Effect of Incretin Analogues and Dipeptidyl-peptidase-IV inhibitors on colorectal cancer risk

Investigators – Phyo Htoo, Til Sturmer, Mugdha Gokhale, Virginia Pate, Jennifer Lund, John Buse

University of North Carolina at Chapel Hill

Background

Incretin analogs (GLP-1 agonists) and Dipeptidyl-peptidase-IV (DPP-IV) inhibitors are second-line oral antidiabetic drugs used in type II Diabetes Mellitus (DM). GLP-1 agonists are analogues to incretin hormones, which promote glucose dependent insulin secretion, suppress glucagon secretion and delay gastric emptying. DPP-IV is the enzyme which degrades incretin hormones and DPP-IV inhibitors inhibit this enzyme thereby increasing incretin hormones action.

GLP-1 receptor signaling has been found in genetic mice to stimulate small and large intestinal mucosal expansion, increase polyp number and growth. GLP-1 agonists such as exenatide were found to stimulate growth factor expression in colon polyps and thus play a role in tumorigenesis (Koehler et al., 2015). Currently there are no population-based studies which report the effect of incretin agents on the colorectal cancer incidence.

Objective

Primary objective is to examine the comparative effect of incretin agents (GLP-1 agonists or DPP-IV agonists) versus other second-line anti-diabetic drugs on the colorectal cancer incidence.

Study Design

We will utilize a new user active comparator, cohort study design to identify new users of GLP-1 agonists or DPP-IV agonists, and new users of other oral anti-diabetic drugs (detailed below in 'Exposure groups' section) after 6 months washout period. Utilization of new users of anti-diabetic drugs has an advantage over prevalent users who are more likely to have a different risk factor profile than those who recently initiate drugs. Active comparator drugs selected to be guideline recommended treatment alternatives for GLP-1 and DDP-IV help reduce the potential for confounding by indication, since DM is a known risk factor for colorectal cancer.

Study population/ Inclusion criteria

Our study population consists of 66 years and older Medicare fee-for-service beneficiaries (20% random sample) who were enrolled in Medicare Part A, B, and D plans for at least one calendar month during 2007-2012. For those meeting these criteria in 2007, we also have access to Medicare parts A, B data from 2006.

New initiators of one of the following classes of medications:

- GLP-1ra (exenatide, liraglutide),

- DPP-4i (sitagliptin, saxagliptin) [note: linagliptin and alogliptin not available until after 2010]
- Thiazolidinediones (pioglitazone, rosiglitazone)
- Sulfonylureas (glyburide, glipizide, glimipiride)
- Long acting insulin (premixed, NPH, glargine, detemir).

New users are defined as those who initiate drugs of interest or their active comparator after at least 6 months of drug free period (participants are allowed to have other anti-diabetic drugs during this period but not the drugs being compared, for e.g. for Insulin, GLP1ra comparison cohort, patients must be new users of these two classes of drugs but can be on other anti-diabetic drugs).

All patients are required to have at least 2 prescriptions of the same drug within 30 days grace period after the days-supply of the first prescription in order to increase the probability that they actually take the drug and continue to remain on the drug during the study period. Follow up will start from after six months lag period following second prescription date to allow for induction and latent periods.

Study participants are also required to have at least 12 months of continuous part A, B and 6 months of part D coverage before the first prescription date. Earliest pharmacy data (part D claims) available is January 1st, 2007, so earliest possible first prescription date will be July 1st, 2007.

Exclusion criteria

Patients with any cancer diagnosis or procedures (except non-melanoma skin cancer) will be identified using a sensitive definition (Table 1.) during a 1 year period before the date of first prescription through to the second prescription date and will be excluded from the study.

Table 1. Codes Used to Identify Prevalent Cancer at Baseline

ICD-9-CM diagnostic codes*: 140·0–208·92 (except 173·X), 209·00–209·36, 209·70-209·79, 230·X, 231·X, 233·X, 234·X, 235·X, 236·X, 237·0-237·1, 237·3, 237·5-237·6, 237·7, 237·9, 238·4, 238·6, 238·7 (all but 238·78), 239·6, 239·7, 273·2, 273·3, 277·89, 288·4, 795·06, 795·16, 796·76, V10·X, V87·41, V66·1, V66·2, V67·1, V67·2, V71·1
HCPCS codes†: G8371, G8372, G8377, J9999, G0355, G0356, G8376, G8377, G8380, G8381, G8464, G8465, G8518, G8519, G8520, G9050-G9054, G9063-G9067, G9069-G9117, G9131-G9133, G9118-G9130, G9134- G9139, G9714-G9715, G9726, G0256, G0261
CPT‡: 49220, 3271F, 3272F, 3273F, 3274F, 3300F – 3318F, 3321F, 3370F, 3372F, 3374F, 3376F, 3378F, 3380F, 3382F, 3384F, 3386F, 3388F, 3390F, 4163F, 4164F, 4180F, 4201F

*ICD-9-CM International Classification of Disease, Ninth Revision, Clinical Modification

†HCPCS Healthcare Common Procedure Coding System

‡CPT Current Procedural Terminology

Exposure groups

Primary drugs of interest of GLP-1 agonists and DPP-IV inhibitors. We will utilize three active comparator cohorts where (1) GLP-1 agonists are compared with insulin, (2) DPP-IV inhibitors with sulfonylurea (SU) and (3) with thiazolinediones (TZD).

Outcome

Primary outcome of interest is colorectal cancer (CRC). A secondary analysis will be performed combining CRC with carcinoma in situ and benign colorectal tumors (polyps, adenoma, excluding carcinoid tumors) separately since prior animal model studies showed that incretin analogues promote colon adenomas and polyps. Colorectal cancer will be defined if there are at least two incident cancer diagnosis codes during 2 months period. This definition has been shown to be highly specific although not specific, thereby decreasing chances of identifying false positive cases. The same definition with diagnosis code will be required for secondary outcome and patients will be censored at the time secondary outcomes develop.

Table 2. Codes used to identify outcome

ICD-9 CM codes	**Outcome**
Diagnosis codes	
153.0	Malignant neoplasm of colon 153.0 Hepatic flexure 153.1 Transverse colon 153.2 Descending colon 153.3 Sigmoid colon 153.4 Cecum, Ileocecal valve 153.5 Appendix 153.6 Ascending colon 153.7 Splenic flexure 153.8 Malignant neoplasm of contiguous or overlapping sites of colon whose point of origin cannot be determined 153.9 Colon, unspecified

154.0	Malignant neoplasm of rectum 154.0 Rectosigmoid junction 154.1 Rectum 154.8 Other Anorectum Cloacogenic zone Malignant neoplasm of contiguous or overlapping sites of rectum, rectosigmoid junction, and anus whose point of origin cannot be determined
211.3	Benign tumors of colon - Appendix - Cecum - Ileocecal valve - Large intestine NOS
211.4	Benign tumors of rectum and anal canal - Anal canal or sphincter - Anus NOS - Rectosigmoid junction
230.3	Carcinoma in situ of Colon - Appendix - Cecum - Ileocecal valve - Large intestine NOS
230.4	Carcinoma in situ of Rectum - Rectosigmoid junction
Procedure codes	
48.36	Endoscopic polypectomy of rectum

45.42	Endoscopic polypectomy of large intestine

Follow-up and analysis

Main analysis will be as treated analysis where patients are followed up six months after the date of second prescription (lag period to allow for empirical induction period of cancer) up to the date of the outcome of interest, or date of switching, stopping or augmenting the drug plus 6 months lag, or death from any cause or end of study period or enrollment in Part A, B, and D claims data, whichever comes first. Patients will also be censored if they developed any non-colorectal cancer (except non-melanoma skin cancer) during the six months period after the second prescription or during the time of follow up, with the same rationale as above that diagnostic work-up or treatment of other cancers may affect colorectal cancer outcome.

Stopping the drug is defined as no prescription of the same drug within the days-supply plus 30 days grace period of the last prescription and patients will be censored 6 months after the end of grace period (lag period allowing empirical induction of cancer).

Switching is defined as utilizing a comparator anti-DM drug without filling another prescription of the study drug within days-supply plus 30 days grace period of the last prescription. Patients will be censored 6 months after the date of filling a comparator drug.

Augmenting is defined as filling the prescription of a comparator drug while on the study drug during the days-supply plus 30 days grace period. Patients will be censored 6 months after the date of filling a comparator drug.

Table 3. Codes used to define any incident cancer during follow up

***Any Cancer ICD-9-CM diagnostic codes:**
140·0–208·92 (except 173·X), 209·00 – 209·36, 209·70-209·79,
233·0, 236·0, 237·0-237·1, 237·5-237·6, 237·72, 237·9, 238·4, 238·6, 238·7X (all but 238·78),
239·6, 239·7, 273·2, 273·3, 277·89, 288·4, 795·06, 795·16, 796·76

*ICD-9-CM International Classification of Disease, Ninth Revision, Clinical Modification

In a secondary analysis, patients will be eligible to re-enter the cohort as a new observation if they fulfill the definition of new users and our study entry criteria after getting censored during the follow up for stopping or switching.

In addition, intention to treat analysis (first treatment carried forward) will also be performed where patients are not censored for switching, stopping or augmenting the drug. Patients are still censored for the development of any non-colorectal cancer during the follow up.

Assessment of diagnostic work-up

Those with differential diagnostic work up have higher chance of being diagnosed with cancer. Therefore in order to ensure that our comparison groups do not have differential diagnostic work up thereby potentially biasing our study results, we will assess the following codes **during the following up**.

Table 4. Codes used to identify diagnostic work-up

Procedure Code	**Type Description**
45.21	Transabdominal endoscopy of LI
45.22	Endoscopy of LI through artificial stroma
45.23	Colonoscopy
45.24	Flexible sigmoidoscopy
45.28	Other diagnostic procedures on LI
45.29	Other diagnostic procedures on intestine site unspecified
48.21	Transabdominal proctosigmoidoscopy
48.22	Proctosigmoidoscopy through artificial stoma
48.23	Rigid proctosigmoidoscopy
89.34	microscopic examination of specimen from rectum (90.91-90.99)
87.64	microscopic examination of specimen from rectum (90.91-90.99)
90.91-90.99	microscopic examination of specimen from rectum (90.91-90.99)
CPT/HCPCS	Colonoscopy
CPT/HCPCS	Fecal for occult blood

Covariates assessment

Potential confounders will be assessed during the twelve months period before the first prescription date. They are chosen either as known risk factors of colorectal cancer or markers of old age or frailty.

Demographics

- Age
- Sex
- Race/ethnicity

Comorbidities

- Diabetes mellitus
- Hypertension
- Chronic obstructive pulmonary disease
- Congestive heart failure
- Myocardial infarction
- Chronic kidney disease
- Connective tissue disease
- Depression
- Tobacco use
- Alcohol use
- Gastrointestinal disorders (inflammatory bowel disease, GI infections, etc.)
- Diabetic complications (neuropathy, nephropathy, cataract, retinopathy)

Comedications

- Insulin
- Metformin
- TZD (unless used as comparator)
- SU (unless used as comparator)
- Angiotensin converting enzyme inhibitors
- Angiotensin receptor blockers

- Statin
- Loop diuretics
- Other diuretics
- Beta blockers
- Calcium channel blockers
- Aspirin (note rarely coded in claims data)
- NSAIDs
- Hormone replacement therapy

Healthcare utilization

- Number of hospital admissions
- Duration of hospital admissions
- Physician office visits
- Emergency department visits
- Colonoscopies
- Fecal occult blood tests
- Blood test
- Lipid panel
- Flu vaccination

Statistical analysis

Propensity Score (PS) methods will be used to control for confounding based on the measured covariates. Using propensity score weighting methods, Inverse Probability of Treatment Weighting (IPTW) and Standardized Morbidity Ratio Weighting (SMRW), we will implement COX models overall and stratified by time since initiation. Balance of the covariates will be assessed in the weighted pseudo-population and within deciles of the propensity score. Inverse probability weighted Kaplan-Meyer survival functions will be compared between our cohorts, adjusted for the same baseline covariates. The main effect measure estimate will be standardized hazard ratios with the assumption that there is no unmeasured confounding.

Sensitivity analyses

(1) We will vary lag periods (after initiation and after stopping) from 6 periods to 0, 12, 24 months, depending on availability of data.

(2) We will perform various asymmetric and symmetric trimming of propensity scores to assess the significance of any populations treated contrary to expectation (i.e. populations treated despite low PS, or not treated despite high PS) and the effect they have on the overall weighting and the effect measure estimate (Sturmer, Rothman, Avorn, & Glynn, 2010).

(3) We will allow new users who are re-eligible after being censored into the cohort

(4) We will perform intention-to-treat analysis (first treatment carried forward) and also as treated analysis without censoring those who augmented with the comparator drug.

References

Koehler, J. A., Baggio, L. L., Yusta, B., Longuet, C., Rowland, K. J., Cao, X., . . . Drucker, D. J. (2015). GLP-1R agonists promote normal and neoplastic intestinal growth through mechanisms requiring Fgf7. *Cell Metabolism,21*(3), 379-391. doi:10.1016/j.cmet.2015.02.005 [doi]

Sturmer, T., Rothman, K., Avorn, J., & Glynn, R. (2010). Treatment effects in the presence of unmeasured confounding: Dealing with observations in the tails of the propensity score distribution—a simulation study. *American Journal of Epidemiology*, *172*(7), 843-854.