmacy claims data on dispensed prescriptions, it is possible that patients did not actually initiate the drugs. We attempted to minimize this problem by requiring a second prescription of the same drug class before entering the cohorts. The median duration between the first and second scripts

was 30 days for DPP-4i cohorts (44 days for GLP-1ra cohort) and we lost approximately 30% of each of our cohort pairs due to this requirement. Yet, the proportion of patients excluded was similar between incretins and their comparators, which minimizes the chance of selection bias (Online Resource Appendix Table S13).

While our study represents the real world pattern of drug utilization, our major limitation is the short duration of treatment and thus our findings should be interpreted cautiously. We observed consistent hazard ratios even 2 years after initiation but both the number of long-term users and events were small. To minimize the limitation due to short duration of treatment, we looked at the effect of anti-hyperglycemic drugs initiation on the colorectal cancer precursors (polyps, adenomas and in situ cases) and results were similar to our primary analyses. We could not distinguish between polyps and adenoma cases due to the absence of separate billing codes in the claims data. The small number of events in our study especially among the GLP-1ra initiators is another limitation of our study. Many GLP-1ra initiators were previously on short and long acting insulin and thus were excluded from our study. This exclusion is, however, necessary to avoid comparing patients not doing well on the established treatment, most likely to be switched to the newest treatment on the market [24-27].

A final limitation of our study is that we could not adequately control for smoking, alcohol consumption, and body mass index (BMI), all risk factors for colorectal cancer [28-33]. We need to point out that while many of these are related to diabetes control and would likely confound any comparison of treated with untreated patients, our active comparator new user design limits confounding by these variables to the extent that these would influence the choice between two guideline recommended treatment alternatives. In addition, we adjusted chronic obstructive pulmonary disease as a proxy for smoking and major comorbid conditions related to obesity to partially account for confounding by these unmeasured factors [34].

In summary, we found evidence for no effect of real world patterns of treatment with incretin-based antihyperglycemic drugs (DPP-4i and GLP-1ra) on the short-term risk for colorectal cancer. Although our study is limited by a short median duration of treatment, our findings currently offer the best available evidence based on real world patterns of these treatments and thus should help clinicians make decisions about the relative benefit harm balance of these treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Conflict of Interest statement:

TS receives investigator-initiated research funding and support as Principal Investigator (R01 AG023178) from the National Institute on Aging (NIA), and as Co-Investigator (R01 CA174453; R01 HL118255, R21-HD080214), National Institutes of Health (NIH). He also receives salary support as Director of the Comparative Effectiveness Research (CER) Strategic Initiative, NC Translational and Clinical Sciences (TraCS) Institute, UNC Clinical and Translational Science Award (UL1TR001111) and as Director of the Center for Pharmacoepidemiology (current

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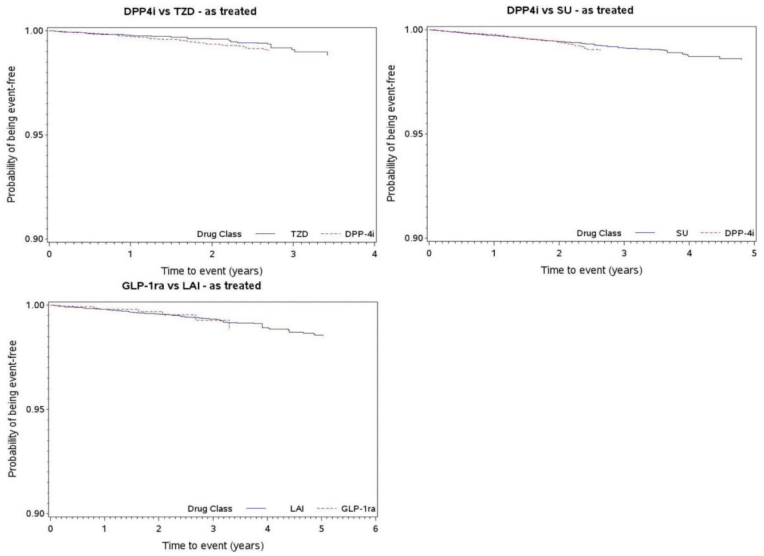

Fig 1.

Propensity score weighted Kaplan-Meier plots of time to colorectal cancer between dipeptidyl peptidase-4 inhibitors (DPP-4i) versus thiazolidinediones (TZD) or sulphonylureas (SU) initiators, and glucagon-like peptide-1 receptor agonists (GLP-1ra) versus long acting insulin (LAI) initiators from 2007-2013 Medicare data[a]

[a] Initiation or new use defined as dispensing at least 2 prescriptions within 30 days (90 days for GLP-1ra) after the days' supply of the first prescription, after 12 months drug free period (6 months for GLP-1ra). Primary as treated analyses with 6 months lag period, in which follow-up started from 6 months after the date of the second prescription until the event or the earliest of any non-colorectal incident cancer (except non-melanoma skin cancer), discontinuation, switching or augmentation with the comparator drug, death, end of enrollment or Dec 31st, 2013. Propensity score weighting is accomplished by standardized morbidity ratio weighting in which a weight of 1 given to DPP-4i or GLP-1ra users and the propensity odds to TZD, SU or LAI users. This weighting balances the covariate distributions between comparator cohorts at baseline, controlling for measured confounders in Tables 1 and 2.

Eur J Clin Pharmacol. Author manuscript; available in PMC 2017 August 01.

Table 1

Distribution of selected baseline characteristics among initiators of dipeptidyl peptidase-4 inhibitors (DPP-4i) versus thiazolidinediones (TZD) and sulphonylureas (SU)[a]

	DPP-4i versus TZD cohort					DPP-4i versus SU cohort				
	DPP-4i[b]		TZD		SMR weighted TZD[c]	DPP-4i[b]		SU		SMR weighted SU[d]
	N 46,720	%	N 28,099	%	%	N 31,527	%	N 87,048	%	%
Age Mean (S.D.)	75.9 (7.4)		74.3 (7.2)		75.8 (9.5)	75.5 (7.2)		75.4 (7.7)		75.5 (4.4)
66 - 70 years	13,591	29.1	10,637	37.9	29.3	9,545	30.3	28,667	32.9	30.5
71 - 75 years	11,986	25.7	6,958	24.8	25.3	8,258	26.2	20,763	23.9	26.2
76 - 80 years	8,822	18.9	4,877	17.4	19.0	6,048	19.2	15,224	17.5	18.9
81 - 85 years	6,529	14.0	3,175	11.3	14.2	4,192	13.3	11,552	13.3	13.4
≥86 years	5,792	12.4	2,452	8.7	12.2	3,484	11.1	10,842	12.5	1.0
Sex										
Male	17,089	36.6	11,496	40.9	36.8	11,571	36.7	34,811	40.0	36.5
Race										
White	34,499	73.8	19,745	70.3	74.7	22,535	71.5	66,084	75.9	71.5
Black	5,290	11.3	3,621	12.9	10.7	3,548	11.3	11,269	12.9	11.3
Other races	6,931	14.8	4,733	16.8	14.7	5,444	17.3	9,695	11.1	17.2
Year of initiation										
2008	4,674	10.0	7,217	25.7	10.0	3,433	10.9	14,704	16.9	10.9
2009	5,581	11.9	7,650	27.2	12.0	3,662	11.6	16,459	18.9	11.6
2010	6,609	14.1	5,998	21.3	14.2	4,502	14.3	15,296	17.6	14.3
2011	9,365	20.0	3,575	12.7	19.9	6,845	21.7	14,379	16.5	21.5
2012	10,586	22.7	1,856	6.6	22.0	7,249	23.0	13,309	15.3	22.9
2013	9,905	21.2	1,803	6.4	21.9	5,836	18.5	12,901	14.8	18.8
Comorbid conditions [e]										
Diabetic neuropathy	10,145	21.7	4,705	16.7	22.4	6,555	20.8	13,279	15.3	21.0

	DPP-4i versus TZD cohort					DPP-4i versus SU cohort				
	DPP-4i[b]		TZD		SMR weighted TZD[c]	DPP-4i[b]		SU		SMR weighted SU[d]
	N 46,720	%	N 28,099	%	%	N 31,527	%	N 87,048	%	%
Diabetic nephropathy	4,526	9.7	2,087	7.4	9.9	2,722	8.6	5,890	6.8	8.8
Diabetic retinopathy	7,657	16.4	4,141	14.7	16.6	4,969	15.8	9,971	11.5	16.0
Congestive heart failure	11,676	25.0	4,503	16.0	25.1	7,366	23.4	20,160	23.2	23.6
Myocardial infarction	1,116	2.4	354	1.3	2.6	663	2.1	2,259	2.6	2.1
Chronic obstructive pulmonary disease	9,693	20.7	4,650	16.5	20.8	6,553	20.8	18,155	20.9	20.7
Chronic kidney disease	14,658	31.4	6,673	23.7	31.4	9,024	28.6	24,032	27.6	28.9
Connective tissue disease	15,231	32.6	7,316	26.0	32.7	10,547	33.5	24,411	28.0	33.5
Depression	8,102	17.3	3,870	13.8	17.4	5,506	17.5	14,288	16.4	17.6
Co-medications [f]										
Metformin	31,674	67.8	17,799	63.3	68.0	21,169	67.1	49,240	56.6	67.7
GLP-1 agonists	825	1.8	483	1.7	2.5	544	1.7	1,101	1.3	1.8
Short acting Insulin	4,414	9.4	2,286	8.1	10.0	3,196	10.1	6,871	7.9	10.3
Long acting insulin	8,500	18.2	4,590	16.3	17.9	6,349	20.1	12,018	13.8	20.7
Thiazolidinediones						8,145	25.8	13,098	15.0	25.9
Sulfonylureas	22,767	48.7	13,498	48.0	50.0					
Angiotensin converting enzyme inhibitors	22,924	49.1	14,364	51.1	48.7	14,446	45.8	43,096	49.5	45.8
Angiotensin receptor blockers	14,884	31.9	7,260	25.8	32.5	10,754	34.1	20,054	23.0	34.3
Statins	33,286	71.2	18,232	64.9	71.3	22,479	71.3	54,254	62.3	71.4

	DPP-4i versus TZD cohort					DPP-4i versus SU cohort				
	DPP-4i[b]		TZD		SMR weighted TZD[c]	DPP-4i[b]		SU		SMR weighted SU[d]
	N 46,720	%	N 28,099	%	%	N 31,527	%	N 87,048	%	%
Loop diuretics	14,052	30.1	6,136	21.8	30.9	8,818	28.0	25,311	29.1	28.1
Other diuretics	18,793	40.2	10,724	38.2	40.6	12,705	40.3	33,295	38.2	40.3
Beta blockers	26,042	55.7	12,878	45.8	56.2	16,472	52.2	44,478	51.1	52.3
Calcium channel blockers	18,050	38.6	9,579	34.1	38.1	11,684	37.1	30,556	35.1	36.9
Health service utilization [e]										
Colonoscopy	3,879	8.3	2,029	7.2	8.3	2,659	8.4	6,528	7.5	8.5
Fecal for Occult Blood	3,837	8.2	2,066	7.4	8.1	2,723	8.6	6,208	7.1	8.7
Lipid tests										
0	8,529	18.3	7,471	26.6	17.5	5,766	18.3	25,257	29.0	18.2
1	13,615	29.1	8,099	28.8	29.1	9,099	28.9	26,565	30.5	28.8
2	12,377	26.5	6,532	23.2	26.7	8,329	26.4	19,661	22.6	26.5
>=3	12,199	26.1	5,997	21.3	26.7	8,333	26.4	15,565	17.9	26.5
Flu vaccination	24,609	52.7	12,632	45.0	53.5	16,414	52.1	40,827	46.9	51.9
Hospital admissions										
0	25,885	55.4	12,347	43.9	55.3	17,907	56.8	42,003	48.3	56.8
1	6,678	14.3	4,660	16.6	14.3	4,549	14.4	13,346	15.3	14.4
2 or 3	6,994	15.0	5,171	18.4	15.4	4,628	14.7	14,927	17.1	14.7
4-6	3,994	8.5	3,291	11.7	8.4	2,492	7.9	9,302	10.7	7.9
>6	3,169	6.8	2,630	9.4	6.6	1,951	6.2	7,470	8.6	6.3
Outpatient visits										
0	3,157	6.8	3,563	12.7	6.6	2,110	6.7	10,689	12.3	6.7
1	1,834	3.9	1,901	6.8	3.8	1,325	4.2	6,157	7.1	4.2
2 or 3	4,406	9.4	3,409	12.1	9.1	3,063	9.7	11,116	12.8	9.7
4-6	9,129	19.5	5,903	21.0	19.3	6,294	20.0	18,041	20.7	19.9
>6	28,194	60.3	13,323	47.4	61.3	18,735	59.4	41,045	47.2	59.5

Eur J Clin Pharmacol. Author manuscript; available in PMC 2017 August 01.

	DPP-4i versus TZD cohort					DPP-4i versus SU cohort				
	DPP-4i[b]		TZD		SMR weighted TZD[c]	DPP-4i[b]		SU		SMR weighted SU[d]
	N 46,720	%	N 28,099	%	%	N 31,527	%	N 87,048	%	%
Emergency room visits										
0	28,549	61.1	19,264	68.6	61.7	20,009	63.5	52,747	60.6	63.3
1	8,929	19.1	4,726	16.8	19.1	5,787	18.4	16,990	19.5	18.3
>=2	9,242	19.8	4,109	14.6	19.2	5,731	18.2	17,311	19.9	18.4

SMR, standardized morbidity ratio (weight of 1 given to DPP-4i users and PS/(1-PS) to TZD or SU users, where PS stands for propensity score); s.d., standard deviation.

[a] Initiation or new use defined as dispensing at least 2 prescriptions within 30 days after the days' supply of the first prescription, after 12 months drug free period.

[b] In the DPP-4i versus TZD cohort pair, patients were allowed to be on antihyperglycemic drugs other than DPP-4i and TZD during the washout period. Similarly, in the DPP-4i versus SU cohort pair, patients could be on antihyperglycemic drugs other than DPP-4i and SU during the washout.

[c] Pseudo-population of TZD initiators weighted to the distribution of covariates of the DPP-4i initiators using the propensity score to balance covariates (and therefore control for confounding).

[d] Pseudo-population of SU initiators weighted to the distribution of covariates of the DPP-4i initiators using the propensity score to balance covariates (and therefore control for confounding).

[e] Measured in the 12 months before drug initiation (the date of the first prescription).

[f] Measured in the 6 months before drug initiation (the date of the first prescription)

Table 2

Distribution of selected baseline characteristics in initiators of glucagon-like peptide-1 receptor agonists (GLP-1ra) versus long acting insulin (LAI) initiators[a]

	GLP-1ra		LAI		PS model parameters[b]		SMR weighted LAI[d]
	N 6,594	%	N 63,909	%	OR[c]	95% CI	%
Age (years), mean (S.D.)	71.8 (5.0)		74.5 (7.7)				71.8 (1.7)
66 - 70	3,264	49.5	25,168	39.4	1.00	(reference)	49.5
71 - 75	1,990	30.2	14,125	22.1	0.80	(0.75, 0.86)	30.3
76 - 80	887	13.5	10,237	16.0	0.55	(0.51, 0.60)	13.4
81 - 85	326	4.9	7,580	11.9	0.33	(0.30, 0.38)	4.9
≥86 years	127	1.9	6,799	10.6	0.19	(0.15, 0.22)	1.9
Sex							
Male	2,650	40.2	25,666	40.2	0.85	(0.81, 0.90)	40.3
Race							
White	5,764	87.4	47,112	73.7	1.00	(reference)	87.5
Black	399	6.1	9,535	14.9	0.42	(0.37, 0.47)	6.0
Other races	431	6.5	7,262	11.4	0.42	(0.38, 0.47)	6.5
Year of initiation							
2007	255	3.9	2,420	3.8	1.01	(0.87, 1.18)	3.9
2008	965	14.6	10,683	16.7	1.00	(reference)	14.5
2009	625	9.5	10,306	16.1	0.63	(0.57, 0.70)	9.4
2010	774	11.7	9,771	15.3	0.77	(0.70, 0.86)	11.6
2011	1,073	16.3	10,238	16.0	0.94	(0.85, 1.04)	16.3
2012	1,403	21.3	10,783	16.9	1.07	(0.97, 1.18)	21.2
2013	1,499	22.7	9,708	15.2	1.27	(1.15, 1.40)	23.1
Comorbid conditions[e]							
Diabetic neuropathy	1,375	20.9	14,202	22.2	0.97	(0.91, 1.04)	20.8
Diabetic nephropathy	511	7.7	7,605	11.9	0.91	(0.81, 1.03)	7.7
Diabetic retinopathy	1,007	15.3	10,928	17.1	0.77	(0.71, 0.83)	15.3
Congestive heart failure	978	14.8	18,244	28.5	0.86	(0.79, 0.93)	14.8
Myocardial infarction	56	0.8	2,152	3.4	0.62	(0.47, 0.82)	0.9
Chronic obstructive pulmonary disease	1,019	15.5	14,543	22.8	0.90	(0.83, 0.98)	15.6
Chronic kidney disease	1,489	22.6	22,847	35.7	0.76	(0.70, 0.82)	22.4
Connective tissue disease	2,100	31.8	17,595	27.5	1.25	(1.17, 1.33)	32.1
Depression	875	13.3	11,072	17.3	0.91	(0.84, 0.99)	13.3
Co-medications[f]							
Metformin	4,779	72.5	32,905	51.5	1.47	(1.38, 1.57)	73.0
Thiazolidinediones	2,020	30.6	13,708	21.4	1.40	(1.31, 1.49)	31.4

	GLP-1ra		LAI		PS model parameters[b]		SMR weighted LAI [d]
	N 6,594	%	N 63,909	%	OR [c]	95% CI	%
Sulfonylureas	3,657	55.5	33,714	52.8	0.74	(0.69, 0.78)	56.5
Angiotensin converting enzyme inhibitors	3,150	47.8	31,448	49.2	0.88	(0.82, 0.93)	47.6
Angiotensin receptor blockers	2,229	33.8	15,027	23.5	1.38	(1.29, 1.48)	34.2
Statins	4,758	72.2	39,629	62.0	1.15	(1.07, 1.22)	72.3
Loop diuretics	1,666	25.3	22,512	35.2	1.00	(0.94, 1.08)	25.3
Other diuretics	2,882	43.7	22,652	35.4	1.16	(1.09, 1.23)	43.9
Beta blockers	3,132	47.5	33,294	52.1	0.91	(0.85, 0.95)	47.5
Calcium channel blockers	2,101	31.9	22,502	35.2	0.94	(0.89, 1.00)	31.9
Health service utilization [e]							
Colonoscopy	666	10.1	4,555	7.1	1.15	(1.05, 1.27)	10.3
Fecal for Occult Blood	567	8.6	3,945	6.2	1.12	(1.01, 1.23)	8.7
Lipid tests							
0	1,039	15.8	21,885	34.2	1.00	(reference)	15.6
1	1,874	28.4	18,059	28.3	1.43	(1.30, 1.56)	28.3
2	1,795	27.2	12,713	19.9	1.69	(1.54, 1.86)	27.3
>=3	1,886	28.6	11,252	17.6	1.92	(1.74,2.11)	28.9
Flu vaccination	3,654	55.4	27,962	43.8	1.18	(1.11, 1.25)	55.5
Hospital admissions							
0	4,178	63.4	26,730	41.8	1.00	(reference)	63.7
1	967	14.7	9,605	15.0	0.82	(0.75, 0.88)	14.7
2 or 3	778	11.8	11,809	18.5	0.62	(0.57, 0.67)	11.6
4-6	421	6.4	8,208	12.8	0.57	(0.51, 0.64)	6.3
>6	250	3.8	7,557	11.8	0.43	(0.37, 0.49)	3.7
Outpatient visits							
0	339	5.1	9,697	15.2	0.49	(0.41, 0.58)	5.1
1	241	3.7	4,787	7.5	0.69	(0.58, 0.81)	3.6
2 or 3	538	8.2	6,749	10.6	1.00	(reference)	8.0
4-6	1,281	19.4	11,028	17.3	1.21	(1.09, 1.36)	19.2
>6	4,195	63.6	31,648	49.5	1.55	(1.39, 1.72)	64.1
Emergency room visits							
0	4,962	75.3	35,477	55.5	1.00	(reference)	75.5
1	1,042	15.8	13,151	20.6	0.67	(0.62, 0.72)	15.7
>=2	590	8.9	15,281	23.9	0.44	(0.40, 0.49)	8.9

PS, propensity scores; OR, odds ratio; CI, confidence intervals; SMR, standardized morbidity ratio (weight of 1 given to GLP-1ra users and PS/(1-PS) to LAI users, where PS stands for propensity score); s.d., standard deviation.

[a] Initiation or new use defined as dispensing at least 2 prescriptions within 90 days after the days' supply of the first prescription, after 6 months drug free period.

[b] Association between each covariate and the initiation of GLP-1ra versus initiation of LAI as estimated from the propensity score model; odds ratios from multivariable logistic regression model; odds ratios >1.0 indicate more likely to be initiated on GLP-1ra than LAI.

[c] Age is defined as the linear plus quadratic term in the propensity score estimation model but the odds ratios for individual age groups are displayed here for easy interpretation.

[d] Pseudo-population of LAI initiators weighted to the distribution of covariates of the GLP-1ra initiators using the propensity score to balance covariates (and therefore control for confounding).

[e] Measured in the 12 months before drug initiation (the date of the first prescription).

[f] Measured in the 6 months before drug initiation (the date of the first prescription).

Table 3

Effects of the initiation[a] of dipeptidyl-peptidase-4 inhibitors (DPP-4i) vs thiazolidinediones (TZD)/ sulphonylureas (SU) and glucagon-like peptide-1 receptor agonists (GLP-1ra] vs long acting insulin (LAI) on colorectal cancer incidence (invasive only) from 2007-2013 Medicare data

Cohort	Drugs	Total new users [a]	Events	Median duration of treatment (IQR)	Incident rates [per 100,000 person years]	Unadjusted HR [95% CI] [b]	Age, race, and sex adjusted HR [95% CI] [c]	SMR weighted HR [95%CI] [d]
As treated analyses with 6 months lag period								
DPP-4i vs TZD	DPP-4i[e]	39,334	104	0.8 (0.4, 1.6)	277.9	1.11 (0.81, 1.51)	1.04 (0.75, 1.44)	1.17 (0.88, 1.71)
	TZD	25,786	63	0.7 (0.3, 1.4)	251.9	1.00 (reference)	1.00 (reference)	1.00 (reference)
DPP-4i vs SU	DPP-4i[e]	27,047	73	0.8 (0.4, 1.5)	285.0	0.92 (0.71, 1.19)	0.97 (0.75, 1.26)	0.98 (0.74, 1.30)
	SU	76,012	266	0.9 (0.4, 1.8)	310.9	1.00 (reference)	1.00 (reference)	1.00 (reference)
GLP-1ra vs LAI	GLP-1ra	5,600	NR[f]	0.8 (0.5, 1.5)	182.4	0.51 (0.27, 0.96)	0.53 (0.28, 1.01)	0.82 (0.42, 1.58)
	LAI	54,767	276	1.2 (0.6, 2.3)	359.4	1.00 (reference)	1.00 (reference)	1.00 (reference)
First treatment carried forward analyses with 6 months lag period								
DPP-4i vs TZD	DPP-4i	39,333	218	2.0 (1.2, 3.3)	299.6	1.06 (0.87, 1.28)	1.03 (0.84, 1.25)	1.05 (0.83, 1.32)
	TZD	25,785	198	3.3 (2.0, 4.5)	280.6	1.00 (reference)	1.00 (reference)	1.00 (reference)
DPP-4i vs SU	DPP-4i	27,047	173	2.1 (1.3, 3.3)	336.4	1.10 (0.92, 1.31)	1.15 (0.96, 1.36)	1.19 (0.99, 1.44)
	SU	76,010	508	2.5 (1.4, 3.9)	305.3	1.00 (reference)	1.00 (reference)	1.00 (reference)
GLP-1ra vs LAI	GLP-1ra	5,600	23	2.2 (1.2, 3.8)	192.2	0.52 (0.34, 0.80)	0.54 (0.35, 0.82)	0.75 (0.48, 1.16)
	LAI	54,765	426	2.3 (1.3, 3.8)	366.8	1.00 (reference)	1.00 (reference)	1.00 (reference)

IQR, interquartile range; HR, hazard ratios; CI, confidence interval; SMR, standardized morbidity ratio (weight of 1 given to DPP-4i or GLP-1ra users and PS/(1-PS) to TZD, SU or LAI users, where PS stands for propensity score); NR, not reported.

[a] Initiation or new use defined as dispensing at least 2 prescriptions within 30 days (90 days for GLP-1ra) after the days' supply of the first prescription, after 12 months drug free period (6 months for GLP-1ra). Note that the number of new users presented here represent the cohort to which the lag period of 6 months has been applied.

[b] Hazard ratios and 95% confidence intervals from Cox proportional hazards model for colorectal cancer with baseline treatment as the only independent variable.

[c] Age is included as linear and quadratic terms.

[d] Hazard ratios and 95% confidence intervals from propensity-score weighted Cox proportional hazards model (standardized to DPP-4i or GLP-1ra population). Variables used in SMR weighting include demographics (age, age-square, race, sex), comorbidities (such as connective tissue disorder, congestive heart failure, chronic obstructive pulmonary disease, myocardial infarction, depression, gastrointestinal diseases, diabetes mellitus, hypertension, diabetes complications), co-medications (antihypertensives, oral antihyperglycemic drugs, statin, NSAIDs, aspirin, tobacco smoking, alcohol), indicators of health system utilization (number of hospital admissions, emergency department visits, outpatient visits, fecal for occult blood testing, colonoscopy, lipid test, flu shots).

[e] Number of people initiating DPP-4i treatment different in both cohorts because in the DPP-4i versus TZD cohort pair, patients were allowed to be on anti-hyperglycemic drugs other than DPP-4i and TZD during the washout period. Similarly, in the DPP-4i versus SU cohort pair, patients could be on anti-hyperglycemic drugs other than DPP-4i and SU during the washout.

[f] Not reported due to small cell size according to data use agreement with the Center for Medicare and Medicaid Services.

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