SUPPLEMENTARY DATA

Supplement to: Tiansheng Wang[1], Jeff Y Yang[1], John B Buse[2], Virginia Pate[1], Huilin Tang[3], Edward L Barnes[4], Robert S Sandler[4], Til Stürmer[1]. **Dipeptidyl peptidase-4 inhibitors and risk of inflammatory bowel disease: Real World Evidence in US Adults**

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**Supplementary Table 1. Codes used for outcome definition and key covariates*.**

| **Primary and secondary outcome** | **ICD-9 Codes** | **ICD-10 Codes*** |
|---|---|---|
| Inflammatory bowel disease (including Crohn's disease and Ulcerative colitis) | 555.0, 555.1, 555.2, 555.9, 556.0, 556.1, 556.2, 556.3, 556.4, 556.5, 556.6, 556.8, 556.9 | K5000, K5010, K5080, K5090, K5180, K5180, K5120, K5130, K5140, K5150, K5100, K5180, K5190 |
| Crohn's disease | 555.0, 555.1, 555.2, 555.9 | K5000, K5010, K5080, K5090, |
| Ulcerative colitis | 556.0, 556.1, 556.2, 556.4, 556.8, 556.9 | K5180, K5180, K5120, K5130, K5140, K5150, K5100, K5180, K5190 |
| **Other specific gastroenterological diseases** | **ICD-9 Codes** | |
| Diverticulitis | 562.01, 562.03, 562.11, 562.13 | |
| Ischemic colitis | 557.0, 557.1, 557.9 | |
| Pseudomembranous colitis | 008.45 | |
| Unspecific colitis | 558.9 | |
| **Other gastroenterological disease categories** | **ICD-9 Codes** | |
| Diseases Of Esophagus, Stomach, And Duodenum | 530 - 539 | |
| Appendicitis | 540 - 543 | |
| Hernia Of Abdominal Cavity | 550 - 553 | |
| Noninfective Enteritis And Colitis | 555 - 558 | |
| Other Diseases Of Intestines And Peritoneum | 560 - 569 | |
| Other Diseases Of Digestive System | 570 - 579 | |
| **Procedures for endoscopy and biopsy** | **CPT Codes** | |
| Colorectal cancer screening | G0104, G0105, G0106, G0120, G0121 | |
| Colonoscopy | 44388, 44390, 44391, 44393, 44394, 44397, 44401, 44402, 44403, 44404, 44405, 44406, 45355, 45378, 45379, 45381, 45382, 45383, 45385, 45386, 45387, 45388, 45389, 45390, 45391, 45393, 45398, | |
| Colonoscopy involving biopsy | 44389, 44392, 44407, 45380, 45384, 45392 | |
| Sigmoidoscopy | 45300, 45302, 45303, 45307, 45309, 45310, 45317, 45320, 45321, 45327 45330, 45332, 45334, 45335, 45338, 45339, 45340, 45341, 45345, 45346, 45347, 45349, | |

| | | |
|---|---|---|
| | 45350,<br>G6022, G6023, | |
| Sigmoidoscopy involving biopsy | 45305, 45308,<br>45315,<br>45331, 45333, 45336<br>45342, | |
| Biopsy | 88300, 88302, 88304, 88305, 88307, 88309 | |
| **Procedures for endoscopy and biopsy** | **ICD-9 procedure code** | **ICD-10 procedure Codes*** |
| Colonoscopy | 4522, 4523, 4524, 4822, 4823, 4921 | 0DJD8ZZ |
| Colonoscopy involving biopsy | 4525 | 0D9H3ZX, 0D9H4ZX, 0D9H8ZX, 0D9H7ZX, 0D9E3ZX, 0D9E4ZX, 0D9E8ZX, 0D9E7ZX, 0D9N3ZX, 0D9N4ZX, 0D9N8ZX, 0D9N7ZX, 0DBH3ZX, 0DBH4ZX, 0DBH8ZX, 0DBH7ZX, 0DBE3ZX, 0DBE4ZX, 0DBE8ZX, 0DBE7ZX, 0DBN3ZX, 0DBN4ZX, 0DBN8ZX, 0DBN7ZX |
| Sigmoidoscopy | 4511, 4521, 4522, 4523, 4524, 4821, 4822, 4823, 4921 | 0DJD4ZZ, 0DJD8ZZ, |
| Screening | 4511, 4521, 4522, 4523, 4524, 4543, 4821, 4822, 4823, 4921 | 0DJD4ZZ, 0DJD8ZZ, 0D5E4ZZ |
| Biopsy | 4514, 4515, 4516, 4525, 4824, 4526, 4527 | 0DB83ZX, 0DB84ZX, 0DB88ZX, 0DB87ZX, 0DB80ZX, 0DB88ZX, 0DBE3ZX, 0DBE4ZX, 0DBE8ZX, 0DBE7ZX, 0D9H0ZX, 0D9E0ZX, 0D9N0ZX, 0DBH0ZX, 0DBE0ZX, 0DBN0ZX, 0D9P3ZX, 0D9P4ZX, 0D9P8ZX, 0D9P7ZX, 0DBP3ZX, 0DBP4ZX, 0DBP8ZX, 0DBP7ZX |
| **Procedures for colectomy, colostomy, ileostomy, and ostomy supplies** | **CPT Codes** | |
| Partial colectomy | 44140, 44141, 44143, 44144, 44145, 44146, 44147,<br>44160,<br>44204, 44205, 44206, 44207, 44208 | |
| Total colectomy | 44150, 44151, 44155, 44156, 44157, 44158, 44210, 44211, 44212 | |
| Colostomy | 44188, 44206, 44208, 50810, 57307 | |

| | | |
|---|---|---|
| Ileostomy | 44186, 44187, 44136 | |
| Ostomy supplies | A4331, A4357,<br>A4361, A4362, A4363, A4364, A4366,<br>A4367, A4368, A4369,<br>A4371, A4372, A4373, A4375, A4376,<br>A4377, A4378, A4379,<br>A4380, A4381, A4382, A4383, A4384,<br>A4385, A4386, A4387, A4388, A4389,<br>A4390,<br>A4402, A4404, A4405, A4406, A4407,<br>A4408, A4409,<br>A4410, A4411, A4412, A4413, A4414,<br>A4415, A4416, A4417, A4418, A4419,<br>A4420, A4421, A4422, A4423, A4424,<br>A4425, A4426, A4427, A4428 A4429,<br>A4430, A4431, A4432, A4433, A4434,<br>A4435,<br>A4450, A4452, A4455, A4456,<br>A5051, A5052, A5053, A5054, A5055,<br>A5056, A5057,<br>A5061, A5062, A5063,<br>A5071, A5072, A5073,<br>A5081, A5082, A5083,<br>A5093,<br>A5102,<br>A5120, A5121, A5122, A5126,<br>A5131,<br>A6216,<br>A9270 | |
| **Procedures for colectomy, colostomy, ileostomy, and ostomy supplies** | **ICD-9 procedure Codes** | **ICD-10 procedure Codes*** |
| Total colectomy | 4581, 4582, 4583 | 0DTE4ZZ, 0DTE0ZZ,<br>0DTE7ZZ, 0DTE8ZZ |

*The latest possible index date is September 30, 2015 (ICD-9 and ICD-10 code switching occurred on October 1, 2015). As all covariates are measured during baseline period, we only need to consider ICD-9 and ICD-10 mapping for outcome.

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**Supplementary Table 2A. Medications considered as inflammatory bowel disease therapy*.**

| Class | Medications |
|---|---|
| Aminosalicylates | Sulfasalazine, |
| | Mesalazine |
| | Olsalazine |
| | Balsalazide |
| Anti-Tumor Necrosis Factor (anti-TNF) | Infliximab |
| | Adalimumab |
| | Certolizumab pegol |
| | Natalizumab |
| | Vedolizumab |
| | Golimumab |
| | Ustekinumab |
| Corticosteroid† | Enteral budesonide |
| Immunosuppressive and immunoregulatory agents | Azathioprine |
| | Mercaptopurine |
| | Methotrexate |
| | Intravenous cyclosporine |

*Due to the wide indications, antibiotics are not considered as therapy to treat inflammatory bowel disease.

†Due to the wide indications, only enteral budesonide is considered as the corticosteroid therapy to treat inflammatory bowel disease.

**Reference**

1. Podolsky DK. Inflammatory Bowel Disease. *N Engl J Med* 2002 Aug 8;347(6):417-29

2. Feuerstein JD, Nguyen GC, Kupfer SS et al. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology 2017 Sep;153(3):827-834.

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**Supplementary Table 2B. Drugs may induce inflammatory bowel disease[1].**

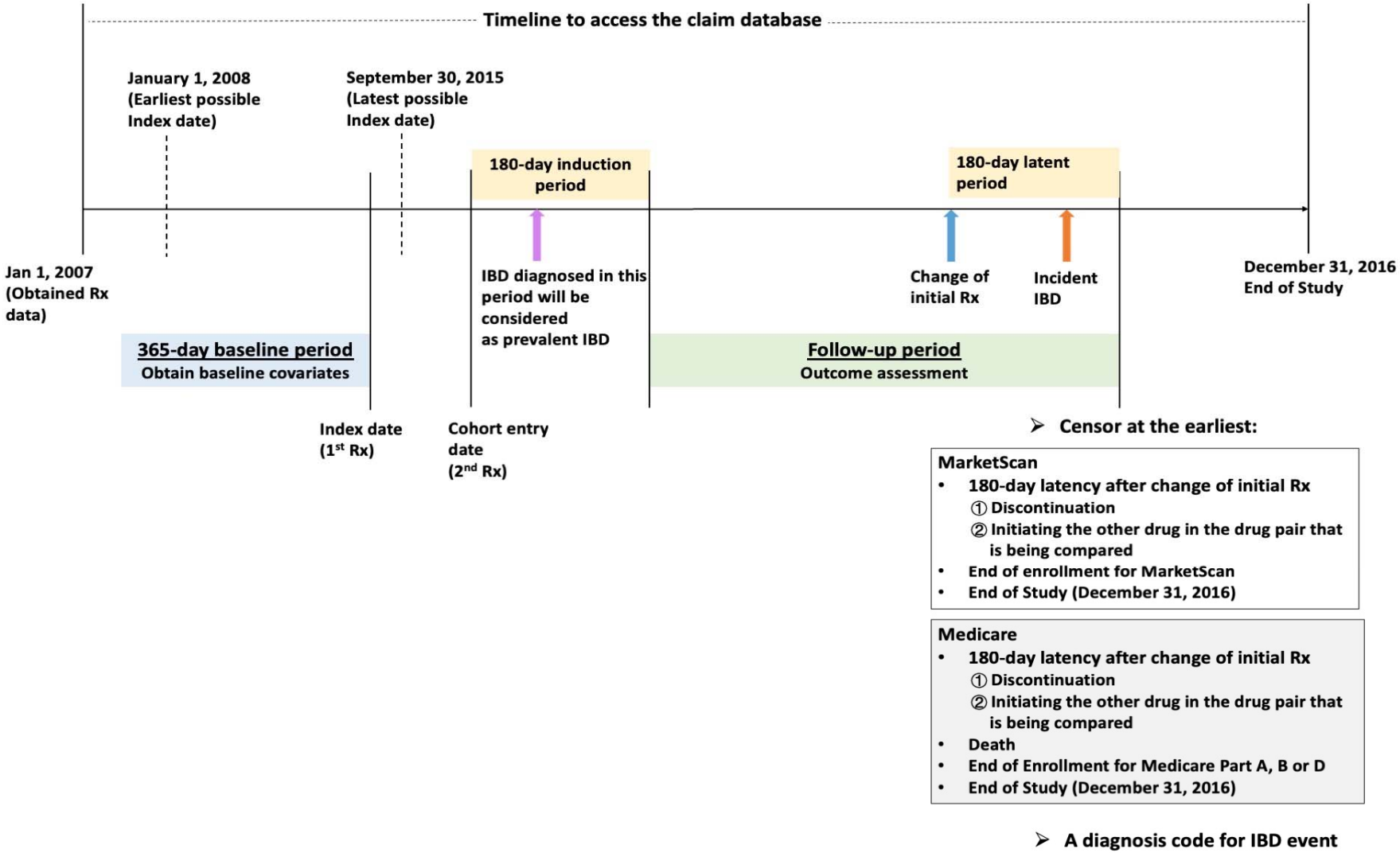
| Drug |
|---|
| Oral contraceptives |
| Hormonal replacement therapy |
| Aspirin |
| Nonsteroidal Anti-inflammatory Drugs (NSAIDs) |
| Isotretinoin |
| Mycophenolate mofetil |
| Etanercept |
| Ipilimumab |
| Rituximab |

**Reference**

Dubeau M-F, Lacucci M, Beck PL, et al. Drug-indcued inflammatory bowel disease and IBD-like conditions. Inflamm Bowel Dis 2013 Feb;19(2):445-56.

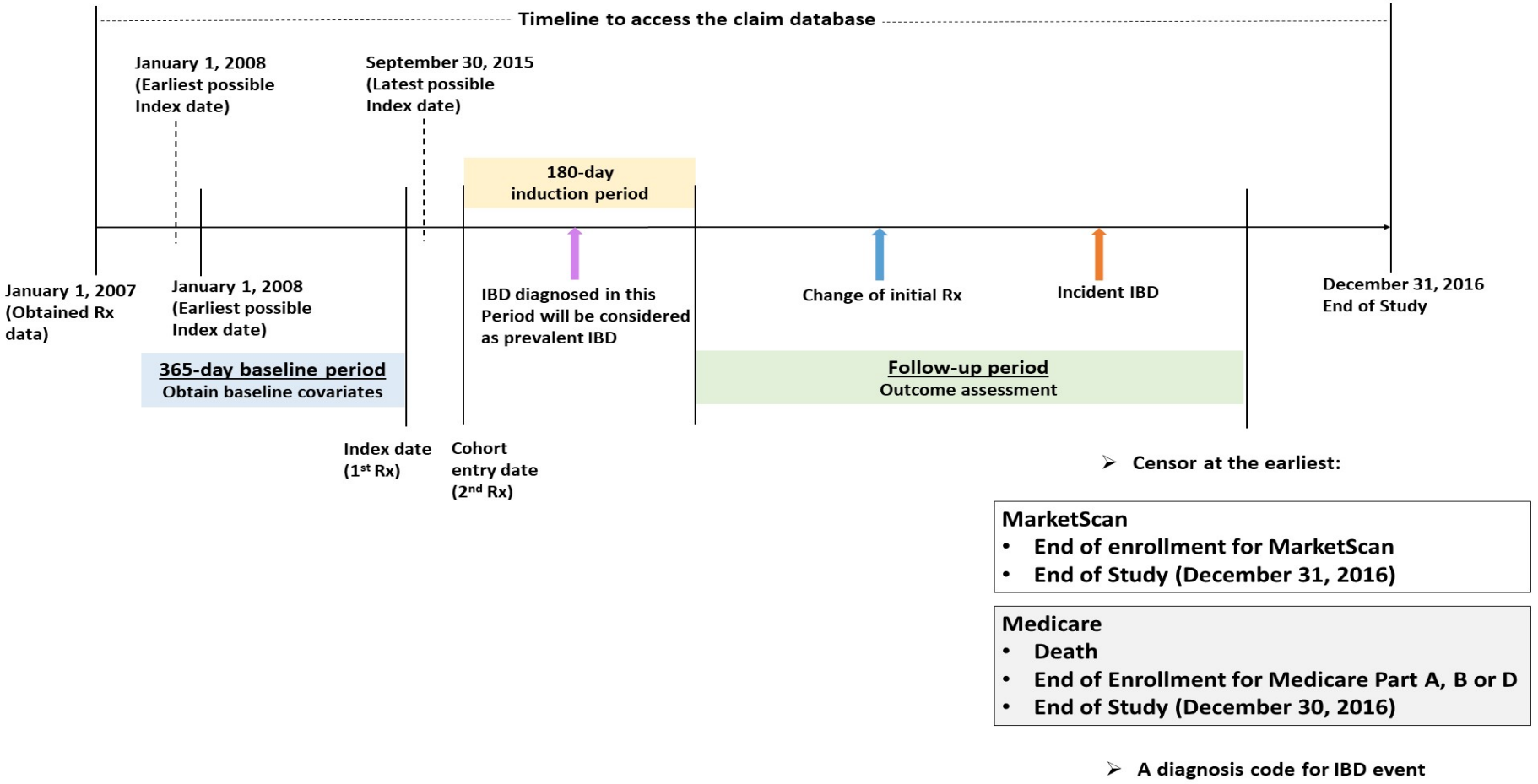
SUPPLEMENTARY DATA

**Supplementary Figure 1A. Overview of study design and new user cohort for as-treated analysis.** Rx, prescription. We assume that the clinical diagnosis of IBD is not made immediately after symptom onset, thus start follow-up for the outcome 180 days after the second prescription (induction period) and exclude patients with the outcome within 180 days after their second prescription. We allow patients with discontinuation, switching, or addition of a drug from comparator within 180 days after their second prescription to contribute to the person-time. Similarly, follow-up for IBD events will continue 180 days (the latency period) after treatment changes.



SUPPLEMENTARY DATA

**Supplementary Figure 1B. Overview of study design and new user cohort for initial-treatment analysis.** Rx, prescription. We assume that the clinical diagnosis of IBD is not made immediately after symptom onset, thus start follow-up for the outcome 180 days after the second prescription (induction period) and exclude patients with the outcome within 180 days after their second prescription. We allow patients with discontinuation, switching, or addition of a drug from comparator to contribute to the person-time. Follow-up for IBD events will end at the earliest of the following event: death (Medicare only); the end of insurance enrolment; end of study; or an incident IBD event.



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**Supplementary Figure 2. Outcome definitions.** The primary outcome was incident IBD, defined by the first IBD diagnosis that was preceded by a colonoscopy/sigmoidoscopy and biopsy within 30 days before diagnosis, and followed by IBD treatment within 30 days after diagnosis. In sensitivity analysis, we modified our primary outcome to 1) use the date of IBD treatment instead of diagnosis as event date; 2) remove the biopsy requirement; 3) remove both colonoscopy/sigmoidoscopy and biopsy requirements; 4) define IBD patients as those with at least three diagnoses on different days within 90 days. Black arrow/box represents the event date.

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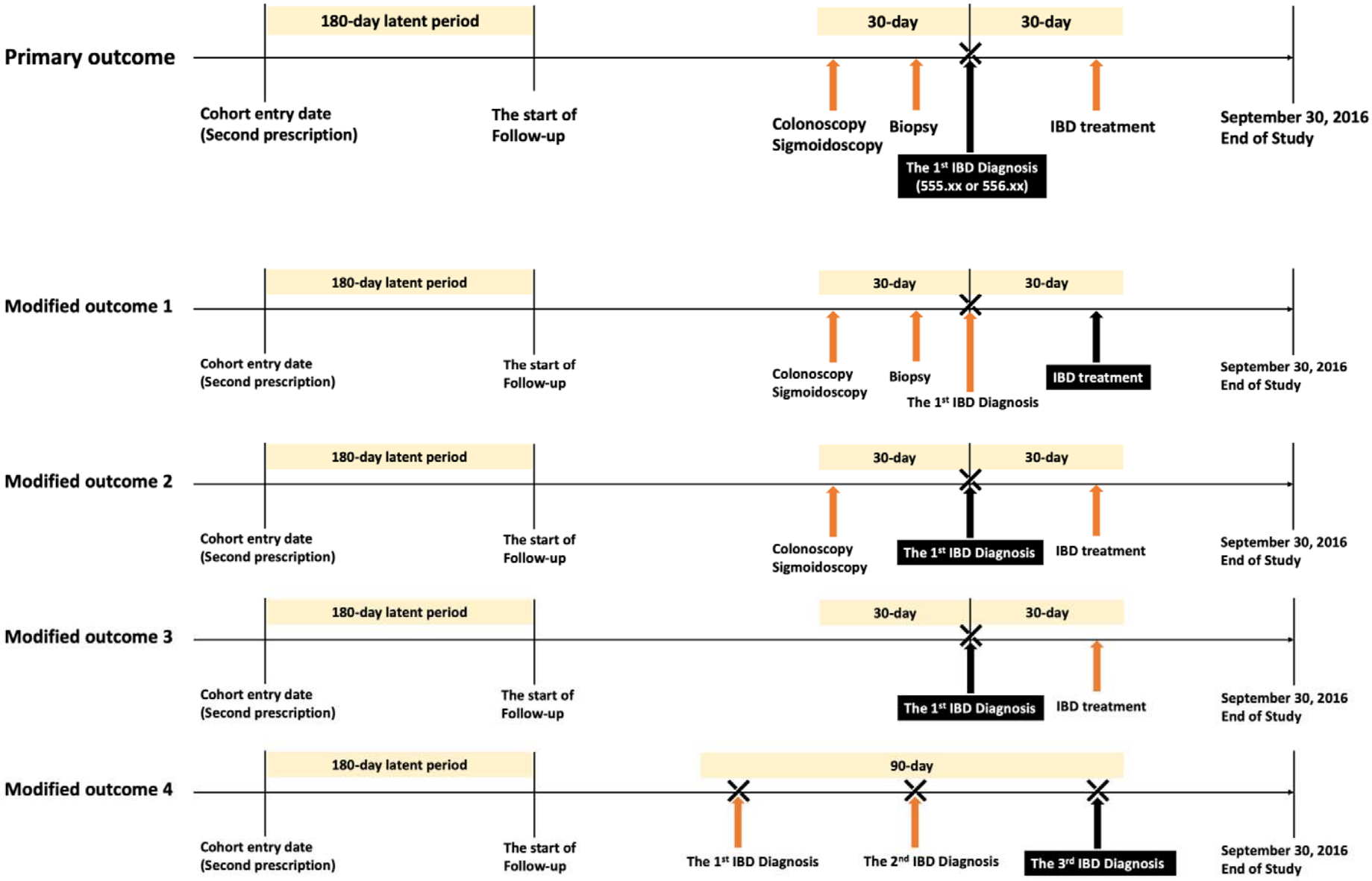

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**Supplementary Figure 3. Number of Patients in the base cohort and study cohort.** Initiation defined as having no prescriptions of either drug class during the 12 months prior to initiation. A patient could be a new user of DPP4i or comparator in different periods according to the 12-month washout period definition, thus could be selected in both DPP4i and comparator cohorts in different period. The number of patients in the bottom box in each column is the number of patients entered cohort, before propensity score trimming.

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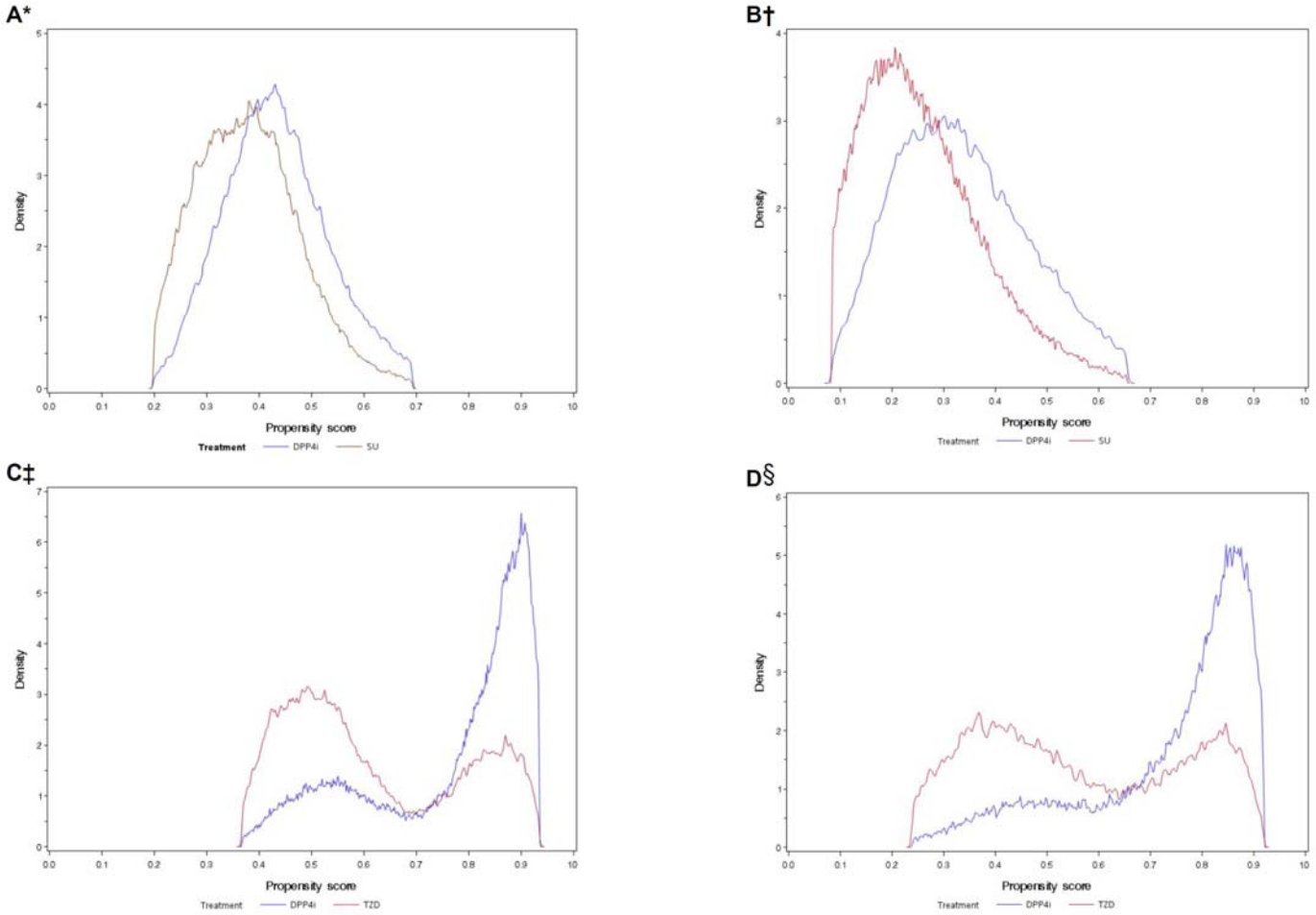
**Supplementary Figure 4**. **Propensity score distribution. DPP4i vs SU cohort in MarketScan (panel A); DPP4i vs SU cohort in Medicare (panel B); DPP4i vs TZD cohort in MarketScan (panel C); DPP4i vs TZD cohort in Medicare (panel D).** The "double peak" shape of plot for the propensity score distribution of TZD in DPP4i vs TZD comparison is mainly due to the calendar year dummy variables, i.e. a function of the increased use of DPP4i and decreased use of TZD overtime. Asymmetric PS trimming was applied to exclude those patients who were treated most contrary to prediction, using a cut point corresponding to the 0.5th and 99.5th percentiles of the PS distribution in the treated and untreated patients, respectively.



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**Supplementary Table 3A. Patient characteristics of DPP4i and comparator initiators for MarketScan population*.**

| Characteristic | DPP4i vs SU | | | | | DPP4i vs TZD | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | DPP4i (N†=137,341) | SU (N†=234,727) | Unweighted Standardized Difference | Weighted SU‡ (N=154,551) | Weighted Standardized Difference | DPP4i (N†=171,576) | TZD (N†=69,222) | Unweighted Standardized Difference | Weighted TZD‡ (N=181,586) | Weighted Standardized Difference |
| **Age, mean (SD)** | 52.4(8.32) | 51.0(9.47) | 0.157 | 51.8(8.87) | 0.071 | 52.4(8.32) | 52.1(8.52) | 0.029 | 52.4(8.46) | 0.003 |
| **Male, n (%)** | 75,267 (54.8) | 124,949 (53.2) | 0.032 | 82,088 (53.1) | 0.034 | 94,839 (55.3) | 40,283 (58.2) | 0.059 | 98,797 (54.4) | 0.017 |
| **Calendar year of initiating, n (%)** | | | | | | | | | | |
| 2008 | 10,487 (7.6) | 18,884 (8.0) | 0.015 | 11,583 (7.5) | 0.005 | 11,191 (6.5) | 11,780 (17.0) | 0.330 | 11,984 (6.6) | 0.003 |
| 2009 | 13,520 (9.8) | 32,120 (13.7) | 0.119 | 15,034 (9.7) | 0.004 | 15,952 (9.3) | 18,544 (26.8) | 0.467 | 16,913 (9.3) | 0.001 |
| 2010 | 15,785 (11.5) | 32,268 (13.7) | 0.068 | 17,833 (11.5) | 0.001 | 18,895 (11.0) | 14,592 (21.1) | 0.277 | 20,171 (11.1) | 0.003 |
| 2011 | 24,018 (17.5) | 34,613 (14.7) | 0.075 | 27,001 (17.5) | 0.000 | 28,185 (16.4) | 8,207 (11.9) | 0.131 | 30,410 (16.7) | 0.009 |
| 2012 | 26,534 (19.3) | 36,542 (15.6) | 0.099 | 30,095 (19.5) | 0.004 | 29,715 (17.3) | 3,944 (5.7) | 0.370 | 32,194 (17.7) | 0.011 |
| 2013 | 17,122 (12.5) | 30,782 (13.1) | 0.019 | 19,799 (12.8) | 0.010 | 24,191 (14.1) | 4,185 (6.0) | 0.270 | 25,234 (13.9) | 0.006 |
| 2014 | 17,428 (12.7) | 29,892 (12.7) | 0.001 | 19,550 (12.6) | 0.001 | 25,114 (14.6) | 4,597 (6.6) | 0.262 | 26,115 (14.4) | 0.007 |
| 2015 | 12,447 (9.1) | 19,626 (8.4) | 0.025 | 13,656 (8.8) | 0.008 | 18,333 (10.7) | 3,373 (4.9) | 0.218 | 18,566 (10.2) | 0.015 |
| **Diabetes comorbidities, n (%)** | | | | | | | | | | |
| Retinopathy | 7,399 (5.4) | 10,267 (4.4) | 0.047 | 7,905 (5.1) | 0.012 | 10,212 (6.0) | 4,089 (5.9) | 0.002 | 10,974 (6.0) | 0.004 |
| Nephropathy | 3,607 (2.6) | 5,980 (2.5) | 0.005 | 4,055 (2.6) | 0.000 | 5,190 (3.0) | 2,114 (3.1) | 0.002 | 5,620 (3.1) | 0.004 |
| Neuropathy | 6,759 (4.9) | 10,098 (4.3) | 0.030 | 7,272 (4.7) | 0.010 | 9,863 (5.7) | 3,578 (5.2) | 0.026 | 10,606 (5.8) | 0.004 |
| **Autoimumue comorbidities, n (%)** | | | | | | | | | | |
| Psoriasis | 1,153 (0.8) | 1,758 (0.7) | 0.010 | 1,299 (0.8) | 0.000 | 1,397 (0.8) | 491 (0.7) | 0.012 | 1,497 (0.8) | 0.001 |
| Systemic vasculitis | 146 (0.1) | 307 (0.1) | 0.007 | 184 (0.1) | 0.004 | 143 (0.1) | 56 (0.1) | 0.001 | 241 (0.1) | 0.015 |
| Rheumatoid | 747 (0.5) | 1,109 | 0.010 | 800 (0.5) | 0.004 | 807 (0.5) | 258 (0.4) | 0.015 | 866 (0.5) | 0.001 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| arthritis | | (0.5) | | | | | | | | |
| Sjogren's syndrome | 126 (0.1) | 176 (0.1) | 0.006 | 155 (0.1) | 0.003 | 106 (0.1) | 26 (0.0) | 0.011 | 88 (0.0) | 0.006 |
| Systemic lupus erythematosus | 285 (0.2) | 439 (0.2) | 0.005 | 348 (0.2) | 0.004 | 291 (0.2) | 103 (0.1) | 0.005 | 377 (0.2) | 0.009 |
| Celiac disease | 92 (0.1) | 132 (0.1) | 0.004 | 105 (0.1) | 0.000 | 103 (0.1) | 38 (0.1) | 0.002 | 109 (0.1) | 0.000 |
| **Gastrointestinal comorbidities§, n (%)** | | | | | | | | | | |
| Diseases of esophagus, stomach, and duodenum | 14,729 (10.7) | 22,247 (9.5) | 0.041 | 16,171 (10.5) | 0.008 | 17,985 (10.5) | 6,236 (9.0) | 0.050 | 18,799 (10.4) | 0.004 |
| Appendicitis | 153 (0.1) | 323 (0.1) | 0.007 | 175 (0.1) | 0.001 | 197 (0.1) | 75 (0.1) | 0.002 | 231 (0.1) | 0.004 |
| Hernia of abdominal cavity | 3,071 (2.2) | 4,848 (2.1) | 0.012 | 3,346 (2.2) | 0.005 | 3,752 (2.2) | 1,349 (1.9) | 0.017 | 3,871 (2.1) | 0.004 |
| Noninfective enteritis and colitis | 25 (0.0) | 43 (0.0) | 0.000 | 30 (0.0) | 0.001 | 19 (0.0) | NTSR | 0.002 | 39 (0.0) | 0.008 |
| Other diseases of intestines and peritoneum | 9,317 (6.8) | 14,239 (6.1) | 0.029 | 10,324 (6.7) | 0.004 | 11,202 (6.5) | 4,109 (5.9) | 0.025 | 11,949 (6.6) | 0.002 |
| Other diseases of digestive system | 9,532 (6.9) | 15,630 (6.7) | 0.011 | 10,642 (6.9) | 0.002 | 12,172 (7.1) | 4,545 (6.6) | 0.021 | 13,310 (7.3) | 0.009 |
| **Cardiovascular comorbidities, n (%)** | | | | | | | | | | |
| Hypertension | 82,345 (60.0) | 130,557 (55.6) | 0.088 | 89,452 (57.9) | 0.042 | 104,687 (61.0) | 38,565 (55.7) | 0.108 | 109,224 (60.2) | 0.018 |
| Dyslipidemia | 82,879 (60.3) | 119,265 (50.8) | 0.193 | 87,940 (56.9) | 0.070 | 105,033 (61.2) | 38,931 (56.2) | 0.101 | 109,689 (60.4) | 0.017 |
| Coronary artery disease | 13,263 (9.7) | 20,419 (8.7) | 0.033 | 14,262 (9.2) | 0.015 | 14,996 (8.7) | 5,517 (8.0) | 0.028 | 15,672 (8.6) | 0.004 |
| Cerebrovascular disease | 4,801 (3.5) | 7,762 (3.3) | 0.010 | 5,389 (3.5) | 0.000 | 5,723 (3.3) | 2,094 (3.0) | 0.018 | 6,162 (3.4) | 0.003 |
| Peripheral vascular disease | 3,314 (2.4) | 4,619 (2.0) | 0.030 | 3,509 (2.3) | 0.009 | 3,839 (2.2) | 1,343 (1.9) | 0.021 | 4,105 (2.3) | 0.002 |
| Congestive heart Failure‖ | 3,231 (2.4) | 5,976 (2.5) | 0.013 | 3,625 (2.3) | 0.000 | NA | NA | NA | NA | NA |
| **Other comorbidities, n (%)** | | | | | | | | | | |
| Chronic obstructive pulmonary disease | 3,718 (2.7) | 6,662 (2.8) | 0.008 | 4,076 (2.6) | 0.004 | 4,063 (2.4) | 1,492 (2.2) | 0.014 | 4,008 (2.2) | 0.011 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Depression | 9,816 (7.1) | 16,241 (6.9) | 0.009 | 11,087 (7.2) | 0.001 | 11,874 (6.9) | 4,108 (5.9) | 0.040 | 13,067 (7.2) | 0.011 |
| Cancer | 6,856 (5.0) | 10,826 (4.6) | 0.018 | 7,666 (5.0) | 0.001 | 8,003 (4.7) | 2,883 (4.2) | 0.024 | 8,515 (4.7) | 0.001 |
| Chronic kidney disease¶ | 7,379 (5.4) | 13,109 (5.6) | 0.009 | 8,363 (5.4) | 0.002 | 9,097 (5.3) | 3,288 (4.7) | 0.025 | 9,818 (5.4) | 0.005 |
| **Co-medications, n (%)** | | | | | | | | | | |
| Metformin | 114,686 (83.5) | 170,299 (72.6) | 0.267 | 124,346 (80.5) | 0.079 | 145,477 (84.8) | 55,188 (79.7) | 0.133 | 152,163 (83.8) | 0.027 |
| SU‖ | NA | 234,727 (100.0) | NA | NA | NA | 62,101 (36.2) | 28,397 (41.0) | 0.099 | 66,876 (36.8) | 0.013 |
| TZD‖ | 23,222 (16.9) | 24,889 (10.6) | 0.184 | 24,320 (15.7) | 0.032 | NA | 69,222 (100.0) | NA | NA | NA |
| DPP4i‖ | 137,341 (100.0) | NA | NA | NA | NA | 171,576 (100.0) | NA | NA | NA | NA |
| GLP1RA | 6,740 (4.9) | 9,964 (4.2) | 0.032 | 7,028 (4.5) | 0.017 | 8,857 (5.2) | 5,025 (7.3) | 0.087 | 9,157 (5.0) | 0.005 |
| SGLT2i | 1,751 (1.3) | 1,024 (0.4) | 0.091 | 1,589 (1.0) | 0.023 | 3,780 (2.2) | 722 (1.0) | 0.092 | 3,573 (2.0) | 0.016 |
| LAI | 15,343 (11.2) | 18,587 (7.9) | 0.111 | 16,412 (10.6) | 0.018 | 19,506 (11.4) | 8,089 (11.7) | 0.010 | 20,127 (11.1) | 0.009 |
| Alpha glucosidase inhibitor | 307 (0.2) | 365 (0.2) | 0.016 | 363 (0.2) | 0.002 | 562 (0.3) | 230 (0.3) | 0.001 | 797 (0.4) | 0.018 |
| Meglitinide | 1,911 (1.4) | 1,615 (0.7) | 0.069 | 1,903 (1.2) | 0.014 | 1,999 (1.2) | 844 (1.2) | 0.005 | 2,250 (1.2) | 0.007 |
| ACE inhibitors | 57,376 (41.8) | 99,885 (42.6) | 0.016 | 62,382 (40.4) | 0.029 | 76,517 (44.6) | 32,038 (46.3) | 0.034 | 80,689 (44.4) | 0.003 |
| ARBs | 33,912 (24.7) | 41,161 (17.5) | 0.176 | 36,134 (23.4) | 0.031 | 40,818 (23.8) | 14,579 (21.1) | 0.065 | 42,558 (23.4) | 0.008 |
| Beta-blockers | 34,159 (24.9) | 62,317 (26.5) | 0.038 | 38,862 (25.1) | 0.006 | 42,071 (24.5) | 15,872 (22.9) | 0.037 | 44,602 (24.6) | 0.001 |
| CCBs | 25,956 (18.9) | 42,379 (18.1) | 0.022 | 28,561 (18.5) | 0.011 | 33,049 (19.3) | 12,562 (18.1) | 0.029 | 35,212 (19.4) | 0.003 |
| Statins | 78,516 (57.2) | 114,397 (48.7) | 0.170 | 84,516 (54.7) | 0.050 | 98,732 (57.5) | 39,178 (56.6) | 0.019 | 104,233 (57.4) | 0.003 |
| Loop diuretics | 8,721 (6.3) | 14,409 (6.1) | 0.009 | 9,476 (6.1) | 0.009 | 8,488 (4.9) | 3,177 (4.6) | 0.017 | 9,490 (5.2) | 0.013 |
| Other diuretics | 44,413 (32.3) | 71,214 (30.3) | 0.043 | 48,294 (31.2) | 0.023 | 55,311 (32.2) | 21,951 (31.7) | 0.011 | 58,944 (32.5) | 0.005 |
| **Drugs may induce IBD** | | | | | | | | | | |
| Oral | 2,220 (3.6) | 5,387 | 0.049 | 3,178 (4.4) | 0.033 | 2,654 (3.5) | 1,086 (3.8) | 0.002 | 3,035 (3.7) | 0.010 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| contraceptives** | | (4.9) | | | | | | | | |
| Hormonal therapy** | 6,915 (11.1) | 11,630 (10.6) | 0.004 | 8,713 (12.0) | 0.027 | 8,083 (10.5) | 3,294 (11.4) | 0.002 | 9,226 (11.1) | 0.017 |
| Aspirin | 4,770 (3.5) | 6,849 (2.9) | 0.032 | 5,120 (3.3) | 0.009 | 5,869 (3.4) | 2,256 (3.3) | 0.009 | 6,117 (3.4) | 0.003 |
| NSAIDs | 34,549 (25.2) | 55,152 (23.5) | 0.039 | 38,233 (24.7) | 0.010 | 43,134 (25.1) | 16,973 (24.5) | 0.014 | 45,903 (25.3) | 0.003 |
| Other drugs may induce IBD | 577 (0.4) | 1,245 (0.5) | 0.016 | 704 (0.5) | 0.005 | 675 (0.4) | 249 (0.4) | 0.006 | 711 (0.4) | 0.000 |
| **Health care utilization** | | | | | | | | | | |
| **Severe hyperglycemia diagnoses††** | | | | | | | | | | |
| 0 | 84,151 (61.3) | 155,476 (66.2) | 0.103 | 98,114 (63.5) | 0.046 | 99,365 (57.9) | 41,624 (60.1) | 0.045 | 107,716 (59.3) | 0.029 |
| 1 | 39,415 (28.7) | 60,718 (25.9) | 0.064 | 42,142 (27.3) | 0.032 | 51,449 (30.0) | 19,779 (28.6) | 0.031 | 52,219 (28.8) | 0.027 |
| 2 | 13,775 (10.0) | 18,533 (7.9) | 0.075 | 14,295 (9.2) | 0.026 | 20,762 (12.1) | 7,819 (11.3) | 0.025 | 21,651 (11.9) | 0.005 |
| ≥3 | NTSR | NTSR | NA | NA | NA | NTSR | NTSR | NA | NA | NA |
| **Hospitalization due to diabetes** | 983 (0.7) | 2,223 (0.9) | 0.025 | 1,207 (0.8) | 0.008 | 1,292 (0.8) | 562 (0.8) | 0.007 | 1,227 (0.7) | 0.009 |
| **ED visit due to diabetes** | | | | | | | | | | |
| 0 | 135,634 (98.8) | 230,695 (98.3) | 0.039 | 152,550 (98.7) | 0.005 | 169,002 (98.5) | 68,245 (98.6) | 0.007 | 178,880 (98.5) | 0.001 |
| 1 | 1,568 (1.1) | 3,713 (1.6) | 0.038 | 1,847 (1.2) | 0.005 | 2,332 (1.4) | 887 (1.3) | 0.007 | 2,462 (1.4) | 0.000 |
| ≥2 | 139 (0.1) | 319 (0.1) | 0.010 | 154 (0.1) | 0.000 | 242 (0.1) | 90 (0.1) | 0.003 | 244 (0.1) | 0.002 |
| **Physician encounters** | | | | | | | | | | |
| 0 | 3,368 (2.5) | 9,405 (4.0) | 0.088 | 3,884 (2.5) | 0.004 | 4,335 (2.5) | 2,272 (3.3) | 0.045 | 4,836 (2.7) | 0.009 |
| 1-3 | 39,527 (28.8) | 82,469 (35.1) | 0.137 | 46,368 (30.0) | 0.027 | 48,858 (28.5) | 21,062 (30.4) | 0.043 | 51,712 (28.5) | 0.000 |
| 4-6 | 44,901 (32.7) | 71,131 (30.3) | 0.051 | 49,455 (32.0) | 0.015 | 57,290 (33.4) | 22,838 (33.0) | 0.008 | 59,148 (32.6) | 0.017 |
| ≥7 | 49,545 (36.1) | 71,722 (30.6) | 0.117 | 54,844 (35.5) | 0.012 | 61,093 (35.6) | 23,050 (33.3) | 0.049 | 65,889 (36.3) | 0.014 |
| **Gastroenterologis encounters** | | | | | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 129,218 (94.1) | 224,254 (95.5) | 0.066 | 146,194 (94.6) | 0.022 | 161,662 (94.2) | 65,710 (94.9) | 0.031 | 171,161 (94.3) | 0.002 |
| 1-3 | 5,632 (4.1) | 7,144 (3.0) | 0.057 | 5,515 (3.6) | 0.028 | 6,872 (4.0) | 2,363 (3.4) | 0.031 | 6,948 (3.8) | 0.009 |
| 4-6 | 1,694 (1.2) | 2,191 (0.9) | 0.029 | 1,867 (1.2) | 0.002 | 2,028 (1.2) | 754 (1.1) | 0.009 | 2,314 (1.3) | 0.008 |
| ≥7 | 797 (0.6) | 1,138 (0.5) | 0.013 | 974 (0.6) | 0.006 | 1,014 (0.6) | 395 (0.6) | 0.003 | 1,164 (0.6) | 0.006 |
| **ED visit** | | | | | | | | | | |
| 0 | 113,067 (82.3) | 187,321 (79.8) | 0.064 | 126,447 (81.8) | 0.013 | 141,079 (82.2) | 57,687 (83.3) | 0.029 | 149,653 (82.4) | 0.005 |
| 1 | 17,434 (12.7) | 33,398 (14.2) | 0.045 | 20,081 (13.0) | 0.009 | 21,857 (12.7) | 8,311 (12.0) | 0.022 | 22,556 (12.4) | 0.010 |
| ≥2 | 6,840 (5.0) | 14,008 (6.0) | 0.043 | 8,023 (5.2) | 0.010 | 8,640 (5.0) | 3,224 (4.7) | 0.018 | 9,376 (5.2) | 0.006 |
| **Flu vaccine** | 38,131 (27.8) | 59,913 (25.5) | 0.051 | 42,749 (27.7) | 0.002 | 47,518 (27.7) | 17,499 (25.3) | 0.055 | 50,477 (27.8) | 0.002 |
| **Smoking‡‡** | 7,047 (5.1) | 13,504 (5.8) | 0.027 | 8,024 (5.2) | 0.003 | 8,844 (5.2) | 3,079 (4.4) | 0.033 | 9,073 (5.0) | 0.007 |
| **Appendectomy** | 120 (0.1) | 252 (0.1) | 0.006 | 134 (0.1) | 0.000 | 153 (0.1) | 65 (0.1) | 0.002 | 202 (0.1) | 0.007 |

Abbreviations: GLP1RA, Glucagon-like peptide-1 receptor agonist; SGLT2i, Sodium-glucose Cotransporter 2 inhibitor; LAI, long acting insulin; ACE inhibitors, Angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCBs, calcium-channel blockers; NA, not applicable; No, number.

* The comparisons were defined by use of IBT and PS-weighted comparator. Covariates were measured in 12 months before the first prescription including the index date (New users appear to 100% have the treatment at baseline). Initiation defined as having no prescriptions of either drug class during the 12 months prior to initiation.

† The size of the population for a specific drug differed across cohorts because of the requirement not to have been treated prior to index date with the comparator drug class. As shown in **Supplementary Figure 3**, before PS trimming, the sample size for MarketScan population is 140,641 vs 241,834 in DPP4i vs SU comparison, and 178,036 vs 71,714 in DPP4i vs TZD comparison, respectively.

‡ Weighted by standardizing to their distribution in incretin-based therapy initiators by using weights of 1 for DPP4i initiators and the odds of the estimated propensity score for comparator initiators.

§ Gastrointestinal disease was grouped according to the ICD9 classification (http://www.icd9data.com/2012/Volume1/520-579/default.htm).

|| Patients with congestive baseline heart failure were excluded for DPP4i vs TZD comparison; and patients are required not to have been treated prior to index date with the comparator drug class.

¶ Diabetic nephropathy codes (250.40-250.43) were not included to identify chronic kidney disease (ICD-9-CM codes: 016.0; 095.4; 189.0; 189.9; 223.0; 236.91; 271.4; 274.1; 283.11; 403; 404; 440.1; 442.1; 572.4; 581-588; 591; 753.12-753.19; 753.2; 794.4).

# Other drugs may induce inflammatory bowel disease include Isotretinoin, Mycophenolate mofetil, Etanercept, Ipilimumab, and Rituximab (Supplementary Tables 2B).

** The denominator of percentage is number of female patients.

†† Severe hyperglycemia diagnoses include diabetes with ketoacidosis (ICD-9-CM codes 2501), diabetes with hyperosmolarity (ICD-9-CM codes 2502),

and diabetes with other coma (ICD-9-CM codes 2503), and uncontrolled diabetes (ICD-9-CM codes 25002, 25003).

‡‡ Smoking was defined using a previously validated algorithm that was a composite of tobacco use diagnosis codes or consultation CPT codes or prescription filled for smoking cessation. Although perfect specificity and positive predictive value, this measure has poor sensitivity (27.9% [95% CI 16.6%-39.1%]) (reference 26)

SUPPLEMENTARY DATA

**Supplementary Table 3B. Patient characteristics of DPP4i and comparator initiators for Medicare population***

| Characteristic | DPP4i vs SU | | | | | DPP4i vs TZD | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | DPP4i (N†=46,518) | SU (N†=117,820) | Unweighted standardized difference | Weighted SU‡ (N=46,375) | Weighted standardized difference | DPP4i (N†=61,283) | TZD (N†=28,532) | Unweighted standardized difference | Weighted TZD‡ (N=61,554) | Weighted standardized difference |
| **Age, mean (SD)** | 74.8(7.29) | 74.4(7.51) | 0.046 | 74.7(7.29) | 0.003 | 74.1(6.91) | 73.3(6.76) | 0.124 | 74.2(6.85) | 0.004 |
| **Male, n (%)** | 19,033 (40.9) | 51,610 (43.8) | 0.058 | 18,930 (40.8) | 0.002 | 25,798 (42.1) | 12,611 (44.2) | 0.042 | 26,323 (42.8) | 0.013 |
| **Race, n (%)** | | | | | | | | | | |
| White | 34,729 (74.7) | 91,280 (77.5) | 0.066 | 34,714 (74.9) | 0.005 | 45,818 (74.8) | 20,887 (73.2) | 0.036 | 46,934 (76.2) | 0.034 |
| Black | 5,436 (11.7) | 14,633 (12.4) | 0.023 | 5,398 (11.6) | 0.001 | 6,865 (11.2) | 3,323 (11.6) | 0.014 | 6,315 (10.3) | 0.030 |
| Others | 6,353 (13.7) | 11,907 (10.1) | 0.110 | 6,262 (13.5) | 0.004 | 8,600 (14.0) | 4,322 (15.1) | 0.032 | 8,305 (13.5) | 0.016 |
| **Calendar year of initiating, n (%)** | | | | | | | | | | |
| 2008 | 2,495 (5.4) | 10,522 (8.9) | 0.139 | 2,501 (5.4) | 0.001 | 2,887 (4.7) | 4,502 (15.8) | 0.371 | 2,893 (4.7) | 0.001 |
| 2009 | 3,503 (7.5) | 15,399 (13.1) | 0.183 | 3,450 (7.4) | 0.003 | 4,459 (7.3) | 6,256 (21.9) | 0.424 | 4,455 (7.2) | 0.001 |
| 2010 | 4,616 (9.9) | 16,173 (13.7) | 0.118 | 4,603 (9.9) | 0.000 | 5,705 (9.3) | 5,578 (19.5) | 0.295 | 5,684 (9.2) | 0.003 |
| 2011 | 7,039 (15.1) | 15,745 (13.4) | 0.051 | 6,983 (15.1) | 0.002 | 8,323 (13.6) | 3,320 (11.6) | 0.059 | 8,186 (13.3) | 0.008 |
| 2012 | 7,281 (15.7) | 14,621 (12.4) | 0.093 | 7,188 (15.5) | 0.004 | 8,850 (14.4) | 1,782 (6.2) | 0.272 | 8,453 (13.7) | 0.020 |
| 2013 | 6,748 (14.5) | 14,793 (12.6) | 0.057 | 6,738 (14.5) | 0.001 | 9,552 (15.6) | 2,000 (7.0) | 0.273 | 9,698 (15.8) | 0.005 |
| 2014 | 7,255 (15.6) | 14,917 (12.7) | 0.084 | 7,292 (15.7) | 0.004 | 10,583 (17.3) | 2,295 (8.0) | 0.280 | 10,845 (17.6) | 0.009 |
| 2015 | 7,581 (16.3) | 15,650 (13.3) | 0.085 | 7,618 (16.4) | 0.004 | 10,924 (17.8) | 2,799 (9.8) | 0.234 | 11,340 (18.4) | 0.016 |
| **Diabetes comorbidities, n (%)** | | | | | | | | | | |
| Retinopathy | 6,388 (13.7) | 12,068 (10.2) | 0.108 | 6,384 (13.8) | 0.001 | 8,878 (14.5) | 3,989 (14.0) | 0.014 | 8,787 (14.3) | 0.006 |
| Nephropathy | 4,133 (8.9) | 7,763 (6.6) | 0.086 | 4,137 (8.9) | 0.001 | 5,021 (8.2) | 1,938 (6.8) | 0.053 | 5,284 (8.6) | 0.014 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Neuropathy | 8,928 (19.2) | 16,961 (14.4) | 0.129 | 8,925 (19.2) | 0.001 | 11,226 (18.3) | 4,412 (15.5) | 0.076 | 11,470 (18.6) | 0.008 |
| **Autoimumue comorbidities, n (%)** | | | | | | | | | | |
| Psoriasis | 505 (1.1) | 1,266 (1.1) | 0.001 | 512 (1.1) | 0.002 | 692 (1.1) | 284 (1.0) | 0.013 | 681 (1.1) | 0.002 |
| Systemic vasculitis | 259 (0.6) | 665 (0.6) | 0.001 | 258 (0.6) | 0.000 | 237 (0.4) | 94 (0.3) | 0.010 | 291 (0.5) | 0.013 |
| Rheumatoid arthritis | 1,281 (2.8) | 2,588 (2.2) | 0.036 | 1,232 (2.7) | 0.006 | 1,308 (2.1) | 578 (2.0) | 0.008 | 1,281 (2.1) | 0.004 |
| Sjogren's syndrome | 105 (0.2) | 181 (0.2) | 0.017 | 105 (0.2) | 0.000 | 109 (0.2) | 41 (0.1) | 0.009 | 122 (0.2) | 0.005 |
| Systemic lupus erythematosus | 155 (0.3) | 293 (0.2) | 0.016 | 153 (0.3) | 0.001 | 136 (0.2) | 54 (0.2) | 0.007 | 152 (0.2) | 0.005 |
| Celiac disease | 51 (0.1) | 114 (0.1) | 0.004 | 52 (0.1) | 0.001 | 42 (0.1) | 15 (0.1) | 0.006 | 36 (0.1) | 0.004 |
| **Gastrointestinal comorbidities§, n (%)** | | | | | | | | | | |
| Diseases of esophagus, stomach, and duodenum | 13,414 (28.8) | 29,455 (25.0) | 0.087 | 13,414 (28.9) | 0.002 | 15,098 (24.6) | 6,188 (21.7) | 0.070 | 14,970 (24.3) | 0.007 |
| Appendicitis | 31 (0.1) | 85 (0.1) | 0.002 | 32 (0.1) | 0.001 | 37 (0.1) | 16 (0.1) | 0.002 | 25 (0.0) | 0.009 |
| Hernia of abdominal cavity | 2,653 (5.7) | 6,307 (5.4) | 0.015 | 2,624 (5.7) | 0.002 | 2,823 (4.6) | 1,156 (4.1) | 0.027 | 2,905 (4.7) | 0.005 |
| Noninfective enteritis and colitis | 20 (0.0) | 67 (0.1) | 0.006 | 20 (0.0) | 0.000 | 25 (0.0) | 16 (0.1) | 0.007 | 29 (0.0) | 0.003 |
| Other diseases of intestines and peritoneum | 8,394 (18.0) | 19,363 (16.4) | 0.043 | 8,367 (18.0) | 0.000 | 9,403 (15.3) | 3,792 (13.3) | 0.059 | 9,599 (15.6) | 0.007 |
| Other diseases of digestive system | 5,754 (12.4) | 13,135 (11.1) | 0.038 | 5,724 (12.3) | 0.001 | 6,203 (10.1) | 2,588 (9.1) | 0.036 | 6,347 (10.3) | 0.006 |
| **Cardiovascular comorbidities, n (%)** | | | | | | | | | | |
| Hypertension | 40,156 (86.3) | 96,912 (82.3) | 0.112 | 40,030 (86.3) | 0.000 | 52,615 (85.9) | 23,384 (82.0) | 0.106 | 53,009 (86.1) | 0.008 |
| Dyslipidemia | 38,108 (81.9) | 87,537 (74.3) | 0.185 | 38,057 (82.1) | 0.004 | 50,225 (82.0) | 22,012 (77.1) | 0.119 | 50,942 (82.8) | 0.021 |
| Coronary artery disease | 17,432 (37.5) | 40,054 (34.0) | 0.073 | 17,371 (37.5) | 0.000 | 17,937 (29.3) | 7,309 (25.6) | 0.082 | 18,417 (29.9) | 0.014 |
| Cerebrovascular disease | 9,948 (21.4) | 22,855 (19.4) | 0.049 | 9,954 (21.5) | 0.002 | 10,447 (17.0) | 4,233 (14.8) | 0.060 | 10,345 (16.8) | 0.006 |
| Peripheral vascular | 9,481 (20.4) | 19,941 | 0.089 | 9,406 | 0.002 | 9,730 (15.9) | 3,833 (13.4) | 0.069 | 9,692 (15.7) | 0.004 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| disease | | (16.9) | | (20.3) | | | | | | |
| Congestive heart failure‖ | 9,713 (20.9) | 23,056 (19.6) | 0.033 | 9,690 (20.9) | 0.000 | NA | NA | NA | NA | NA |
| **Other comorbidities, n (%)** | | | | | | | | | | |
| Chronic obstructive pulmonary disease | 8,895 (19.1) | 22,167 (18.8) | 0.008 | 8,847 (19.1) | 0.001 | 7,707 (12.6) | 3,405 (11.9) | 0.020 | 7,681 (12.5) | 0.003 |
| Depression | 7,558 (16.2) | 17,070 (14.5) | 0.049 | 7,534 (16.2) | 0.000 | 7,991 (13.0) | 3,182 (11.2) | 0.058 | 7,861 (12.8) | 0.008 |
| Cancer | 7,466 (16.0) | 18,246 (15.5) | 0.015 | 7,446 (16.1) | 0.000 | 8,975 (14.6) | 3,644 (12.8) | 0.054 | 9,089 (14.8) | 0.003 |
| Chronic kidney disease¶ | 12,403 (26.7) | 27,998 (23.8) | 0.067 | 12,363 (26.7) | 0.000 | 13,256 (21.6) | 5,049 (17.7) | 0.099 | 13,411 (21.8) | 0.004 |
| **Co-medications, n (%)** | | | | | | | | | | |
| Metformin | 29,720 (63.9) | 67,079 (56.9) | 0.143 | 29,875 (64.4) | 0.011 | 43,172 (70.4) | 18,855 (66.1) | 0.094 | 43,513 (70.7) | 0.005 |
| SU‖ | NA | 117,820 (100.0) | NA | NA | NA | 30,897 (50.4) | 14,955 (52.4) | 0.040 | 31,373 (51.0) | 0.011 |
| TZD‖ | 8,203 (17.6) | 13,577 (11.5) | 0.174 | 8,184 (17.6) | 0.000 | NA | 28,532 (100.0) | NA | NA | NA |
| DPP4i‖ | 46,518 (100.0) | NA | NA | NA | NA | 61,283 (100.0) | NA | NA | NA | NA |
| GLP1RA | 927 (2.0) | 1,662 (1.4) | 0.045 | 944 (2.0) | 0.003 | 1,277 (2.1) | 723 (2.5) | 0.030 | 1,290 (2.1) | 0.001 |
| SGLT2i | 199 (0.4) | 235 (0.2) | 0.041 | 207 (0.4) | 0.003 | 413 (0.7) | 108 (0.4) | 0.041 | 431 (0.7) | 0.003 |
| LAI | 8,862 (19.1) | 14,793 (12.6) | 0.179 | 8,894 (19.2) | 0.003 | 8,969 (14.6) | 3,916 (13.7) | 0.026 | 9,099 (14.8) | 0.004 |
| Alpha glucosidase inhibitor | 243 (0.5) | 394 (0.3) | 0.029 | 250 (0.5) | 0.002 | 457 (0.7) | 205 (0.7) | 0.003 | 514 (0.8) | 0.010 |
| Meglitinide | 1,642 (3.5) | 2,472 (2.1) | 0.087 | 1,633 (3.5) | 0.001 | 1,436 (2.3) | 613 (2.1) | 0.013 | 1,581 (2.6) | 0.015 |
| ACE inhibitors | 20,193 (43.4) | 54,905 (46.6) | 0.064 | 20,098 (43.3) | 0.001 | 28,632 (46.7) | 14,134 (49.5) | 0.056 | 28,468 (46.2) | 0.009 |
| ARBs | 15,033 (32.3) | 27,843 (23.6) | 0.194 | 15,017 (32.4) | 0.001 | 18,837 (30.7) | 7,404 (25.9) | 0.106 | 19,138 (31.1) | 0.008 |
| Beta-blockers | 24,134 (51.9) | 59,727 (50.7) | 0.024 | 24,056 (51.9) | 0.000 | 29,406 (48.0) | 12,213 (42.8) | 0.104 | 29,781 (48.4) | 0.008 |
| CCBs | 16,703 (35.9) | 40,483 (34.4) | 0.032 | 16,580 (35.8) | 0.003 | 21,871 (35.7) | 9,497 (33.3) | 0.051 | 21,815 (35.4) | 0.005 |
| Statins | 32,624 (70.1) | 74,008 (62.8) | 0.155 | 32,543 (70.2) | 0.001 | 43,072 (70.3) | 18,974 (66.5) | 0.081 | 43,403 (70.5) | 0.005 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Loop diuretics | 11,994 (25.8) | 30,305 (25.7) | 0.001 | 11,977 (25.8) | 0.001 | 9,531 (15.6) | 3,949 (13.8) | 0.048 | 9,625 (15.6) | 0.002 |
| Other diuretics | 17,979 (38.6) | 43,787 (37.2) | 0.031 | 17,888 (38.6) | 0.002 | 23,744 (38.7) | 10,883 (38.1) | 0.012 | 23,932 (38.9) | 0.003 |
| **Drugs may induce IBD** | | | | | | | | | | |
| Oral contraceptives** | NTSR | NTSR | NA | NA | NA | NTSR | NTSR | NA | NTSR | NA |
| Hormonal therapy** | 1,178 (4.3) | 2,667 (4.0) | 0.018 | 1,173 (4.3) | 0.000 | 1,488 (4.2) | 725 (4.6) | 0.007 | 1,462 (4.1) | 0.003 |
| Aspirin | 2,150 (4.6) | 4,107 (3.5) | 0.058 | 2,130 (4.6) | 0.001 | 2,093 (3.4) | 935 (3.3) | 0.008 | 2,124 (3.5) | 0.002 |
| NSAIDs | 12,192 (26.2) | 25,560 (21.7) | 0.106 | 12,109 (26.1) | 0.002 | 15,674 (25.6) | 7,082 (24.8) | 0.017 | 15,562 (25.3) | 0.007 |
| Other drugs may induce IBD | 80 (0.2) | 169 (0.1) | 0.007 | 78 (0.2) | 0.001 | 84 (0.1) | 41 (0.1) | 0.002 | 82 (0.1) | 0.001 |
| **Health care utilization** | | | | | | | | | | |
| **Severe hyperglycemia diagnoses††** | | | | | | | | | | |
| 0 | 26,459 (56.9) | 74,734 (63.4) | 0.134 | 26,360 (56.8) | 0.001 | 33,228 (54.2) | 16,415 (57.5) | 0.067 | 33,384 (54.2) | 0.000 |
| 1 | 6,145 (13.2) | 15,456 (13.1) | 0.003 | 6,106 (13.2) | 0.001 | 8,175 (13.3) | 3,640 (12.8) | 0.017 | 7,993 (13.0) | 0.010 |
| 2 | 3,410 (7.3) | 7,722 (6.6) | 0.031 | 3,387 (7.3) | 0.001 | 4,745 (7.7) | 2,089 (7.3) | 0.016 | 4,784 (7.8) | 0.001 |
| ≥3 | 10,504 (22.6) | 19,908 (16.9) | 0.143 | 10,522 (22.7) | 0.003 | 15,135 (24.7) | 6,388 (22.4) | 0.054 | 15,393 (25.0) | 0.007 |
| **Hospitalization due to diabetes** | 712 (1.5) | 1,600 (1.4) | 0.014 | 693 (1.5) | 0.003 | 713 (1.2) | 308 (1.1) | 0.008 | 680 (1.1) | 0.006 |
| **ED visit due to diabetes** | | | | | | | | | | |
| 0 | 45,163 (97.1) | 114,622 (97.3) | 0.012 | 45,022 (97.1) | 0.000 | 59,623 (97.3) | 27,814 (97.5) | 0.012 | 59,947 (97.4) | 0.006 |
| 1 | 1,088 (2.3) | 2,683 (2.3) | 0.004 | 1,083 (2.3) | 0.000 | 1,391 (2.3) | 608 (2.1) | 0.009 | 1,355 (2.2) | 0.005 |
| ≥2 | 267 (0.6) | 515 (0.4) | 0.019 | 269 (0.6) | 0.001 | 269 (0.4) | 110 (0.4) | 0.008 | 252 (0.4) | 0.005 |
| **Physician encounters** | | | | | | | | | | |
| 0 | 3,641 (7.8) | 14,055 (11.9) | 0.138 | 3,593 (7.7) | 0.003 | 4,576 (7.5) | 2,945 (10.3) | 0.100 | 4,328 (7.0) | 0.017 |
| 1-3 | 6,564 (14.1) | 22,470 | 0.134 | 6,524 | 0.001 | 8,913 (14.5) | 5,140 (18.0) | 0.094 | 8,738 (14.2) | 0.010 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | (19.1) | | (14.1) | | | | | | |
| 4-6 | 8,724 (18.8) | 23,460 (19.9) | 0.029 | 8,727 (18.8) | 0.002 | 12,891 (21.0) | 6,357 (22.3) | 0.030 | 12,881 (20.9) | 0.003 |
| ≥7 | 27,589 (59.3) | 57,835 (49.1) | 0.206 | 27,531 (59.4) | 0.001 | 34,903 (57.0) | 14,090 (49.4) | 0.152 | 35,607 (57.8) | 0.018 |
| **Gastroenterologist encounters** | | | | | | | | | | |
| 0 | 42,331 (91.0) | 109,632 (93.1) | 0.076 | 42,264 (91.1) | 0.005 | 56,264 (91.8) | 26,636 (93.4) | 0.059 | 56,682 (92.1) | 0.010 |
| 1-3 | 2,473 (5.3) | 5,123 (4.3) | 0.045 | 2,446 (5.3) | 0.002 | 3,042 (5.0) | 1,147 (4.0) | 0.046 | 2,854 (4.6) | 0.015 |
| 4-6 | 1,044 (2.2) | 1,826 (1.5) | 0.051 | 953 (2.1) | 0.013 | 1,209 (2.0) | 449 (1.6) | 0.030 | 1,250 (2.0) | 0.004 |
| ≥7 | 670 (1.4) | 1,239 (1.1) | 0.035 | 712 (1.5) | 0.008 | 768 (1.3) | 300 (1.1) | 0.019 | 768 (1.2) | 0.000 |
| **ED visit** | | | | | | | | | | |
| 0 | 31,207 (67.1) | 78,650 (66.8) | 0.007 | 31,080 (67.0) | 0.001 | 45,561 (74.3) | 21,919 (76.8) | 0.058 | 45,931 (74.6) | 0.006 |
| 1 | 7,758 (16.7) | 19,801 (16.8) | 0.003 | 7,733 (16.7) | 0.000 | 9,329 (15.2) | 4,016 (14.1) | 0.032 | 9,325 (15.1) | 0.002 |
| ≥2 | 7,553 (16.2) | 19,369 (16.4) | 0.005 | 7,561 (16.3) | 0.002 | 6,393 (10.4) | 2,597 (9.1) | 0.045 | 6,298 (10.2) | 0.007 |
| **Flu vaccine** | 24,498 (52.7) | 56,327 (47.8) | 0.097 | 24,501 (52.8) | 0.003 | 32,500 (53.0) | 13,647 (47.8) | 0.104 | 33,453 (54.3) | 0.026 |
| **Low income subsidy** | 22,093 (47.5) | 50,759 (43.1) | 0.089 | 21,905 (47.2) | 0.005 | 26,742 (43.6) | 13,561 (47.5) | 0.078 | 25,033 (40.7) | 0.060 |
| **Smoking‡‡** | 5,535 (11.9) | 13,635 (11.6) | 0.010 | 5,542 (12.0) | 0.002 | 6,076 (9.9) | 2,075 (7.3) | 0.094 | 6,052 (9.8) | 0.003 |
| **Appendectomy** | 15 (0.0) | 46 (0.0) | 0.004 | 15 (0.0) | 0.000 | 26 (0.0) | 14 (0.0) | 0.003 | 22 (0.0) | 0.004 |

Abbreviations: GLP1RA, Glucagon-like peptide-1 receptor agonist; SGLT2i, Sodium-glucose Cotransporter 2 inhibitor; LAI, long acting insulin; ACE inhibitors, Angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCBs, calcium-channel blockers; NA, not applicable; No, number.

* The comparisons were defined by use of IBT and PS-weighted comparator. Covariates were measured in 12 months before the first prescription including the index date (New users appear to 100% have the treatment at baseline). Initiation defined as having no prescriptions of either drug class during the 12 months prior to initiation.

† The size of the population for a specific drug differed across cohorts because of the requirement not to have been treated prior to index date with the comparator drug class. As shown in **Supplementary Figure 3**, before PS trimming, the sample size is 47,927 vs 122,399 in DPP4i vs SU comparison, and 63,474 vs 30,059 in DPP4i vs TZD comparison, respectively.

‡ Weighted by standardizing to their distribution in incretin-based therapy initiators by using weights of 1 for DPP4i initiators and the odds of the estimated propensity score for comparator initiators.

§ Gastrointestinal disease was grouped according to the ICD9 classification (http://www.icd9data.com/2012/Volume1/520-579/default.htm).

|| Patients with congestive baseline heart failure were excluded for DPP4i vs TZD comparison; and patients are required not to have been treated prior to index date with the comparator drug class.

¶ Diabetic nephropathy codes (250.40-250.43) were not included to identify chronic kidney disease (ICD-9-CM codes: 016.0; 095.4; 189.0; 189.9; 223.0; 236.91; 271.4; 274.1; 283.11; 403; 404; 440.1; 442.1; 572.4; 581-588; 591; 753.12-753.19; 753.2; 794.4).

# Other drugs may induce inflammatory bowel disease include Isotretinoin, Mycophenolate mofetil, Etanercept, Ipilimumab, and Rituximab (Supplementary Tables 2B).

** The denominator of percentage is number of female patients.

†† Hyperglycemia diagnoses include diabetes with ketoacidosis (ICD-9-CM codes 2501), diabetes with hyperosmolarity (ICD-9-CM codes 2502), and diabetes with other coma (ICD-9-CM codes 2503), and uncontrolled diabetes (ICD-9-CM codes 25002, 25003).

‡‡ Smoking was defined using a previously validated algorithm that was a composite of tobacco use diagnosis codes or consultation CPT codes or prescription filled for smoking cessation. Although perfect specificity and positive predictive value, this measure has poor sensitivity (27.9% [95% CI 16.6%-39.1%]) (reference 26)

SUPPLEMENTARY DATA

**Supplementary Table 4A. The time between first and second prescription and length of treatment duration and follow-up time in the analyzed cohort*.**

| | | | MarketScan | | | | Medicare | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | DPP4i vs SU | | DPP4i vs TZD | | DPP4i vs SU | | DPP4i vs TZD | |
| | | | DPP4i (N†=117,548) | SU (N†=199,744) | DPP4i (N†=146,880) | TZD (N†=60,237) | DPP4i (N†=44,064) | SU (N†=110,806) | DPP4i (N†=58,690) | TZD (N†=27,306) |
| Days between first and second prescription (median) | | | 35 (28-65) | 33 (27-61) | 35 (28-63) | 35 (28-66) | 32 (27-61) | 33 (27-71) | 32 (27-63) | 32 (28-63) |
| Duration of treatment (years) ‡ | | median | 1.21 (0.73-2.04) | 1.12 (0.66-1.96) | 1.27 (0.75-2.13) | 1.09 (0.67-1.88) | 1.42 (0.75-2.49) | 1.69 (0.90-2.91) | 1.50 (0.81-2.57) | 1.27 (0.74-2.18) |
| | | mean | 1.59 (1.26) | 1.53 (1.25) | 1.66 (1.28) | 1.48 (1.20) | 1.88 (1.53) | 2.17 (1.68) | 1.95 (1.53) | 1.71 (1.42) |
| | | maximum | 8.75 | 8.75 | 8.75 | 8.74 | 8.75 | 8.75 | 8.75 | 8.75 |
| Length of follow-up (years): | As-treated analysis§ | median | 0.84 (0.43-1.65) | 0.78 (0.41-1.57) | 0.89 (0.47-0.71) | 0.80 (0.42-1.55) | 1.08 (0.53-2.12) | 1.28 (0.64-2.49) | 1.14 (0.59-2.17) | 1.01 (0.52-1.91) |
| | | mean | 1.24 (1.19) | 1.19 (1.18) | 1.29 (1.22) | 1.18 (1.15) | 1.57 (1.44) | 1.83 (1.61) | 1.62 (1.44) | 1.46 (1.35) |
| | | maximum | 8.21 | 8.18 | 8.20 | 8.17 | 8.19 | 8.19 | 8.18 | 8.15 |
| | Initial-treatment analysis‖ | median | 1.79 (0.86-3.35) | 1.78 (0.85-3.30) | 1.72 (0.84-3.16) | 2.13 (0.97-4.12) | 2.58 (1.34-4.33) | 2.77 (1.37-4.76) | 2.51 (1.34-4.24) | 3.86 (1.76-6.04) |
| | | mean | 2.29 (1.83) | 2.28 (1.85) | 2.20 (1.77) | 2.71 (2.12) | 2.97 (1.95) | 3.19 (2.11) | 2.93 (1.93) | 3.95 (2.34) |
| | | maximum | 8.25 | 8.24 | 8.25 | 8.21 | 8.24 | 8.24 | 8.24 | 8.21 |

* median (interquartile range); mean (standard deviation).

† The sample size is equal to the sample size in Table 2, which is the number of population when follow-up started.

‡ The duration of treatment is longer than the follow-up time because 1) follow-up started 180 days post the second prescription; 2) when patients are censored due to end of coverage, death (Medicare only), or end of study, the 180-day lag period cannot be applied after stopping.

§Analysis was based on as-treated exposure definition, follow-up started from 180 days (induction period) post the second prescription, ended at the earliest of the following events: 1) 180 days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016), or 5) observation of an incident IBD event.

‖ Initial-treatment analysis is defined as completely ignoring treatment changes during follow-up (this mimics the intention-to-treat analysis in a randomized trial and is equivalent to an indefinite induction period). The follow-up ends with the earliest of the following events: death (for Medicare beneficiaries only), end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries), or incident IBD event.

SUPPLEMENTARY DATA

**Supplementary Table 4B. Number of prescriptions for overall analyzed population and patients with incident IBD during follow-up*.**

| | MarketScan | | | | Medicare | | | |
|---|---|---|---|---|---|---|---|---|
| | DPP4i vs SU | | DPP4i vs TZD | | DPP4i vs SU | | DPP4i vs TZD | |
| **Overall analyzed cohort** | **DPP4i (N†=117,548)** | **SU (N†=199,744)** | **DPP4i (N†=146,880)** | **TZD (N†=60,237)** | **DPP4 (N†=46,511)** | **SU (N†=117,792)** | **DPP4i (N†=61,275)** | **TZD (N†=28,530)** |
| Number of prescriptions during follow-up: (median (IQR)) | 8 (5-15) | 8 (4-14) | 8 (5-15) | 7 (4-13) | 11 (6-22) | 12 (6-22) | 11 (5-21) | 9 (5-17) |
| **Patients with incident IBD** | **DPP4i (N=35)** | **SU (N=53)** | **DPP4i (N=40)** | **TZD (N=23)** | **DPP4i (N=NTSR)** | **SU (N=44)** | **DPP4i (N=17)** | **TZD (N=12)** |
| Number of prescriptions during follow-up: (median (IQR)) | 9 (6-14) | 10 (6-16) | 9 (5.5-12.5) | 6 (5-12) | 12.5 (3.5-15.5) | 11 (7.5-20.5) | 15 (12-18) | 12.5 (6.5-22.5) |

IQR (interquartile range), 25th and 75th percentile.
* Based on primary analysis (as-treated).
†The sample size is equal to the sample size in Table 2, which is the number of population when follow-up started.

SUPPLEMENTARY DATA

**Supplementary Table 4C. Reasons for censoring of follow-up in primary analysis*.**

| Censoring reason | MarketScan | | | | Medicare | | | |
|---|---|---|---|---|---|---|---|---|
| | DPP4i vs SU | | DPP4i vs TZD | | DPP4i vs SU | | DPP4i vs TZD | |
| | DPP4i (N†=117,548) | SU (N†=199,744) | DPP4i (N†=146,880) | TZD (N†=60,237) | DPP4i (N†=44,064) | SU (N†=110,806) | DPP4i (N†=58,690) | TZD (N†=27,306) |
| **Switching or augmenting**‡ | 15971 (13.6) | 18293 (9.2) | 6042 (4.1) | 6759 (11.2) | 6778 (15.4) | 10851 (9.8) | 2530 (4.3) | 3313 (12.1) |
| **Discontinuation of treatment** | 45053 (38.3) | 88339 (44.2) | 63959 (43.5) | 30748 (51.0) | 19028 (43.2) | 48351 (43.6) | 30295(51.6) | 16188 (59.3) |
| **End of coverage**§ | 56562 (48.1) | 93178 (46.6) | 76925 (52.4) | 22754 (37.8) | 18275 (41.5) | 51616 (46.6) | 25880 (44.1) | 7810 (28.6) |
| **Death** | NA | NA | NA | NA | 4183 (9.5) | 14066 (12.7) | 4455 (7.6) | 1725 (6.3) |
| **End of study (12/31/2016)** | 15085 (12.8) | 22909 (11.5) | 22954 (15.6) | 3922 (6.5) | 10836 (24.6) | 28477 (25.7) | 16596 (28.3) | 4172 (15.3) |
| ***Outcome***‖ | 35 (0.0) | 53 (0.0) | 40 (0.0) | 23 (0.0) | 8 (0.0) | 44 (0.0) | 17 (0.0) | 12 (0.0) |

NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (% is not shown in this case to block the number of event).

* Censoring reason for each category is not mutually exclusive.

† The sample size is equal to the sample size in Table 2, which is the number of population when follow-up started, i.e. after propensity-score trimming and excluding those patients had IBD events, with discontinuation of enrollment in the 180 days (induction period) post the second prescription.

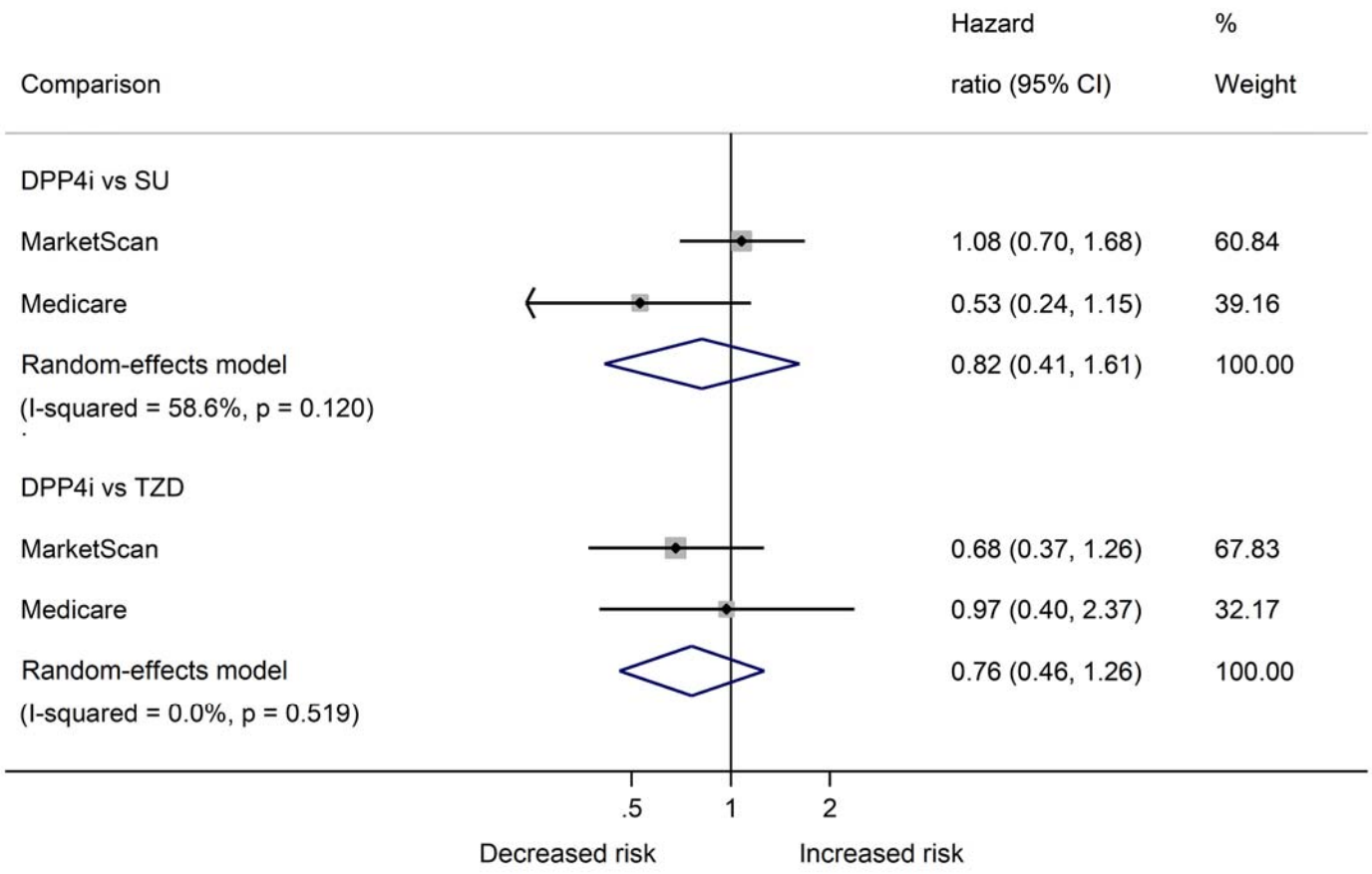
‡ Initiating the other drug in the drug pair that is being compared

§ For Medicare data, this is entirely driven by losing part D.

‖ Outcome is also included for comparison purpose.

SUPPLEMENTARY DATA

**Supplementary Figure 5.** Association between Treatment with DPP4i and the Risk of IBD in primary analysis. The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 5. Crude and adjusted hazard ratios for Crohn's disease associated with use of DPP4i compared with therapeutic alternatives*.**

| Comparison | Database | Cohort | No. of Patients† | Median duration (yr) of treatment (IQR) | Person-yr | No. of CD events | CD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting‡ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| DPP4i vs SU | MarketScan | DPP4i | 117,548 | 1.21 (0.73-2.04) | 146,197 | 13 | 8.9 (5.2-15.3) | 1.32 (0.64-2.75) | 1.38 (0.65-2.93) |
| | | SU | 199,744 | 1.12 (0.66-1.97) | 238,603 | 16 | 6.7 (4.1-10.9) | | |
| | Medicare | DPP4i | 44,064 | 1.42 (0.75-2.49) | NA | NTSR | 1.4 (0.2-10.3) | 0.35 (0.04-2.79) | 0.44 (0.05-3.59) |
| | | SU | 110,806 | 1.69 (0.90-2.91) | NA | NTSR | 4.0 (2.0-7.9) | | |
| DPP4i vs TZD | MarketScan | DPP4i | 146,880 | 1.27 (0.75-2.13) | 190,019 | 16 | 8.4 (5.2-13.7) | 0.69 (0.30-1.55) | 0.84 (0.35-2.00) |
| | | TZD | 60,237 | 1.09 (0.67-1.88) | 71,275 | 9 | 12.6 (6.6-24.3) | | |
| | Medicare | DPP4i | 58,690 | 1.50 (0.81-2.57) | NA | NTSR | 4.2 (1.6-11.2) | 0.27 (0.08-0.92) | 0.50 (0.13-1.94) |
| | | TZD | 27,306 | 1.27 (0.74-2.18) | NA | NTSR | 15.1 (6.8-33.5) | | |

Abbreviations: Yr, year; IQR, interquartile range; HR, hazard ratio; CD, Crohn's disease; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

* Analysis was based on as-treated exposure definition, follow-up started from 180 days (induction period) post the second prescription, ended at the earliest of the following events: 1) 180 days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016), or 5) observation of an incident IBD event.

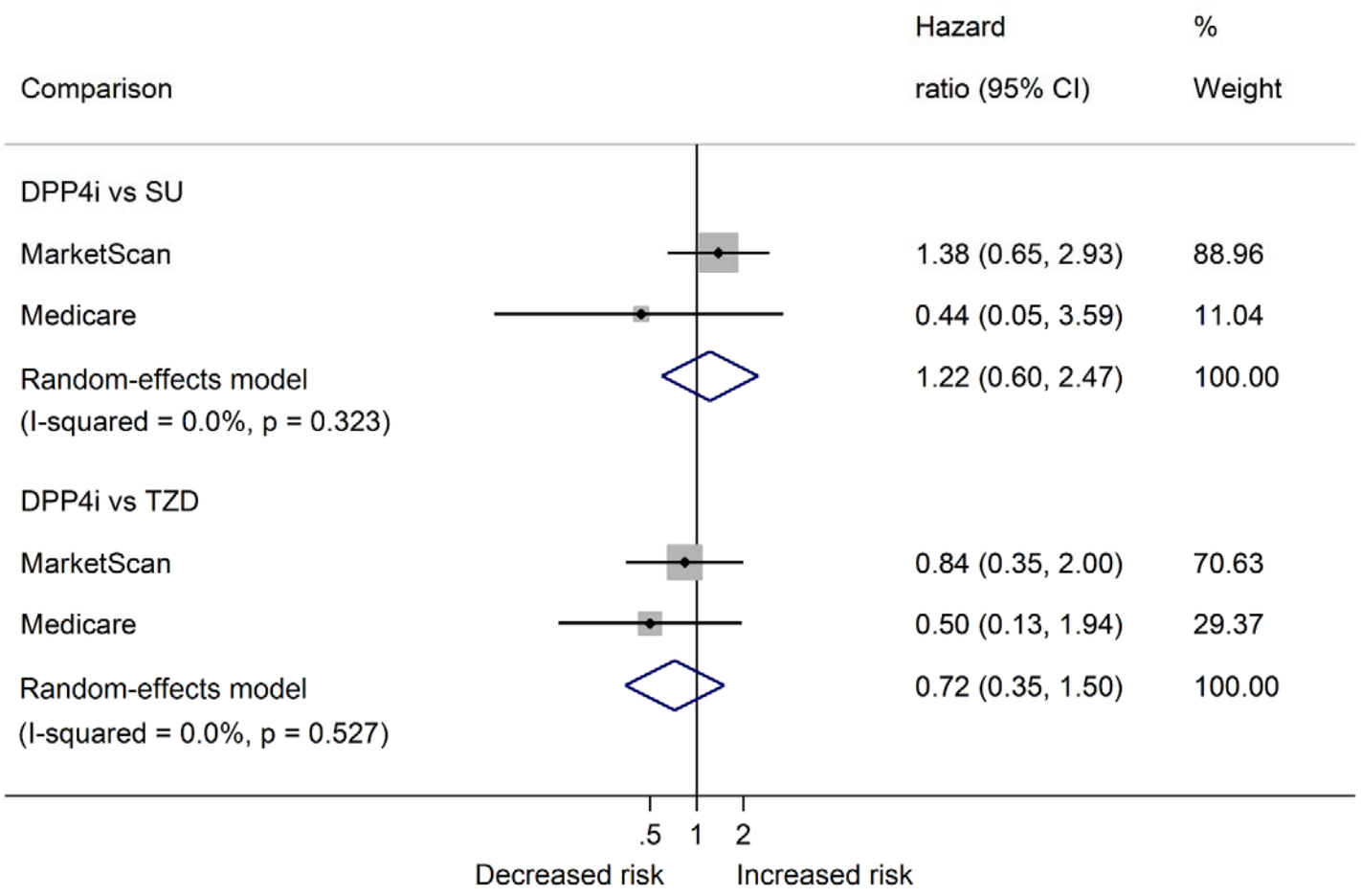
† Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

‡ Propensity score weighted HRs were standardized to the distribution of baseline covariates in DPP4i initiators.

§ Median duration of treatment is not shown due to number of event is too small to report.

SUPPLEMENTARY DATA

**Supplementary Figure 6. Forest plot of the association between use of DPP4i and CD risk.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 6. Crude and adjusted hazard ratios for ulcerative colitis associated with use of DPP4i compared with therapeutic alternatives*.**

| Comparison | Database | Cohort | No. of Patients† | Median duration (yr) of treatment (IQR) | Person-yr | No. of UC events | UC rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting‡ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| DPP4i vs SU | MarketScan | DPP4i | 117,548 | 1.21 (0.73-2.04) | 146,185 | 26 | 17.8 (12.1-26.1) | 0.94 (0.58-1.53) | 0.93 (0.56-1.52) |
| | | SU | 199,744 | 1.12 (0.66-1.96) | 238,563 | 45 | 18.9 (14.1-25.3) | | |
| | Medicare | DPP4i | 44,064 | 1.42 (0.75-2.49) | NA | NTSR | 10.1 (4.8-21.2) | 0.52 (0.23-1.15) | 0.51 (0.22-1.18) |
| | | SU | 110,806 | 1.69 (0.90-2.91) | 202,393 | 39 | 19.3 (14.1-26.4) | | |
| DPP4i vs TZD | MarketScan | DPP4i | 146,880 | 1.27 (0.75-2.13) | 190,008 | 28 | 14.7 (10.2-21.3) | 0.59 (0.33-1.07) | 0.58 (0.28-1.20) |
| | | TZD | 60,237 | 1.09 (0.67-1.88) | 71,275 | 18 | 25.3 (15.9-40.1) | | |
| | Medicare | DPP4i | 58,690 | 1.50 (0.81-2.57) | 95,352 | 15 | 15.7 (9.5-26.1) | 0.77 (0.33-1.80) | 1.27 (0.43-3.76) |
| | | TZD | 27,306 | 1.27 (0.74-2.18) | NA | NTSR | 20.1 (10.0-40.2) | | |

Abbreviations: Yr, year; IQR, interquartile range; HR, hazard ratio; PS, propensity score; CI, confidence interval; UC, ulcerative colitis; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

* Analysis was based on as-treated exposure definition, follow-up started from 180 days (induction period) post the second prescription, ended at the earliest of the following events: 1) 180 days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016), or 5) observation of an incident IBD event.

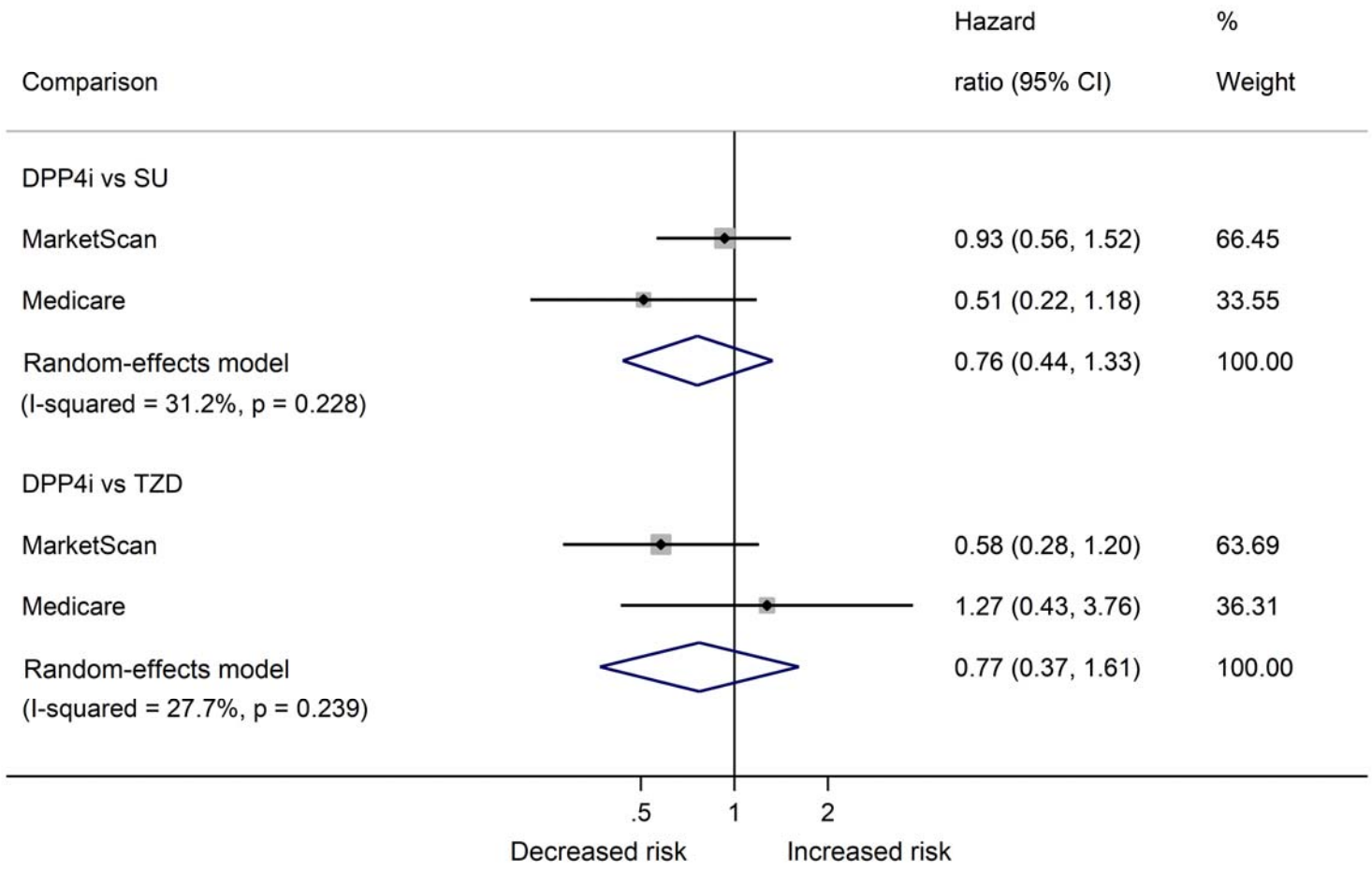
† Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

‡ Propensity score weighted HRs were standardized to the distribution of baseline covariates in DPP4i initiators.

§ Median duration of treatment is not shown due to number of event is too small to report.

SUPPLEMENTARY DATA

**Supplementary Figure 7. Forest plot of the association between use of DPP4i and UC risk.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 7. Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of DPP4i compared with therapeutic alternatives stratified by age*.**

| Database | Stratum | Comparison | Cohort | No. of Patients† | Median duration (yr) of treatment (IQR) | Person-yr | No. of IBD disease events | IBD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting‡ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Age** | | | | | | | | | |
| MarketScan | 18≤age<50 | DPP4i vs SU | DPP4i | 36,726 | 1.07 (0.66-1.82) | 42,356 | 10 | 23.6 (12.7-43.9) | 1.22 (0.55-2.69) | 1.48 (0.66-3.34) |
| | | | SU | 72,612 | 0.90 (0.56-1.66) | 76,698 | 15 | 19.6 (11.8-32.4) | | |
| | | DPP4i vs TZD | DPP4i | 45,807 | 1.13 (0.69-1.94) | 55,729 | 11 | 19.7 (10.9-35.6) | 0.88 (0.31-2.53) | 1.73 (0.59-5.01) |
| | | | TZD | 19,759 | 0.98 (0.62-1.71) | 22,070 | 5 | 22.7 (9.4-54.4) | | |
| | 50≤age<65 | DPP4i vs SU | DPP4i | 80,741 | 1.27 (0.75-2.14) | 103,731 | 24 | 23.1 (15.5-34.5) | 0.98 (0.59-1.63) | 0.94 (0.55-1.59) |
| | | | SU | 126,289 | 1.26 (0.74-2.12) | 161,159 | 38 | 23.6 (17.2-32.4) | | |
| | | DPP4i vs TZD | DPP4i | 101,055 | 1.33 (0.78-2.22) | 134,304 | 29 | 21.6 (15.0-31.1) | 0.61 (0.34-1.09) | 0.55 (0.28-1.10) |
| | | | TZD | 40,524 | 1.15 (0.71-1.97) | 49,188 | 18 | 36.6 (23.1-58.1) | | |
| Medicare | 65≤age<75 | DPP4i vs SU | DPP4i | 24,387 | 1.43 (0.75-2.51) | NA | NTSR | 15.4 (6.9-34.3) | 0.65 (0.27-1.56) | 0.64 (0.25-1.61) |
| | | | SU | 64,217 | 1.74 (0.92-2.99) | 121,684 | 28 | 23.0 (15.9-33.3) | | |
| | | DPP4i vs TZD | DPP4i | 34,048 | 1.50 (0.82-2.58) | 55,775 | 15 | 26.9 (16.2-44.6) | 0.98 (0.40-2.39) | 1.26 (0.39-4.04) |
| | | | TZD | 17,481 | 1.30 (0.74-2.24) | NA | NTSR | 26.7 (12.7-55.9) | | |
| | age≥75 | DPP4i vs SU | DPP4i | 19,626 | 1.42 (0.75-2.46) | NA | NTSR | 6.6 (1.7-26.5) | 0.33 (0.08-1.44) | 0.33 (0.07-1.50) |
| | | | SU | 46,747 | 1.63 (0.87-2.75) | 81,242 | 16 | 19.7 (12.1-32.1) | | |
| | | DPP4i vs TZD | DPP4i | 24,830 | 1.50 (0.80-2.55) | NA | NTSR | 5.0 (1.3-20.0) | 0.18 (0.03-0.99) | 0.46 (0.08-2.70) |
| | | | TZD | 9,954 | 1.24 (0.71-2.08) | NA | NTSR | 28.8 (10.8-76.8) | | |

Abbreviations: Yr, year; IQR, interquartile range; HR, hazard ratio; PS, propensity score; CI, confidence interval; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

***** Analysis was based on as-treated exposure definition, follow-up started from 180 days (induction period) post the second prescription, ended at the earliest of the following events: 1) 180 days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016), or 5) observation of an incident IBD event. † Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

‡ Propensity score weighted HR were standardized to the distribution of baseline covariates in DPP4i initiators.

SUPPLEMENTARY DATA

**Supplementary Table 8. Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of DPP4i compared with therapeutic alternatives stratified by sex*.**

| Stratum | Comparison | Database | Cohort | No. of Patients† | Median duration (yr) of treatment (IQR) | Person-yr | No. of IBD disease events | IBD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting‡ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Gender** | | | | | | | | | | |
| Female | DPP4i vs SU | MarketScan | DPP4i | 53,195 | 1.16 (0.70-1.97) | 64,630 | 17 | 26.3 (16.4-42.3) | 0.95 (0.52-1.73) | 1.01 (0.55-1.88) |
| | | | SU | 91,235 | 1.01 (0.60-1.82) | 101,816 | 28 | 27.5 (19.0-39.8) | | |
| | | Medicare | DPP4i | 26,109 | 1.42 (0.75-2.51) | NA | NTSR | 2.4 (0.3-17.1) | 0.15 (0.02-1.11) | 0.13 (0.02-1.04) |
| | | | SU | 62,085 | 1.66 (0.87-2.90) | 113,161 | 18 | 15.9 (10.0-25.2) | | |
| | DPP4i vs TZD | MarketScan | DPP4i | 67,617 | 1.23 (0.74-2.05) | 85,408 | 19 | 22.2 (14.2-34.9) | 0.57 (0.27-1.17) | 0.56 (0.24-1.31) |
| | | | TZD | 24,749 | 1.00 (0.63-1.73) | 27,133 | 11 | 40.5 (22.4-73.2) | | |
| | | Medicare | DPP4i | 34,379 | 1.51 (0.81-2.61) | NA | NTSR | 10.5 (4.7-23.5) | 0.45 (0.14-1.45) | 0.46 (0.13-1.59) |
| | | | TZD | 15,091 | 1.23 (0.71-2.14) | NA | NTSR | 23.0 (9.6-55.4) | | |
| Male | DPP4i vs SU | MarketScan | DPP4i | 64,358 | 1.24 (0.74-2.09) | 81,536 | 18 | 22.1 (13.9-35.0) | 1.20 (0.65-2.19) | 1.14 (0.60-2.14) |
| | | | SU | 106,719 | 1.23 (0.73-2.09) | 135,726 | 25 | 18.4 (12.4-27.3) | | |
| | | Medicare | DPP4i | 17,934 | 1.42 (0.75-2.45) | NA | NTSR | 25.2 (12.0-52.9) | 0.86 (0.38-1.95) | 0.88 (0.37-2.11) |
| | | | SU | 48,904 | 1.73 (0.93-2.92) | 89,639 | 26 | 29.0 (19.7-42.6) | | |
| | DPP4i vs TZD | MarketScan | DPP4i | 79,973 | 1.31 (0.76-2.19) | 105,467 | 21 | 19.9 (13.0-30.5) | 0.69 (0.34-1.38) | 0.88 (0.38-2.00) |
| | | | TZD | 35,595 | 1.16 (0.70-2.00) | 44,324 | 13 | 29.3 (17.0-50.5) | | |
| | | Medicare | DPP4i | 24,337 | 1.48 (0.81-2.50) | 38,476 | 11 | 28.6 (15.8-51.6) | 0.85 (0.32-2.28) | 2.81 (1.02-7.76) |
| | | | TZD | 12,242 | 1.33 (0.74-2.23) | NA | NTSR | 33.0 (14.8-73.4) | | |

Abbreviations: Yr, year; IQR, interquartile range; HR, hazard ratio; PS, propensity score; CI, confidence interval; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

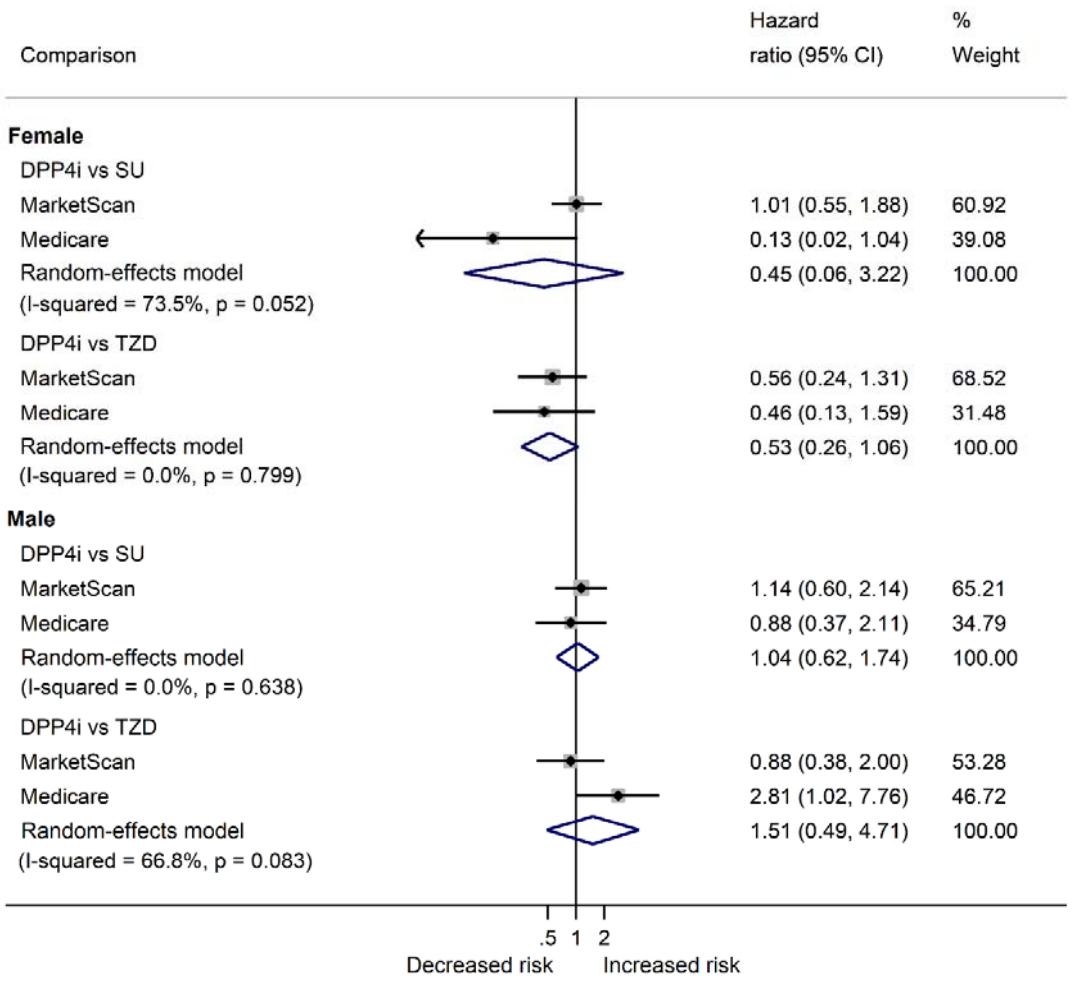
***** Analysis was based on as-treated exposure definition, follow-up started from 180 days (induction period) post the second prescription, ended at the earliest of the following events: 1) 180 days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016), or 5) observation of an incident IBD event.

† Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

‡ Propensity score weighted HR were standardized to the distribution of baseline covariates in DPP4i initiators.

SUPPLEMENTARY DATA

**Supplementary Figure 8. Forest plot of the association between use of DPP4i and IBD risk stratified by sex.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 9. Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of DPP4i compared with therapeutic alternatives stratified by duration of treatment*.**

| Stratum | Comparison | Database | Cohort | No. of Patients† | Median duration (yr) of treatment (IQR) ‡ | Person-yr | No. of IBD events | IBD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting§ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Duration of treatment** | | | | | | | | | | |
| ≤12 months‖ | DPP4i vs SU | MarketScan | DPP4i | 117,544 | 1.00 (0.73-1.00) | 76,583 | 22 | 28.7 (18.9-43.6) | 1.21 (0.70-2.10) | 1.21 (0.69-2.13) |
| | | | SU | 199,668 | 1.00 (0.66-1.00) | 127,600 | 30 | 23.5 (16.4-33.6) | | |
| | | Medicare | DPP4i | 44,063 | 1.00 (0.75-1.00) | NA | NTSR | 19.2 (8.6-42.7) | 0.98 (0.38-2.50) | 0.91 (0.33-2.48) |
| | | | SU | 110,806 | 1.00 (0.90-1.00) | 81,543 | 16 | 19.6 (12.0-32.0) | | |
| | DPP4i vs TZD | MarketScan | DPP4i | 146,878 | 1.00 (0.75-1.00) | 98,263 | 27 | 27.5 (18.8-40.1) | 0.56 (0.31-1.02) | 0.55 (0.27-1.11) |
| | | | TZD | 60,228 | 1.00 (0.67-1.00) | 38,808 | 19 | 49.0 (31.2-76.8) | | |
| | | Medicare | DPP4i | 58,689 | 1.00 (0.81-1.00) | NA | NTSR | 16.3 (7.8-34.2) | 0.51 (0.17-1.52) | 0.92 (0.22-3.79) |
| | | | TZD | 27,306 | 1.00 (0.74-1.00) | NA | NTSR | 31.0 (13.9-69.1) | | |
| >12 months¶ | DPP4i vs SU | MarketScan | DPP4i | 92,352 | 1.49 (0.99-2.36) | 69,746 | 27 | 18.6 (10.8-32.1) | 0.90 (0.46-1.78) | 0.91 (0.45-1.85) |
| | | | SU | 150,640 | 1.46 (0.94-2.33) | 111,176 | 38 | 20.7 (13.7-31.1) | | |
| | | Medicare | DPP4i | 37,165 | 1.68 (1.02-2.78) | NA | NTSR | 9.3 (3.9-22.5) | 0.40 (0.16-1.01) | 0.40 (0.15-1.05) |
| | | | SU | 97,042 | 1.91 (1.17-3.15) | 162,930 | 37 | 22.7 (16.5-31.3) | | |
| | DPP4i vs TZD | MarketScan | DPP4i | 118,360 | 1.52 (1.02-2.41) | 91,929 | 27 | 15.2 (9.0-25.7) | 1.24 (0.40-3.78) | 1.99 (0.60-6.63) |
| | | | TZD | 46,891 | 1.38 (0.89-2.19) | 32,533 | 11 | 12.3 (4.6-32.8) | | |
| | | Medicare | DPP4i | 51,234 | 1.71 (1.04-2.80) | 73,985 | 14 | 18.9 (11.2-32.0) | 0.56 (0.25-1.25) | 1.18 (0.46-3.04) |
| | | | TZD | 23,129 | 1.50 (0.92-2.44) | NA | NTSR | 33.3 (17.9-61.9) | | |

Abbreviations: Yr, year; IQR, interquartile range; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event). NA, not applicable.

***** Analysis was based on as-treated exposure definition, follow-up started from 180 days (induction period) post the second prescription, ended at the earliest of the following events: 1) 180 days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016), or 5) observation of an incident IBD event.

† Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

‡ The actual duration of treatment received was shown for patients with a duration of treatment of more than 12 months.

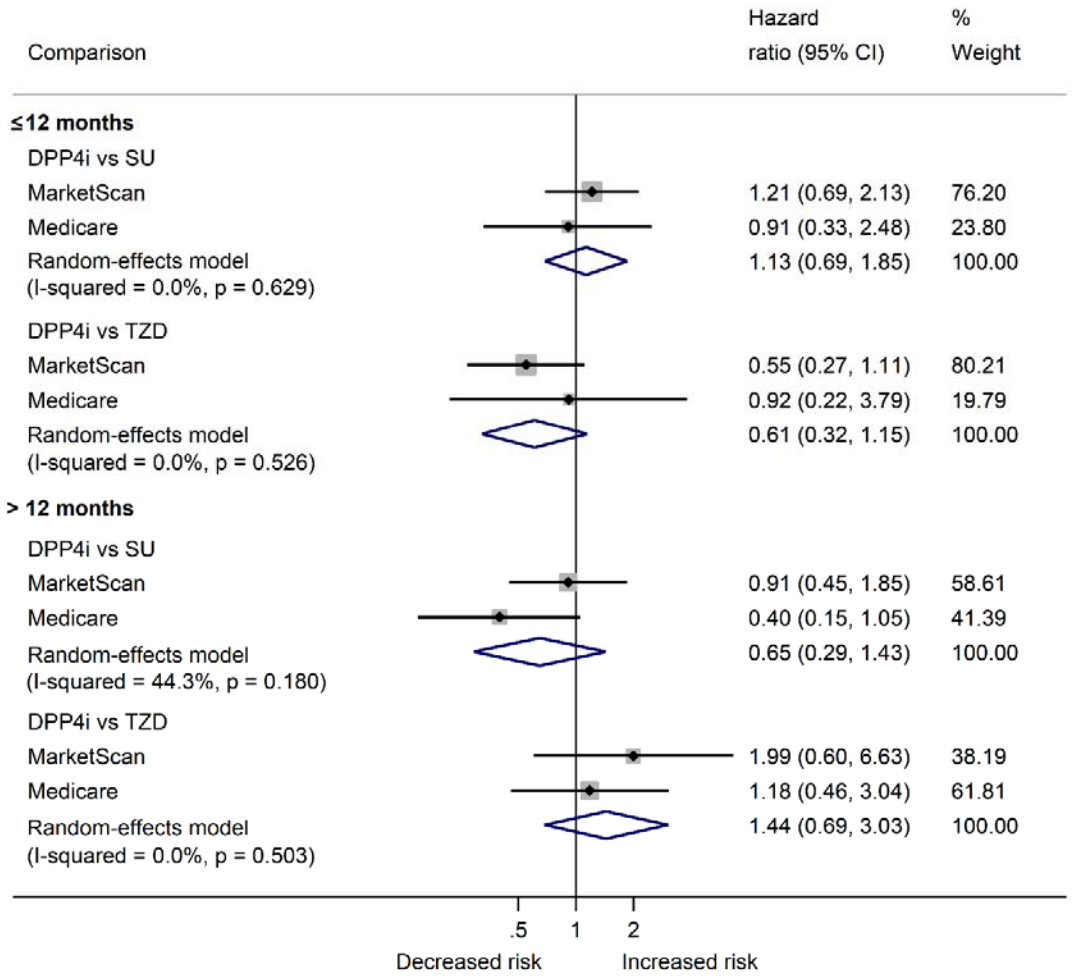
§Propensity score weighted HR were standardized to the distribution of baseline covariates in DPP4i initiators.

‖ In the stratified ≤12 months cohorts, patients were excluded if the end of 12 months treatment is prior to the start of follow-up (180 days post the second prescription), thus the numbers of patients were slightly less than those in the analyzed cohort in Table 2. Patients with a duration of treatment of more than 12 months were censored at 18 months postinitiation (12 months treatment plus 6 months latent period).

¶ In the stratified >12 months cohorts, follow-up started at 18 months post-initiation (12 months treatment plus 6 months induction period), patients with duration of treatment less than 12 months were excluded.

SUPPLEMENTARY DATA

**Supplementary Figure 9. Forest plot of the association between use of DPP4i and IBD risk stratified by time since the first prescription.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 10. Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of DPP4i compared with therapeutic alternatives according to pre-existing gastroenterological disease*.**

| Comparison | Stratum | Database | Cohort | No. of Patients† | Median duration (yr) of treatment (IQR) | Person-yr | No. of IBD events | IBD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting‡ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| No pre-existing GI disease | DPP4i vs SU | MarketScan | DPP4i | 93,563 | 1.22 (0.73-2.06) | 117,766 | 29 | 24.6 (17.1-35.4) | 1.24 (0.77-2.01) | 1.29 (0.78-2.14) |
| | | | SU | 162,851 | 1.12 (0.66-1.98) | 196,805 | 39 | 19.8 (14.5-27.1) | | |
| | | Medicare | DPP4i | 25,451 | 1.46 (0.77-2.51) | NA | NTSR | 14.9 (6.7-33.1) | 0.91 (0.37-2.23) | 1.23 (0.49-3.06) |
| | | | SU | 69,621 | 1.78 (0.95-2.98) | 131,162 | 21 | 16.0 (10.4-24.6) | | |
| | DPP4i vs TZD | MarketScan | DPP4i | 116,754 | 1.28 (0.75-2.15) | 152,704 | 35 | 22.9 (16.5-31.9) | 0.81 (0.46-1.45) | 0.71 (0.35-1.44) |
| | | | TZD | 49,497 | 1.10 (0.67-1.91) | 59,511 | 17 | 28.6 (17.8-46.0) | | |
| | | Medicare | DPP4i | 36,603 | 1.53 (0.82-2.58) | NA | NTSR | 15.0 (7.8-28.9) | 0.46 (0.18-1.17) | 0.89 (0.31-2.51) |
| | | | TZD | 18,520 | 1.32 (0.74-2.24) | NA | NTSR | 32.4 (16.8-62.2) | | |
| With pre-existing GI disease | DPP4i vs SU | MarketScan | DPP4i | 23,974 | 1.17 (0.71-1.96) | 28,388 | 6 | 21.1 (9.5-47.0) | 0.63 (0.24-1.64) | 0.58 (0.22-1.53) |
| | | | SU | 36,829 | 1.09 (0.66-1.87) | 41,694 | 14 | 33.6 (19.9-56.7) | | |
| | | Medicare | DPP4i | 18,615 | 1.39 (0.74-2.46) | NA | NTSR | 6.9 (1.7-27.7) | 0.21 (0.05-0.90) | 0.20 (0.05-0.86) |
| | | | SU | 41,391 | 1.56 (0.82-2.75) | 71,834 | 23 | 32.0 (21.3-48.2) | | |
| | DPP4i vs TZD | MarketScan | DPP4i | 30,198 | 1.26 (0.74-2.04) | 37,374 | 5 | 13.4 (5.6-32.1) | 0.28 (0.09-0.92) | 0.49 (0.14-1.68) |
| | | | TZD | 10,794 | 1.03 (0.66-1.77) | 11,837 | 6 | 50.7 (22.8-112.9) | | |
| | | Medicare | DPP4i | 22,344 | 1.46 (0.77-2.54) | NA | NTSR | 22.3 (11.2-44.7) | 1.26 (0.28-5.79) | 1.03 (0.18-5.80) |
| | | | TZD | 8,878 | 1.18 (0.67-2.07) | NA | NTSR | 16.4 (4.1-65.6) | | |

Abbreviations: Yr, year; IQR, interquartile range; GI, gastroenterological; NA, not applicable; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

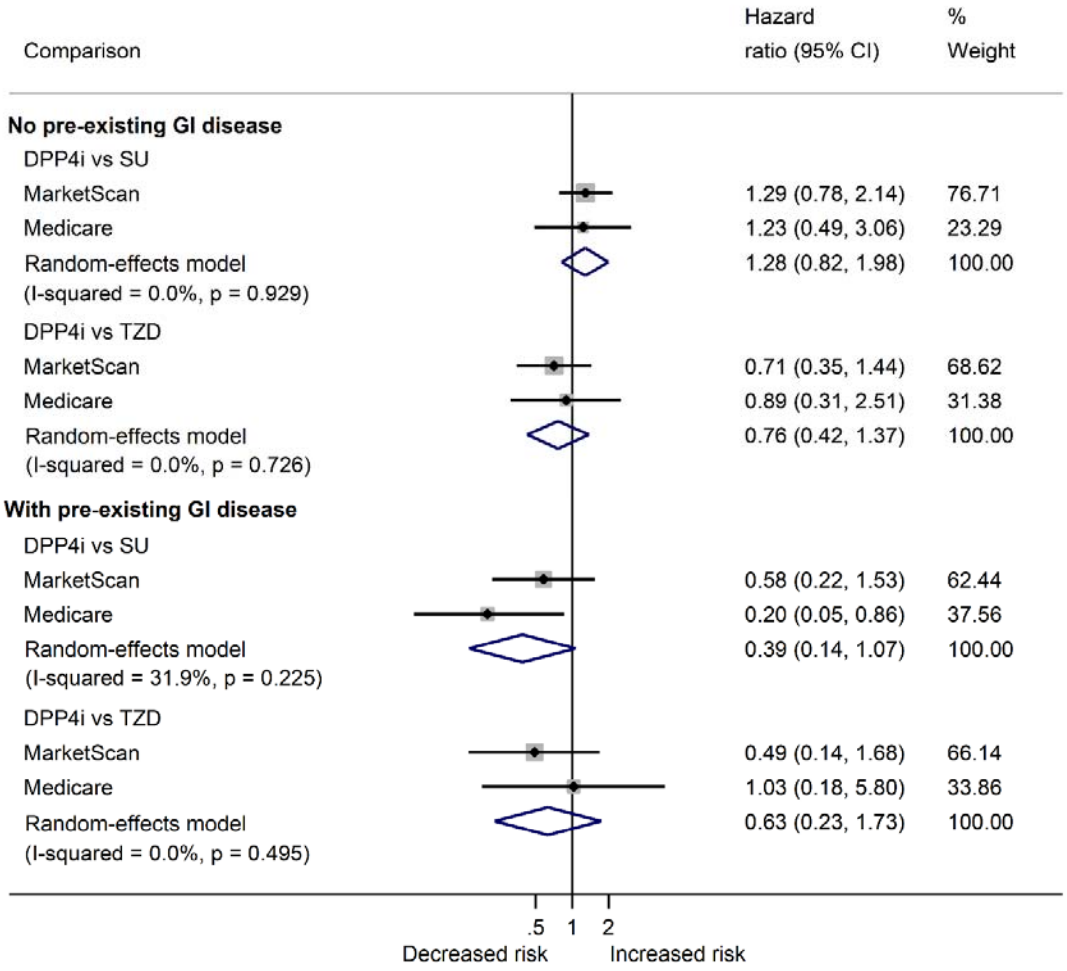
***** Analysis was based on as-treated exposure definition, follow-up started from 180 days (induction period) post the second prescription, ended at the earliest of the following events: 1) 180 days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016), or 5) observation of an incident IBD event.

† Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

‡ Propensity score weighted HR were standardized to the distribution of baseline covariates in DPP4i initiators.

SUPPLEMENTARY DATA

**Supplementary Figure 10. Forest plot of the association between use of DPP4i and IBD risk stratified by pre-existing gastrointestinal disease.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 11**. **Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of DPP4i compared with therapeutic alternatives restricted to patient with no pre-existing autoimmune disease.**

| Comparison | Database | Cohort | No. of Patient† | Median duration (yr) of treatment (IQR) | Person-yr | No. of IBD events | IBD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting ‡ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| DPP4i vs SU | MarketScan | DPP4i | 115,455 | 1.21 (0.73-2.05) | 143,744 | 34 | 23.7 (16.9-33.1) | 1.07 (0.69-1.65) | 1.08 (0.69-1.68) |
| | | SU | 196,618 | 1.12 (0.66-1.97) | 235,115 | 52 | 22.1 (16.9-29.0) | | |
| | Medicare | DPP4i | 41,938 | 1.43 (0.75-2.49) | NA | NTSR | 10.6 (5.1-22.3) | 0.50 (0.23-1.10) | 0.50 (0.22-1.14) |
| | | SU | 106,375 | 1.70 (0.91-2.92) | 195,089 | 41 | 21.0 (15.5-28.5) | | |
| DPP4i vs TZD | MarketScan | DPP4i | 144,296 | 1.27 (0.75-2.13) | 186,876 | 38 | 20.3 (14.8-27.9) | 0.63 (0.38-1.06) | 0.65 (0.35-1.20) |
| | | TZD | 59,400 | 1.09 (0.67-1.88) | 70,269 | 23 | 32.7 (21.7-49.3) | | |
| | Medicare | DPP4i | 56,330 | 1.50 (0.81-2.57) | 91,562 | 17 | 18.6 (11.5-29.9) | 0.59 (0.28-1.22) | 0.97 (0.40-2.38) |
| | | TZD | 26,359 | 1.28 (0.74-2.19) | 38,639 | 12 | 31.1 (17.6-54.7) | | |

Abbreviations: Yr, year; IQR, interquartile range; NA, not applicable; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

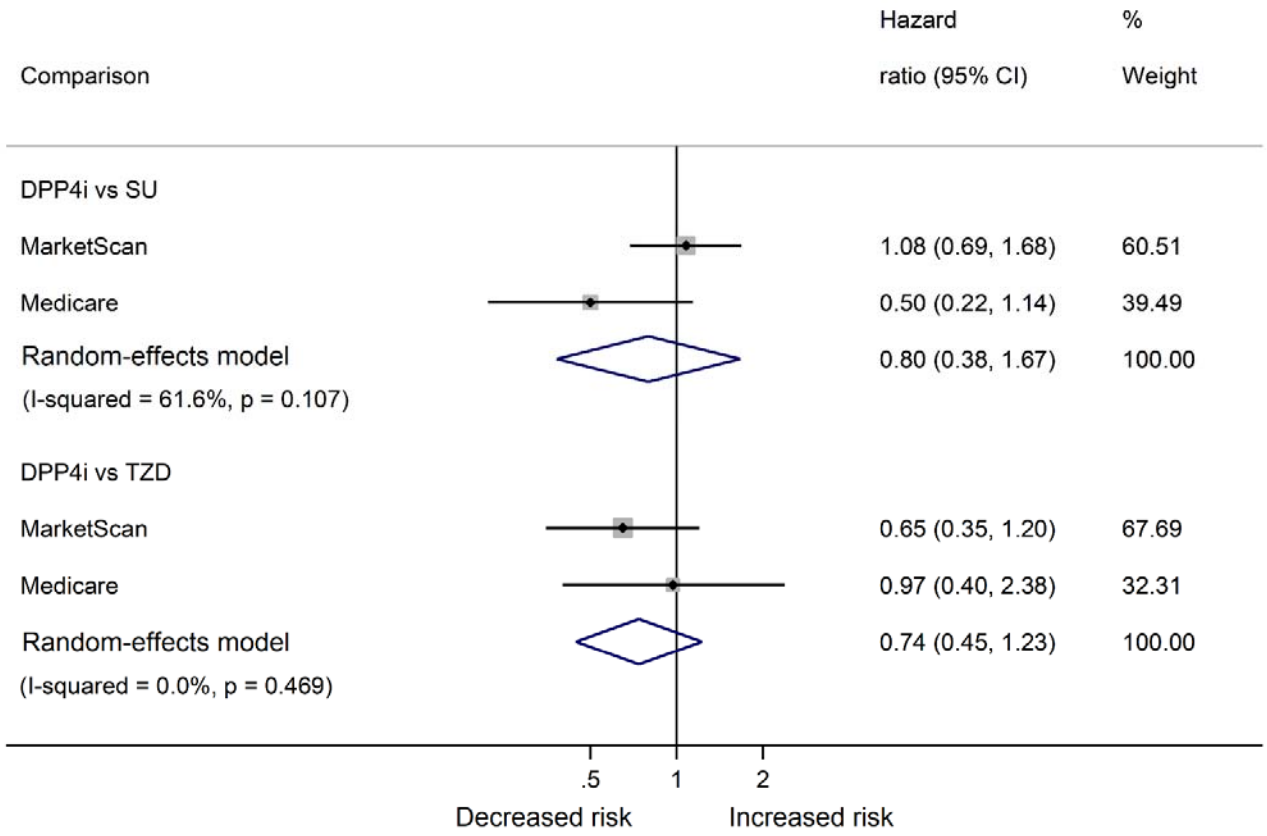
*****Analysis was based on as-treated exposure definition, follow-up started from 180 days (induction period) post the second prescription, ended at the earliest of the following events: 1) 180 days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016), or 5) observation of an incident IBD event.

† Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

‡ Propensity score weighted HR were standardized to the distribution of baseline covariates in DPP4i initiators.

SUPPLEMENTARY DATA

**Supplementary Figure 11. Forest plot of the association between use of DPP4i and IBD risk in patients with no pre-existing autoimmune disease.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 12. Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of each individual DPP4i compared with therapeutic alternatives*.**

| Comparison | Stratum† | Comparison | Cohort | No. of Patients‡ | Median duration (yr) of treatment (IQR) | Person-yr | No. of IBD events | IBD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting§ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| DPP4i vs SU | Sitagliptin vs SU | MarketScan | Sitagliptin | 85,504 | 1.21 (0.73-2.03) | 105,713 | 27 | 25.5 (17.5-37.2) | 1.18 (0.74-1.87) | 1.21 (0.75-1.95) |
| | | | SU | 199,773 | 1.12 (0.66-1.97) | 238,891 | 52 | 21.8 (16.6-28.6) | | |
| | | Medicare | Sitagliptin | 33,293 | 1.39 (0.74-2.46) | NA | NTSR | 11.6 (5.2-25.8) | 0.53 (0.23-1.24) | 0.51 (0.21-1.23) |
| | | | SU | 111,745 | 1.69 (0.90-2.91) | 204,598 | 44 | 21.5 (16.0-28.9) | | |
| | Saxagliptin vs SU | MarketScan | Saxagliptin | 22,081 | 1.10 (0.69-1.89) | 24,256 | 5 | 20.6 (8.6-49.5) | 0.91 (0.36-2.28) | 0.96 (0.37-2.45) |
| | | | SU | 173,205 | 1.09 (0.66-1.91) | 196,619 | 45 | 22.9 (17.1-30.7) | | |
| | | Medicare | Saxagliptin | 5,860 | 1.26 (0.71-2.23) | NA | NTSR | 12.7 (1.8-90.5) | 0.63 (0.09-4.61) | 0.52 (0.08-3.58) |
| | | | SU | 87,849 | 1.66 (0.91-2.74) | 147,182 | 30 | 20.4 (14.3-29.2) | | |
| | Linaglitpin vs SU | MarketScan | Linaglitpin | 8,329 | 1.05 (0.67-1.69) | 7,781 | 1 | 12.9 (1.8-91.2) | 0.61 (0.08-4.52) | 0.61 (0.08-4.66) |
| | | | SU | 124,920 | 1.09 (0.66-1.85) | 132,175 | 28 | 21.2 (14.6-30.7) | | |
| | | Medicare | Linaglitpin | 4,434 | 1.28 (0.74-1.95) | NA | NTSR | 20.6 (2.9-146.4) | 1.06 (0.14-7.96) | 1.28 (0.15-10.63) |
| | | | SU | 59,012 | 1.62 (0.91-2.46) | 84,909 | 16 | 18.8 (11.5-30.8) | | |
| DPP4i vs TZD | Sitagliptin vs TZD | MarketScan | Sitagliptin | 107,915 | 1.26 (0.75-2.11) | 138,446 | 30 | 21.7 (15.2-31.0) | 0.67 (0.39-1.14) | 0.69 (0.37-1.31) |
| | | | TZD | 60,602 | 1.09 (0.67-1.89) | 71,782 | 24 | 33.4 (22.4-49.9) | | |
| | | Medicare | Sitagliptin | 44,828 | 1.47 (0.79-2.55) | 72,113 | 14 | 19.4 (11.5-32.8) | 0.71 (0.32-1.55) | 1.04 (0.42-2.55) |
| | | | TZD | 27,582 | 1.27 (0.74-2.19) | 40,389 | 11 | 27.2 (15.1-49.2) | | |
| | Saxagliptin vs TZD | MarketScan | Saxagliptin | 26,588 | 1.17 (0.74-1.98) | 30,826 | 3 | 9.7 (3.1-30.2) | 0.26 (0.08-0.89) | 0.37 (0.11-1.32) |
| | | | TZD | 43,514 | 1.03 (0.66-1.75) | 47,502 | 18 | 37.9 (23.9-60.1) | | |
| | | Medicare | Saxagliptin | 7,653 | 1.31 (0.74-2.28) | NA | NTSR | 9.5 (1.3-67.6) | 0.36 (0.05-2.93) | 0.60 (0.07-4.80) |
| | | | TZD | 17,331 | 1.29 (0.74-2.05) | NA | NTSR | 25.5 (11.5-56.8) | | |
| | Linagliptin vs TZD | MarketScan | Linaglitpin | 11,009 | 1.12 (0.72-1.73) | 10,630 | 2 | 18.8 (4.7-75.2) | 0.60 (0.12-2.99) | 0.44 (0.09-2.23) |
| | | | TZD | 20,029 | 1.00 (0.65-1.69) | 19,621 | 6 | 30.6 (13.7-68.1) | | |
| | | Medicare | Linaglitpin | 5,734 | 1.32 (0.75-1.98) | NA | NTSR | 15.8 (2.2-111.9) | 0.59 (0.06-5.63) | 0.62 (0.06-6.17) |
| | | | TZD | 9,034 | 1.46 (0.79-2.14) | NA | NTSR | 25.9 (8.4-80.4) | | |

Abbreviations: Yr, year; IQR, interquartile range; NA, not applicable; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

***** Analysis was based on as-treated exposure definition, follow-up started from 180 days (induction period) post the second prescription, ended at the earliest of the following events: 1) 180 days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016); 5) an incident IBD event.

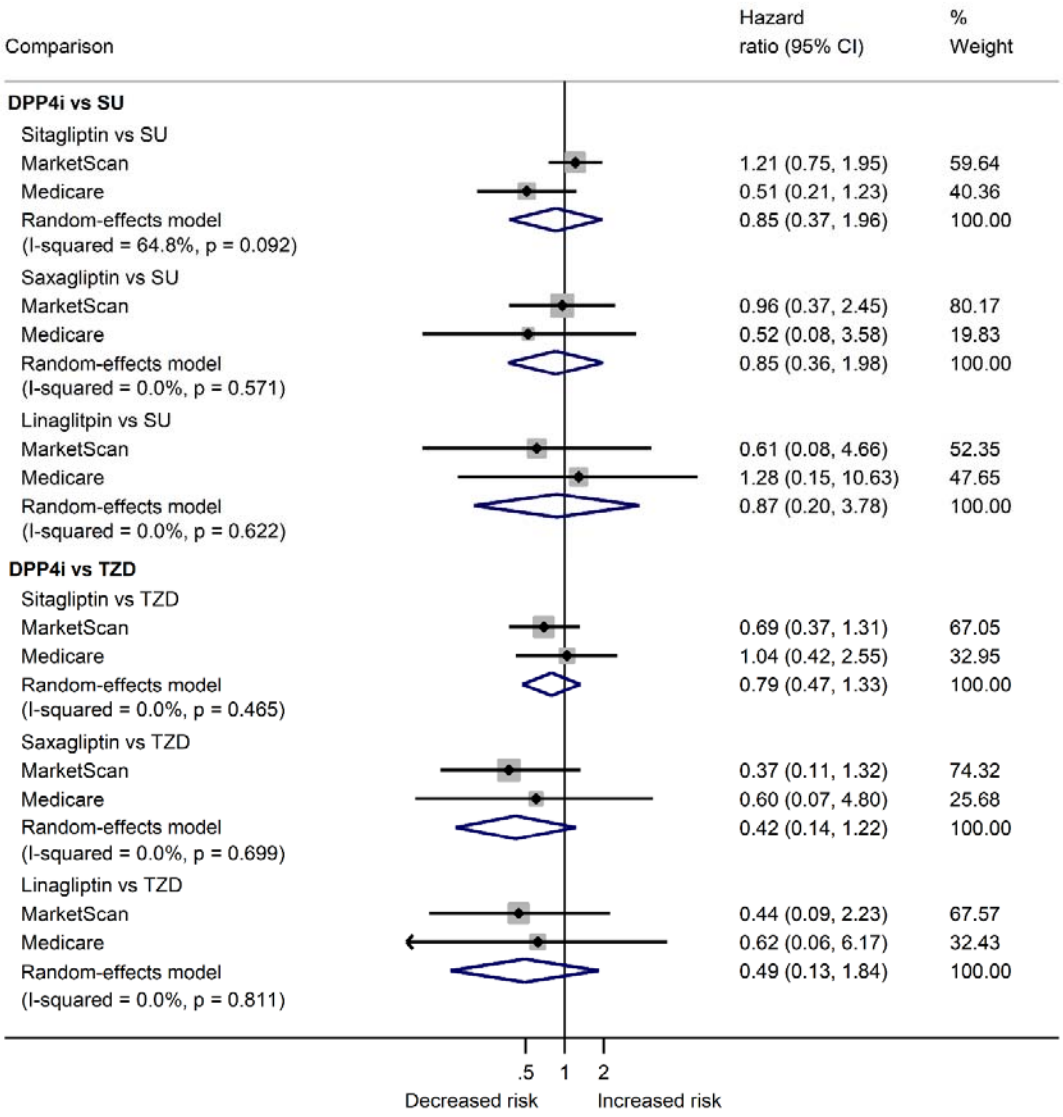
† Patients initiated two DPP4i (e.g. sitagliptin and saxagliptin) on the same day were excluded. Patients were censored when switching from one DPP4i to another DPP4i (e.g. from sitagliptin to saxagliptin). Alogliptin is not assessed due to small sample size.

SUPPLEMENTARY DATA

‡ Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.
§ Propensity score weighted HR were standardized to the distribution of baseline covariates in DPP4i initiators

SUPPLEMENTARY DATA

**Supplementary Figure 12. Forest plot of the association between use of individual DPP4i and IBD risk.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 13. Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of DPP4i compared with therapeutic alternatives by different lag periods*.**

| Comparison | Lag period† (days) | Database | Cohort | No. of Patients‡ | Median duration (yr) of treatment (IQR) | Person-yr | No. of IBD events | IBD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting§ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| DPP4i vs SU | 0-day lag period | MarketScan | DPP4i | 137,217 | 1.00 (0.56-1.84) | 176,064 | 45 | 25.6 (19.1-34.2) | 1.14 (0.78-1.66) | 1.16 (0.78-1.72) |
| | | | SU | 234,514 | 0.92 (0.51-1.76) | 287,916 | 65 | 22.6 (17.7-28.8) | | |
| | | Medicare | DPP4i | 46,511 | 1.34 (0.68-2.39) | NA | NTSR | 10.3 (5.1-20.5) | 0.51 (0.24-1.07) | 0.51 (0.23-1.10) |
| | | | SU | 117,792 | 1.57 (0.78-2.80) | 227,477 | 45 | 19.8 (14.8-26.5) | | |
| | 90-day lag period | MarketScan | DPP4i | 127,381 | 1.10 (0.64-1.94) | 160,649 | 43 | 26.8 (19.9-36.1) | 1.17 (0.79-1.74) | 1.20 (0.80-1.81) |
| | | | SU | 217,024 | 1.01 (0.58-1.86) | 262,436 | 60 | 22.9 (17.8-29.4) | | |
| | | Medicare | DPP4i | 45,303 | 1.38 (0.74-2.44) | NA | NTSR | 12.2 (6.4-23.5) | 0.60 (0.30-1.23) | 0.59 (0.28-1.24) |
| | | | SU | 114,288 | 1.63 (0.83-2.85) | 215,031 | 43 | 20.0 (14.8-27.0) | | |
| | 365-day lag period | MarketScan | DPP4i | 100,661 | 1.39 (0.76-2.25) | 118,901 | 29 | 24.4 (16.9-35.1) | 1.16 (0.72-1.87) | 1.17 (0.71-1.92) |
| | | | SU | 170,019 | 1.32 (0.69-2.17) | 193,940 | 41 | 21.1 (15.6-28.7) | | |
| | | Medicare | DPP4i | 41,587 | 1.51 (0.78-2.59) | NA | NTSR | 15.1 (7.9-29.0) | 0.64 (0.31-1.32) | 0.67 (0.31-1.43) |
| | | | SU | 103,711 | 1.80 (0.99-3.01) | 175,760 | 40 | 22.8 (16.7-31.0) | | |
| DPP4i vs TZD | 0-day lag period | MarketScan | DPP4i | 171,417 | 1.07 (0.59-1.92) | 230,487 | 52 | 22.6 (17.2-29.6) | 0.79 (0.49-1.29) | 0.79 (0.44-1.42) |
| | | | TZD | 69,166 | 0.94 (0.55-1.72) | 83,213 | 24 | 28.8 (19.3-43.0) | | |
| | | Medicare | DPP4i | 61,275 | 1.44 (0.74-2.49) | 107,720 | 18 | 16.7 (10.5-26.5) | 0.60 (0.29-1.24) | 1.48 (0.61-3.60) |
| | | | TZD | 28,530 | 1.22 (0.67-2.11) | 43,600 | 12 | 27.5 (15.6-48.5) | | |
| | 90-day lag period | MarketScan | DPP4i | 159,000 | 1.17 (0.67-2.02) | 209,629 | 46 | 21.9 (16.4-29.3) | 0.72 (0.44-1.17) | 0.68 (0.38-1.21) |
| | | | TZD | 64,686 | 1.00 (0.61-1.79) | 77,076 | 24 | 31.1 (20.9-46.5) | | |
| | | Medicare | DPP4i | 60,038 | 1.47 (0.77-2.53) | 101,643 | 18 | 17.7 (11.2-28.1) | 0.61 (0.29-1.27) | 1.41 (0.59-3.36) |
| | | | TZD | 27,950 | 1.24 (0.70-2.14) | 41,743 | 12 | 28.7 (16.3-50.6) | | |
| | 365-day lag period | MarketScan | DPP4i | 125,676 | 1.46 (0.83-2.33) | 152,809 | 27 | 17.7 (12.1-25.8) | 0.67 (0.36-1.24) | 0.69 (0.32-1.49) |
| | | | TZD | 52,309 | 1.25 (0.71-2.05) | 60,379 | 16 | 26.5 (16.2-43.3) | | |
| | | Medicare | DPP4i | 55,779 | 1.58 (0.84-2.65) | 81,705 | 16 | 19.6 (12.0-32.0) | 0.63 (0.30-1.36) | 1.30 (0.54-3.14) |
| | | | TZD | 26,025 | 1.34 (0.74-2.25) | 35,786 | 11 | 30.7 (17.0-55.5) | | |

Abbreviations: Yr, year; IQR, interquartile range; NA, not applicable; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

***** Analysis was based on as-treated exposure definition, follow-up started from a lag period post the second prescription, ended at the earliest of the following events: 1) the same lag period days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016); 5) an incident IBD event.

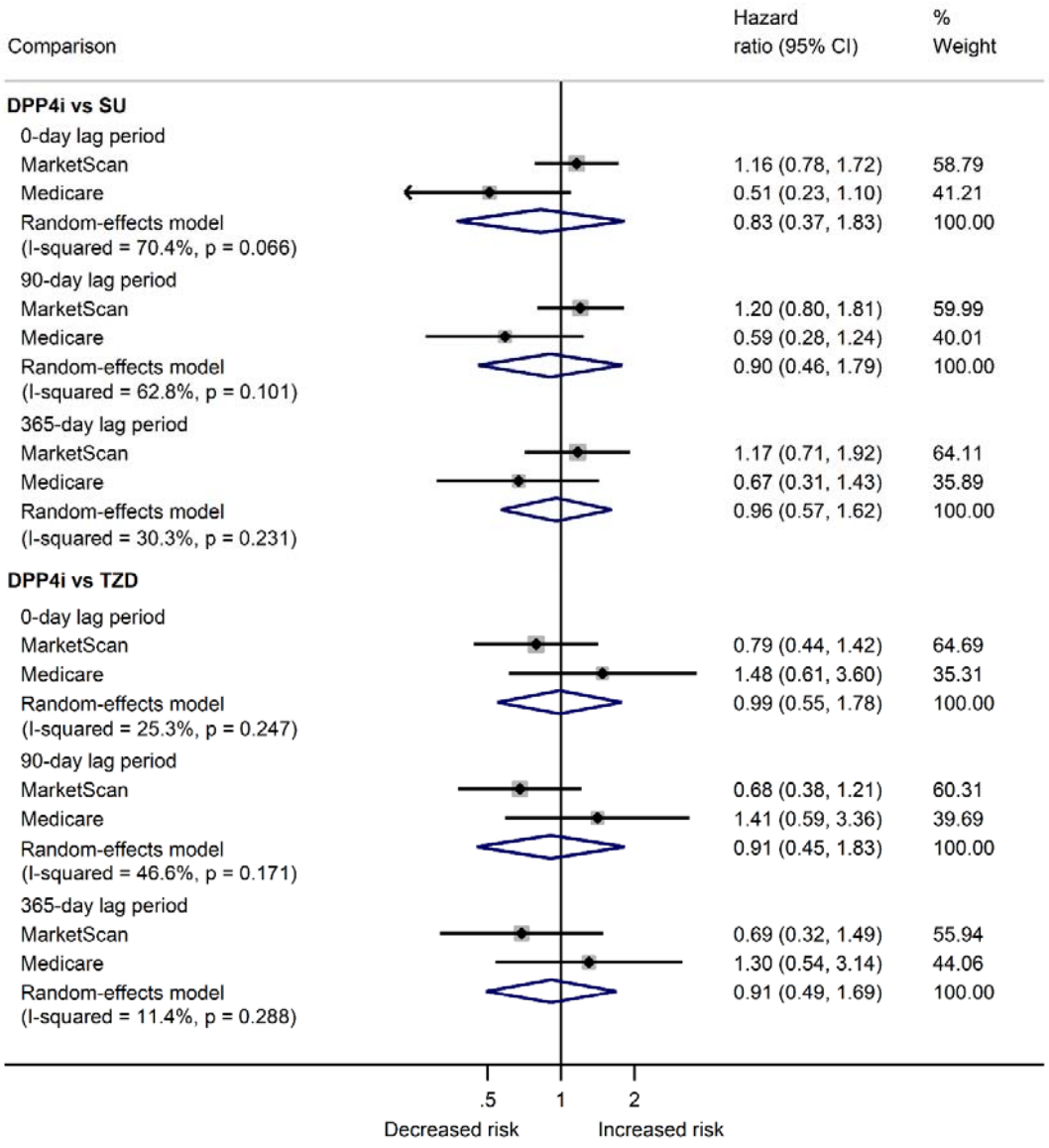
† The lag period is 0, 90, and 365, respectively.

‡ Before the start of follow-up (i.e. 0 day, 90 days, or 365 days post the second prescription, respectively), patients with IBD events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

§ Propensity score weighted HRs were standardized to the distribution of baseline covariates in DPP4i initiators.

SUPPLEMENTARY DATA

**Supplementary Figure 13. Forest plot of the association between use of DPP4i and IBD risk by different lag period.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 14. Crude and adjusted hazard ratios for Crohn's disease associated with use of DPP4i compared with therapeutic alternatives by different lag period*.**

| Comparison | Lag period† (days) | Database | Cohort | No. of Patients‡ | Median duration (yr) of treatment (IQR) | Person-yr | No. of CD events | CD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting§ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| DPP4i vs SU | 0-day lag period | MarketScan | DPP4i | 137,217 | 1.00 (0.56-1.84) | 176,098 | 18 | 10.2 (6.4-16.2) | 1.48 (0.78-2.81) | 1.66 (0.86-3.20) |
| | | | SU | 234,514 | 0.92 (0.51-1.76) | 287,968 | 20 | 6.9 (4.5-10.8) | | |
| | | Medicare | DPP4i | 46,511 | 1.34 (0.68-2.39) | NA | NTSR | 1.3 (0.2-9.1) | 0.23 (0.03-1.80) | 0.32 (0.04-2.53) |
| | | | SU | 117,792 | 1.57 (0.78-2.80) | 227,537 | 12 | 5.3 (3.0-9.3) | | |
| | 90-day lag period | MarketScan | DPP4i | 127,381 | 1.10 (0.64-1.94) | 160,683 | 15 | 9.3 (5.6-15.5) | 1.36 (0.69-2.71) | 1.40 (0.68-2.87) |
| | | | SU | 217,024 | 1.01 (0.58-1.86) | 262,479 | 18 | 6.9 (4.3-10.9) | | |
| | | Medicare | DPP4i | 45,303 | 1.38 (0.74-2.44) | NA | NTSR | 1.4 (0.2-9.6) | 0.31 (0.04-2.47) | 0.38 (0.05-3.05) |
| | | | SU | 114,288 | 1.63 (0.83-2.85) | NA | NTSR | 4.2 (2.2-8.0) | | |
| | 365-day lag period | MarketScan | DPP4i | 100,661 | 1.39 (0.76-2.25) | 118,922 | 10 | 8.4 (4.5-15.6) | 1.25 (0.54-2.87) | 1.22 (0.52-2.85) |
| | | | SU | 170,019 | 1.32 (0.69-2.17) | 193,977 | 13 | 6.7 (3.9-11.5) | | |
| | | Medicare | DPP4i | 41,587 | 1.51 (0.78-2.59) | NA | NTSR | 3.4 (0.8-13.4) | 1.10 (0.22-5.49) | 1.11 (0.21-5.74) |
| | | | SU | 103,711 | 1.80 (0.99-3.01) | NA | NTSR | 2.8 (1.2-6.8) | | |
| DPP4i vs TZD | 0-day lag period | MarketScan | DPP4i | 171,417 | 1.07 (0.59-1.92) | 230,530 | 21 | 9.1 (5.9-14.0) | 0.87 (0.40-1.89) | 0.92 (0.39-2.16) |
| | | | TZD | 69,166 | 0.94 (0.55-1.72) | 83,223 | 9 | 10.8 (5.6-20.8) | | |
| | | Medicare | DPP4i | 61,275 | 1.44 (0.74-2.50) | NA | NTSR | 3.7 (1.4-9.9) | 0.26 (0.07-0.92) | 0.56 (0.13-2.35) |
| | | | TZD | 28,530 | 1.22 (0.67-2.11) | NA | NTSR | 13.8 (6.2-30.6) | | |
| | 90-day lag period | MarketScan | DPP4i | 159,000 | 1.17 (0.67-2.02) | 209,672 | 18 | 8.6 (5.4-13.6) | 0.68 (0.32-1.46) | 0.76 (0.33-1.73) |
| | | | TZD | 64,686 | 1.00 (0.61-1.79) | 77,085 | 10 | 13.0 (7.0-24.1) | | |
| | | Medicare | DPP4i | 60,038 | 1.47 (0.77-2.53) | NA | NTSR | 3.9 (1.5-10.5) | 0.27 (0.08-0.95) | 0.53 (0.13-2.18) |
| | | | TZD | 27,950 | 1.24 (0.70-2.14) | NA | NTSR | 14.4 (6.5-32.0) | | |
| | 365-day lag period | MarketScan | DPP4i | 125,676 | 1.46 (0.83-2.33) | 152,831 | 10 | 6.5 (3.5-12.2) | 0.66 (0.24-1.82) | 1.07 (0.36-3.12) |
| | | | TZD | 52,309 | 1.25 (0.71-2.05) | 60,383 | 6 | 9.9 (4.5-22.1) | | |
| | | Medicare | DPP4i | 55,779 | 1.58 (0.84-2.65) | NA | NTSR | 4.9 (1.8-13.0) | 0.35 (0.10-1.26) | 0.61 (0.15-2.56) |
| | | | TZD | 26,025 | 1.34 (0.74-2.25) | NA | NTSR | 14.0 (5.8-33.6) | | |

Abbreviations: Yr, year; IQR, interquartile range; NA, not applicable; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

***** Analysis was based on as-treated exposure definition, follow-up started from a lag period post the second prescription, ended at the earliest of the following events: 1) the same lag period days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016); 5) an incident IBD event.

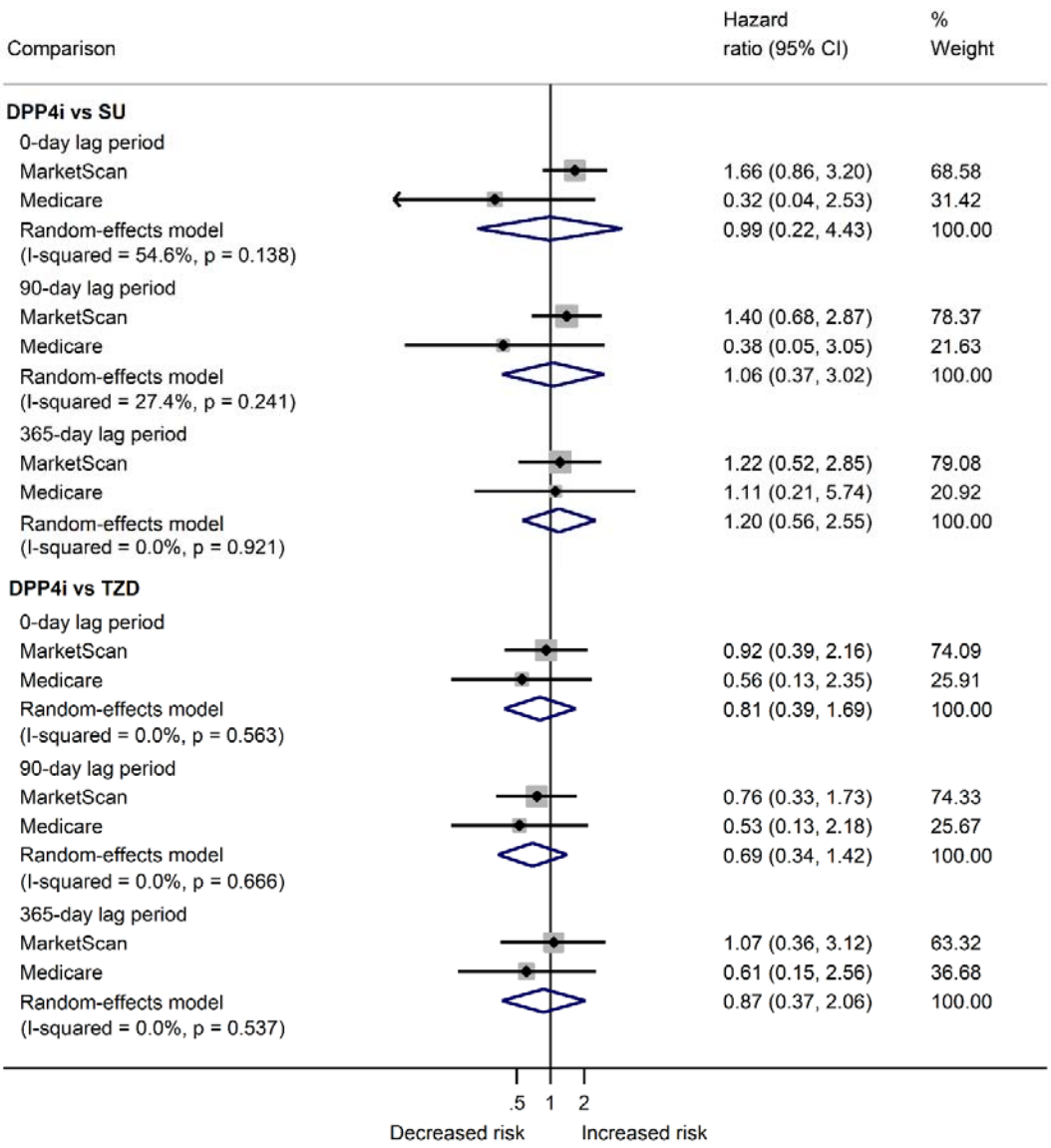
† The lag period is 0, 90, and 365, respectively.

‡ Before the start of follow-up (i.e. 0 day, 90 days, or 365 days post the second prescription, respectively), patients with IBD events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

§ Propensity score weighted HRs were standardized to the distribution of baseline covariates in DPP4i initiators.

SUPPLEMENTARY DATA

**Supplementary Figure 14. Forest plot of the association between use of DPP4i and CD risk by different lag period**. The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 15. Crude and adjusted hazard ratios for ulcerative colitis associated with use of DPP4i compared with therapeutic alternatives by different latency period*.**

| Comparison | Lag period† (days) | Database | Cohort | No. of Patients‡ | Median duration (yr) of treatment (IQR) | Person-yr | No. of UC events | UC rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting§ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| DPP4i vs SU | 0-day lag period | MarketScan | DPP4i | 137,217 | 1.00 (0.56-1.84) | 176,083 | 33 | 18.7 (13.3-26.4) | 1.04 (0.67-1.61) | 1.03 (0.66-1.62) |
| | | | SU | 234,514 | 0.92 (0.51-1.76) | 287,925 | 52 | 18.1 (13.8-23.7) | | |
| | | Medicare | DPP4i | 46,511 | 1.34 (0.68-2.39) | NA | NTSR | 9.0 (4.3-18.8) | 0.55 (0.25-1.21) | 0.52 (0.23-1.20) |
| | | | SU | 117,792 | 1.57 (0.78-2.80) | 227,493 | 37 | 16.3 (11.8-22.4) | | |
| | 90-day lag period | MarketScan | DPP4i | 127,381 | 1.10 (0.64-1.94) | 160,665 | 33 | 20.5 (14.6-28.9) | 1.08 (0.70-1.68) | 1.08 (0.68-1.70) |
| | | | SU | 217,024 | 1.01 (0.58-1.86) | 262,443 | 50 | 19.1 (14.4-25.1) | | |
| | | Medicare | DPP4i | 45,303 | 1.38 (0.74-2.44) | NA | NTSR | 10.9 (5.4-21.7) | 0.63 (0.29-1.33) | 0.60 (0.27-1.33) |
| | | | SU | 114,288 | 1.63 (0.83-2.85) | 215,039 | 37 | 17.2 (12.5-23.7) | | |
| | 365-day lag period | MarketScan | DPP4i | 100,661 | 1.39 (0.76-2.25) | 118,909 | 21 | 17.7 (11.5-27.1) | 1.05 (0.61-1.81) | 1.08 (0.61-1.91) |
| | | | SU | 170,019 | 1.32 (0.69-2.17) | 193,943 | 33 | 17.0 (12.1-23.9) | | |
| | | Medicare | DPP4i | 41,587 | 1.51 (0.78-2.59) | NA | NTSR | 11.7 (5.6-24.6) | 0.54 (0.24-1.22) | 0.56 (0.24-1.31) |
| | | | SU | 103,711 | 1.80 (0.99-3.01) | 175,765 | 37 | 21.1 (15.3-29.1) | | |
| DPP4i vs TZD | 0-day lag period | MarketScan | DPP4i | 171,417 | 1.07 (0.59-1.92) | 230,513 | 36 | 15.6 (11.3-21.7) | 0.77 (0.43-1.38) | 0.73 (0.36-1.49) |
| | | | TZD | 69,166 | 0.94 (0.55-1.72) | 83,220 | 17 | 20.4 (12.7-32.9) | | |
| | | Medicare | DPP4i | 61,275 | 1.44 (0.74-2.49) | 107,721 | 17 | 15.8 (9.8-25.4) | 0.96 (0.40-2.33) | 2.77 (0.97-7.89) |
| | | | TZD | 28,530 | 1.22 (0.67-2.11) | NA | NTSR | 16.1 (7.7-33.7) | | |
| | 90-day lag period | MarketScan | DPP4i | 159,000 | 1.17 (0.67-2.02) | 209,652 | 32 | 15.3 (10.8-21.6) | 0.70 (0.39-1.26) | 0.62 (0.31-1.26) |
| | | | TZD | 64,686 | 1.00 (0.61-1.79) | 77,083 | 17 | 22.1 (13.7-35.5) | | |
| | | Medicare | DPP4i | 60,038 | 1.47 (0.77-2.53) | 101,643 | 17 | 16.7 (10.4-26.9) | 0.87 (0.37-2.01) | 2.35 (0.90-6.17) |
| | | | TZD | 27,950 | 1.24 (0.70-2.14) | NA | NTSR | 19.2 (9.6-38.3) | | |
| | 365-day lag period | MarketScan | DPP4i | 125,676 | 1.46 (0.83-2.33) | 152,821 | 19 | 12.4 (7.9-19.5) | 0.54 (0.27-1.08) | 0.52 (0.22-1.21) |
| | | | TZD | 52,309 | 1.25 (0.71-2.05) | 60,379 | 14 | 23.2 (13.7-39.2) | | |
| | | Medicare | DPP4i | 55,779 | 1.58 (0.84-2.65) | 81,706 | 14 | 17.1 (10.1-28.9) | 0.76 (0.32-1.81) | 1.82 (0.70-4.73) |
| | | | TZD | 26,025 | 1.34 (0.74-2.25) | NA | NTSR | 22.4 (11.2-44.7) | | |

Abbreviations: Yr, year; IQR, interquartile range; NA, not applicable; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

***** Analysis was based on as-treated exposure definition, follow-up started from a lag period post the second prescription, ended at the earliest of the following events: 1) the same lag period days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016); 5) an incident IBD event.

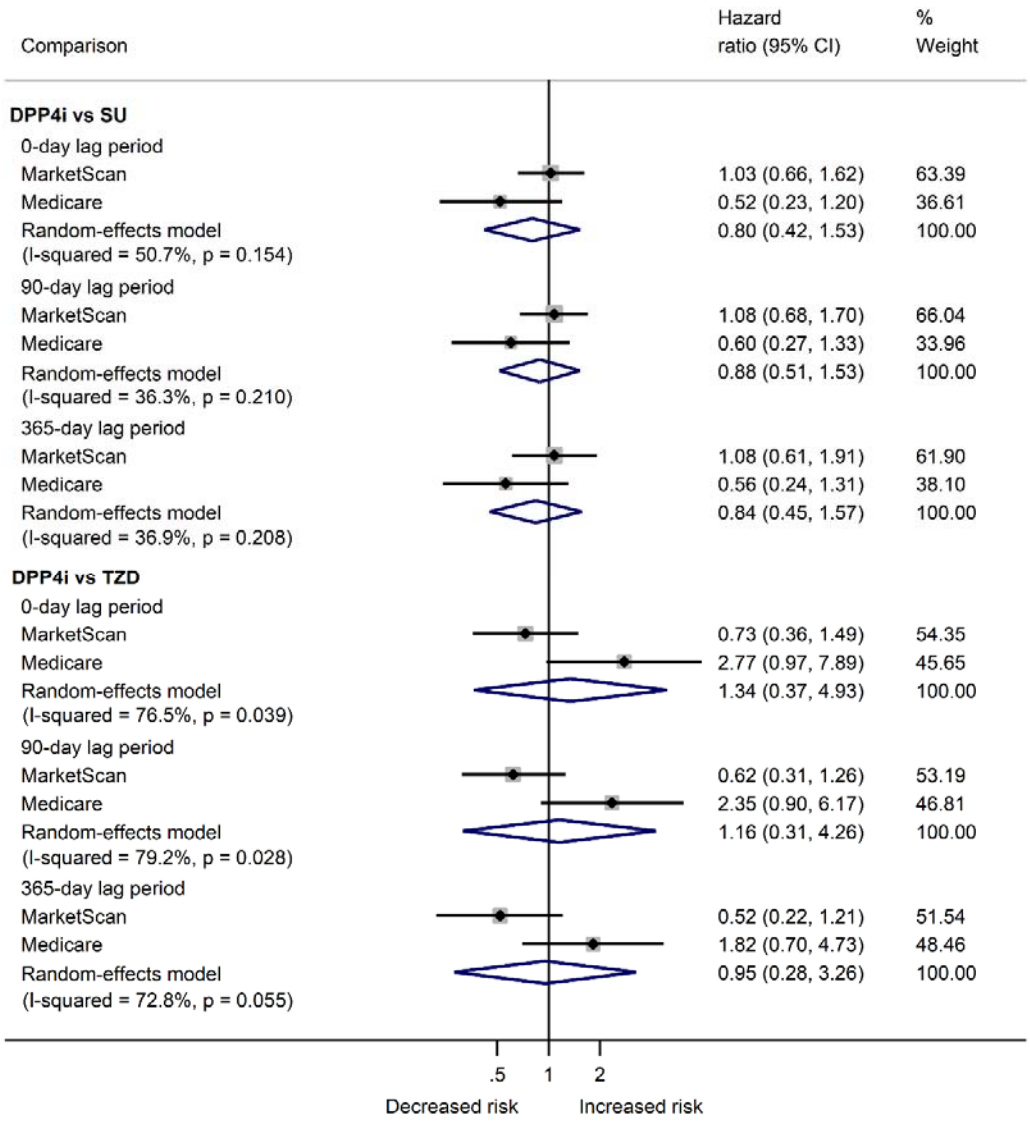
† The lag period is 0, 90, and 365, respectively.

‡ Before the start of follow-up (i.e. 0 day, 90 days, or 365 days post the second prescription, respectively), patients with IBD events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

§ Propensity score weighted HRs were standardized to the distribution of baseline covariates in DPP4i initiators.

SUPPLEMENTARY DATA

**Supplementary Figure 15. Forest plot of the association between use of DPP4i and UC risk by different lag period.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 16**. **Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of DPP4i compared with therapeutic alternatives based on initial-treatment analysis*.**

| Comparison | Database | Cohort | No. of Patient† | Median follow-up time (yr) (IQR) | Person-yr | No. of IBD disease events | IBD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting ‡ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| DPP4i vs SU | MarketScan | DPP4i | 117,548 | 1.79 (0.86-3.35) | 268,667 | 66 | 24.6 (19.3-31.3) | 1.06 (0.78-1.44) | 1.02 (0.74-1.40) |
| | | SU | 199,744 | 1.78 (0.85-3.30) | 456,826 | 106 | 23.2 (19.1-28.1) | | |
| | Medicare | DPP4i | 44,064 | 2.58 (1.34-4.33) | 130,816 | 28 | 21.4 (14.6-31.4) | 0.92 (0.59-1.44) | 0.94 (0.59-1.49) |
| | | SU | 110,806 | 2.77 (1.37-4.76) | 353,662 | 81 | 22.9 (18.4-28.5) | | |
| DPP4i vs TZD | MarketScan | DPP4i | 146,880 | 1.72 (0.84-3.16) | 323,806 | 75 | 23.2 (18.5-29.0) | 0.75 (0.52-1.08) | 0.72 (0.47-1.11) |
| | | TZD | 60,237 | 2.13 (0.97-4.12) | 163,463 | 49 | 30.0 (22.7-39.7) | | |
| | Medicare | DPP4i | 58,690 | 2.51 (1.34-4.24) | 172,094 | 34 | 19.8 (14.1-27.6) | 0.79 (0.47-1.33) | 1.15 (0.62-2.12) |
| | | TZD | 27,306 | 3.86 (1.76-6.04) | 107,808 | 27 | 25.0 (17.2-36.5) | | |

Abbreviations: Yr, year; IQR, interquartile range;

* Initial-treatment analysis is defined as completely ignoring treatment changes during follow-up (this mimics the intention-to-treat analysis in a randomized trial and is equivalent to an indefinite induction period). The follow-up ends with the earliest of the following events: death (for Medicare beneficiaries only), end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries), or incident IBD event.

† Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

‡ Propensity score weighted HR were standardized to the distribution of baseline covariates in DPP4i initiators.

SUPPLEMENTARY DATA

**Supplementary Table 17. Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of DPP4i compared with therapeutic alternatives stratified by time since the first prescription on initial-treatment analysis*.**

| Stratum | Comparison | Database | Cohort | No. of Patients† | Median follow-up time in each strata (yr) (IQR)‡ | Person-yr | No. of IBD events | IBD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting§ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Time since the first prescription** | | | | | | | | | | |
| ≤ 2 year‖ | DPP4i vs SU | MarketScan | DPP4i | 117,548 | 1.69 (0.86-1.90) | 160,301 | 40 | 25.0 (18.3-34.0) | 1.00 (0.67-1.47) | 1.02 (0.68-1.53) |
| | | | SU | 199,744 | 1.69 (0.85-1.91) | 272,202 | 68 | 25.0 (19.7-31.7) | | |
| | | Medicare | DPP4i | 44,064 | 1.82 (1.34-1.92) | 69,383 | 15 | 21.6 (13.0-35.9) | 0.88 (0.49-1.59) | 0.85 (0.46-1.57) |
| | | | SU | 110,806 | 1.81 (1.37-1.92) | 175,344 | 43 | 24.5 (18.2-33.1) | | |
| | DPP4i vs TZD | MarketScan | DPP4i | 146,880 | 1.67 (0.84-1.90) | 198,355 | 45 | 22.7 (16.9-30.4) | 0.65 (0.41-1.03) | 0.64 (0.37-1.10) |
| | | | TZD | 60,237 | 1.76 (0.97-1.91) | 85,943 | 30 | 34.9 (24.4-49.9) | | |
| | | Medicare | DPP4i | 58,690 | 1.81 (1.34-1.92) | 92,638 | 15 | 16.2 (9.8-26.9) | 0.52 (0.25-1.08) | 0.82 (0.34-1.96) |
| | | | TZD | 27,306 | 1.88 (1.65-1.92) | 45,232 | 14 | 31.0 (18.3-52.3) | | |
| > 2 - 4 years¶ | DPP4i vs SU | MarketScan | DPP4i | 70,234 | 1.56 (0.66-2.00) | 75,257 | 31 | 29.2 (19.2-44.4) | 1.94 (1.05-3.59) | 1.81 (0.96-3.41) |
| | | | SU | 118,388 | 1.52 (0.64-2.00) | 126,137 | 29 | 15.1 (9.6-23.6) | | |
| | | Medicare | DPP4i | 31,871 | 2.00 (0.91-2.00) | 40,591 | NTSR | 17.2 (8.2-36.2) | 0.72 (0.31-1.67) | 0.76 (0.31-1.85) |
| | | | SU | 81,849 | 2.00 (0.97-2.00) | 109,355 | 34 | 23.8 (16.2-34.9) | | |
| | DPP4i vs TZD | MarketScan | DPP4i | 85,555 | 1.44 (0.62-2.00) | 88,094 | 34 | 26.1 (17.3-39.3) | 1.01 (0.50-2.03) | 1.29 (0.58-2.90) |
| | | | TZD | 39,196 | 1.98 (0.82-2.00) | 47,526 | 18 | 25.2 (14.3-44.5) | | |
| | | Medicare | DPP4i | 42,456 | 1.89 (0.84-2.00) | 52,558 | 13 | 22.8 (13.0-40.2) | 1.29 (0.48-3.50) | 2.69 (0.95-7.56) |
| | | | TZD | 21,892 | 2.00 (1.47-2.00) | 33,438 | NTSR | 17.9 (8.1-39.9) | | |
| > 4 years# | DPP4i vs SU | MarketScan | DPP4i | 29,049 | 1.14 (0.51-2.18) | 33,328 | 7 | 12.0 (4.5-32.0) | 0.37 (0.13-1.10) | 0.29 (0.10-0.88) |
| | | | SU | 48,117 | 1.27 (0.55-2.34) | 58,855 | 22 | 32.3 (20.6-50.6) | | |
| | | Medicare | DPP4i | 16,574 | 1.25 (0.54-2.32) | 21,096 | NTSR | 28.4 (12.8-63.3) | 1.63 (0.61-4.38) | 2.06 (0.76-5.60) |
| | | | SU | 45,406 | 1.60 (0.74-2.67) | 70,085 | 15 | 17.1 (9.7-30.2) | | |
| | DPP4i vs TZD | MarketScan | DPP4i | 33,110 | 1.16 (0.52-2.15) | 37,616 | 10 | 18.6 (8.9-39.0) | 0.77 (0.27-2.24) | 0.44 (0.13-1.46) |
| | | | TZD | 19,368 | 1.74 (0.84-2.74) | 30,130 | 7 | 23.2 (11.1-48.7) | | |
| | | Medicare | DPP4i | 21,129 | 1.31 (0.57-2.36) | 27,228 | 11 | 25.7 (12.3-53.9) | 1.01 (0.36-2.82) | 1.06 (0.31-3.65) |
| | | | TZD | 14,955 | 2.17 (1.27-3.11) | 29,477 | NTSR | 23.7 (11.3-49.8) | | |

Abbreviations: Yr, year; IQR, interquartile range; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event). NA, not applicable.

* Initial-treatment analysis is defined as completely ignoring treatment changes during follow-up (this mimics the intention-to-treat analysis in a randomized trial and is equivalent to an indefinite induction period). The follow-up ends with the earliest of the following events: 3 years after initiation, death (for Medicare beneficiaries), end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries), or incident IBD event.

SUPPLEMENTARY DATA

† Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

‡ The follow-up time in each strata period was shown, i.e. time in previous period was excluded (e.g., for strata 1.1-3 years, follow-up time in the first year was excluded). And a 180-day lag was applied for each strata period.

§ Propensity score weighted HR were standardized to the distribution of baseline covariates in DPP4i initiators.

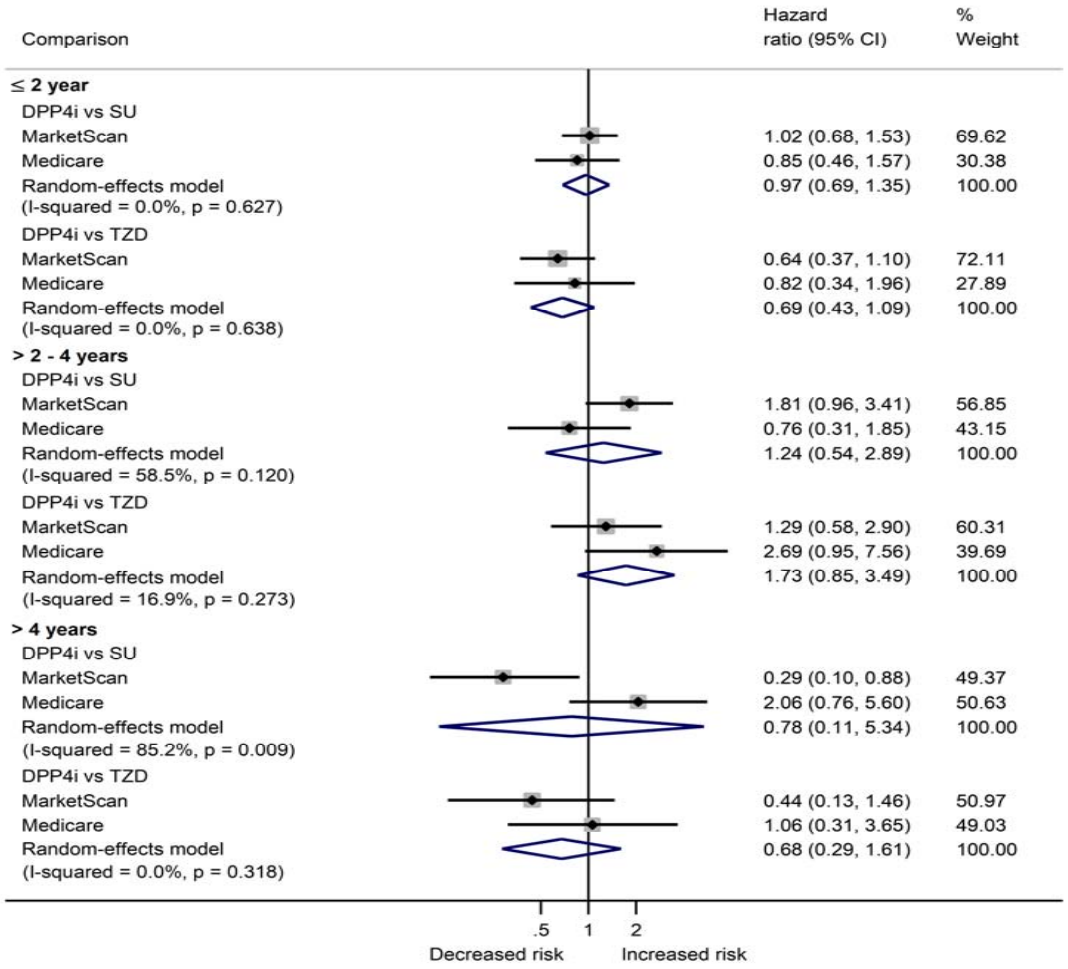
|| Patients with a duration of treatment of more than 2 years were censored at 30 months post-initiation (2-year treatment plus 6 months latent period).

¶ In the stratified cohort with 2.1-4 years (i.e. 2<follow-up≤4) treatment, follow-up started at 30 months post-initiation (2-year treatment plus 6 months induction period), patients with follow-up less than 30 months were excluded. Patients with a duration of treatment of more than 4 years were censored at 54 months post-initiation (4-year treatment plus 6 months latent period).

# In the stratified cohorts with >4 years treatment, follow-up started at 54 months post-initiation (4-year treatment plus 6 months induction period), patients with follow-up less than 54 months were excluded.

SUPPLEMENTARY DATA

**Supplementary Figure 17. Forest plot of the association between use of DPP4i and IBD risk stratified by duration of use in initial-treatment analysis.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 18. Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of DPP4i compared with therapeutic alternatives, follow-up started on the 180th day post to the first prescription*.**

| Comparison | Database | Cohort | No. of Patients† | Median duration (yr) of treatment (IQR) | Person-yr | No. of IBD events | IBD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting‡ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| DPP4i vs SU | MarketScan | DPP4i | 152,368 | 0.88 (0.50-1.71) | 171,547 | 42 | 24.5 (18.1-33.1) | 1.09 (0.74-1.61) | 1.13 (0.75-1.68) |
| | | SU | 274,119 | 0.75 (0.42-1.57) | 286,494 | 64 | 22.3 (17.5-28.5) | | |
| | Medicare | DPP4i | 44,064 | 1.42 (0.75-2.49) | NA | NTSR | 11.6 (5.8-23.1) | 0.52 (0.25-1.10) | 0.53 (0.24-1.15) |
| | | SU | 110,806 | 1.69 (0.90-2.91) | 202,385 | 44 | 21.7 (16.2-29.2) | | |
| DPP4i vs TZD | MarketScan | DPP4i | 189,782 | 0.93 (0.50-1.79) | 222,577 | 46 | 20.7 (15.5-27.6) | 0.68 (0.42-1.09) | 0.71 (0.41-1.23) |
| | | TZD | 84,631 | 0.74 (0.42-1.49) | 86,913 | 27 | 31.1 (21.3-45.3) | | |
| | Medicare | DPP4i | 58,690 | 1.50 (0.81-2.57) | 95,351 | 17 | 17.8 (11.1-28.7) | 0.58 (0.28-1.21) | 0.97 (0.40-2.37) |
| | | TZD | 27,306 | 1.27 (0.74-2.18) | 39,834 | 12 | 30.1 (17.1-53.0) | | |

Abbreviations: Yr, year; IQR, interquartile range; NA, not applicable; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

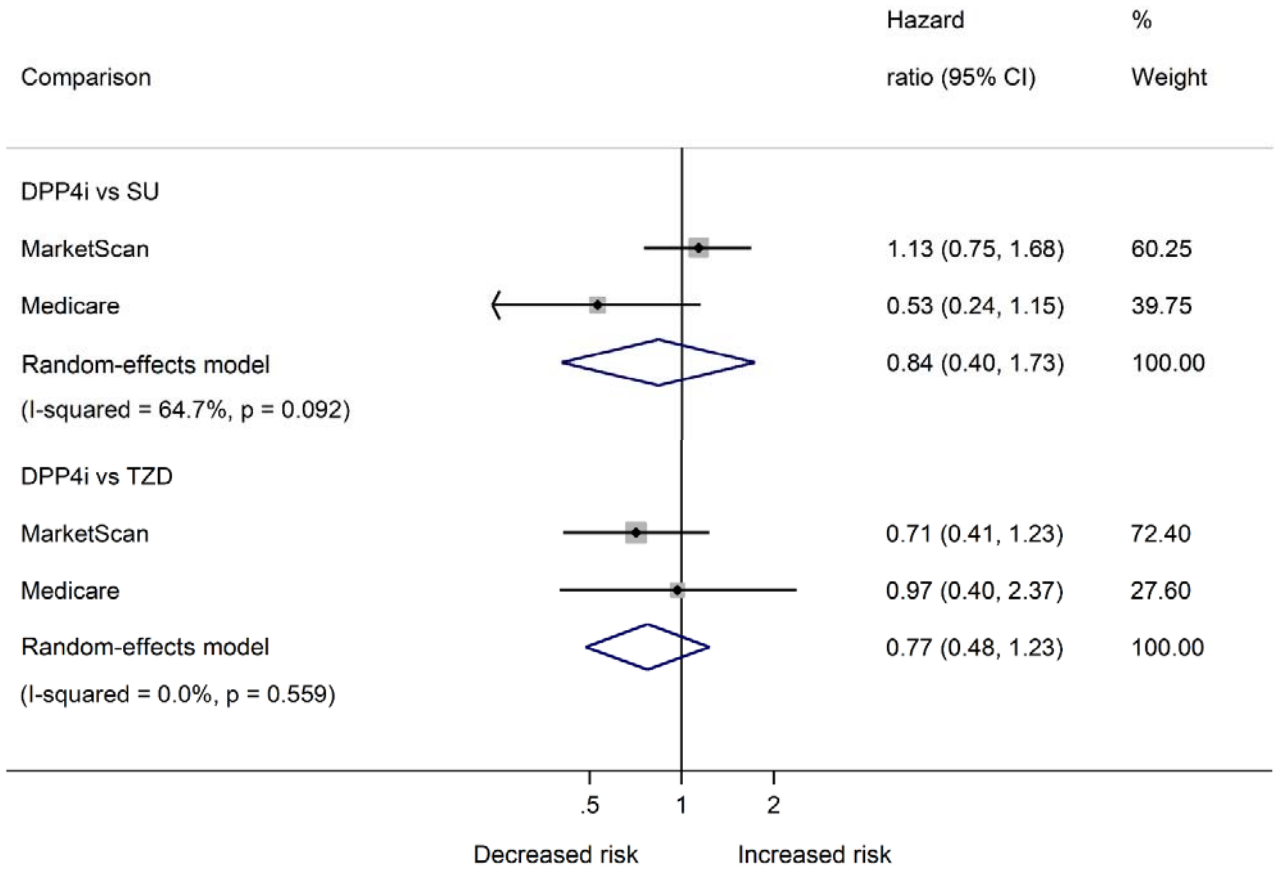
*Analysis was based on as-treated exposure definition, follow-up started from a lag period post the first prescription, ended at the earliest of the following events: 1) the same lag period days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016), or 5) observation of an incident IBD event.

† Before the start of follow-up (180 days post the first prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

‡ Propensity score weighted HRs were standardized to the distribution of baseline covariates in DPP4i initiators.

SUPPLEMENTARY DATA

**Supplementary Figure 18. Forest plot of the association between use of DPP4i and IBD risk, follow-up started on the 180th day post to first prescription.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 19. Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of DPP4i compared with therapeutic alternatives using the first new user period *.**

| Comparison | Database | Cohort | No. of Patients† | Median duration (yr) of treatment (IQR) | Person-yr | No. of IBD events | IBD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting‡ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| DPP4i vs SU | MarketScan | DPP4i | 114,672 | 1.22 (0.73-2.05) | 143,430 | 35 | 24.4 (17.5-34.0) | 1.09 (0.71-1.68) | 1.11 (0.71-1.73) |
| | | SU | 194,139 | 1.12 (0.66-1.97) | 232,703 | 52 | 22.3 (17.0-29.3) | | |
| | Medicare | DPP4i | 42,792 | 1.43 (0.75-2.51) | NA | NTSR | 11.8 (5.9-23.6) | 0.52 (0.25-1.11) | 0.53 (0.24-1.15) |
| | | SU | 108,489 | 1.70 (0.91-2.92) | 199,469 | 44 | 22.1 (16.4-29.6) | | |
| DPP4i vs TZD | MarketScan | DPP4i | 142,828 | 1.27 (0.75-2.14) | 185,592 | 40 | 21.6 (15.8-29.4) | 0.67 (0.40-1.12) | 0.68 (0.37-1.26) |
| | | TZD | 59,295 | 1.09 (0.67-1.89) | 70,379 | 23 | 32.7 (21.7-49.2) | | |
| | Medicare | DPP4i | 56,844 | 1.51 (0.82-2.58) | 93,005 | 17 | 18.3 (11.4-29.4) | 0.59 (0.28-1.22) | 0.96 (0.39-2.34) |
| | | TZD | 26,854 | 1.27 (0.74-2.18) | 39,271 | 12 | 30.6 (17.4-53.8) | | |

Abbreviations: Yr, year; IQR, interquartile range; NA, not applicable; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

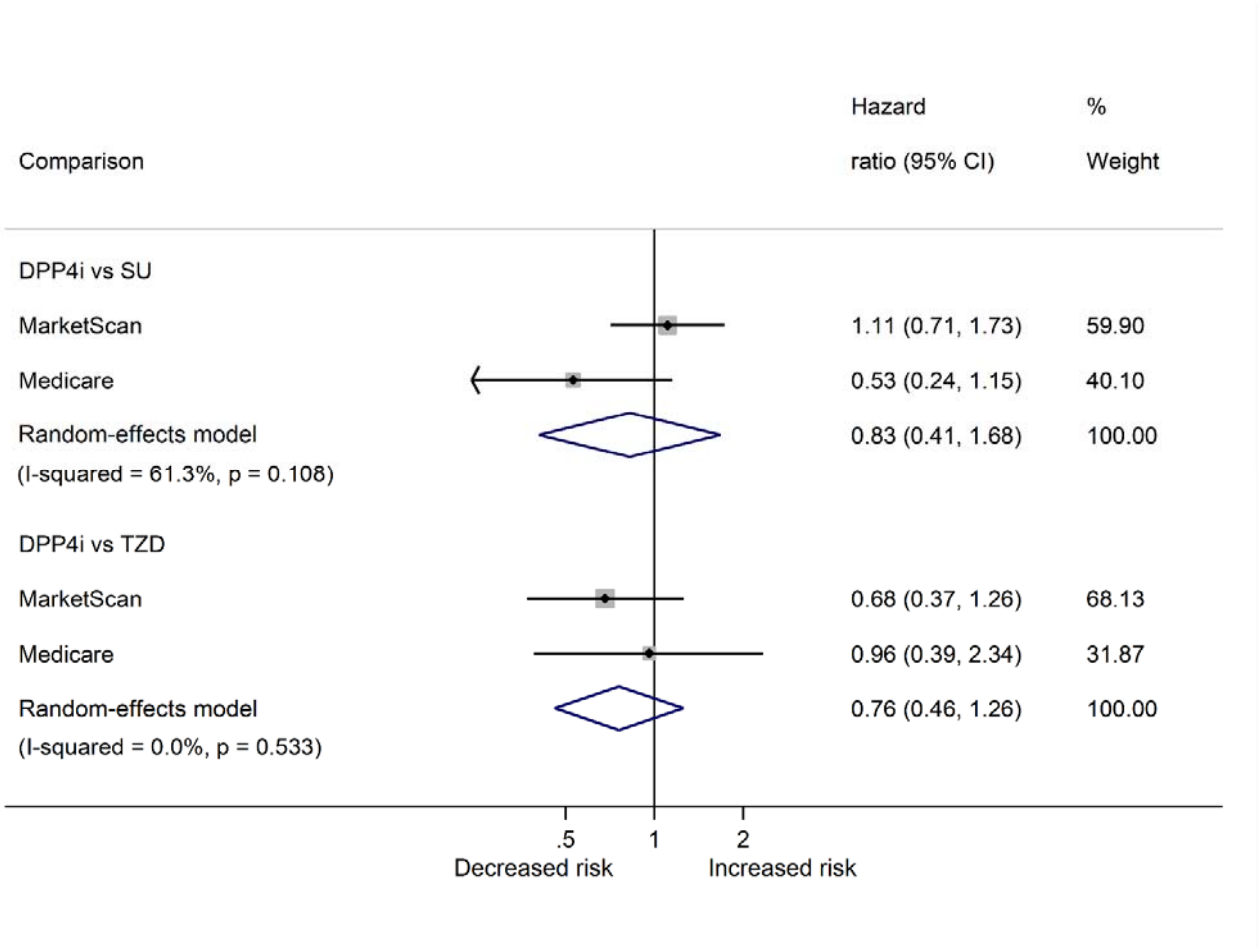
*The cohorts were built based on the first new user period, i.e., patients were allowed to enter a cohort only once. Analysis was based on as-treated exposure definition, follow-up started from a lag period post the second prescription, ended at the earliest of the following events: 1) the same lag period days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016), or 5) observation of an incident IBD event.

† Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

‡ Propensity score weighted HRs were standardized to the distribution of baseline covariates in DPP4i initiators.

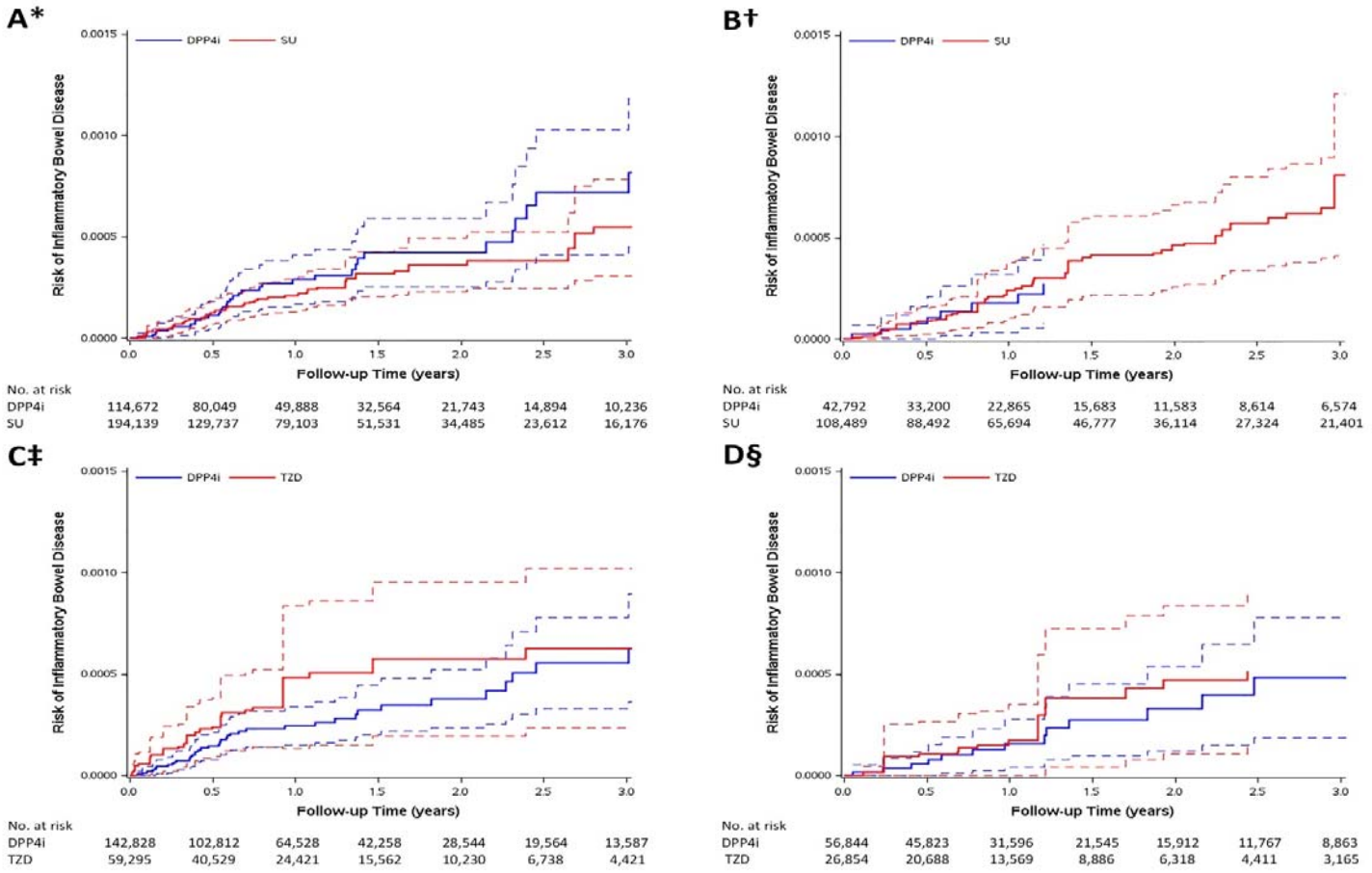
SUPPLEMENTARY DATA

**Supplementary Figure 19 A. Forest plot of the association between use of DPP4i and IBD risk using the first new user period.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Figure 19B. Standardized mortality/morbidity ratio weighted Kaplan Meier plots of inflammatory bowel disease in analysis according to the first ever new user period: DPP4i vs SU cohort in commercial insurance (panel A); DPP4i vs SU cohort in Medicare (panel B); DPP4i vs TZD cohort in commercial insurance (panel C); DPP4i vs TZD cohort in Medicare (panel D).** Follow-up started for the outcome 180 days (induction period) after the second prescription (cohort entry date). SMR weights create a pseudo-population of the untreated (comparators: SU or TZD) which has the same covariate distribution as the treated (DPP4i). Every patient receiving DPP4i has a weight of 1, while every patient in the comparator group is weighted by (PS/(1-PS)). The risks on the y axis were obtained by SMR weighted Cox model (weighting comparator drug initiators by the propensity score odds (PS/(1-PS)). HR treating comparators as reference, adjusted HR<1 indicates a lower risk for DPP4i. *HR 1.11 (0.71-1.73). † HR 0.53 (0.24-1.15). ‡ HR 0.68 (0.37-1.26). §HR 0.96 (0.39-2.34). Dotted lines around the survival curve point estimates represent 95% confidence bands.



SUPPLEMENTARY DATA

**Supplementary Table 20. Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of DPP4i compared with therapeutic alternatives using all-available history to completely avoid including prevalent IBD cases*.**

| Comparison | Database | Cohort | No. of Patients† | Median duration (yr) of treatment (IQR) | Person-yr | No. of IBD events | IBD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting‡ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| DPP4i vs SU | MarketScan | DPP4i | 85,042 | 1.18 (0.71-2.00) | 104,959 | 19 | 18.1 (11.5-28.4) | 1.38 (0.76-2.52) | 1.44 (0.77-2.67) |
| | | SU | 154,807 | 1.08 (0.64-1.93) | 183,036 | 24 | 13.1 (8.8-19.6) | | |
| | Medicare | DPP4i | 24,205 | 1.45 (0.76-2.47) | NA | NTSR | 13.1 (5.5-31.5) | 0.83 (0.32-2.17) | 0.93 (0.34-2.53) |
| | | SU | 68,978 | 1.73 (0.91-2.93) | 127,815 | 20 | 15.6 (10.1-24.3) | | |
| DPP4i vs TZD | MarketScan | DPP4i | 105,965 | 1.25 (0.74-2.10) | 136,549 | 22 | 16.1 (10.6-24.5) | 0.51 (0.28-0.96) | 0.55 (0.25-1.22) |
| | | TZD | 47,711 | 1.07 (0.66-1.88) | 56,578 | 18 | 31.8 (20.0-50.5) | | |
| | Medicare | DPP4i | 32,874 | 1.55 (0.83-2.60) | 54,390 | 11 | 20.2 (11.2-36.5) | 0.60 (0.25-1.43) | 0.85 (0.29-2.44) |
| | | TZD | 18,021 | 1.31 (0.74-2.22) | NA | NTSR | 33.3 (17.3-64.0) | | |

Abbreviations: Yr, year; IQR, interquartile range; NA, not applicable; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

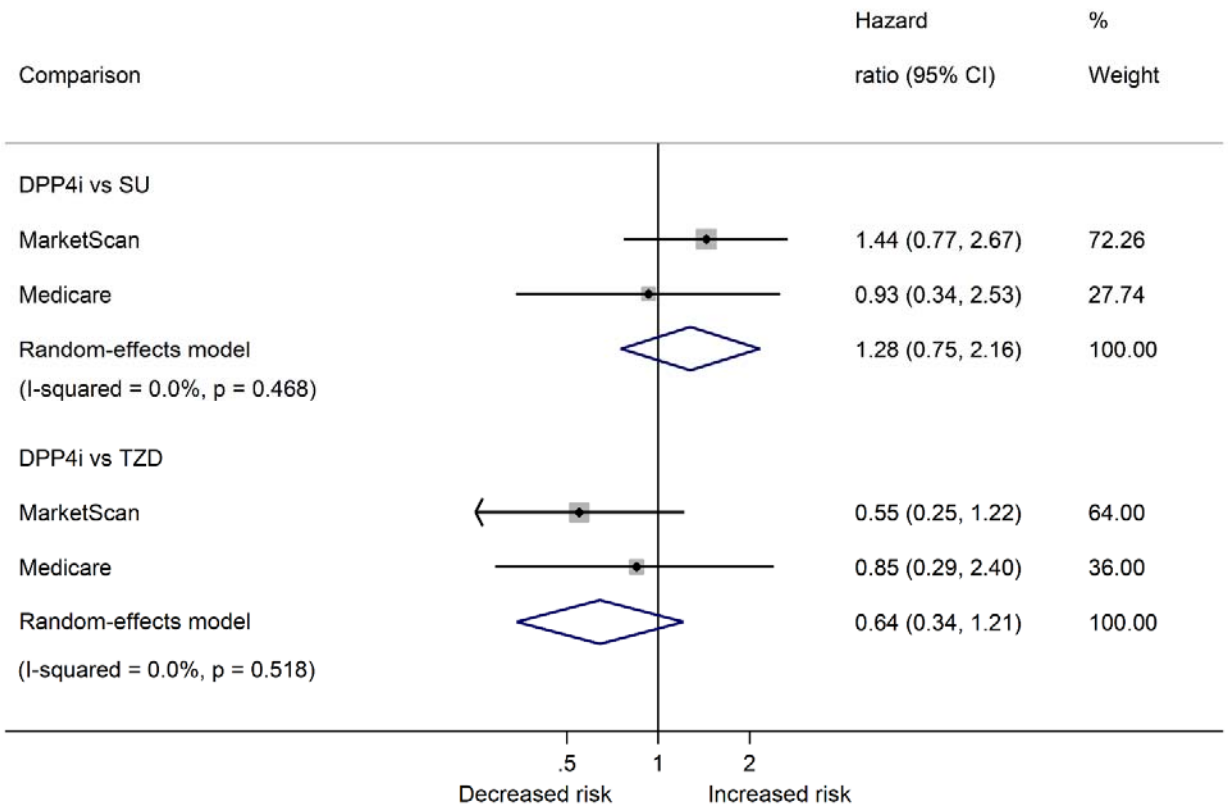
*Analysis was based on as-treated exposure definition, follow-up started from a lag period post the second prescription, ended at the earliest of the following events: 1) the same lag period days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016), or 5) observation of an incident IBD event.

† Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

‡ Propensity score weighted HRs were standardized to the distribution of baseline covariates in DPP4i initiators.

SUPPLEMENTARY DATA

**Supplementary Figure 20. Forest plot of the association between use of DPP4i and IBD risk using all-available history.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 21. Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of DPP4i compared with therapeutic alternatives based on modified outcome defintions*.**

| Comparison | Modified Outcome | Databse | Cohort | No. of Patients† | Median duration (yr) of treatment (IQR) | Person-yr | No. of IBD events | IBD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting‡ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| DPP4i vs SU | Modified outcome using IBD treatment date as event date§ | MarketScan | DPP4i | 117,549 | 1.21 (0.73-2.04) | 146,172 | 36 | 24.6 (17.8-34.1) | 1.13 (0.74-1.73) | 1.15 (0.74-1.78) |
| | | | SU | 199,744 | 1.12 (0.66-1.96) | 238,559 | 52 | 21.8 (16.6-28.6) | | |
| | | Medicare | DPP4i | 44,064 | 1.35 (0.75-2.41) | NA | NTSR | 12.1 (6.0-24.1) | 0.55 (0.26-1.16) | 0.55 (0.25-1.21) |
| | | | SU | 110,806 | 1.60 (0.90-2.80) | 194,778 | 42 | 21.6 (15.9-29.2) | | |
| | Modified outcome without requiring biopsy‖ | MarketScan | DPP4i | 117,548 | 1.21 (0.73-2.04) | 146,169 | 36 | 24.6 (17.8-34.1) | 1.07 (0.70-1.63) | 1.07 (0.70-1.66) |
| | | | SU | 199,744 | 1.12 (0.66-1.96) | 238,556 | 55 | 23.1 (17.7-30.0) | | |
| | | Medicare | DPP4i | 44,064 | 1.35 (0.75-2.41) | NA | NTSR | 13.6 (7.1-26.1) | 0.60 (0.29-1.22) | 0.60 (0.28-1.26) |
| | | | SU | 110,806 | 1.60 (0.90-2.80) | 194,774 | 43 | 22.1 (16.4-29.8) | | |
| | Modified outcome without requiring colonoscopy or biopsy¶ | MarketScan | DPP4i | 117,542 | 1.21 (0.73-2.04) | 146,147 | 46 | 31.5 (23.6-42.0) | 0.98 (0.68-1.41) | 0.97 (0.66-1.41) |
| | | | SU | 199,735 | 1.12 (0.66-1.96) | 238,518 | 77 | 32.3 (25.8-40.4) | | |
| | | Medicare | DPP4i | 44,063 | 1.35 (0.75-2.40) | 66,307 | 12 | 18.1 (10.3-31.9) | 0.55 (0.30-1.02) | 0.56 (0.29-1.06) |
| | | | SU | 110,802 | 1.60 (0.90-2.80) | 194,735 | 62 | 31.8 (24.8-40.8) | | |
| | Outcome defined by requiring three diagnoses in 90 days# | MarketScan | DPP4i | 117,548 | 1.21 (0.73-2.04) | 146,157 | 43 | 29.4 (21.8-39.7) | 1.11 (0.75-1.64) | 1.05 (0.70-1.57) |
| | | | SU | 199,737 | 1.12 (0.66-1.96) | 238,522 | 63 | 26.4 (20.6-33.8) | | |
| | | Medicare | DPP4i | 44,062 | 1.35 (0.75-2.40) | 66,271 | 35 | 52.8 (37.9-73.6) | 0.98 (0.67-1.44) | 1.09 (0.73-1.63) |
| | | | SU | 110,788 | 1.60 (0.90-2.80) | 194,711 | 103 | 52.9 (43.6-64.2) | | |
| DPP4i vs TZD | Modified outcome using IBD treatment date as event date§ | MarketScan | DPP4i | 146,880 | 1.27 (0.75-2.13) | 189,988 | 40 | 21.1 (15.4-28.7) | 0.67 (0.40-1.11) | 0.68 (0.37-1.26) |
| | | | TZD | 60,237 | 1.09 (0.67-1.88) | 71,268 | 23 | 32.3 (21.4-48.6) | | |
| | | Medicare | DPP4i | 58,690 | 1.42 (0.81-2.47) | 90,905 | 16 | 17.6 (10.8-28.7) | 0.61 (0.28-1.31) | 1.27 (0.52-3.13) |
| | | | TZD | 27,306 | 1.24 (0.74-2.14) | 38,725 | 11 | 28.4 (15.7-51.3) | | |
| | Modified outcome without requiring biopsy‖ | MarketScan | DPP4i | 146,880 | 1.27 (0.75-2.13) | 189,985 | 41 | 21.6 (15.9-29.3) | 0.65 (0.39-1.08) | 0.67 (0.37-1.23) |
| | | | TZD | 60,237 | 1.09 (0.67-1.88) | 71,267 | 24 | 33.7 (22.6-50.2) | | |
| | | Medicare | DPP4i | 58,690 | 1.42 (0.81-2.47) | 90,902 | 18 | 19.8 (12.5-31.4) | 0.63 (0.31-1.31) | 1.03 (0.42-2.51) |
| | | | TZD | 27,306 | 1.24 (0.74-2.14) | 38,725 | 12 | 31.0 (17.6-54.6) | | |
| | Modified outcome without requiring colonoscopy or biopsy¶ | MarketScan | DPP4i | 146,875 | 1.27 (0.75-2.13) | 189,948 | 61 | 32.1 (25.0-41.3) | 0.66 (0.44-1.00) | 0.61 (0.37-1.00) |
| | | | TZD | 60,235 | 1.09 (0.67-1.88) | 71,251 | 35 | 49.1 (35.3-68.4) | | |
| | | Medicare | DPP4i | 58,690 | 1.42 (0.81-2.47) | 90,895 | 23 | 25.3 (16.8-38.1) | 0.70 (0.36-1.36) | 1.23 (0.54-2.79) |
| | | | TZD | 27,306 | 1.24 (0.74-2.14) | 38,720 | 14 | 36.2 (21.4-61.1) | | |
| | Outcome defined by requiring three diagnoses in 90 days# | MarketScan | DPP4i | 146,878 | 1.27 (0.75-2.13) | 189,991 | 52 | 27.4 (20.9-35.9) | 0.87 (0.53-1.42) | 0.76 (0.41-1.41) |
| | | | TZD | 60,234 | 1.09 (0.67-1.88) | 71,265 | 23 | 32.3 (21.4-48.6) | | |
| | | Medicare | DPP4i | 58,686 | 1.42 (0.81-2.47) | 90,877 | 47 | 51.7 (38.9-68.8) | 1.11 (0.65-1.91) | 1.26 (0.63-2.53) |
| | | | TZD | 27,303 | 1.24 (0.74-2.14) | 38,722 | 18 | 46.5 (29.3-73.8) | | |

Abbreviations: Yr, year; IQR, interquartile range; NA, not applicable; NTSR: numbers too small (<11) to report based on Center for Medicare and

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Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

* Analysis was based on as-treated exposure definition, follow-up started from a lag period post the second prescription, ended at the earliest of the following events: 1) the same lag period days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016), or 5) observation of an incident IBD event.

†† Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper. The number of patients are slightly different than **Table 2** due to various outcome definitions (different number of patients with IBD events were excluded).

‡ Propensity score weighted HR were standardized to the distribution of baseline covariates in DPP4i initiators.

§ Use the date of IBD treatment instead of the date of IBD diagnosis as event date, to quantify the potential for time related bias in our primary outcome definition.

|| outcome defined as the date of first IBD diagnosis with a colonoscopy/sigmoidoscopy within 30 days prior and an IBD treatment within 30 days after (remove the biopsy requirement as some colonoscopy codes already include biopsy).

¶ outcome defined as: the date of first IBD diagnosis with an IBD treatment claims within 30 days after (remove both colonoscopy/sigmoidoscopy and biopsy requirements).

# Used an outcome definition adapted from a previously validated definition (29), that defines IBD patients as those with at least three health care contacts, on different days within 90 days, with an ICD-9 diagnosis code for CD (555.xx) or UC (556.xx). The third diagnosis date will be considered as the event date.

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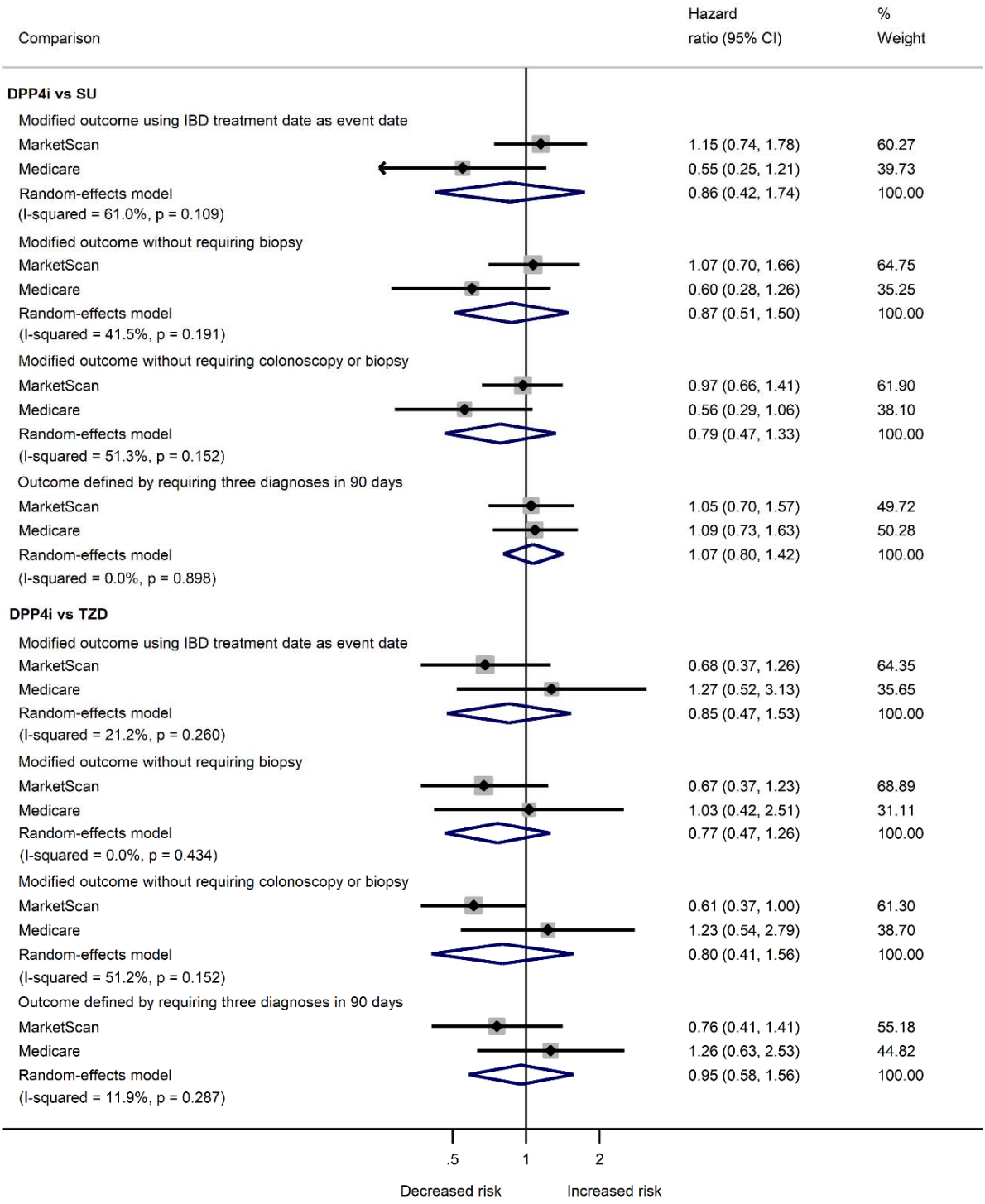
**Supplementary Figure 21. Forest plot of the association between use of DPP4i and IBD risk by modified outcome definitions.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



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**Supplementary Table 22. Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of DPP4i compared with therapeutic alternatives based relaxed exclusion criteria*.**

| Comparison | Outcome | Database | Cohort | No. of Patients† | Median duration (yr) of treatment (IQR) | Person-yr | No. of events | Rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting‡ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| DPP4i vs SU | IBD | MarketScan | DPP4i | 119,969 | 1.21 (0.72-2.04) | 148,967 | 35 | 23.5 (16.9-32.7) | 1.08 (0.70-1.65) | 1.08 (0.70-1.68) |
| | | | SU | 203,432 | 1.11 (0.66-1.96) | 242,787 | 53 | 21.8 (16.7-28.6) | | |
| | | Medicare | DPP4i | 48,736 | 1.40 (0.75-2.44) | 75,354 | 13 | 17.3 (10.0-29.7) | 0.78 (0.42-1.43) | 0.80 (0.42-1.53) |
| | | | SU | 122,643 | 1.66 (0.89-2.86) | 220,382 | 48 | 21.8 (16.4-28.9) | | |
| | CD | MarketScan | DPP4i | 119,969 | 1.21 (0.72-2.04) | 148,997 | 12 | 8.1 (4.6-14.2) | 1.22 (0.58-2.58) | 1.28 (0.59-2.75) |
| | | | SU | 203,432 | 1.11 (0.66-1.96) | 242,831 | 16 | 6.6 (4.0-10.8) | | |
| | | Medicare | DPP4i | 48,736 | 1.40 (0.75-2.44) | NA | NTSR | 2.7 (0.7-10.6) | 0.70 (0.15-3.26) | 0.89 (0.19-4.26) |
| | | | SU | 122,643 | 1.66 (0.89-2.86) | NA | NTSR | 3.6 (1.8-7.3) | | |
| | UC | MarketScan | DPP4i | 119,969 | 1.21 (0.72-2.04) | 148,981 | 27 | 18.1 (12.4-26.4) | 0.98 (0.61-1.58) | 0.96 (0.59-1.57) |
| | | | SU | 203,432 | 1.11 (0.66-1.96) | 242,792 | 45 | 18.5 (13.8-24.8) | | |
| | | Medicare | DPP4i | 48,736 | 1.40 (0.75-2.44) | 75,356 | 11 | 14.6 (8.1-26.4) | 0.74 (0.38-1.42) | 0.75 (0.37-1.50) |
| | | | SU | 122,643 | 1.66 (0.89-2.86) | 220,390 | 43 | 19.5 (14.5-26.3) | | |
| DPP4i vs TZD | IBD | MarketScan | DPP4i | 149,789 | 1.27 (0.75-2.13) | 193,487 | 42 | 21.7 (16.0-29.4) | 0.64 (0.39-1.06) | 0.69 (0.38-1.25) |
| | | | TZD | 61,401 | 1.08 (0.67-1.88) | 72,567 | 25 | 34.5 (23.3-51.0) | | |
| | | Medicare | DPP4i | 64,032 | 1.49 (0.80-2.54) | 102,764 | 19 | 18.5 (11.8-29.0) | 0.64 (0.31-1.30) | 1.08 (0.45-2.60) |
| | | | TZD | 29,275 | 1.26 (0.74-2.17) | 42,319 | 12 | 28.4 (16.1-49.9) | | |
| | CD | MarketScan | DPP4i | 149,789 | 1.27 (0.75-2.13) | 193,519 | 18 | 9.3 (5.9-14.8) | 0.63 (0.30-1.33) | 0.84 (0.38-1.88) |
| | | | TZD | 61,401 | 1.08 (0.67-1.88) | 72,574 | 11 | 15.2 (8.4-27.4) | | |
| | | Medicare | DPP4i | 64,032 | 1.49 (0.80-2.54) | NA | NTSR | 3.9 (1.5-10.4) | 0.26 (0.08-0.91) | 0.51 (0.13-1.95) |
| | | | TZD | 29,275 | 1.26 (0.74-2.17) | NA | NTSR | 14.2 (6.4-31.6) | | |
| | UC | MarketScan | DPP4i | 149,789 | 1.27 (0.75-2.13) | 193,509 | 29 | 15.0 (10.4-21.6) | 0.58 (0.33-1.04) | 0.59 (0.29-1.20) |
| | | | TZD | 61,401 | 1.08 (0.67-1.88) | 72,576 | 19 | 26.2 (16.7-41.0) | | |
| | | Medicare | DPP4i | 64,032 | 1.49 (0.80-2.54) | 102,765 | 17 | 16.5 (10.3-26.6) | 0.85 (0.37-1.96) | 1.43 (0.49-4.18) |
| | | | TZD | 29,275 | 1.26 (0.74-2.17) | NA | NTSR | 18.9 (9.5-37.8) | | |

Abbreviations: Yr, year; IQR, interquartile range; NA, not applicable; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

* Analysis was based on as-treated exposure definition, follow-up started from a lag period post the second prescription, ended at the earliest of the following events: 1) the same lag period days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016); 5) an incident IBD event.

† Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper. More patients were included due to relaxed exclusion criteria.

‡ Propensity score weighted HRs were standardized to the distribution of baseline covariates in DPP4i initiators.

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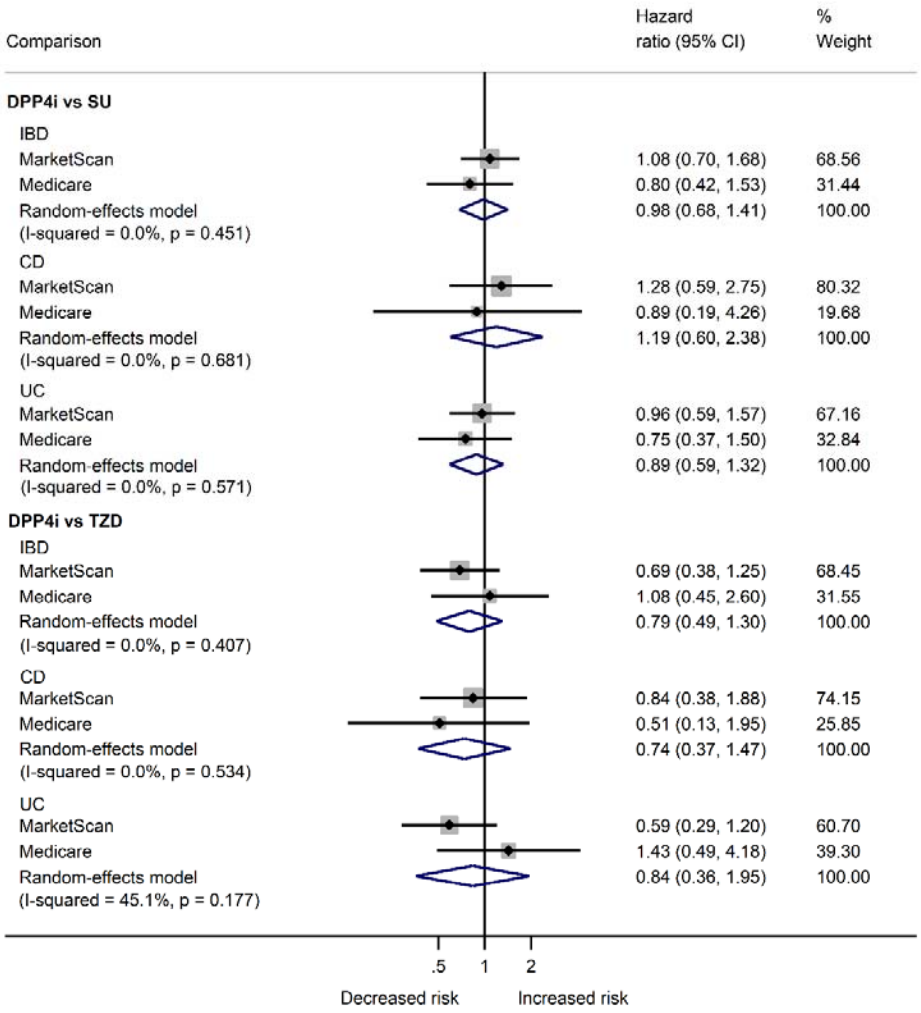
**Supplementary Figure 22. Forest plot of the association between use of DPP4i and IBD risk based on relaxed exclusion criteria.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 23. Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of DPP4i compared with therapeutic alternatives after censoring patients receiving medications that may induce inflammatory bowel disease*.**

| Comparison | Database | Cohort | No. of Patient† | Median duration (yr) of treatment (IQR) | Person-yr | No. of IBD events | IBD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting § HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| DPP4i vs SU | MarketScan | DPP4i | 117,548 | 0.79 (0.41-1.47) | 88,567 | 19 | 21.5 (13.7-33.6) | 1.15 (0.64-2.08) | 1.25 (0.68-2.29) |
| | | SU | 199,744 | 0.74 (0.41-1.41) | 145,282 | 27 | 18.6 (12.7-27.1) | | |
| | Medicare | DPP4i | 41,208 | 0.77 (0.33-1.45) | NA | NTSR | 15.8 (6.6-38.0) | 0.70 (0.27-1.81) | 0.60 (0.22-1.64) |
| | | SU | 105,969 | 0.92 (0.44-1.81) | 103,332 | 23 | 22.3 (14.8-33.5) | | |
| DPP4i vs TZD | MarketScan | DPP4i | 146,880 | 0.82 (0.43-1.52) | 114,268 | 21 | 18.4 (12.0-28.2) | 0.69 (0.34-1.40) | 0.67 (0.30-1.48) |
| | | TZD | 60,237 | 0.75 (0.41-1.38) | 44,046 | 12 | 27.2 (15.5-48.0) | | |
| | Medicare | DPP4i | 54,492 | 0.82 (0.41-1.53) | NA | NTSR | 18.1 (9.0-36.1) | 0.54 (0.20-1.49) | 0.66 (0.20-2.22) |
| | | TZD | 26,380 | 0.76 (0.38-1.40) | NA | NTSR | 33.8 (16.1-70.8) | | |

Abbreviations: Yr, year; IQR, interquartile range; NA, not applicable; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

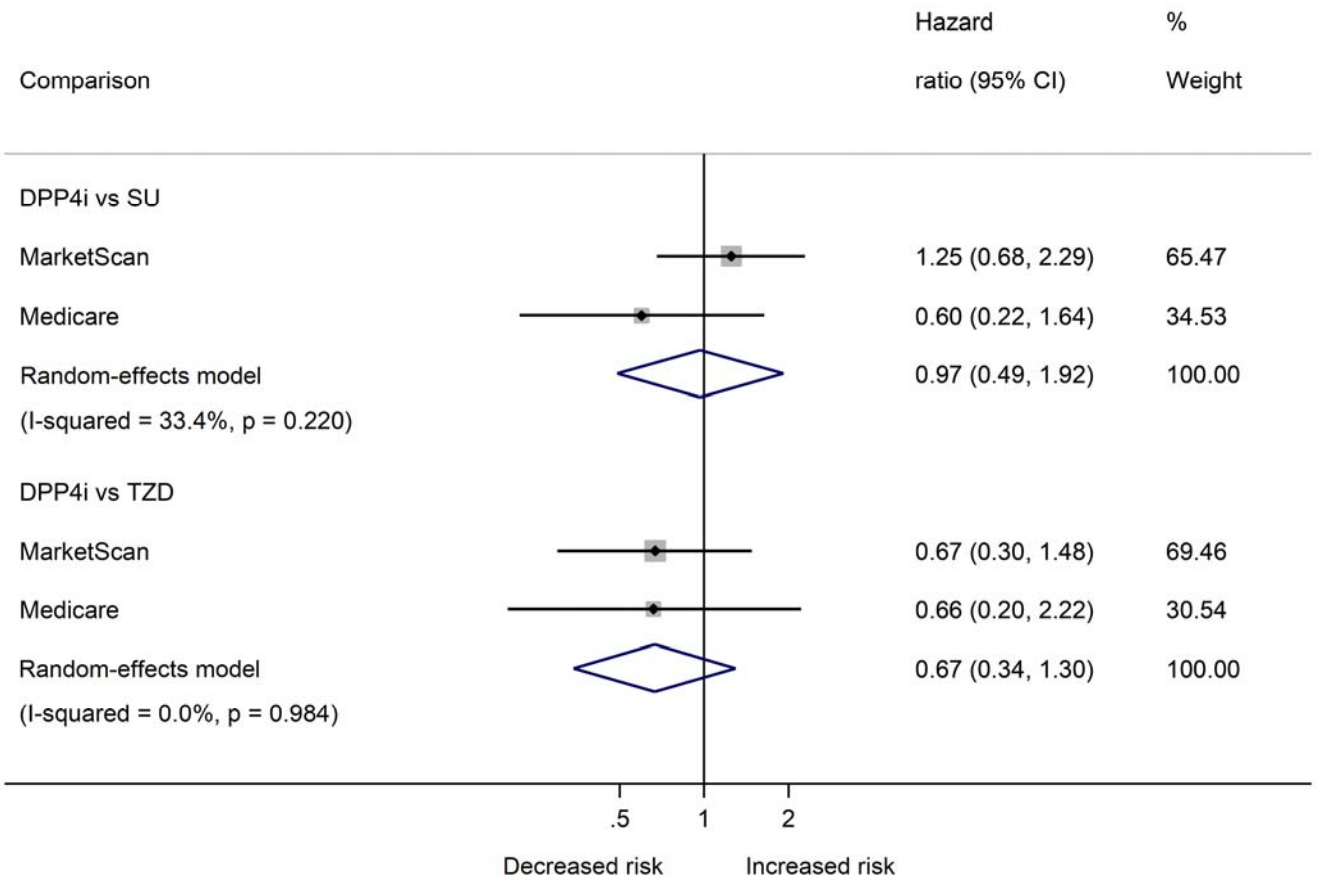
* Analysis was based on as-treated exposure definition, follow-up started from a lag period post the second prescription, ended at the earliest of the following events: 1) the same lag period days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016), or 5) observation of an incident IBD event.

† Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

‡ Propensity score weighted HR were standardized to the distribution of baseline covariates in DPP4i initiators.

SUPPLEMENTARY DATA

**Supplementary Figure 23. Forest plot of the association between use of DPP4i and IBD risk censoring patients receiving medications may induce IBD.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 24. Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of DPP4i compared with therapeutic alternatives based on multivariate Cox regression model*.**

| Comparison | Database | Cohort | No. of Patient† | Median duration (yr) of treatment (IQR) | Person-yr | No. of IBD events | IBD rate per 100,000 patient-yr | Crude HR (95% CI) | Adjusted ‡ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| DPP4i vs SU | MarketScan | DPP4i | 120,391 | 1.21 (0.73-2.04) | 149,418 | 35 | 23.4 (16.8-32.6) | 1.06 (0.69-1.63) | 1.20 (0.73-2.00) |
| | | SU | 205,602 | 1.11 (0.66-1.96) | 244,680 | 54 | 22.1 (16.9-28.8) | | |
| | Medicare | DPP4i | 45,381 | 1.43 (0.75-2.49) | NA | NTSR | 11.2 (5.6-22.4) | 0.51 (0.24-1.09) | 0.54 (0.24-1.20) |
| | | SU | 115,007 | 1.69 (0.90-2.92) | 211,814 | 45 | 21.2 (15.9-28.5) | | |
| DPP4i vs TZD | MarketScan | DPP4i | 152,038 | 1.27 (0.75-2.13) | 196,829 | 42 | 21.3 (15.8-28.9) | 0.67 (0.41-1.11) | 0.68 (0.37-1.26) |
| | | TZD | 62,377 | 1.08 (0.67-1.88) | 73,804 | 24 | 32.5 (21.8-48.5) | | |
| | Medicare | DPP4i | 60,766 | 1.50 (0.81-2.57) | 98,786 | 17 | 17.2 (10.7-27.7) | 0.55 (0.27-1.13) | 0.63 (0.28-1.44) |
| | | TZD | 28,762 | 1.28 (0.74-2.22) | 42,624 | 13 | 30.5 (17.7-52.5) | | |

Abbreviations: Yr, year; IQR, interquartile range; NA, not applicable; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

*Analysis was based on as-treated exposure definition, follow-up started from a lag period post the second prescription, ended at the earliest of the following events: 1) the same lag period days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO for Medicare beneficiaries); 3) death (for Medicare beneficiaries only); 4) administrative study end (December 31, 2016), or 5) observation of an incident IBD event.

† Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from original cohort, i.e. the cohort without PS trimming (the sample size is shown in **Supplementary Figure 3**).

‡Adjusted HRs from multivariate Cox regression model were based on original population without weighting.

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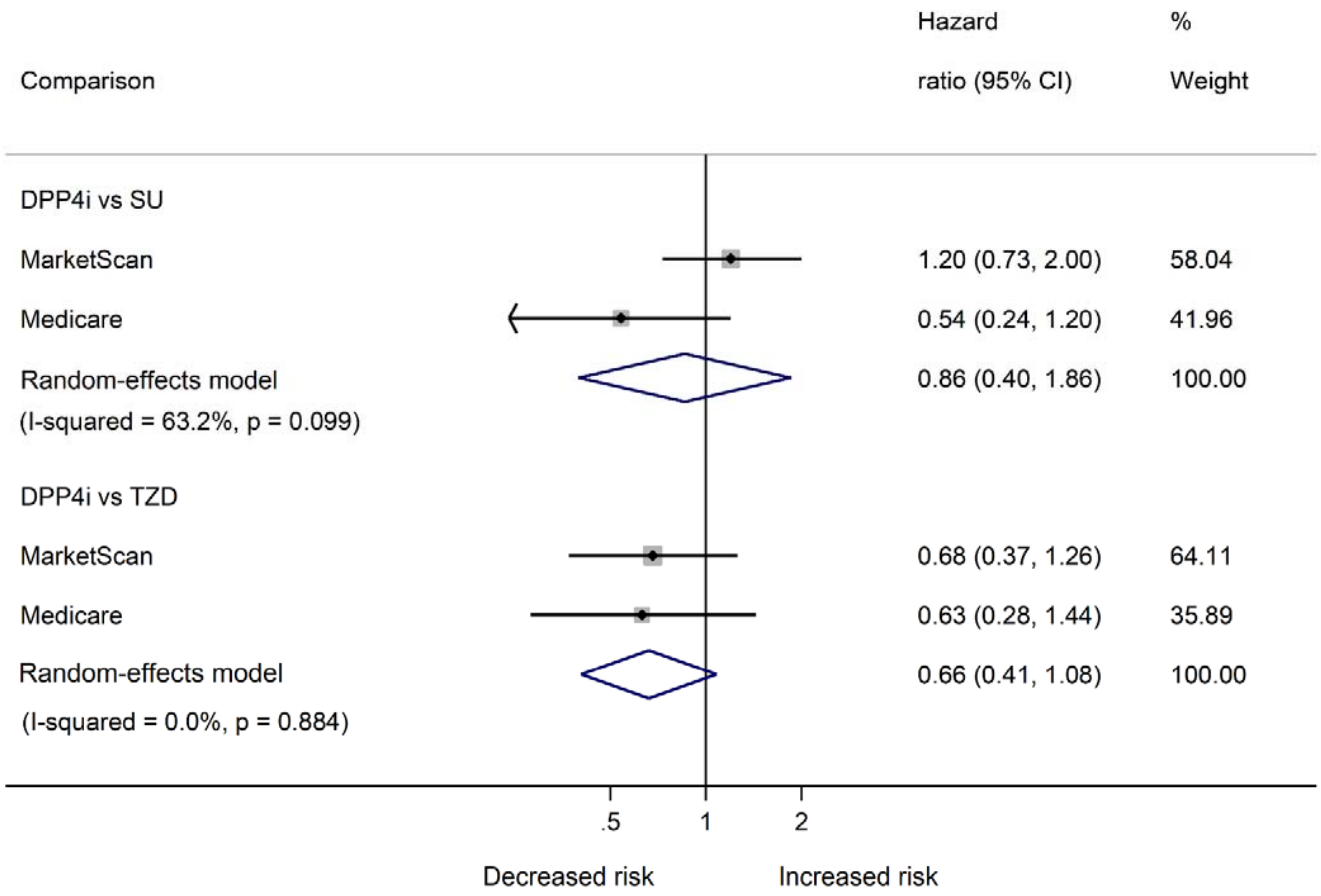
**Supplementary Figure 24. Forest plot of the association between use of DPP4i and IBD risk based on multivariate Cox regression model.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-



SUPPLEMENTARY DATA

**Supplementary Table 25**. **Crude and adjusted hazard ratios for inflammatory bowel disease associated with use of DPP4i compared with therapeutic alternatives excluding patients originally qualified for Medicare due to end stage renal disease and disability.**

| Comparison | Database | Cohort | No. of Patients† | Median duration (yr) of treatment (IQR) | Person-yr | No. of IBD events | IBD rate per 100,000 patient-yr | Crude HR (95% CI) | PS weighting‡ HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| DPP4i vs SU | MarketScan§ | DPP4i | 117,548 | 1.21 (0.73-2.04) | 146,171 | 35 | 23.9 (17.2-33.3) | 1.08 (0.70-1.65) | 1.08 (0.70-1.68) |
| | | SU | 199,744 | 1.12 (0.66-1.96) | 238,558 | 53 | 22.2 (17.0-29.1) | | |
| | Medicare | DPP4i | 35,407 | 1.42 (0.75-2.50) | NA | NTSR | 12.5 (6.0-26.2) | 0.55 (0.24-1.22) | 0.52 (0.22-1.22) |
| | | SU | 83,404 | 1.69 (0.90-2.91) | 153,053 | 34 | 22.2 (15.9-31.1) | | |
| DPP4i vs TZD | MarketScan§ | DPP4i | 146,880 | 1.27 (0.75-2.13) | 189,987 | 40 | 21.1 (15.4-28.7) | 0.67 (0.40-1.11) | 0.68 (0.37-1.26) |
| | | TZD | 60,237 | 1.09 (0.67-1.88) | 71,268 | 23 | 32.3 (21.4-48.6) | | |
| | Medicare | DPP4i | 47,739 | 1.49 (0.80-2.55) | NA | NTSR | 11.6 (6.0-22.3) | 0.57 (0.20-1.62) | 1.44 (0.47-4.42) |
| | | TZD | 20,591 | 1.25 (0.73-2.12) | NA | NTSR | 20.5 (9.2-45.6) | | |

Abbreviations: Yr, year; IQR, interquartile range; NA, not applicable; NTSR: numbers too small (<11) to report based on Center for Medicare and Medicaid Services (CMS) rules and data use agreement (Person-yr is not shown in this case to block the number of event).

*Analysis was based on as-treated exposure definition, follow-up started from a lag period post the second prescription, ended at the earliest of the following events: 1) the same lag period days after the date of prescription change including discontinuation or initiating the other drug in the drug pair that is being compared; 2) the end of enrolment (the end of enrolment for parts A, B or D or enrolment for HMO); 3) death; 4) administrative study end (December 31, 2016), or 5) observation of an incident IBD event.

† Before the start of follow-up (180 days post the second prescription), patients with events, discontinuation of enrollment, death, or reached the end of study (December 31, 2016) were excluded from PS trimmed cohort, as explained in the notes of **Table 2** in the main paper.

‡ Propensity score weighted HR were standardized to the distribution of baseline covariates in DPP4i initiators

§ Results for MarketScan population are the same as primary analysis **(Table 2)**.

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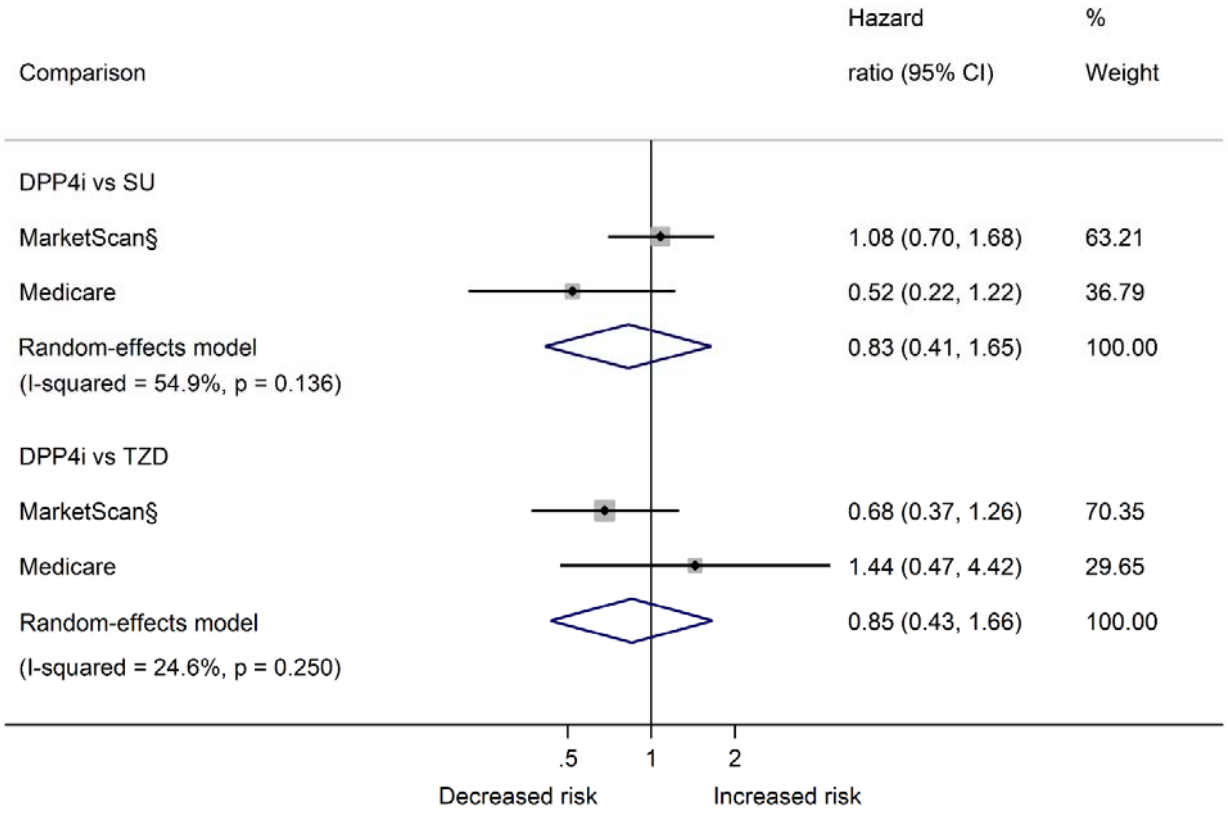
**Supplementary Figure 25. Forest plot of the association between use of DPP4i and IBD risk excluding patients originally qualified for Medicare due to end stage renal disease and disability.** The size of the boxes for database's point estimate is proportional to the weight of that database in the random-effects meta-analysis.



SUPPLEMENTARY DATA

**Supplementary Table 26**. **Summary of meta-analysis results.**

| Analysis | DPP4i vs SU | | | DPP4i vs TZD | | |
|---|---|---|---|---|---|---|
| | Random-effect | Fixed-Effect | $I^2$(%) | Random-effect | Fixed-Effect | $I^2$(%) |
| IBD | 0.82(0.41-1.61) | 0.91 (0.62-1.34) | 58.6 | 0.76 (0.46-1.26) | 0.76 (0.46-1.26) | 0 |
| CD | 1.22 (0.60-2.47) | 1.22 (0.60-2.47) | 0 | 0.72 (0.35-1.50) | 0.72 (0.35-1.50) | 0 |
| UC | 0.76 (0.44-1.33) | 0.79 (0.52-1.22) | 31.2 | 0.77 (0.37-1.61) | 0.74 (0.40-1.35) | 27.7 |
| Men | 1.04 (0.62-1.74) | 1.04 (0.62-1.74) | 0 | 1.51 (0.49-4.71) | 1.40 (0.74-2.67) | 66.8 |
| Women | 0.45 (0.06-3.22) | 0.84 (0.47-1.52) | 73.5 | 0.53 (0.26-1.06) | 0.53 (0.26-1.06) | 0 |
| Duration of treatment ≤12 months | 1.13 (0.69-1.85) | 1.13 (0.69-1.85) | 0 | 0.61 (0.32-1.15) | 0.61 (0.32-1.15) | 0 |
| Duration of treatment >12 months | 0.65(0.29-1.43) | 0.69 (0.39-1.21) | 44.3 | 1.44 (0.69-3.03) | 1.44 (0.69-3.03) | 0 |
| No GI disease | 1.28 (0.82-1.98) | 1.28 (0.82-1.98) | 0 | 0.76 (0.42-1.37) | 0.76 (0.42-1.37) | 0 |
| With GI disease | 0.39 (0.14-1.07) | 0.41 (0.19-0.92) | 31.9 | 0.63 (0.23-1.73) | 0.63 (0.23-1.73) | 0 |
| No autoimmune disease | 0.80 (0.38-1.67) | 0.91 (0.61-1.34) | 61.6 | 0.74 (0.45-1.23) | 0.74 (0.45-1.23) | 0 |
| Sitagliptin | 0.85 (0.37-1.96) | 1.00 (0.65-1.52) | 64.8 | 0.79 (0.47-1.33) | 0.79 (0.47-1.33) | 0 |
| Saxagliptin | 0.85 (0.36-1.98) | 0.85 (0.36-1.98) | 0 | 0.42 (0.14-1.22) | 0.42 (0.14-1.22) | 0 |
| Linagliptin | 0.87 (0.20-3.78) | 0.87 (0.20-3.78) | 0 | 0.49 (0.13-1.84) | 0.49 (0.13-1.84) | 0 |
| IBD, 0-day lag period | 0.83 (0.37-1.83) | 0.98 (0.69-1.40) | 70.4 | 0.99 (0.55-1.78) | 0.96 (0.59-1.56) | 25.3 |
| IBD, 90-day lag period | 0.90 (0.46-1.79) | 1.02 (0.71-1.46) | 62.8 | 0.91 (0.45-1.83) | 0.85 (0.53-1.38) | 46.6 |
| IBD, 365-day lag period | 0.96 (0.57-1.62) | 0.99 (0.65-1.50) | 30.3 | 0.91 (0.49-1.69) | 0.91 (0.51-1.62) | 11.4 |
| CD, 0-day lag period | 0.99 (0.22-4.43) | 1.43 (0.76-2,67) | 54.6 | 0.81 (0.39-1.69) | 0.81 (0.39-1.69) | 0 |
| CD, 90-day lag period | 1.06 (0.37-3.02) | 1.21(0.62-2.40) | 27.4 | 0.69 (0.34-1.42) | 0.69 (0.34-1.42) | 0 |
| CD, 365-day lag period | 1.20 (0.56-2.55) | 1.20 (0.56-2.55) | 0 | 0.87 (0.37-2.06) | 0.87 (0.37-2.06) | 0 |
| UC, 0-day lag period | 0.80 (0.42-1.53) | 0.88 (0.59-1.31) | 50.7 | 1.34 (0.37-4.93) | 1.11 (0.62-2.00) | 76.5 |
| UC, 90-day lag period | 0.88 (0.51-1.53) | 0.93 (0.63-1.39) | 36.3 | 1.16 (0.31-4.26) | 0.98 (0.56-1.73) | 79.2 |
| UC, 365-day lag period | 0.84 (0.45-1.57) | 0.88 (0.55-1.41) | 36.9 | 0.95 (0.28-3.26) | 0.91 (0.48-1.71) | 72.8 |
| Initial-treatment analysis | 0.99 (0.76-1.29) | 0.99 (0.76-1.29) | 0 | 0.86 (0.55-1.35) | 0.84 (0.59-1.19) | 33.2 |
| ≤ 2 year | 0.97 (0.69-1.35) | 0.97 (0.69-1.35) | 0 | 0.69 (0.43-1.09) | 0.69 (0.43-1.09) | 0 |
| >2 - 4 years | 1.24 (0.54-2.89) | 1.35 (0.81-2.27) | 58.5 | 1.73 (0.85-3.49) | 1.70 (0.90-3.21) | 16.9 |
| > 4 years | 0.78 (0.11-5.34) | 0.84 (0.40, 1.75) | 85.2 | 0.68 (0.29-1.61) | 0.68 (0.29-1.61) | 0 |
| Start follow-up on 180-day post first Rx | 0.84 (0.40-1.73) | 0.96 (0.67-1.38) | 64.7 | 0.77 (0.48-1.23) | 0.77 (0.48-1.23) | 0 |
| Cohorts based on the first new user period | 0.83 (0.41-1.68) | 0.93 (0.63-1.36) | 61.3 | 0.76 (0.46-1.26) | 0.76 (0.46-1.26) | 0 |
| Cohorts based on all-available history | 1.28 (0.75-2.16) | 1.28 (0.75-2.16) | 0 | 0.64 (0.34-1.21) | 0.64 (0.34-1.21) | 0 |
| Outcome using treatment date as event date | 0.86 (0.42-1.74) | 0.97 (0.66-1.42) | 61 | 0.85 (0.47-1.53) | 0.83 (0.50-1.38) | 21.2 |
| IBD defined without biopsy | 0.87 (0.51-1.50) | 0.93 (0.64-1.35) | 41.5 | 0.77 (0.47-1.26) | 0.77 (0.47-1.26) | 0 |
| IBD defined without colonoscopy/biopsy | 0.79 (0.47-1.33) | 0.84 (0.61-1.17) | 51.3 | 0.80 (0.41-1.56) | 0.74 (0.48-1.13) | 51.2 |
| IBD defined by three diagnoses in 90 days | 1.07 (0.80-1.42) | 1.07 (0.80-1.42) | 0 | 0.95 (0.58-1.56) | 0.95 (0.60-1.51) | 11.9 |
| IBD, relaxed exclusion criteria | 0.98 (0.68-1.41) | 0.98 (0.68-1.41) | 0 | 0.79 (0.49-1.30) | 0.79 (0.49-1.30) | 0 |
| CD, relaxed exclusion criteria | 1.19 (0.60-2.38) | 1.19 (0.60-2.38) | 0 | 0.74 (0.37-1.47) | 0.74 (0.37-1.47) | 0 |
| UC, relaxed exclusion criteria | 0.89 (0.59-1.32) | 0.89 (0.59-1.32) | 0 | 0.84 (0.36-1.95) | 0.77 (0.43-1.40) | 45.1 |
| Censor at drugs may induce IBD | 0.97 (0.49-1.92) | 1.03 (0.61-1.73) | 33.4 | 0.67 (0.34-1.30) | 0.67 (0.34-1.30) | 0 |
| Cox regression model | 0.86 (0.40-1.86) | 0.96 (0.63-1.47) | 63.2 | 0.66 (0.41-1.08) | 0.66 (0.41-1.08) | 0 |
| Exclude ESRD/disability in Medicare* | 0.83 (0.41-1.65) | 0.93 (0.63-1.37) | 54.9 | 0.85 (0.43-1.66) | 0.81 (0.47-1.38) | 24.6 |

NA, not applicable (only estimate from one database is available); GI, gastrointestinal; Rx, prescription; ESRD, end stage renal disease.

* excluding patients originally qualified for Medicare due to end stage renal disease and disability.

SUPPLEMENTARY DATA

**Supplementary Figure 26. Modelling DPP4i treatment as time-varying variable.** Abbreviations: $T_o$, the time follow up starts; SGLT2i, Sodium-glucose cotransporter 2 inhibitors; GLP1RA, Glucagon-like peptide-1 receptor agonists; GLD, glucose-lowering drugs. When modeling the use of DPP4i as a time-varying exposure (allowing the same patient to contribute both unexposed and exposed person-time), Abrahami et al. only analyzed DPP4i and active comparators in the same way, i.e. analogous to initial-treatment analysis, when patients initiated DPP4i or initiated non-DPP4i GLDs and never switched DPP4i (scenario 2 or 3). However, if patients started non-DPP4i GLDs and then switched to DPP4i (scenario 1), such patients were actually analyzed by as-treated analysis first until switching (only consider switching to DPP4i as prescription change), then switchers (after enter DPP4i group) were analyzed by initial-treatment analysis (like scenario 2).