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The use of drugs acting on the renin–angiotensin system and the incidence of pancreatic cancer

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Background: Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are commonly used antihypertensives. Recently, these drugs have been associated with a protective effect against pancreatic cancer, but data on this putative association remain limited. Thus, the objective of this study was to determine whether the use of ACEIs and/or ARBs is associated with a decreased risk of pancreatic cancer.

Methods: We conducted a population-based cohort study, using a nested case–control analysis within the UK Clinical Practice Research Datalink population. The cohort consisted of all patients newly treated with antihypertensive drugs between 1 January 1995 and 31 December 2009, with follow-up until 31 December 2010. Cases were patients with newly diagnosed pancreatic cancer, which were matched with up to 10 controls on age, sex, calendar year of cohort entry, and duration of follow-up. Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of pancreatic cancer incidence associated with ever use of ACEIs and ARBs. A secondary analysis was conducted to assess whether the incidence of pancreatic cancer varied with cumulative duration of use of these drugs.

Results: A cohort of 547 566 was assembled. During 3040 332 person-years of follow-up, a total of 866 patients were newly diagnosed with pancreatic cancer (rate: 3/10 000 per year) and matched to 8636 controls. Overall, when compared with other antihypertensive drugs, the use of ACEIs was not associated with a decreased risk of pancreatic cancer overall (OR: 1.01, 95% CI: 0.86–1.17) or according to cumulative duration of use. The use of ARBs was not associated with a decreased risk of pancreatic cancer overall (OR: 0.93, 95% CI: 0.75–1.15), whereas a cumulative duration of use of 1–3 years was associated with a 38% decrease (OR: 0.62, 95% CI: 0.41–0.94), which returned to the null after >3 years of use (OR: 1.04, 95% CI: 0.74–1.46).

Conclusions: The use of ARBs and ACEIs was not associated with an overall decreased risk of pancreatic cancer when compared with patients using other antihypertensive drugs. Additional research is needed to determine whether ARBs may confer a short-term protective effect.

The role of the renin–angiotensin system (RAS) in the homeostasis of blood pressure, electrolytes, and volume status is well established (Peach, 1977). There is also evidence that the RAS exists in other tissues, such as the pancreas where it is thought to mediate growth and may have a role in carcinogenesis (Fujimoto *et al*, 2001; Lam and Leung, 2002; Anandanadesan *et al*, 2008;

Perez-Diaz *et al*, 2011; Chauhan *et al*, 2013). Although the exact role of RAS in carcinogenesis remains to be elucidated, it is thought to be implicated in several pathways that may lead to cancer via angiogenesis, inhibition of apoptosis, and influence on stromal cells (Fujimoto *et al*, 2001; Arafat *et al*, 2007; Anandanadesan *et al*, 2008; Chauhan *et al*, 2013; Masamune *et al*, 2013).

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Given the involvement of RAS in the development of pancreatic cancer, it is biologically plausible that drugs that interfere with this system may have chemopreventive effects. Indeed, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are two drug classes used in the treatment of hypertension via the blockade of RAS whose use may decrease the risk of pancreatic cancer. In line with this hypothesis, *in vitro* and animal studies have shown that the use of ACEIs or ARBs inhibited tumour growth by inhibiting angiogenesis or inducing apoptosis (Fujimoto *et al*, 2001; Arafat *et al*, 2007; Noguchi *et al*, 2009; Doi *et al*, 2010; Fendrich *et al*, 2010; Arnold *et al*, 2012; Chauhan *et al*, 2013; Masamune *et al*, 2013). Furthermore, it has been demonstrated that hypertension itself may be protective against pancreatic cancer (Eijgenraam *et al*, 2013). It may be postulated that this effect may be driven by the use of antihypertensive drugs such as ACEIs and ARBs. However, other studies have failed to show an association between hypertension and pancreatic cancer (Stolzenberg-Solomon *et al*, 2002; Rosato *et al*, 2011). This is possibly due to the influence of certain antihypertensive drugs.

To date, no observational study has been conducted to assess whether there is an association between the use of ACEIs or ARBs on the incidence of pancreatic cancer. Thus, the objective of this large population-based study was to determine whether the use of ACEIs or ARBs is associated with a decreased risk of pancreatic cancer in patients newly treated with antihypertensive drugs.

MATERIALS AND METHODS

Data source. We conducted a retrospective population-based cohort study, using a nested case-control analysis using the United Kingdom Clinical Practice Research Datalink (CPRD) database. The CPRD includes over 13 million patients followed in general practice in over 680 offices in the United Kingdom. The CPRD records demographic data, diagnoses, procedures, and prescriptions written by general practitioners. The information recorded in the CPRD has been shown to have excellent validity (Garcia Rodriguez and Perez Gutthann, 1998; Lawrenson *et al*, 1999; Jick *et al*, 2003; Herrett *et al*, 2010).

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 15_038R) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Study cohort. The cohort consisted of all patients newly treated with antihypertensive drugs (diuretics, beta-blockers, ACEIs, ARBs, calcium channel blockers (CCBs), alpha-adrenergic receptor blocking drugs (alpha-blockers), and other antihypertensives) between 1 January 1995 and 31 December 2009, with follow-up until 31 December 2010. Cohort entry was the date of the first-ever prescription for an antihypertensive drug. To be included in the study, patients were required to have at least 1 year of medical history in the CPRD prior to cohort entry and to have at least 1 year of follow-up after cohort entry, which was necessary for latency considerations. Patients with a history of cystic fibrosis at any time prior to cohort entry were excluded as this is considered to be a risk factor for chronic pancreatitis and thus pancreatic cancer as well (Becker *et al*, 2014).

Thus, all patients meeting the study inclusion criteria were followed until a first-ever diagnosis of pancreatic cancer, death from any cause, end of registration with the general practice, or end of the study period (31 December 2010), whichever occurred first.

Case-control selection. All patients newly diagnosed with pancreatic cancer during follow-up were identified on the basis of Read codes (available in Supplementary Material, Appendix II).

The event date of each case's pancreatic cancer diagnosis was defined as their index date.

Using risk set sampling, up to 10 controls were randomly selected and matched to each case on age, sex, calendar year of cohort entry, and duration of follow-up. The matched controls inherited the index date of their respective cases. Thus, by definition, all controls were alive, not previously diagnosed with pancreatic cancer, and registered with their general practice when matched to a given case, and thus had equal duration of follow-up at the index date.

Exposure assessment. For all cases and matched controls, we obtained information on the antihypertensive prescriptions received between cohort entry and index date. These consisted of diuretics, beta-blockers, ACEIs, ARBs, CCBs, alpha-blockers, and other antihypertensive drugs.

The use of ACEIs or ARBs was entered as two non-mutually exclusive exposure categories in the models. Ever use was defined as receiving at least one prescription for an ACEI or ARB at any time but excluding the year before index date. The exclusion of exposures initiated in the year immediately prior to index date was to account for a biologically meaningful latency time window, as it was unlikely that a drug would have an effect on the incidence of pancreatic cancer after short exposure durations. This was considered the primary exposure definition.

We also considered four secondary exposure definitions. The first three definitions assessed whether there was a duration-response relationship in terms of cumulative duration of use, number of prescriptions received, and time since initiation. Thus, for patients deemed to be ever users ACEIs or ARBs, we calculated their cumulative duration of use as the sum of all prescription durations received between cohort entry and the index date. Similarly, number of prescriptions received was calculated by summing all prescriptions received between cohort entry and index date. Time since initiation was calculated as time between the first prescription and index date. These three secondary exposure definitions were categorised into tertiles based on the distribution of use in the controls. Finally, the fourth definition reclassified ever use of ACEIs or ARBs into three mutually exclusive categories: ACEIs alone, ARBs alone, and ever use of both ACEIs and ARBs.

Statistical analysis. The overall incidence rate of pancreatic cancer was estimated by dividing the total number of cases by the total person-years of follow-up, with 95% confidence intervals (CIs) based on the Poisson distribution. Conditional logistic regression was used to estimate odds ratios (ORs) with 95% CIs of pancreatic cancer associated with ever use of ACEIs or ARBs, when compared with never use. We also assessed whether there was a duration- and dose-response relationship in terms of cumulative duration, number of prescriptions, and time since initiation. Finally, we assessed whether smoking was an effect modifier of the association by including an exposure-smoking product term in the models.

In addition to age, sex, calendar year of cohort entry, and duration of follow-up on which the logistic regression was conditioned, all models were adjusted for the potential confounders measured at cohort entry based on their known association with the outcome (development of pancreatic cancer) and may possibly influence the prescribing of an ACEI or an ARB. These included excessive alcohol use, smoking status, body mass index, chronic pancreatitis, history of previous cancer (other than non-melanoma skin cancers), history of type 2 diabetes, and ever use of anti-diabetic drugs (metformin, sulfonylureas, thiazolidinediones, insulins, and others, entered individually as non-mutually exclusive variables), aspirin, non-steroidal anti-inflammatory drugs, and statins. The models were also adjusted for the ever use of diuretics, CCBs, alpha-blockers, beta-blockers, and other antihypertensive drugs, all measured between cohort entry and the

year immediately before index date, and all entered as non-mutually exclusive variables.

Sensitivity analyses. We conducted three sensitivity analyses. The first consisted of repeating the primary analysis after applying longer lag periods of 2 and 3 years before index date, given uncertainties related to the latency time window (as it is not possible to delineate the timeline for the development of pancreatic cancer). Second, the primary analysis was repeated using an alternate exposure definition, consisting of receiving at least four prescriptions within a 12-month period of ACEIs or ARBs. Finally, to account for the missing information on smoking status, sensitivity analyses were conducted using multiple imputation methods.

RESULTS

A total of 547 566 patients were included in the cohort (Figure 1). The mean (s.d.) age at entry of the cohort was 68.6 (10.4) years and 51.4% were males. The cohort generated 3 040 332 person-years of follow-up during which 866 patients were newly diagnosed with pancreatic cancer (crude incidence rate: 28.5 (95% CI: 26.6–30.4 per 100 000 person-years)).

The baseline characteristics of the cases and matched controls are listed in Table 1. Compared with matched controls, cases were more likely to have a lower body mass index, but more likely to have a history of excessive alcohol use, to have ever smoked, and to have ever used anti-diabetic drugs. Cases were more likely to have been diagnosed with type 2 diabetes than controls (10.2% vs 7.6%, respectively), whereas the prevalence of previous cancer was similar in both groups (Table 1).

Table 2 presents the results of the primary and secondary analyses for ACEIs. Overall, compared with the use of other antihypertensive drugs, the use of ACEIs was not associated with a decreased risk of pancreatic cancer (OR: 1.01, 95% CI: 0.86–1.17). In addition, there was no evidence of a duration- or dose-response relationship, with all ORs around null the value for the different secondary exposure definitions (Table 2). Smoking status did not modify the association (p -interaction = 0.27; Supplementary Table 1).

Table 3 presents the results of the primary and secondary analyses for ARBs. Overall, compared with the use of other antihypertensive drugs, the use of ARBs was not associated with a decreased risk of pancreatic cancer (OR: 0.93, 95% CI: 0.75–1.15). In secondary analyses, cumulative durations of 12–36 months and receiving between 12 and 36 prescriptions were associated with 38% and 39% risk reductions, respectively (Table 3). The time since initiation of ARBs did not influence the incidence of pancreatic cancer (Table 3). Smoking did not significantly modify the association (p -interaction = 0.20; Supplementary Table 1). Finally, compared with never use of any ACEI or ARB, ever use of ACEIs alone, ARBs alone, or history of both ACEIs and ARBs was not associated with a decreased incidence of pancreatic cancer (Supplementary Table 2).

Sensitivity analyses. Similar findings were observed when repeating the primary analyses using alternate lag periods (2 and 3 years) (Supplementary Table 3), and using a stricter exposure definition for ACEIs and ARBs (Supplementary Tables 4 and 5). For the latter, a decreased risk of pancreatic cancer remained in the 12–36 months cumulative duration category (Supplementary Table 5). Finally, similar findings

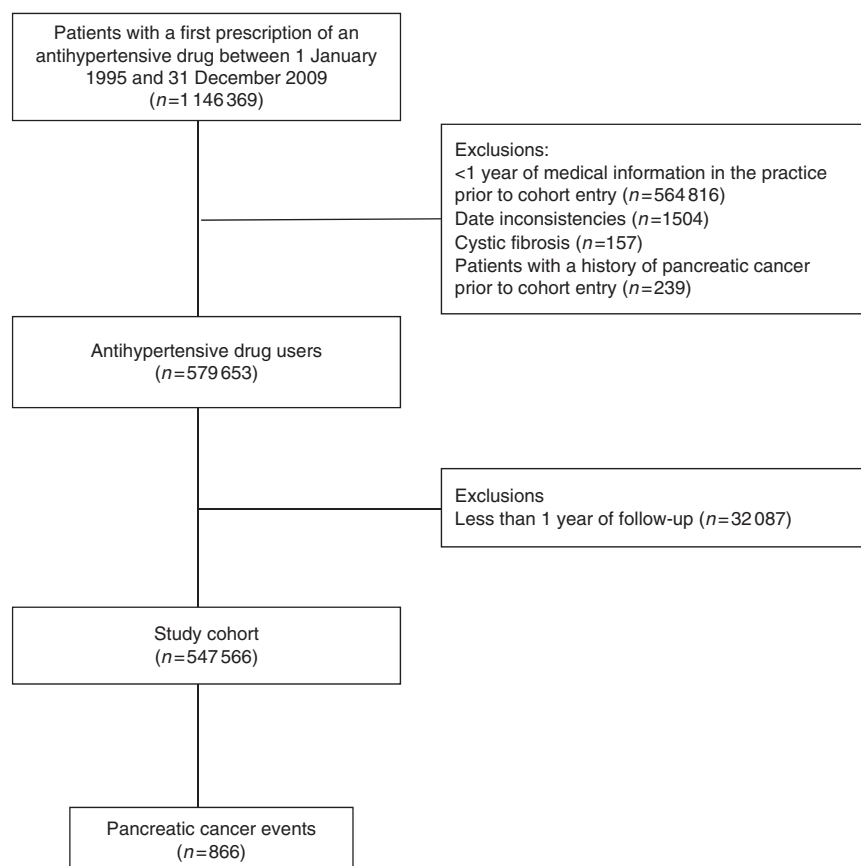


Figure 1. Study flow chart.

were obtained when using multiple imputation methods for patients with missing smoking information (Supplementary Table 6).

Table 1. Characteristics of pancreatic cancer cases and matched controls

Characteristics	Cases (n = 866)	Controls (n = 8636)
At index date		
Duration of follow-up, years, mean (s.d.) ^a	5.2 (3.1)	5.2 (3.1)
At cohort entry		
Age, years, mean (s.d.) ^a	68.6 (10.4)	68.6 (10.3)
Male, n (%) ^a	447 (51.6)	4448 (51.5)
Excessive alcohol use, n (%)	51 (5.9)	362 (4.2)
Smoking status, n (%)		
Ever	368 (42.5)	3350 (38.8)
Never	361 (41.7)	3995 (46.3)
Unknown	137 (15.8)	1291 (15.0)
Body mass index, n (%)		
< 18.5 kg m ⁻²	11 (1.3)	64 (0.7)
18.5–25 kg m ⁻²	182 (21.0)	1899 (22.0)
25–30 kg m ⁻²	211 (24.4)	2221 (25.7)
≥ 30 kg m ⁻²	119 (13.7)	1258 (14.6)
Unknown	343 (39.6)	3194 (37.0)
Chronic pancreatitis, n (%)	7 (0.8)	55 (0.6)
Anti-diabetic drugs, n (%) ^b		
Metformin	49 (5.7)	363 (4.2)
Sulfonylureas	56 (6.5)	368 (4.3)
TZD	6 (0.7)	41 (0.5)
Insulins	19 (2.2)	126 (1.5)
Others	4 (0.5)	38 (0.4)
Type 2 diabetes, n (%)	88 (10.2)	660 (7.6)
Aspirin, n (%)	220 (25.4)	2253 (26.1)
Other NSAIDs, n (%)	382 (44.1)	3820 (44.2)
Statins, n (%)	136 (15.7)	1328 (15.4)
Previous cancer, n (%)	80 (9.2)	794 (9.2)

^aMatching variables (along with year of cohort entry).
^bNot mutually exclusive.

DISCUSSION

To our knowledge, this is the first population-based study to investigate the association between the use of ACEIs and ARBs on the incidence of pancreatic cancer. Overall, there was no association between the use of ACEIs and ARBs on this outcome when compared with patients using other antihypertensive drugs. However, in a secondary analysis, we observed a 38% decreased risk of pancreatic in patients whose ARB cumulative duration of use varied between one and three years. Overall, sensitivity analyses yielded findings consistent with those of the primary analyses.

The data related to cancer development and use of ACEIs and ARBs remains vague. Initially, there were concerns that ACEIs and ARBs may increase the risk of developing cancer, but subsequent studies did not substantiate these claims (Lever *et al*, 1998; Coleman *et al*, 2008; Bangalore *et al*, 2011; Collaboration, 2011; Mc Menamin *et al*, 2012). Furthermore, to our knowledge, no study has investigated the impact of ACEIs and ARBs on pancreatic cancer incidence specifically. One study investigated their effect on treatment outcomes in a cohort of 155 patients with pancreatic cancer receiving gemcitabine chemotherapy (Nakai *et al*, 2010). Overall, the use of ACEIs or ARBs was associated with an improvement in overall survival compared with hypertensive and non-hypertensive patients (15.1 months vs 8.9 months and 9.5 months, respectively), generating a 42% risk reduction compared with the group without hypertension (HR: 0.58, 95% CI: 0.34–0.95) (Nakai *et al*, 2010). However, this study was likely affected by immortal time bias (Suissa, 2008), which was introduced by misclassifying the time between diagnosis and the first ACEI or ARB prescription as exposed. Moreover, by design, patients necessarily had to survive to be subsequently considered exposed, otherwise they would have been considered unexposed. This bias may have greatly exaggerated the purported effects of these agents on overall survival.

From a biological standpoint, there exists a body of pre-clinical data, which seems to indicate that the RAS has an important role in carcinogenesis and that its blockade may result in a protective effect against cancer (Fujimoto *et al*, 2001; Arafat *et al*, 2007; Anandanadesan *et al*, 2008; Chauhan *et al*, 2013; Masamune *et al*, 2013). Several

Table 2. The use of ACEIs and the incidence of pancreatic cancer

Use of ACEIs	Cases (n = 866)	Controls (n = 8636)	Crude OR	Adjusted OR (95% CI) ^a
Primary analysis				
Use of antihypertensive drugs other than ACEIs, n (%)	464 (53.6)	4708 (54.5)	1.00	1.00 (Reference)
Ever use of ACEIs, n (%)	402 (46.4)	3928 (45.5)	1.05	1.01 (0.86–1.17)
Cumulative duration of use, n (%)				
≤ 1 year	158 (18.2)	1551 (18.0)	1.04	1.02 (0.84–1.25)
1–3 years	114 (13.2)	1148 (13.3)	1.01	0.97 (0.78–1.22)
> 3 years	130 (15.0)	1229 (14.2)	1.09	1.01 (0.80–1.28)
				p-heterogeneity: 0.99
Number of prescriptions, n (%)				
≤ 12	181 (20.9)	1824 (21.1)	1.01	0.99 (0.82–1.21)
12–36	121 (14.0)	1215 (14.1)	1.02	0.97 (0.78–1.22)
> 36	100 (11.6)	889 (10.3)	1.17	1.08 (0.84–1.39)
				p-heterogeneity: 0.91
Time since initiation, n (%)				
≤ 2 years	81 (9.4)	788 (9.1)	1.04	1.01 (0.77–1.32)
2–3 years	65 (7.5)	669 (7.8)	0.98	0.96 (0.72–1.28)
> 3 years	256 (30.0)	2471 (28.6)	1.06	1.02 (0.85–1.23)
				p-heterogeneity: 0.98

Abbreviations: ACEIs = angiotensin-converting enzyme inhibitors; CI = confidence interval; OR = odds ratio.
^aAdjusted for excessive alcohol use, smoking status, acute or chronic pancreatitis, previous cancer, metformin, sulfonylureas, thiazolidinediones, insulins, other oral anti-hypoglycaemic agents, aspirin, non-steroidal anti-inflammatory drugs, statins, and diagnosis of type 2 diabetes at baseline. Angiotensin receptor blockers, calcium channel blockers, beta-blockers, diuretics, other antihypertensive drugs, measured between cohort entry and the year immediately before index date.

Table 3. Use of ARBs and the risk of pancreatic cancer

Use of ARBs	Cases (n = 866)	Controls (n = 8636)	Crude OR	Adjusted OR (95% CI) ^a
Primary analysis				
Use of antihypertensive drugs other than ARBs, n (%)	754 (87.1)	7468 (86.5)	1.00	1.00 (Reference)
Ever use of ARBs, n (%)	112 (12.9)	1168 (13.5)	0.95	0.93 (0.75–1.15)
Cumulative duration of use, n (%)				
≤ 1 year	44 (5.1)	373 (4.3)	1.17	1.14 (0.82–1.58)
1–3 years	25 (2.9)	391 (4.5)	0.63	0.62 (0.41–0.94)
> 3 years	43 (5.0)	404 (1.7)	1.06	1.04 (0.74–1.46)
				p-heterogeneity: 0.12
Number of prescriptions, n (%)				
12	49(5.7)	456 (5.3)	1.06	1.03 (0.76–1.40)
12–36	28 (3.2)	451 (5.2)	0.61	0.60 (0.41–0.90)
36	35 (4.0)	261 (3.0)	1.33	1.32 (0.91–1.92)
				p-heterogeneity: 0.03
Time since initiation, n (%)				
≤ 2 years	29 (3.4)	231 (2.7)	1.24	1.21 (0.81–1.80)
2–3 years	21 (2.4)	224 (2.6)	0.93	0.91 (0.58–1.44)
> 3 years	62 (7.2)	713 (8.3)	0.85	0.84 (0.63–1.11)
				p-heterogeneity: 0.44
Abbreviations: ARB = angiotensin receptor blockers; CI = confidence interval; OR = odds ratio.				
^a Adjusted for excessive alcohol use, smoking status, acute or chronic pancreatitis, previous cancer, metformin, sulfonylureas, thiazolidinediones, insulins, other oral anti-hypoglycaemic agents, aspirin, non-steroidal anti-inflammatory drugs, statins, and diagnosis of type 2 diabetes at baseline. ACE inhibitors, calcium channel blockers, beta-blockers, diuretics, other antihypertensive drugs, measured between cohort entry and the year immediately before index date.				

mechanisms have been proposed to explain a possible protective effect of ACEIs and ARBs. Vascular endothelial growth factor (VEGF) is a well-known factor in neoplasm formation, as well as a target for drug therapies and mediates tumour growth via its role in the formation of new blood vessels (Dvorak *et al*, 1995). In one study, RAS and VEGF expression in the pancreas were shown to be related and exposure of an ARB *in vitro* diminished the expression of VEGF and cell growth (Arafat *et al*, 2007; Fendrich *et al*, 2010). Other proposed mechanisms implicate the blockade of RAS in apoptosis; one study showing an interaction with NF-kappa b and another through pancreatic stellate cell deactivation (Amaya *et al*, 2004; Gong *et al*, 2010; Masamune *et al*, 2013).

There are several possibilities why our findings are generally inconsistent with the pre-clinical data. First, the doses used in experimental studies may be different from the ones used in the clinical setting. Second, the treatment of hypertension often requires multi-agent therapy (Campbell *et al*, 2010; McManus *et al*, 2012), and thus the risk of the outcome may have been influenced by the use of other antihypertensive drugs. Although our models adjusted for the use of other antihypertensive drugs, it is possible that the doses of ACEIs and ARBs were adjusted when used in combination therapy with other antihypertensive drugs. This may explain why decreased risk observed with ARBs was lost after > 3 years of use, and may thus reflect, at least in part, a change in the dosing regimen. It is also possible that this analysis lacked statistical power, as it was based on 43 exposed cases generating a wide CI.

This study has several strengths. First, we assembled a large population-based cohort of patients initially treated with antihypertensive drugs, which generated a significant number of cases. Second, confounding by indication was likely minimised by restricting the cohort to patients using antihypertensive drugs. Third, the use of a nested case-control analysis with risk set sampling allowed us to assess exposure in a time-dependent fashion, thereby eliminating immortal time bias (Suissa, 2008). Finally, the use of the CPRD allowed us to adjust the models for a number of potential confounders often absent in administrative databases, such as smoking and body mass index.

This study also has some limitations. First, given the observational nature of the study, there may be some concerns regarding residual confounding owing to unmeasured covariates, such as

the severity of hypertension. However, a relationship between hypertension and pancreatic cancer incidence has never been documented as there have been many conflicting reports (Stolzenberg-Solomon *et al*, 2002; Rosato *et al*, 2011; Eijgenraam *et al*, 2013). Second, exposure misclassification is a possibility, as the CPRD records prescriptions written by general practitioners and not specialists. Furthermore, patient compliance with the pharmacotherapy is unknown. Such misclassifications would tend to bias the point estimates toward the null. Misclassification of the outcome (pancreatic cancer) is also possible, although we do not expect this misclassification to be differential between patients exposed and unexposed to ACEIs and ARBs in this cohort of patients using antihypertensive drugs. Finally, the average cohort follow-up was 5.5 years, and thus this may be considered a short duration to observe the long-term effects of ACEIs and ARBs, although the maximal follow-up was 16 years.

In summary, this is the first large population-based study investigating the association between the use of agents acting on RAS and the incidence of pancreatic cancer in patients receiving antihypertensive drugs. Our findings suggest that, overall, there is no association between the use of ACEIs and ARBs on the incidence of pancreatic cancer in this population. However, in secondary analyses, 1–3 years of ARB use was associated with a decreased risk of pancreatic cancer. These findings will need to be replicated in studies conducted in other settings.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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