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ORIGINAL RESEARCH

Dihydropyridine Calcium Channel Blockers and Risk of Pancreatic Cancer: A Population-Based Cohort Study

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BACKGROUND: Recent studies have reported that dihydropyridine calcium channel blockers (dCCBs) may increase the risk of pancreatic cancer, but these studies had methodological limitations. We thus aimed to determine whether dCCBs are associated with an increased risk of pancreatic cancer compared with thiazide diuretics, a clinically relevant comparator.

METHODS AND RESULTS: We conducted a new user, active comparator, population-based cohort study using the UK Clinical Practice Research Datalink. We identified new users of dCCBs and new users of thiazide diuretics between 1990 and 2018, with follow-up until 2019. Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% CIs for pancreatic cancer, comparing dCCBs with thiazide diuretics. Models were weighted using standardized morbidity ratio weights based on calendar time-specific propensity scores. We also conducted secondary analyses by cumulative duration of use, time since initiation, and individual drugs and assessed for the presence of effect modification by age, sex, smoking status, body mass index, history of chronic pancreatitis, and diabetes. The cohort included 344 480 initiators of dCCBs and 357 968 initiators of thiazide diuretics, generating 3 360 745 person-years of follow-up. After a median follow-up of 4.5 years, the weighted incidence rate per 100 000 person-years was 37.2 (95% CI, 34.1–40.4) for dCCBs and 39.4 (95% CI, 36.1–42.9) for thiazide diuretics. Overall, dCCBs were not associated with an increased risk of pancreatic cancer (weighted HR, 0.93; 95% CI, 0.80–1.09). Similar results were observed in secondary analyses.

CONCLUSIONS: In this large, population-based cohort study, dCCBs were not associated with an increased risk of pancreatic cancer compared with thiazide diuretics. These findings provide reassurance regarding the long-term pancreatic cancer safety of these drugs.

Key Words: antihypertensive drugs ■ calcium channel blockers ■ cancer ■ cohort study ■ pancreatic cancer ■ propensity score ■ thiazide diuretics

Dihydropyridine calcium channel blockers (dCCBs) are among the most commonly prescribed antihypertensive drugs in primary care practices.[1–3] This drug class is recommended as a first-line treatment for the management of hypertension and has a favorable cardiovascular safety profile comparable with other antihypertensive drugs.[4–6]

Recently, however, there have been concerns that dCCBs might be associated with an increased risk of pancreatic cancer. Indeed, to date, 3 large meta-analyses of randomized controlled trials (RCTs) investigated the safety of antihypertensive drugs with respect to cancer outcomes.[7–9] Of these, 2 reported an increased risk of any cancer with the use of dCCBs,[8,9] although none of the RCTs included in these meta-analyses were designed to specifically address the long-term cancer safety of antihypertensive drugs. In observational studies, 5 of 6 studies investigating the

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CLINICAL PERSPECTIVE

What Is New?

- Two large meta-analyses of randomized controlled trials reported a 6% increased risk of any cancer in patients using dihydropyridine calcium channel blockers (dCCBs).
- Observational studies have also reported a potential association between dCCBs and pancreatic cancer, but these had important limitations and did not compare dCCBs with a clinically relevant comparator.
- In this large, population-based cohort study of 702 448 patients, representing 3.3 million person-years of follow-up, dCCBs were not associated with an increased risk of pancreatic cancer when compared with thiazide diuretics, another commonly prescribed antihypertensive drug.

What Are the Clinical Implications?

- There was no association between long-term use of dCCBs and the risk of pancreatic cancer.
- Overall, dCCBs appear safe with respect to pancreatic cancer.

Nonstandard Abbreviations and Acronyms

CPRD	Clinical Practice Research Datalink
dCCBs	dihydropyridine calcium channel blockers
sRAGE	soluble receptor for advanced glycation end products

association between calcium channel blockers (CCBs; ie, dCCBs and non-dCCBs) and cancer reported numerically elevated effect estimates for pancreatic cancer ranging between 1.10 and 2.07, with the CI crossing the null value in some studies.[10–14] One study reported an effect estimate below the null (0.85).[15] Importantly, several studies investigating this association had small sample sizes, potentially important methodological limitations such as prevalent user bias and confounding by indication,[16] or did not distinguish between dCCBs and non-dCCBs. Finally, the inconclusive findings from previous studies mirror the conflicting biological mechanisms associating dCCBs with cancer, with laboratory studies suggesting that dCCBs may inhibit apoptosis and promote tumor growth or, conversely, may have antitumor effects.[17–19]

Given the limited and conflicting evidence available from RCTs and observational studies on the long-term pancreatic cancer safety of dCCBs, we conducted a large, new-user, population-based cohort study to investigate whether dCCBs are associated with an increased risk of pancreatic cancer compared with thiazide diuretics, another commonly prescribed antihypertensive drug class.

METHODS

Ethics Approval

The study protocol was approved by the Clinical Practice Research Datalink (CPRD) Research Data Governance (number 22_001791) and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada. General practices have consented for the CPRD to collect deidentified patient records.

Availability of Data and Materials

This study is based in part on data from the CPRD obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the UK National Health Service as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone. Because electronic health records are classified as sensitive data by the UK Data Protection Act, information governance restrictions (to protect patient confidentiality) prevent data sharing via public deposition. Data are available with approval through the individual constituent entities controlling access to the data. Specifically, the primary care data can be requested via application to the CPRD (https://www.cprd.com).

Data Source

We conducted this study using the UK CPRD Gp OnLine Data (GOLD). The CPRD GOLD is an electronic primary care database containing the health records of >20.7 million patients and has been shown to be representative of the UK general population in terms of age and sex.[20] A key strength of the CPRD is the inclusion of anthropometric data (eg, body mass index) and lifestyle information (eg, smoking status, alcohol use). It also includes medical diagnoses and procedures, recorded using Read codes, and prescriptions recorded using the British National Formulary dictionary.[20] Pancreatic cancer is well recorded in the CPRD, with a positive predictive value of 96% and sensitivity of 92% when compared with the UK National Cancer Data Repository.[21,22]

Study Population

We identified a new-user, active comparator cohort of primary care patients initiating either a dCCB or a thiazide diuretic between January 1, 1990, and March 31, 2018. The cohort consisted of all patients initiating

a dCCB (amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, and nisoldipine, alone or with other antihypertensive drugs except thiazide diuretics) and compared them with patients initiating a thiazide diuretic (hydrochlorothiazide, bendroflumethiazide, chlorothiazide, trichlormethiazide, methyclothiazide, polythiazide, quinethazone, hydroflumethiazide, benzthiazide, cyclopenthiazide, mefruside, indapamide, chlorthalidone, clopamide, xipamide, and metolazone, alone or with other antihypertensive drugs except dCCBs). British National Formulary codes and relevant product codes within British National Formulary codes were selected (British National Formulary codes listed in Tables S1 and S2). Cohort entry was defined as the date of the first prescription for either a dCCB or thiazide diuretic during the study period. We selected dCCBs (rather than all CCBs) as this subclass is usually preferred over non-dCCBs for the treatment of hypertension.[5,6,23] We also selected thiazide diuretics as the active comparator group as this drug class has not been previously associated with pancreatic cancer[12] and to minimize confounding by indication as thiazide diuretics are recommended for the same indication and stage as dCCBs.[4-6]

To be included in the cohort, patients were required to be aged ≥40 years and have a minimum of 1 year of medical history in the CPRD before cohort entry; the latter served as a washout period necessary to identify new users. We excluded patients with concomitant prescriptions for both study drugs at cohort entry as well as those previously diagnosed with rare genetic conditions or interventions that have been associated with an elevated incidence of pancreatic cancer at any time before cohort entry (Lynch syndrome, hereditary pancreatitis, Peutz-Jeghers syndrome, familial atypical multiple mole and melanoma syndrome, ataxia-telangiectasia, hereditary breast and ovarian cancer syndrome, multiple endocrine neoplasia type 1, von Hippel Lindau syndrome, neurofibromatosis type 1, cystic fibrosis, and solid organ transplant).[24–27] To identify incident events during follow-up, we excluded patients previously diagnosed with pancreatic cancer or those who underwent a total pancreatectomy at any time before cohort entry. Finally, patients were required to have at least 1 year of follow-up after cohort entry to allow for a minimum cancer latency period and minimize the detection of prevalent pancreatic cancer events. Thus, person-time at risk started 1 year after the cohort entry date.

Exposure Definition

Patients meeting the inclusion criteria were followed 1 year after cohort entry (ie, the date of the new prescription for a dCCB or a thiazide diuretic) until the first of the following events: an incident diagnosis of pancreatic cancer identified using Read codes (Table S3), 1 year after switching to 1 of the study drugs, death from any cause, end of registration with the general practice, or end of the study period (March 31, 2019). Follow-up was censored if patients switched to the other study drug but not if patients discontinued treatment or switched to other antihypertensive drugs. This exposure definition is more commonly used in studies of drug safety with cancer outcomes, where the effect of the exposure is considered irreversible. Indeed, this definition aligns with the hypothesized biological mechanism, which assumes a permanent and irreversible effect of dCCBs on the development of pancreatic cancer that would persist beyond treatment discontinuation. The exposure definition is depicted in Figure S1.

Potential Confounders

All models were adjusted for the following variables, measured at or before cohort entry and selected from expert knowledge and with evidence as established or potential risk factors for pancreatic cancer: age (modeled flexibly as a continuous variable), sex, body mass index (most recent measurement at or before cohort entry), smoking status (most recent measurement at or before cohort entry), alcohol-related disorders, hypertension (captured as a recorded diagnosis or a minimum of 3 systolic or diastolic blood pressure measurement readings ≥140 mm Hg or ≥90 mm Hg, respectively, in the year prior cohort entry),[28] myocardial infarction, heart failure, stroke, atrial fibrillation, coronary artery disease, peripheral vascular disease, angina, chronic obstructive pulmonary disease, end-stage kidney disease, inflammatory bowel disease (ulcerative colitis, Crohn disease, other), cholecystectomy, previous cancer diagnoses other than nonmelanoma skin cancer, chronic pancreatitis, cirrhosis of the liver, *Helicobacter pylori* infection, and hepatitis B infection. We also included the following prescription drugs, all measured at any time before cohort entry: statins, aspirin and other NSAIDs, glucose-lowering drugs (including insulin, metformin, sulfonylureas, incretin-based drugs, sodium-glucose cotransporter–2 inhibitors, and other glucose-lowering drugs), antihypertensive drugs (other than the study drugs, which included angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, non-dCCBs, diuretics other than thiazide diuretics, β-blockers, and other antihypertensive drugs), proton pump inhibitors, vitamin D supplements, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors. Finally, we considered the following variables in the year before cohort entry as proxies for health care use and health-seeking behaviors: influenza vaccination

and screening procedures, including fecal occult blood test or participation in the national bowel screening program, mammography, and prostate-specific antigen testing.

Statistical Analysis

We used a multivariable logistic regression model to estimate the predicted probability of receiving a dCCB versus a thiazide diuretic conditional on the covariates listed previously, reweighting the study population using calendar time-specific propensity scores estimated within 5-year calendar bands at cohort entry (1990–1993, 1994–1998, 1999–2003, 2004–2008, 2009–2013, 2014–2018). The rationale for using calendar time-specific propensity scores was to account for secular trends in the prescribing of antihypertensive drugs, changes in pancreatic cancer incidence over time, and heterogeneity in the covariates during the study period.[3,29] The calendar bands were selected based on the strata size producing stable weights while allowing the capture of adequate variation in the temporal factors described previously. Propensity scores in the nonoverlapping regions were trimmed. As the average treatment effect in the treated population was the target of inference to obtain the effect estimate if the population was standardized to dCCBs, we used the propensity scores to generate standardized morbidity ratio weights. Patients initiating a dCCB were given a weight of 1, whereas patients initiating a thiazide diuretic were given a weight of the odds of treatment probability.[30,31] Extreme weights were truncated at 0.1 or 10. We evaluated covariate balance for each exposure group using absolute standardized differences, with predefined differences <0.10 indicative of an achieved balance.[32] Finally, we calculated weighted incidence rates of pancreatic cancer with 95% CIs based on the Poisson distribution and presented weighted cumulative incidence using the Kaplan–Meier curves. Weighted Cox proportional hazard models stratified on 5-year calendar bands at cohort entry were fit to estimate hazard ratios (HRs) and 95% CIs of pancreatic cancer associated with dCCBs using robust variance estimators.

Secondary and Sensitivity Analyses

We conducted 4 secondary analyses. First, we assessed the presence of a duration–response relation by modeling cumulative duration of dCCBs in a time-varying fashion. We calculated the duration of each dCCB and thiazide diuretic prescription separately and updated the duration cumulatively at each person-day of follow-up from cohort entry until the risk set date. Cumulative duration categories were set at <5, 5 to 10, and >10 years. Second, we investigated whether the risk of pancreatic cancer increased according to the time since initiation of the study drugs. For this analysis, the duration of follow-up was divided into 3 categories for dCCBs and thiazide diuretics (<5, 5–10, >10 years), and HRs were estimated within each of these categories. Third, we repeated the primary analysis by individual dCCB drug (amlodipine, nifedipine, felodipine, lercanidipine, other dCCBs). Finally, we assessed the presence of effect modification by risk factors for pancreatic cancer, which included sex, age, smoking status, body mass index, chronic pancreatitis, and diabetes.[33–37] This analysis was conducted by including product terms in the primary analysis model.

We conducted 3 sensitivity analyses. First, we modified the length of the lag period to 3 years, 5 years, and 10 years to account for uncertainties related to the latency time window of pancreatic cancer. Second, analogous to an intention-to-treat analysis, we did not censor patients at the time of switch from a dCCB to a thiazide diuretic or from a thiazide diuretic to a dCCB. In this analysis, switching was ignored, and patients were followed until a pancreatic cancer event or censoring on death from any cause, deregistration from the general practice, or end of study period. Third, we investigated the impact of potential informative censoring from drug switching during follow-up and the competing risk of death from any cause.[30] For this analysis, we used stabilized inverse probability of censoring weighting, where we estimated the probabilities of (1) remaining uncensored as a result of switching and (2) death for any cause, separately for dCCBs and thiazide diuretics. The product of the stabilized inverse probability of censoring weighting and the standardized morbidity ratio weights was used to reweigh the cohort (Data S1). Finally, we conducted a post hoc complete case exploratory analysis excluding patients with unknown body mass index and smoking status. For this analysis, the propensity score was reestimated, and standardized morbidity ratio weights were recalculated. All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC) and R (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The cohort included 344 480 dCCB initiators and 357 968 thiazide diuretic initiators (Figure 1) followed for a median of 4.1 and 5.0 years, respectively (including the 1-year lag period). A total of 545 and 707 pancreatic cancer events occurred in the dCCB group and the thiazide diuretic group during the study period, respectively, yielding respective weighted incidence rates of 37.2 (95% CI, 34.1–40.4) and 39.4 (95% CI, 36.1–42.9) per 100 000 person-years.

Baseline patient characteristics are presented in Table 1. Before weighting, the dCCB group and thiazide diuretic group were similar on most characteristics. Initiators of dCCBs were more likely to be men and be prescribed statins, angiotensin-converting enzyme inhibitors, and proton pump inhibitors. All baseline characteristics were well balanced after weighting, with absolute standardized differences ranging between 0.00 and 0.04. Figure S2 displays the distributional overlap of propensity scores before and after propensity score weighting.

Table 2 presents the results of the primary analysis. Overall, dCCBs were not associated with an increased risk of pancreatic cancer when compared with thiazide diuretics, yielding a weighted HR of 0.93 (95% CI, 0.80–1.09). Although the weighted cumulative incidence curves diverged after 10 years of follow-up, with a lower cumulative incidence for dCCBs, the CIs between the 2 groups overlapped (Figure S3).

There was no duration–response relation in secondary analyses investigating cumulative duration of use (Table 2). After >10 years of cumulative duration of use, the weighted HR was 1.25 (95% CI, 0.68–2.31), which had a wide CI and was based on few events. Consistent with the weighted cumulative incidence curve, the time since initiation analysis showed a lower point estimate for dCCBs after >10 years since initiation (weighted HR, 0.77 [95% CI, 0.47–1.26]). However, CIs were wide and overlapping across the different time since initiation categories. In the secondary analysis by individual dCCB agents, there was no evidence of an association with any of the individual agents and risk of pancreatic cancer, with weighted HRs ranging from 0.62 to 1.12 (Table S4). Similarly, there was no evidence of an association in the analyses investigating potential effect modification by sex, age, smoking status, body mass index, history of chronic pancreatitis, and diabetes (Tables S5 through S10).

Results from sensitivity analyses are presented in Figure 2. The sensitivity analyses using different lag periods (3, 5, 10 years) were consistent with the primary analysis, generating weighted hazard ratios ranging between 0.92 and 0.99 (Table S11). The weighted HRs were also highly consistent in the intention-to-treat analysis (0.96 [95% CI, 0.85–1.09]; Table S12) and the inverse probability of censoring weighting (marginal HR, 0.91 [95% CI, 0.78–1.06]; Table S13). Results from the post hoc exploratory analysis yielded similar estimates (Table S14).

DISCUSSION

The findings from this large, new-user, active comparator, population-based cohort study indicate that dCCBs are not associated with an increased risk of pancreatic cancer when compared with thiazide diuretics. Secondary analyses did not find evidence of an association for pancreatic cancer with any of the individual dCCB agents or with long-term cumulative use of dCCBs. Similar findings were observed in other secondary analyses, including time since initiation of dCCBs and effect modification by sex, age, smoking status, body mass index, chronic pancreatitis, and diabetes. Findings were also consistent in several sensitivity analyses addressing different sources of potential bias, including the use of 3-, 5-, and 10-year lag periods; an intention-to-treat analysis; and a stabilized inverse probability of censoring weighting to investigate the impact of potential informative censoring.

The biological mechanisms behind a possible association between dCCBs and pancreatic cancer are limited. It has been suggested that some antihypertensive drug classes, including dCCBs, might improve prognosis and survival in patients with pancreatic cancer.[38] Indeed, it has been shown that high levels of sRAGE (soluble receptor for advanced glycation end products) might play a protective role in pancreatic tumor initiation, and previous studies have shown that some dCCBs increase sRAGE concentrations, thus inhibiting the proinflammatory RAGE (receptor for advanced glycation end products) signaling pathway.[39,40] Contrastingly, sRAGE levels have been reported to be significantly lower in users of some dCCBs compared with users of other antihypertensive drugs and nonusers.[11] Some studies have also suggested that dCCBs may inhibit apoptosis and promote tumor growth through the inhibition of DNA fragmentation.[18,19] Overall, our findings do not support an association between dCCBs and pancreatic cancer. We reported that the weighted cumulative incidence curves diverged after 10 years of follow-up, with a lower cumulative incidence for dCCBs, although the CIs between the 2 groups overlapped. Future population-based studies with additional years of follow-up should further explore this finding. In the secondary analyses assessing the presence of effect modification, treatment effect heterogeneity was not observed across some subgroups, particularly for sex, age, chronic pancreatitis, and diabetes, resulting in the average treatment effect on the treated approximating the average treatment effect. Although there was no evidence of effect modification in the subgroups, future research should be conducted to confirm these findings.

To date, 6 observational studies have investigated a potential association with pancreatic cancer. Two earlier Danish studies reported standardized incidence rates of 1.20 (95% CI, 0.70–1.20) and 0.86 (95% CI, 0.57–1.25) for pancreatic cancer in users of any CCB compared with the general population.[14,15] In a 1998 case control study, the use of any CCB was not associated with an overall increased risk of pancreatic

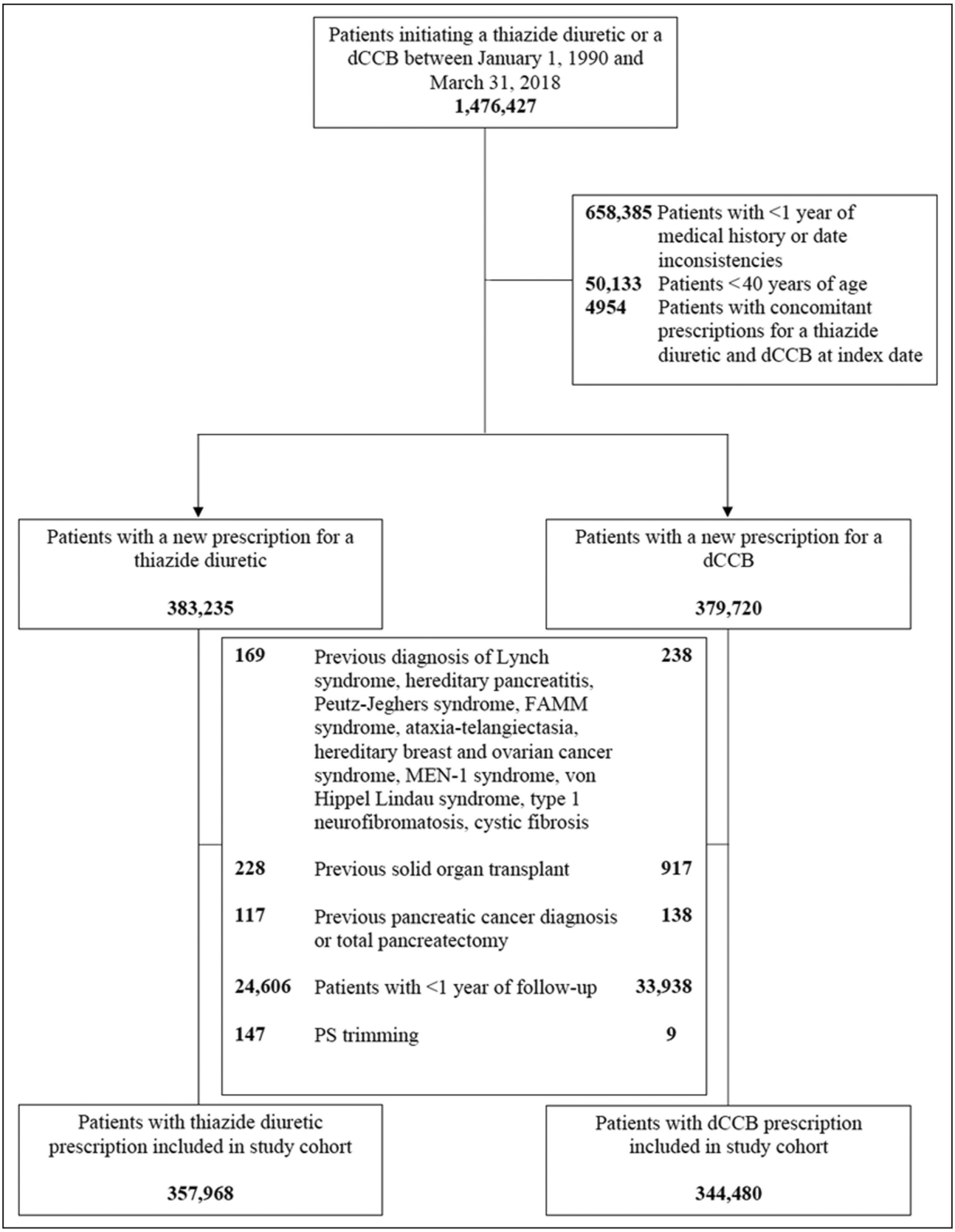

Figure 1. Study flow diagram of patients initiating dihydropyridine calcium channel blockers and thiazide diuretics in the Clinical Practice Research Datalink between January 1, 1990, and March 31, 2018.
dCCB indicates dihydropyridine calcium channel blocker; FAMM, familial atypical multiple mole and melanoma syndrome; MEN-1, multiple endocrine neoplasia type 1; and PS, propensity score.

Table 1. Baseline Characteristics of Initiators of dCCBs and Thiazide Diuretics Before and After Weighting

Characteristics	Before weighting			After weighting*		
	dCCB	Thiazide diuretic	ASD	dCCB	Thiazide diuretic	ASD
Total	344 480	357 968		344 480	339 912	
Mean age, y (SD)	63.6 (11.5)	64.7 (12.1)	0.09	63.6 (11.5)	63.9 (11.3)	0.02
Male sex, n (%)	187 261 (54.3)	143 926 (40.2)	0.28	187 261 (54.3)	183 731 (54.0)	0.00
BMI, n (%)						
<25 kg/m^2	84 924 (24.6)	90 121 (25.1)	0.01	84 924 (24.6)	83 848 (24.6)	0.00
25 to 29.9 kg/m^2	122 243 (35.4)	119 961 (33.5)	0.03	122 243 (35.4)	120 056 (35.3)	0.00
≥30 kg/m^2	99 876 (28.9)	90 217 (25.2)	0.08	99 876 (28.9)	98 837 (29.0)	0.00
Unknown	37 437 (10.8)	57 669 (16.1)	0.15	37 437 (10.8)	37 169 (10.9)	0.00
Smoking status, n (%)						
Ever	166 363 (48.2)	157 524 (44.0)	0.08	166 363 (48.2)	164 129 (48.2)	0.00
Never	164 566 (47.7)	169 315 (47.3)	0.00	164 566 (47.7)	162 259 (47.7)	0.00
Unknown	13 551 (3.9)	31 129 (8.7)	0.19	13 551 (3.9)	13 524 (3.9)	0.00
Alcohol-related disorders, n (%)†	17 076 (4.9)	10 326 (2.8)	0.10	17 076 (4.9)	16 641 (4.9)	0.00
Medical history, n (%)‡						
Hypertension	279 347 (81.0)	281 108 (78.5)	0.06	279 347 (81.0)	277 497 (81.6)	0.01
Myocardial infarction	17 782 (5.1)	10 306 (2.8)	0.11	17 782 (5.1)	19 166 (5.6)	0.02
Heart failure	7430 (2.1)	7498 (2.0)	0.00	7430 (2.1)	8576 (2.5)	0.02
Stroke	12 372 (3.5)	12 945 (3.6)	0.00	12 372 (3.5)	13 320 (3.9)	0.01
Atrial fibrillation	11 353 (3.3)	11 206 (3.1)	0.00	11 353 (3.3)	12 001 (3.5)	0.01
Coronary artery disease	74 438 (21.6)	58 008 (16.2)	0.13	74 438 (21.6)	76 489 (22.5)	0.02
PVD	14 544 (4.2)	9920 (2.7)	0.07	14 544 (4.2)	15 710 (4.6)	0.01
Angina	33 214 (9.6)	18 918 (5.2)	0.16	33 214 (9.6)	34 793 (10.2)	0.01
COPD	31 707 (9.2)	35 850 (10.0)	0.02	31 707 (9.2)	31 791 (9.3)	0.00
End-stage kidney disease	1705 (0.4)	512 (0.1)	0.06	1705 (0.4)	1890 (0.5)	0.00
Ulcerative colitis	2227 (0.6)	1915 (0.5)	0.01	2227 (0.6)	2155 (0.6)	0.00
Crohn disease	1198 (0.3)	973 (0.2)	0.01	1198 (0.3)	1121 (0.3)	0.00
Other IBD	621 (0.1)	403 (0.1)	0.01	621 (0.1)	600 (0.1)	0.00
Cholecystectomy	13 820 (4.0)	14 418 (4.0)	0.00	13 820 (4.0)	13 681 (4.0)	0.00
Previous cancer	19 877 (5.7)	18 462 (5.1)	0.02	19 877 (5.7)	19 744 (5.8)	0.00
History of chronic pancreatitis	388 (0.1)	249 (0.1)	0.01	388 (0.1)	382 (0.1)	0.00
Cirrhosis of the liver	564 (0.1)	409 (0.1)	0.01	564 (0.1)	562 (0.1)	0.00
Helicobacter pylori infection	2399 (0.7)	1403 (0.3)	0.04	2399 (0.7)	2316 (0.6)	0.00
Hepatitis B	223 (0.1)	89 (0.0)	0.01	223 (0.1)	216 (0.1)	0.00
Medications, n (%)						
Statins	115 475 (33.5)	65 394 (18.2)	0.35	115 475 (33.5)	116 710 (34.3)	0.01
Aspirin	95 062 (27.6)	73 981 (20.6)	0.16	95 062 (27.6)	97 557 (28.7)	0.02
Other NSAIDs	218 574 (63.4)	220 083 (61.4)	0.09	218 574 (63.4)	215 130 (63.2)	0.00
Insulin	9169 (2.6)	5230 (1.4)	0.08	9169 (2.6)	10 056 (2.9)	0.01
Metformin	27 285 (7.9)	14 117 (3.9)	0.16	27 285 (7.9)	28 434 (8.3)	0.01
Sulfonylureas	18 544 (5.3)	11 211 (3.1)	0.11	18 544 (5.3)	20 015 (5.8)	0.02
Incretin-based drugs	2773 (0.8)	633 (0.1)	0.09	2773 (0.8)	2772 (0.8)	0.00
SGLT-2 inhibitors	309 (0.1)	60 (0.0)	0.03	309 (0.1)	309 (0.1)	0.00
Other glucose-lowering drugs	6437 (1.8)	3538 (0.9)	0.07	6437 (1.8)	6727 (1.9)	0.00
ACE inhibitors	117 812 (34.2)	74 350 (20.7)	0.30	117 812 (34.2)	122 915 (36.1)	0.04

(*Continued*)

Table 1. Continued

Characteristics	Before weighting			After weighting*		
	dCCB	Thiazide diuretic	ASD	dCCB	Thiazide diuretic	ASD
ARBs	26 181 (7.6)	18 233 (5.0)	0.10	26 181 (7.6)	22 761 (8.1)	0.02
Non-dCCBs	11 768 (3.4)	12 719 (3.5)	0.00	11 768 (3.4)	12 992 (3.4)	0.02
Other diuretics	35 916 (10.4)	34 684 (9.6)	0.02	35 916 (10.4)	38 346 (11.2)	0.02
β-blockers	105 267 (30.5)	94 064 (26.2)	0.09	105 267 (30.5)	106 954 (31.4)	0.01
Other antihypertensive drugs	8950 (2.6)	9258 (2.5)	0.00	8950 (2.6)	9054 (2.6)	0.00
Proton pump inhibitors	126 895 (36.8)	81 532 (22.7)	0.31	126 895 (36.8)	125 233 (36.8)	0.00
Vitamin D supplement	26 089 (7.5)	17 978 (5.0)	0.10	26 089 (7.5)	26 253 (7.7)	0.00
SSRIs and SNRIs	67 858 (19.7)	52 887 (14.7)	0.13	67 858 (19.7)	66 930 (19.6)	0.00
Screening and other health behaviors, n (%)						
Influenza vaccination	105 766 (30.7)	130 167 (36.3)	0.12	105 766 (30.7)	108 062 (31.7)	0.02
Fecal occult blood test§	11 746 (3.4)	3566 (1.0)	0.16	11 746 (3.4)	11 073 (3.2)	0.00
Mammography	23 667 (6.8)	25 994 (7.2)	0.01	23 667 (6.8)	23 373 (6.8)	0.00
PSA test	20.688 (6.0)	11 425 (3.1)	0.13	20.688 (6.0)	20 044 (5.9)	0.00
Cohort entry year, n (%)						
1990 to 1993	8517 (2.4)	16 995 (4.7)	0.12	8517 (2.4)	8831 (2.6)	0.01
1994 to 1998	20 310 (5.9)	42 930 (11.9)	0.21	20 310 (5.9)	20 695 (6.0)	0.00
1999 to 2003	41 410 (12.0)	129 262 (36.1)	0.58	41 410 (12.0)	42 088 (12.3)	0.01
2004 to 2008	99 613 (28.9)	117 570 (32.8)	0.08	99 613 (28.9)	99 929 (29.4)	0.01
2009 to 2013	108 788 (31.6)	41 776 (11.6)	0.50	108 788 (31.6)	108 737 (31.9)	0.00
2014 to 2018	65 788 (19.1)	9435 (2.6)	0.55	65 788 (19.1)	59 631 (17.5)	0.04

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ASD, absolute standardized difference; BMI, body mass index; COPD, chronic obstructive pulmonary disease; dCCB, dihydropyridine calcium channel blocker; IBD, inflammatory bowel disease; PSA, prostate-specific antigen; PVD, peripheral vascular disease; SGLT-2, sodium-glucose cotransporter–2; SNRIs, serotonin-norepinephrine reuptake inhibitors; and SSRIs, selective serotonin reuptake inhibitors.

*Characteristics weighted using standardized morbidity ratio weighting.

†Includes alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and hepatic failure.

‡Not mutually exclusive.

§Includes participation in the national bowel screening program.

cancer (relative risk, 1.1 [95% CI, 0.70–1.80]), although a higher point estimate was observed in patients with >5 years of use (relative risk, 1.80 [95% CI, 0.80–4.00]).[10] Recently, a 2018 Women's Health Initiative cohort study of 145 551 menopausal women reported that ever users of short-acting CCBs, such as the dCCB nifedipine, had a 66% increased risk of pancreatic cancer compared with ever users of other antihypertensive drugs (HR, 1.66 [95% CI, 1.20–2.28]), with a doubling of the risk associated with >3 years of use (HR, 2.07 [95% CI, 1.42–3.02]).[11] A 2019 cohort study of 8311 patients with chronic pancreatitis found that users of any CCB had a 56% increased risk of pancreatic cancer compared with nonusers, although the CIs were wide and crossed the null value (HR, 1.56 [95% CI, 0.76–3.22]).[12] Finally, a 2021 cohort study of 70 549 patients reported a moderately elevated point estimate in users of any CCB compared with nonusers, but with the CI crossing the null value (HR, 1.32 [95% CI, 0.79–2.20]).[13]

Of these 6 studies, however, only 2 were specifically designed to investigate associations between any CCB and pancreatic cancer,[11,12] with 1 of those studies restricted to patients with chronic pancreatitis.[12] Although chronic pancreatitis is an important risk factor for pancreatic cancer, it represents a specific and small subset of the patient population using antihypertensive drugs.[36] Importantly, neither of the 2 studies distinguished between dCCBs and non-dCCBs. This is important because the American College of Cardiology/American Heart Association, Hypertension Canada, and the International Society of Hypertension guidelines more specifically recommend dCCBs over non-dCCBs as a first-line treatment for hypertension because of their more potent vasodilatory effects.[5,6,23] In addition, some of the previous studies had potentially important, conclusion-altering biases, such as prevalent user bias, latency bias, recall bias, and confounding by indication by comparing CCB users with nonusers or the general population.[16,41–43] In addition to these biases, only 2 studies assessed a potential association by duration of use, and none reported analyses by individual agents. Although our study represents the largest study to date on dCCBs and

Table 2. Crude and Adjusted Hazard Ratios for Pancreatic Cancer Comparing dCCBs With Thiazide Diuretics

Exposure	Events	Person-years	Weighted incidence rate (95% CI)*,†	Crude hazard ratio (95% CI)	Weighted hazard ratio (95% CI)†,‡
Primary analysis					
Thiazide diuretics	707	1 895 844	39.4 (36.1–42.9)	1.00 [Reference]	1.00 [Reference]
dCCBs	545	1 464 901	37.2 (34.1–40.4)	1.02 (0.91–1.14)	0.93 (0.80–1.09)
Cumulative duration <5 y§					
Thiazide diuretics	534	1 507 162	38.2 (34.7–42.0)	1.00 [Reference]	1.00 [Reference]
dCCBs	441	1 197 492	36.8 (33.4–40.4)	1.06 (0.93–1.20)	0.96 (0.81–1.14)
Cumulative duration 5 to 10 y§					
Thiazide diuretics	141	317 640	47.0 (37.7–57.9)	1.00 [Reference]	1.00 [Reference]
dCCBs	85	226 527	37.5 (29.9–46.4)	0.85 (0.65–1.12)	0.80 (0.57–1.11)
Cumulative duration >10 y§					
Thiazide diuretics	32	71 042	37.1 (18.5–66.6)	1.00 [Reference]	1.00 [Reference]
dCCBs	19	40 882	46.4 (27.9–72.6)	1.04 (0.59–1.84)	1.25 (0.68–2.31)
Time since initiation <5 y					
Thiazide diuretics	390	1 148 239	36.3 (32.5–40.3)	1.00 [Reference]	1.00 [Reference]
dCCBs	357	1 008 706	35.3 (31.8–39.2)	1.04 (0.89–1.22)	0.97 (0.79–1.18)
Time since initiation 5 to 10 y‖					
Thiazide diuretics	211	528 658	44.5 (37.8–52.0)	1.00 [Reference]	1.00 [Reference]
dCCBs	136	348 898	38.9 (32.7–46.1)	0.97 (0.76–1.21)	0.87 (0.66–1.15)
Time since initiation >10 y‖					
Thiazide diuretics	106	219 119	63.0 (48.6–80.3)	1.00 [Reference]	1.00 [Reference]
dCCBs	52	107 168	48.5 (36.2–63.6)	1.00 (0.68–1.34)	0.77 (0.47–1.26)

dCCBs indicates dihydropyridine calcium channel blockers.
*Per 100 000 person-years.
†Weighted using standardized morbidity ratio weights.
‡Stratified by 5-year calendar bands.
§Cumulative duration was modeled in a time-varying fashion.
‖Propensity score was reestimated, and weights were recalculated for these categories.

pancreatic cancer, additional large, population-based studies would be needed to confirm our findings. This is especially important given that pancreatic cancer is relatively rare, with an incidence between 5.6 and 9.9 per 100 000 person-years in Europe, North America, Australia, and New Zealand, which represent the regions with the highest incidence rates.[44]

Finally, evidence from RCTs is limited. To date, 3 large meta-analyses of RCTs have investigated the safety of antihypertensive drugs with respect to cancer outcomes.[7–9] Of those, 1 meta-analysis reported an odds ratio of 1.06 (95% CI, 1.01–1.12) with dCCBs for any cancer,[8] and 1 meta-analysis reported a HR of 1.06 (95% CI, 1.01–1.11).[9] Both meta-analyses concluded that an excess risk for dCCBs could not be ruled out and that the risk of cancer for this drug class needed to be further investigated.[8,9] However, only 1 of the 3 meta-analyses investigated site-specific cancers,

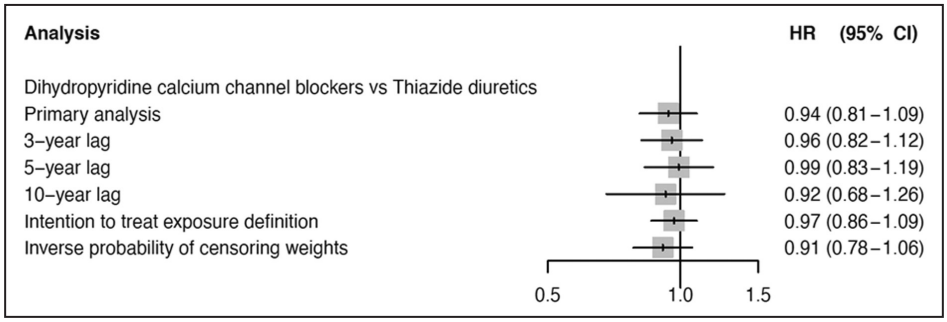

Figure 2. Forest plot presenting weighted hazard ratios and 95% CIs for the primary and sensitivity analyses.
HR indicates hazard ratio.

which included 5 cancer sites (colorectal, breast, lung, prostate, and skin), but not pancreatic cancer.[9] Indeed, to date, no meta-analyses of RCTs have included pancreatic cancer. Furthermore, these meta-analyses had important limitations in their assessment of cancer safety. First, none of the RCTs included in the 3 meta-analyses were designed to assess cancer safety outcomes.[7–9] Second, some site-specific cancers were represented by few RCTs, limiting the sample size available to detect these outcomes.[9] Third, the reported duration of follow-up was relatively short, where the majority of the RCTs included in the site-specific meta-analysis had <5 years of follow-up.[9] Finally, generalizing these findings to the real-world patient population is difficult considering the strict selection of patients in RCTs.

Strengths and Limitations

This study has several strengths. First, we aimed to address the limitations of previous studies by using thiazide diuretics as a clinically relevant comparator. This drug class is prescribed at a similar disease stage as dCCBs,[45–51] thus minimizing the potential for confounding by indication while generating clinically relevant findings. Second, we selected new users of dCCBs and thiazide diuretics to minimize the possibility of left truncation (ie, when there is exposed person-time before cohort entry but is not included in the study) and to properly assess the risk of pancreatic cancer in the cumulative duration of use and time since initiation analyses. Third, the use of the CPRD allowed us to account for important risk factors for pancreatic cancer not present in administrative databases, including smoking status, body mass index, and alcohol use. In addition, it allowed for long follow-up periods, with some patients having up to 28 years of follow-up. Finally, with the inclusion of 703 448 patients representing 3.3 million person-years of follow-up, our study represents the first study sufficiently large to adequately assess the association between dCCBs and pancreatic cancer risk. Furthermore, it was specifically designed to investigate this association, with additional analyses by individual agents, cumulative duration, and time since initiation.

The study has some limitations. First, prescriptions in the CPRD represent those issued by primary care physicians, and therefore no information is available on medications prescribed by specialists, which can potentially lead to some misclassification of the exposure. In the United Kingdom, however, primary care physicians predominantly manage patients treated with antihypertensive drugs.[52,53] Furthermore, the CPRD does not contain information on dispensation of medications, thus not containing information on treatment adherence and possibly leading to additional exposure misclassification. However, our secondary analysis assessing duration–response by cumulative duration of use captures repeated prescriptions and therefore some indication of adherence, which showed findings consistent with the primary analysis. Second, misclassification of pancreatic cancer is possible although unlikely, as it has been shown to have a high positive predictive value and sensitivity compared with the National Cancer Data Repository.[21,22] Third, we were unable to stratify on grade and stage or distinguish between pancreatic ductal adenocarcinoma and other subtypes of pancreatic cancer as these are not well recorded in the CPRD. However, pancreatic ductal adenocarcinoma represents the majority of pancreatic tumors.[54] Finally, although we were unable to capture potential risk factors for pancreatic cancer such as diet and chemical and heavy metal exposure, these variables would be unlikely to be differentially distributed among patients prescribed dCCBs versus thiazide diuretics.

In summary, the results of this large, population-based cohort study of 702 448 primary care patients indicate that dCCBs are not associated with an increased risk of pancreatic cancer compared with thiazide diuretics. The findings were consistent in several secondary and sensitivity analyses, including cumulative duration of dCCB use and individual dCCB agents. Given the long-term use of dCCBs in patients with hypertension, this observational study provides much needed evidence, as well as reassurance to physicians and patients, regarding the safety of this drug class with respect to pancreatic cancer.

ARTICLE INFORMATION

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Rouette conducted the data analysis and drafted the manuscript. L. Azoulay has attested that all authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Disclosures

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Supplemental Material

Data S1
Tables S1–S14
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Inverse probability of censoring weighting

We used inverse probability of censoring weighting (IPCW) to investigate the potential impact of informative censoring due to switching/adding on the other drug under study (i.e., switching from a dCCB to a thiazide diuretic and vice versa). IPCW was also used to account for competing risk of all-cause death. Accordingly, we applied one weight for switching/adding on and one weight for all-cause death as competing risk.

For this analysis, the follow-up period of every patient was divided into one-year intervals in which the covariates were updated based on the previous interval. We updated the covariates (listed under Potential Confounders section in main manuscript) using the same measurement structure. We then estimated the probability of remaining uncensored due to switching at each one-year interval, calculated separately for dCCBs and thiazide diuretics. For this step, we generated the probability by fitting a multivariable logistic regression model stratified by five-year calendar bands, conditional on the covariates included in the primary analysis. Similarly, we estimated the probability of not being censored due to death from any cause, separately for both cohorts and at each one-year interval. We generated the probability by fitting a multivariable logistic regression model stratified by 5-year calendar bands, conditional on the covariates included in the primary analysis.

Finally, we used the conditional probabilities to generate weights at every interval for each patient. The two IPCWs were stabilized using intercept-only models as the numerator, and extreme weights were truncated at the 1st and 99th percentile. We took the product of the stabilized weights and the standardized morbidity ratio weight to obtain a final weight for each patient, then re-weighted the cohort. Weighted Cox proportional hazard models were then used to estimate hazard ratios and confidence intervals of pancreatic cancer associated with dCCBs using robust variance estimators.

Table S1. British National Formulary (BNF) codes for dihydropyridine calcium channel blockers [*]

BNF code	BNF header
2060200	Calcium-channel Blockers
02040000/02060200	Beta-Adrenoceptor Blocking Drugs/Calcium-channel Blockers
02050501/02060200	Angiotensin-converting Enzyme inhibitors/Calcium-channel blockers
02050504/02060200	Angiotensin-ii Receptor Antagonists/Calcium-channel Blockers

[*] BNF codes include chapter and section information for the prescribed product, with every product defined through a unique product code in the Clinical Practice Research Datalink.

Table S2. British National Formulary (BNF) codes for thiazide diuretics *

BNF code	BNF header
2020100	Thiazides And Related Diuretics
2020400	Potassium-sparing Diuretics With Other Diuretics
2020800	Diuretics With Potassium
2040100	Beta-adrenoceptor Blocking Drugs With Diuretic
2050504	Angiotensin-ii Receptor Antagonists With Diuretic
02020100/02040000	Thiazides And Related Diuretics/Beta-adrenoceptor Blocking Drugs
02020100/02050501	Thiazides And Related Diuretics/Angiotensin-Converting Enzyme Inh
02020100/09050102	Thiazides And Related Diuretics/Hypercalcaemia And Hypercalciuria

* BNF codes include chapter and section information for the prescribed product, with every product defined through a unique product code in the Clinical Practice Research Datalink.

Table S3. Read codes for pancreatic cancer

Read code	Read term
BB5B600	[M]Mixed islet cell and exocrine adenocarcinoma
BBA2.00	[M]Acinar cell carcinoma
BB5B100	[M]Islet cell carcinoma
BB5C.00	[M]Gastrinoma and carcinomas
BB5C000	[M]Gastrinoma NOS
BB5C100	[M]Gastrinoma, malignant
BB5Cz00	[M]Gastrinoma or carcinoma NOS
BB5B300	[M]Insulinoma, malignant
BB5B200	[M]Insulinoma NOS
BB5B500	[M]Glucagonoma, malignant
BB5B400	[M]Glucagonoma NOS
BB5y100	[M]Vipoma
B176.00	Somatostatinoma of pancreas
B17yz00	Malignant neoplasm of specified site of pancreas NOS
B17y000	Malignant neoplasm of ectopic pancreatic tissue
B17y.00	Malignant neoplasm of other specified sites of pancreas
B171.00	Malignant neoplasm of body of pancreas
B17z.00	Malignant neoplasm of pancreas NOS
B80z000	Carcinoma in situ of pancreas
BB5Bz00	[M]Pancreatic adenoma or carcinoma NOS
B173.00	Malignant neoplasm of pancreatic duct
B175.00	Malignant neoplasm, overlapping lesion of pancreas
B170.00	Malignant neoplasm of head of pancreas
BB5B.00	[M]Pancreatic adenomas and carcinomas
B17..00	Malignant neoplasm of pancreas
B172.00	Malignant neoplasm of tail of pancreas
B717011	Endocrine tumour of pancreas
B905100	Neoplasm of uncertain behaviour of pancreas
B174.00	Malignant neoplasm of Islets of Langerhans

Table S4. Crude and adjusted hazard ratios for the association between individual dihydropyridine calcium channel blocker agents and risk of pancreatic cancer

Exposure	Events	Person years	Weighted incidence rate (95% CI) [*†]	Crude hazard ratio (95% CI)	Weighted hazard ratio (95% CI) [†‡]
Thiazide diuretics	707	1,895,844	39.4 (36.1-42.9)	1.00 [Reference]	1.00 [Reference]
Individual dCCB agent					
Amlodipine	346	973,458	35.5 (31.8-39.4)	0.98 (0.86-1.12))	0.89 (0.75-1.05)
Nifedipine	120	270,859	44.3 (36.7-52.9)	1.18 (0.97-1.43)	1.12 (0.91-1.39)
Felodipine	64	166,166	38.5 (29.6-49.1)	1.05 (0.81-1.35)	0.97 (0.74-1.28)
Lercanidipine	10	33,719	29.6 (14.2-54.5)	0.82 (0.44-1.53)	0.75 (0.70-1.42)
Other [§]	5	20,699	24.1 (7.8-56.3)	0.64 (0.26-1.55)	0.62 (0.25-1.49)

Abbreviations: dCCBs; dihydropyridine calcium channel blockers, CI; confidence interval

[*]Per 100,000 person-years. [†]Weighted using standardized morbidity ratio weights. [‡] Stratified by 5-year calendar bands.
[§] Other include nimodipine, nisoldipine, nicardipine, isradipine, lacidipine, combinations

Table S5. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (effect modification by sex)

	Male	**Female**	
Events	586	666	
Person-years	1,532,507	1,828,238	
Weighted incidence rate (95% CI) [*†]	39.8 (36.8-43.1)	36.3 (33.1-39.8)	
Crude hazard ratio (95% CI)			
Thiazide diuretics	1.00 [Reference]	1.00 [Reference]	p-interaction=0.83
dCCBs	0.99 (0.84-1.17)	1.02 (0.87-1.20)	
Weighted hazard ratio (95% CI) [†‡]			
Thiazide diuretics	1.00 [Reference]	1.00 [Reference]	p-interaction=0.47
dCCBs	0.89 (0.71-1.10)	0.99 (0.81-1.21)	

Abbreviations: dCCBs; dihydropyridine calcium channel blockers, CI; confidence interval
[*] Per 100,000 person-years. [†] Weighted using standardized morbidity ratio weights. [‡] Stratified by 5-year calendar bands

Table S6. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (effect modification by age)

	Age ≤ 65	**Age > 65**	
Events	426	826	
Person-years	1,965,425	1,395,319	
Weighted incidence rate (95% CI) [*†]	22.5 (20.3-25.0)	60.6 (56.2-65.3)	
Crude hazard ratio (95% CI)			
Thiazide diuretics	1.00 [Reference]	1.00 [Reference]	
dCCBs	1.07 (0.88-1.29)	1.02 (0.89-1.17)	p-interaction=0.68
Weighted hazard ratio (95% CI) [†‡]			
Thiazide diuretics	1.00 [Reference]	1.00 [Reference]	
dCCBs	0.93 (0.72-1.21)	0.93 (0.78-1.12)	p-interaction=0.98

Abbreviations: dCCBs; dihydropyridine calcium channel blockers, CI; confidence interval

[*] Per 100,000 person-years. [†] Weighted using standardized morbidity ratio weights. [‡] Stratified by 5-year calendar bands

Table S7. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (effect modification by smoking status) [*]

	Never smoker	Ever smoker	
Events	523	630	
Person-years	1,598,161	1,490,658	
Weighted incidence rate (95% CI) [†‡]	32.4 (29.4-35.6)	44.5 (41.0-48.3)	
Crude hazard ratio (95% CI)			
Thiazide diuretics	1.00 [Reference]	1.00 [Reference]	p-interaction=0.12
dCCBs	0.89 (0.75-1.07)	1.13 (0.96-1.32)	
Weighted hazard ratio (95% CI) [‡§]			
Thiazide diuretics	1.00 [Reference]	1.00 [Reference]	p-interaction=0.66
dCCBs	0.86 (0.69-1.07)	0.99 (0.79-1.24)	

Abbreviations: dCCBs; dihydropyridine calcium channel blockers, CI; confidence interval

[*] Unknown smoking status considered in the model but not presented in the table. [†] Per 100,000 person-years.
[‡]Weighted using standardized morbidity ratio weights. [§] Stratified by 5-year calendar bands

Table S8. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (effect modification by body mass index) [*]

	BMI <25 kg/m^2	BMI 25-29 kg/m	BMI >29 kg/m^2	
Events	314	478	275	
Person-years	828,538	1,162,735	872,837	
Weighted incidence rate (95% CI) [†‡]	36.9 (32.5-41.7)	46.5 (42.4-50.9)	30.3 (26.5-34.5)	
Crude hazard ratio (95% CI)				
dCCBs	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	
Thiazide diuretics	1.04 (0.83-1.30)	1.11 (0.93-1.34)	0.95 (0.74-1.20)	p-interaction=0.12
Weighted hazard ratio (95% CI) [‡§]				
dCCBs	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	
Thiazide diuretics	1.07 (0.82-1.40)	0.85 (0.66-1.09)	0.98 (0.72-1.33)	p-interaction=0.64

Abbreviations: dCCBs; dihydropyridine calcium channel blockers, CI; confidence interval

[*] Unknown smoking status considered in the model but not presented in the table. [†] Per 100,000 person-years. [‡] Weighted using standardized morbidity ratio weights.
[§] Stratified by 5-year calendar bands

Table S9. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (effect modification by history of chronic pancreatitis)

	No history of chronic pancreatitis	History of chronic pancreatitis	
Events	1,247	5	
Person-years	2,846,256	2554	
Weighted incidence rate (95% CI) [*†]	38.1 (35.8-40.5)	182.7 (61.2-419.3)	
Crude hazard ratio (95% CI)			
Thiazide diuretics	1.00 [Reference]	1.00 [Reference]	
dCCBs	1.02 (0.91-1.14)	0.92 (0.15-5.55)	p-interaction=0.91
Weighted hazard ratio (95% CI) [†‡]			
Thiazide diuretics	1.00 [Reference]	1.00 [Reference]	
dCCBs	0.93 (0.80-1.08)	1.07 (0.17-6.48)	p-interaction=0.88

Abbreviations: dCCBs; dihydropyridine calcium channel blockers, CI; confidence interval

[*] Per 100,000 person-years. [†] Weighted using standardized morbidity ratio weights. [‡] Stratified by 5-year calendar bands

Table S10. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (effect modification by history of diabetes)

	No history of diabetes	History of diabetes	
Events	1,140	112	
Person-years	3,139,965	220,780	
Weighted incidence rate (95% CI) [*†]	36.8 (34.5-39.2)	52.7 (44.2-62.3)	
Crude hazard ratio (95% CI)			
Thiazide diuretics	1.00 [Reference]	1.00 [Reference]	p-interaction=0.89
dCCBs	0.99 (0.88-1.12)	1.02 (0.69-1.50)	
Weighted hazard ratio (95% CI) [†‡]			
Thiazide diuretics	1.00 [Reference]	1.00 [Reference]	p-interaction=0.96
dCCBs	0.93 (0.80-1.09)	0.92 (0.57-1.49)	

Abbreviations: dCCBs; dihydropyridine calcium channel blockers, CI; confidence interval

[*] Per 100,000 person-years. [†] Weighted using standardized morbidity ratio weights. [‡] Stratified by 5-year calendar bands

Table S11. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (different lag periods)

Exposure	Events	Person years	Weighted incidence rate (95% CI) [*†]	Crude hazard ratio (95% CI)	Weighted hazard ratio (95% CI) [†‡]
Primary analysis					
Thiazide diuretics	707	1,895,844	39.4 (36.1-42.9)	1.00 [Reference]	1.00 [Reference]
dCCBs	545	1,464,901	37.2 (34.1-40.4)	1.02 (0.91-1.14)	0.93 (0.80-1.09)
3-year lag period					
Thiazide diuretics	593	1,508,945	40.5 (36.6-44.8)	1.00 [Reference]	1.00 [Reference]
dCCBs	394	1,014,379	38.8 (35.1-42.8)	1.00 (0.88-1.14)	0.95 (0.81-1.12)
5-year lag period					
Thiazide diuretics	480	1,163,182	43.9 (39.0-49.3)	1.00 [Reference]	1.00 [Reference]
dCCBs	297	679,383	43.7 (38.8-48.9)	1.07 (0.92-1.23)	0.99 (0.82-1.18)
10-year lag period					
Thiazide diuretics	221	484,480	51.2 (42.0-61.9)	1.00 [Reference]	1.00 [Reference]
dCCBs	98	205,765	47.6 (38.6-58.0)	1.05 (0.83-1.33)	0.92 (0.68-1.25)

Abbreviations: dCCBs; dihydropyridine calcium channel blockers, CI; confidence interval

[*] Per 100,000 person-years [†] Weighted using standardized morbidity ratio weights [‡] Stratified by 5-year calendar bands

Table S12. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (intention-to-treat exposure definition)

Exposure	Events	Person years	Weighted incidence rate (95% CI) [*†]	Crude hazard ratio (95% CI)	Weighted hazard ratio (95% CI) [†‡]
Primary analysis					
Thiazide diuretics	707	1,895,844	39.4 (36.1-42.9)	1.00 [Reference]	1.00 [Reference]
dCCBs	545	1,464,901	37.2 (34.1-40.4)	1.02 (0.91-1.14)	0.93 (0.80-1.09)
Intention-to-treat exposure definition					
Thiazide diuretics	1134	2,917,427	38.8 (36.1-41.6)	1.00 [Reference]	1.00 [Reference]
dCCBs	731	1,950,057	37.4 (34.8-40.3)	0.99 (0.90-1.09)	0.96 (0.85-1.09)

Abbreviations: dCCBs; dihydropyridine calcium channel blockers, CI; confidence interval

[*] Per 100,000 person-years. [†] Weighted using standardized morbidity ratio weights. [‡] Stratified by 5-year calendar bands

Table S13. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (inverse probability of censoring weighting)

Exposure	Events	Person years	Weighted incidence rate (95% CI) [*†]	Crude hazard ratio (95% CI)	Weighted hazard ratio (95% CI) [†‡]
Primary analysis					
Thiazide diuretics	707	1,895,844	39.4 (36.1-42.9)	1.00 [Reference]	1.00 [Reference]
dCCBs	545	1,464,901	37.2 (34.1-40.4)	1.02 (0.91-1.14)	0.93 (0.80-1.09)
Inverse probability of censoring weighting					
Thiazide diuretics	707	2,088,076	36.8 (33.8-39.9)	1.00 [Reference]	1.00 [Reference]
dCCBs	545	1,651,886	33.8 (31.9-36.7)	0.99 (0.89-1.11)	0.91 (0.78-1.06)

Abbreviations: dCCBs; dihydropyridine calcium channel blockers, CI; confidence interval

[*] Per 100,000 person-years. [†] Weighted using standardized morbidity ratio weights. [‡] Stratified by 5-year calendar bands

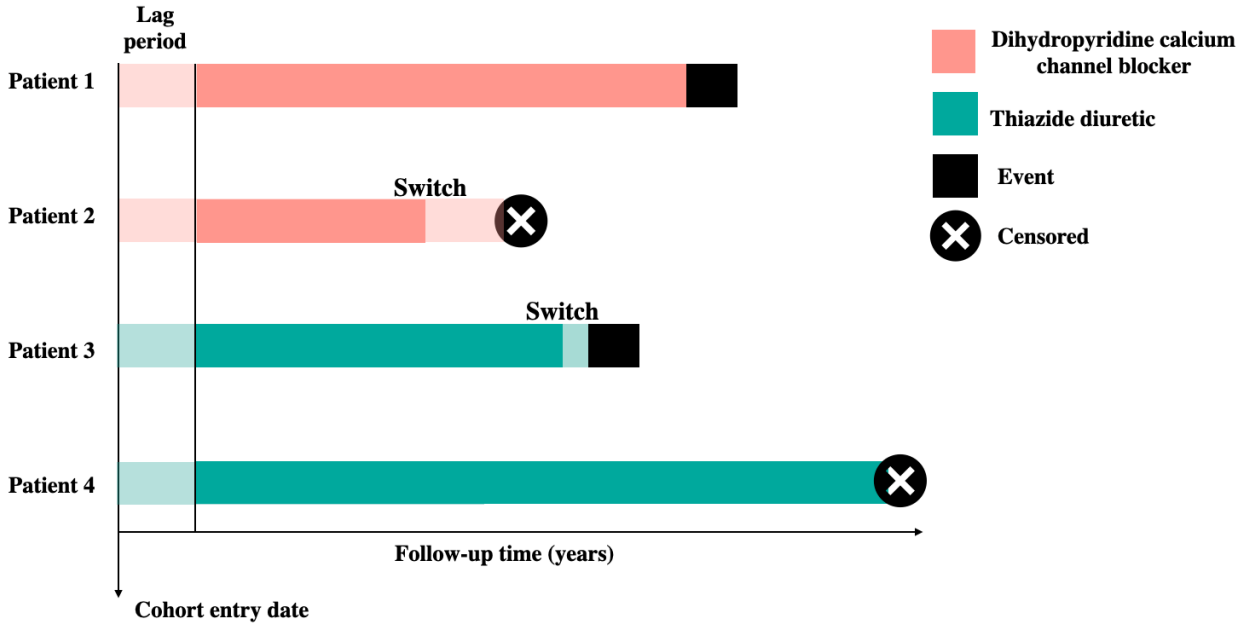
Table S14. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (post-hoc complete case analysis)

Exposure	Events	Person years	Weighted incidence rate (95% CI) [*†]	Crude hazard ratio (95% CI)	Weighted hazard ratio (95% CI) [†‡]
Primary analysis					
Thiazide diuretics	707	1,895,844	39.4 (36.1-42.9)	1.00 [Reference]	1.00 [Reference]
dCCBs	545	1,464,901	37.2 (34.1-40.4)	1.02 (0.91-1.14)	0.93 (0.80-1.09)
Complete case analysis [§]					
Thiazide diuretics	569	1,533,922	40.0 (36.4-43.8)	1.00 [Reference]	1.00 [Reference]
dCCBs	481	1,259,251	38.2 (34.9-41.8)	1.06 (0.94-1.20)	0.95 (0.81-1.12)

Abbreviations: dCCBs; dihydropyridine calcium channel blockers, CI; confidence interval

[*] Per 100,000 person-years. [†] Weighted using standardized morbidity ratio weights. [‡] Stratified by 5-year calendar bands [§] Propensity score was re-estimated and weights were re-calculated for this analysis

Figure S1. Exposure definition



Cohort entry date is the date of the first prescription for either study drug i.e., the first of either a dihydropyridine calcium channel blocker or a thiazide diuretic. All patients were required to have a minimum of one year of follow-up after cohort entry (lag period, considered as unexposed person-time). Therefore, the follow-up started one year after cohort entry for all patients (start of person-time at risk or exposed person-time). Patient 1 initiated a dihydropyridine calcium channel blocker, and was considered exposed starting one year after cohort entry. Follow-up ended on the date of the event, depicted by a black square. Similarly, patient 2 initiated a dihydropyridine calcium channel blocker, and was considered exposed starting one year after cohort entry. Once the patient switched to a thiazide diuretic, a one-year lag period was applied whereas an event occurring during that one-year period would be attributed to the dihydropyridine calcium channel blocker. After the one-year period had elapsed, the patient was censored. Patient 3 initiated a thiazide diuretic and subsequently switched to a dihydropyridine calcium channel blocker. The patient had an event during the one-year period following the switch, which was attributed to the thiazide diuretic. Patient 4 initiated a thiazide diuretic and was subsequently censored at the end of the study period.

Figure S2. Distributional overlap of propensity scores before and after weighting

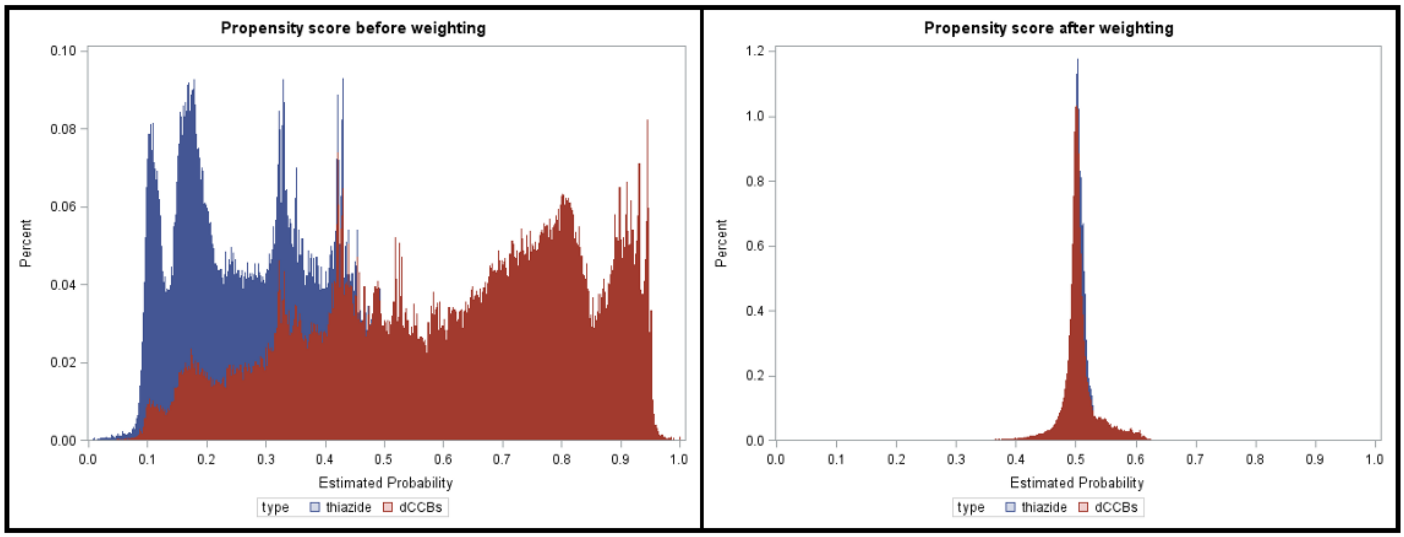
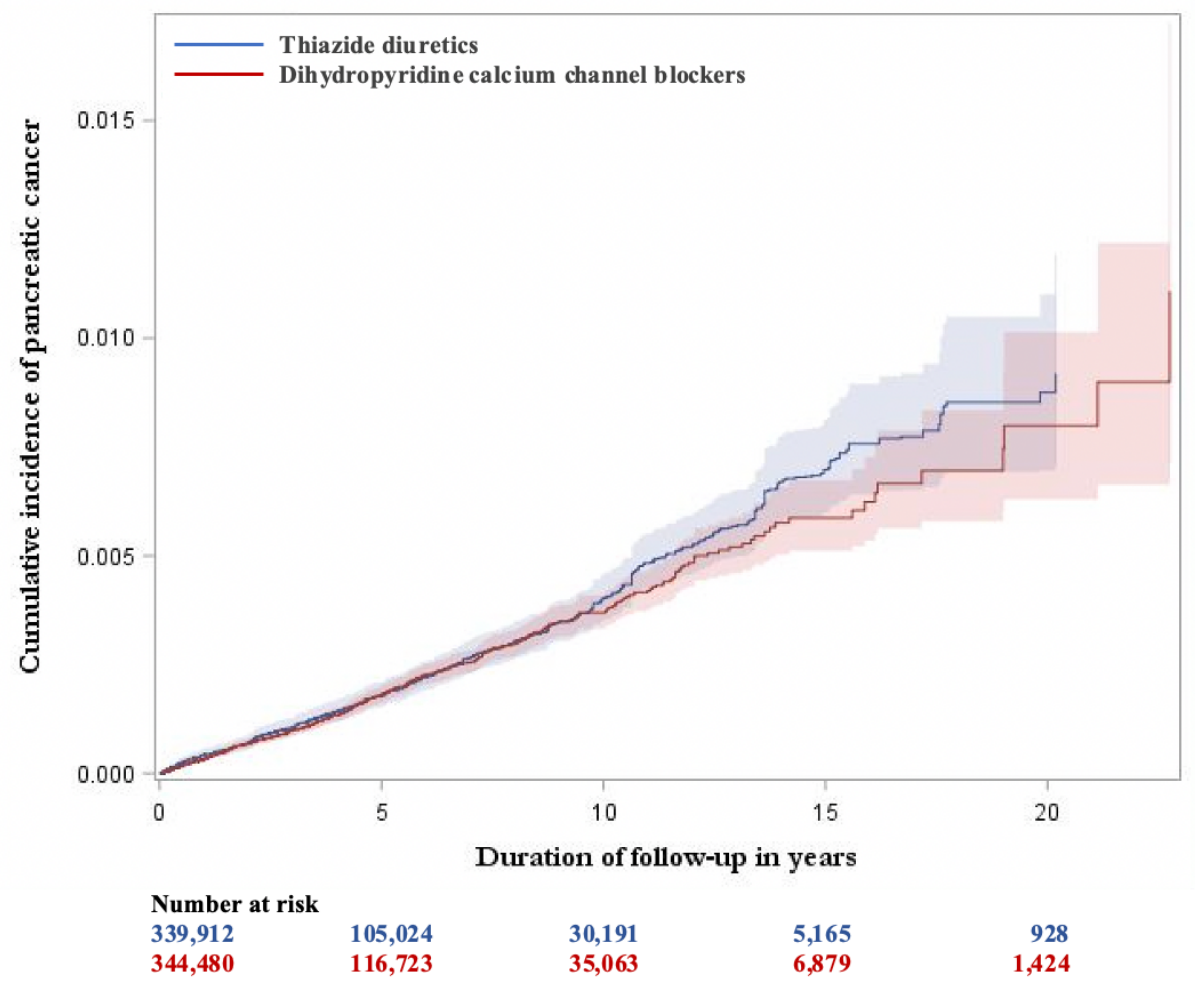


Figure S3. Weighted Kaplan-Meier curve for cumulative incidence of pancreatic cancer [*†]



[*] Weighted using standardized morbidity ratio weights [†] Follow-up starts one year after cohort entry