Effects of RAS inhibitors on all-site cancers and mortality in the Hong Kong diabetes surveillance database (2002-2019)

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Summary

Background Cancer is replacing cardiovascular-disease as a leading cause of death in type 2 diabetes (T2D). The association of RAS-inhibitors (RASi) and cancer, including differences between angiotensin-converting-enzyme-inhibitor (ACEi) and angiotensin-receptor-blocker (ARBs) as well as their associations independent of blood pressure lowering, remains inconclusive in T2D.

Methods We conducted a cohort study with new-user design in 253,491 patients in the Hong-Kong-Diabetes-Surveillance-Database (HKDSD) in 2002-2019. We evaluated the associations of time-varying RASi use (ACEi and ARBs) with all-site cancer, diabetes-related cancers, and cancer-specific mortality including comparison with new-users of calcium-channel-blockers (CCBs) as an active-comparator group.

Findings Of 253,491, 133,730 (52.8%) were new-RASi and 119,761 (47.2%) were non-RASi users with a median follow-up period of 6.3 (interquartile ragne: 3.4-9.2) years (1,678,719 patient-years). After propensity-score weighting and adjustment for time-varying covariables, RASi use was associated with lower risk of all-site cancer (HR=0.76, 95%CI: 0.74-0.79), diabetes-related cancer (HR=0.79, 95%CI: 0.75-0.84), cancer-specific mortality (HR=0.50, 95%CI: 0.47-0.53), and diabetes-related cancer mortality (HR=0.49, 95%CI: 0.45-0.54) versus non-RASi. Amongst RASi users, ARBs use was associated with lower risk of cancer-specific mortality versus ACEi (HR=0.77, 95%CI: 0.66-0.91). Use of RASi was associated with an estimated-prevention of 2.6 (95%CI: 2.3-3.0) all-site cancer per-1000-person-years and 2.2 (95%CI: 2.0-2.5) cancer-related mortality per-1000-person-years. Lower risk of cancer-specific mortality was similarly observed in new-RASi compared with new-CCBs users.

Interpretation RASi use was independently associated with lower cancer risk in T2D with stronger associations in users of ARBs than ACEi. The benefits of RASi in patients with diabetes might go beyond cardiovascular-renal protection if confirmed by other real-world studies and trials.

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Keywords: Angiotensin-converting enzyme inhibitors; Angiotensin receptor antagonists; Cancer; Mortality; Therapeutics; Diabetes

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Research in context

Evidence before this study

We searched PubMed with the terms "diabetes", "antihypertensive agents", "cancer", "mortality" and "death" for original articles and reviews published up to August, 2021. Most studies on the association of renin-angiotensin-system inhibitors (RASi) with cancer risk were randomized-controlled-trials (RCTs) with conflicting evidence. Few real-world-evidence (RWE) is available on the association of RASi and site-specific cancers, including diabetes-related cancers. Data on the link between RASi use and risk of cancer remains inconclusive in people with type 2 diabetes (T2D) and prior studies did not account for time-varying and cumulative treatment effects.

Added value of this study

In this RWE study including over 0.25 million Chinese patients with T2D followed up for a median period of 6.3 years, we comprehensively evaluated the association between long-term RASi use and cancer and related mortality. Our results indicated that compared with non-RASi use, use of RASi was associated with lower risk of all-site cancer, diabetes-related cancer as well as all-cause, all-site cancer, and diabetes-related cancer mortality. These associations were more robust with angiotensin-receptor-blockers (ARBs) when compared directly with angiotensin-converting-enzyme-inhibitor (ACEi). The reduced risk associations of RASi with cancer and related deaths remained stable throughout the observation period. Compared with new-users of calcium-channel blockers, the reduced risk associations of RASi with all-cause and cancer-related mortality were most evident in young adults.

Implications of all the available evidence

Use of RASi was independently associated with reduced risk of cancer, including diabetes-related cancers and cancer-specific mortality in diabetes, supporting the use of RASi in individuals without cardiovascular-renal risk factors for organ protection. If the anti-cancer effects of RASi can be replicated by other RWE or RCTs, the economic benefits of RASi in patients with diabetes might go beyond cardiovascular-renal protection.

Introduction

Globally, cancer has replaced cardiovascular disease (CVD) as the leading cause of death.[1] One in 5 people might develop cancer during their lifetime, and one in 8 men and one in 11 women died from cancer in 2020.[2] Cancer and CVD are leading comorbidities in patients with type 2 diabetes (T2D). T2D is associated with 2-fold increased risk of CVD and 1.3-to-3 fold increased risk of cancer.[3] Improved access to healthcare had led to declining incidence of CVD and related death in part due to better control of cardiovascular risk factors.[4] These changing disease landscape portends the increasing unmet healthcare need due to cancer in an aging population with diabetes.[5] Diabetes, especially T2D, is associated with increased risk for some cancers (liver, pancreas, colon and rectum, gallbladder, endometrial and breast). The increased cancer risk in patients with diabetes might be mediated via hyperglycemia, hyperinsulinemia, inflammation or other risk factors shared by diabetes and cancer, such as obesity.[6-8]

Patients with diabetes are frequently treated with antihypertensive drugs for cardiovascular-renal protection. There is inconsistent evidence regarding the association of hypertension and cancer risk.[9,10] In observational studies, hypertension was associated with increased cancer risk. However, in a Mendelian randomization analysis using genetic variants to explore causality, blood pressure did not appear to be a causal risk factor for cancer.[10] Renin-angiotensin-system (RAS) plays a pivotal role in the regulation of blood pressure through formation of angiotensin-II which is one of the most potent vasoconstrictors with pro-inflammatory effects. Experimental and clinical studies suggested that gluco-lipotoxicity could activate angiotensin-II with increased angiogenesis and cellular adhesion, invasion and proliferation which might promote cancer risk.[11] On the other hand, treatment with RAS inhibitors (RASi) including angiotensin-II type-I receptor blockers (ARBs) or angiotensin-converting-enzyme inhibitors (ACEi) reduced the activity of angiotensin-II with possible anti-cancer effects since many types of cancer express angiotensin-II type-I receptors (ATR1).[4,12] Despite this biological plausibility, compared with the large body of evidence on the benefits of RASi on CVD, the risk association of RASi use with cancer in diabetes remains controversial.[13]

Given the importance of RAS in diabetes and its pluripotent effects, we hypothesized that: 1) RASi use was associated with reduced risk of all-site cancer, diabetes-related cancers, and cancer-specific mortality in T2D; 2) the protective effects of RASi against cancer were class-specific and independent of its antihypertensive effects using calcium-channel blocker (CCBs) as a comparator. In this light, CCBs had been extensively studied regarding its association with cancer,[13] with most studies suggesting neutral risk.[13,14] In an observational case-control drug surveillance study including 9513 patients with incident cancer and 6492 controls, use of CCBs was unrelated to cancer.[14] In this study, we used real-world data from a territory-wide electronic-medical-record (EMR) system and evaluated the time-varying risk associations of RASi with cancer events and related mortality. Due to the different mechanisms of ACEi and ARBs in reducing angiotensin-II activity,[15] we also directly compared the risk associations with cancer between ACEi-only and ARBs-only users.

Methods

Data sources

We conducted a prospective cohort analysis in the territory-wide Hong Kong Diabetes Surveillance Database (HKDSD) including Chinese patients with T2D with comprehensive baseline data captured in the module of the Risk-Assessment-and-Management-Programme-for-Diabetes-Mellitus (RAMP-DM).[16-18] Hong Kong has 7.5 million population mainly of Southern Chinese descent with universal health coverage through care provision by the government-funded Hospital Authority (HA). The latter operates all hospitals and clinics with on-site drug dispensing which share a territory-wide EMR system since 2000. Due to the highly subsidized nature of HA services, over 90% of patients with diabetes were captured in the EMR system.[19] The HKDSD includes all people who have ever had a measurement of either fasting or random plasma glucose, fasting and 2-hour plasma glucose during 75 gram oral glucose tolerance test and/or glycated haemoglobin (HbA1c) in the EMR since 2000. Between 2000 and 2019, the HKDSD included 964,950 patients with diabetes diagnosed by physicians, medication use and/or laboratory values. Of these, 581, 811 people had structured data captured by the RAMP-DM module. As part of a quality improvement program, all patients with diabetes can be referred by their doctors to undergo periodic structured assessments including eye, feet, blood and urine examination in hospital-based diabetes centre and community-based clinics guided by a uniform template in the RAMP-DM module within the HKDSD. Data on income, education, and self-reported lifestyle and history of cancer is available in the RAMP-DM module but not in the overall HKDSD. The data structure of the HKDSD had been reported with clinical outcomes including cancer defined by International Classification of Diseases 9th-Revision (ICD-9) in the HA EMR system, linked to the causes of death coded by the Hong Kong Death Register using ICD-10. Details of the HKDSD data source profile were described elsewhere.[19] The study was approved by the Joint NTEC-CUHK Clinical Research Ethics Committee. This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for cohort study (eTable 1).

Study design and participants

We adopted a new-user design[20,21] to compare the risk associations of new-RASi use versus non-RASi use with cancer risk and related mortality. A patient was defined as a RASi-user if he/she had been exposed to ACEi and/or ARBs for ≥90 days during the observation period. The index-date referred to the first date of dispensing of ACEi/ARBs for RASi users, and the first date of dispensing of glucose-lowering-drugs (GLDs) for non-RASi users after enrolment. The baseline period was defined as up to one year before the index date (eFigure 1). To avoid bias from incomplete case records of diabetes in the first two years of establishment of the EMR system, we excluded patients enrolled in 2000-2001 and in 2019 which was the year of censor (n = 79,881, 13.7%). We excluded patients with observation for <1 year; age<18 years at diagnosis; missing data related to year of diabetes diagnosis (n = 26,222) and relevant laboratory results (see later definition, n = 96,434); prior history of end-stage kidney disease (ESKD), CVD, cancer and gestational-diabetes-mellitus based on ICD-9 codes. Other exclusion criteria included type 1 diabetes (defined as ketotic presentation or continuous requirement of insulin within one year of diagnosis), missing type of diabetes (n = 5038), RASi use for <90 days (n = 5586), and history of RASi use (n = 115,229). A total of 253,491 (133,730 new-RASi and 119,761 non-RASi users) patients enrolled in 2002-2018 and observed until 31 December 2019 were included in the main analysis (eFigure 2).

To investigate whether an association for RASi in cancer was independent of its antihypertensive effects, we compared the risk of cancer and related mortality between new-RASi (n = 30,143) and new-CCBs (n = 18,613) users as a comparator. The index-date referred to the first date of dispensing of RASi or CCBs after enrollment. Users of CCBs were defined by exposure to CCBs for ≥90 days during the observation period without ever exposure to RASi.

Definitions of covariates

Baseline covariates included sociodemographic data, clinical measurements, comorbidities, and medications collected during the structured assessment in the RAMP-DM module (eFigure 1 and Table 1) and the EMR system. We retrieved all laboratory, comorbidities and dispensing records as time-varying covariates during the baseline and observation period using the EMR system. Details on the definition of covariates is provided in *Supplementary Methods*.

Evaluation of RASi and other medications

Patients from the HKDSD-RAMP module had individual-level longitudinal dispensing data including drug name, dose, frequency, dispensing duration (in days), start and end dates in 2000-2019. We analysed medications prescribed during outpatient visits which were dispensed by the on-site HA pharmacy after the consultation at the community- or hospital-based clinics until the next follow-up date. Dispensed drug quantity and duration were curated from the EMR system. We grouped RASi and other medications (GLDs, antihypertensives and lipid-modifying drugs) according to the Anatomical Therapeutic Chemical Classification System (eTable 2).[17] Time-varying exposure to RASi was based on start and end dates of dispensing records during each follow-up year.

Variables	Overall	Before PS overlap-weighting			After PS overlap-weighting		
		Non-RASi	RASi	SMD	Non-RASi	RASi	SMD
N	253,491	119,761 (47.2)	133,730 (52.8)		119,761	133,730	
Men, %	120466 (47.5)	54935 (45.9)	65531 (49.0)	0.063	48.2	48.2	<0.001
Age at index date, years	61.1 (11.9)	59.1 (11.9)	63.0 (11.7)	0.331	61.2 (11.9)	61.2 (11.7)	<0.001
Duration of diabetes, years	5.2 (6.1)	3.4 (5.0)	6.9 (6.6)	0.589	4.7 (6.1)	4.7 (4.8)	<0.001
Family history of diabetes, %	109311 (43.1)	52008 (43.4)	57303 (42.8)	0.012	42.2	42.2	<0.001
Use of tobacco, %				0.085			<0.001
Never	186746 (73.7)	90052 (75.2)	96694 (72.3)		73.7	73.7	
Ever	35192 (13.9)	14785 (12.3)	20407 (15.3)		13.8	13.8	
Current	31553 (12.4)	14924 (12.5)	16629 (12.4)		12.5	12.5	
Use of alcohol, %				0.046			<0.001
Never	48599 (19.2)	23528 (19.6)	25071 (18.7)		19.3	19.3	
Ever	188212 (74.2)	89009 (74.3)	99203 (74.2)		74.1	74.1	
Current	16680 (6.6)	7224 (6.0)	9456 (7.1)		6.6	6.6	
Body mass index, kg/m^2	25.7 (4.1)	25.2 (4.0)	26.2 (4.2)	0.224	25.8 (4.2)	25.8 (4.0)	<0.001
Waist circumference, cm	89.1 (10.2)	87.8 (10.1)	90.3 (10.2)	0.247	89.2 (10.2)	89.2 (10.0)	<0.001
Systolic BP, mmHg	132.3 (13.5)	128.1 (13.3)	136.0 (12.5)	0.609	132.5 (13.5)	132.5 (11.6)	<0.001
Diastolic BP, mmHg	74.4 (8.4)	73.5 (8.3)	75.2 (8.3)	0.207	74.7 (8.5)	74.7 (8.1)	<0.001
HDL-C, mmol/L	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	0.093	1.3 (0.4)	1.3 (0.4)	<0.001
LDL-C, mmol/L	2.8 (0.9)	2.8 (0.9)	2.7 (0.9)	0.140	2.8 (0.9)	2.8 (0.9)	<0.001
Total cholesterol, mmol/L	4.8 (1.0)	4.8 (1.0)	4.7 (1.0)	0.120	4.8 (1.0)	4.8 (1.0)	<0.001
Triglyceride, mmol/L	1.6 (1.3)	1.6 (1.3)	1.7 (1.3)	0.066	1.7 (1.4)	1.7 (1.3)	<0.001
Blood haemoglobin, g/dL	13.7 (1.6)	13.8 (1.5)	13.7 (1.6)	0.073	13.8 (1.5)	13.8 (1.6)	<0.001
HbA1c, %	7.5 (1.6)	7.5 (1.6)	7.4 (1.5)	0.016	7.4 (1.5)	7.4 (1.5)	<0.001
eGFR, mL/min/1.73m^2	85.2 (18.8)	88.6 (17.4)	82.1 (19.5)	0.357	85.4 (18.3)	85.4 (18.4)	<0.001
Medications							
Antihypertensives	16244 (6.4)	5155 (4.3)	11089 (8.3)	0.165	6.0	6.0	<0.001
Diuretics	20372 (8.0)	6445 (5.4)	13927 (10.4)	0.187	7.7	7.7	<0.001
Beta-blockers	55872 (22.0)	20029 (16.7)	35843 (26.8)	0.246	21.5	21.5	<0.001
Calcium-channel blockers	101167 (39.9)	34782 (29.0)	66385 (49.6)	0.431	39.0	39.0	<0.001
Statins	78506 (31.0)	32182 (26.9)	46324 (34.6)	0.169	30.9	30.9	<0.001
Non-statins lipid-modifying	8593 (3.4)	3059 (2.6)	5534 (4.1)	0.088	3.3	3.3	<0.001
Alpha-blockers	5142 (2.0)	2246 (1.9)	2896 (2.2)	0.021	2.0	2.0	<0.001
Glucose-lowering drugs (GLDs)							
Insulin	15844 (6.3)	5391 (4.5)	10453 (7.8)	0.138	5.3	5.3	<0.001
Metformin	169118 (66.7)	69951 (58.4)	99167 (74.2)	0.338	65.4	65.4	<0.001
Sulfonylureas	102867 (40.6)	36371 (30.4)	66496 (49.7)	0.403	38.4	38.4	<0.001
AGIs	1112 (0.4)	365 (0.3)	747 (0.6)	0.039	0.4	0.4	<0.001
TZD	1425 (0.6)	424 (0.4)	1001 (0.7)	0.053	0.5	0.5	<0.001
DPP-4i	3839 (1.5)	1046 (0.9)	2793 (2.1)	0.101	1.3	1.3	<0.001
GLP-1RA	2044 (0.8)	618 (0.5)	1426 (1.1)	0.062	0.8	0.8	<0.001
SGLT2i	247 (0.1)	86 (0.1)	161 (0.1)	0.016	0.1	0.1	<0.001
Number of GLDs				0.501			<0.001
0	61852 (24.4)	39237 (32.8)	22615 (16.9)		25.3	25.3	
1	99886 (39.4)	50598 (42.2)	49288 (36.9)		41.5	41.5	
2	80050 (31.6)	26509 (22.1)	53541 (40.0)		29.4	29.4	
≥3	11703 (4.6)	3417 (2.9)	8286 (6.2)		3.8	3.8	
Hypertension history	153070 (60.4)	56192 (46.9)	96878 (72.4)	0.539	61.1	61.1	<0.001
ASCVD 10-year risk score				0.416			<0.001
low (<7.5)	34801 (13.7)	23217 (19.4)	11584 (8.7)		12.5	12.5	
medium (7.5-19.9)	81499 (32.2)	43504 (36.3)	37995 (28.4)		33.1	33.1	
high (≥20)	137191 (54.1)	53040 (44.3)	84151 (62.9)		54.3	54.3	

Table 1 *(Continued)*

Variables	Overall	Before PS overlap-weighting			After PS overlap-weighting		
		Non-RASi	RASi	SMD	Non-RASi	RASi	SMD
Period of index year				0.202			<0.001
2002-2006	21532 (8.5)	10092 (8.4)	11440 (8.6)		8.9	8.9	
2007-2010	55915 (22.1)	24410 (20.4)	31505 (23.6)		22.6	22.6	
2011-2014	85193 (33.6)	36390 (30.4)	48803 (36.5)		33.2	33.2	
2015-2018	90851 (35.8)	48869 (40.8)	41982 (31.4)		35.3	35.3	

***Table 1*: Clinical profiles of patients categorized by incident-RASi use before and after propensity score (PS) overlap-weighting.**
Abbreviations: SMD, standardized mean difference; RASi, renin angiotensin system inhibitors; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; AGIs: alpha-glucosidase inhibitors; TZDs: thiazolidinediones; DPP-4i: dipeptidyl peptidase 4 inhibitors; GLP1-RA: glucagon-like peptide-1 receptor analogues; SGLT2i: sodium-glucose co-transporter 2 inhibitors; GLDs: glucose-lowering drugs; ASCVD, atherosclerotic-cardiovascular-disease.

Outcomes

The primary outcomes were incidence of all-site cancer, diabetes-related cancers, all-cause mortality, cancer-specific mortality, and diabetes-related cancer mortality. Diabetes-related cancers were identified as those closely associated with diabetes including colorectal, pancreatic, liver, gallbladder, breast, and endometrial cancers.[7,8] Secondary outcomes included top site-specific cancers in Hong Kong including liver, lung, colorectal, breast, prostate, and pancreas.[22] We used principal discharge diagnoses based on ICD-9 codes to define first event of all-site, diabetes-related, and site-specific cancers in the EMR system. Causes of death was defined by ICD-10 codes in the Hong Kong Death Registry and classified as all-cause, cancer-specific, and diabetes-related cancer mortality (eTable 3).

Statistical analysis

All descriptive statistics were reported as counts (percentages), mean (standard deviation, SD), or median (interquartile range, IQR). Standardized mean difference (SMD) was used to check balance of each covariate in the between-group comparisons.

Propensity-score with overlap-weighting

To address confounding by indication,[20,23] we applied propensity-score overlap-weighting (PS-OW)[24] to homogenize baseline data for comparing outcomes between new-RASi and non-RASi users. We calculated propensity-score using a multivariable logistic regression model, and used the effect size of selected baseline covariates to assign weights to the relevant attributes for each patient using the overlap-weighting approach.[24] This overlap-weighting method creates an exact balance of every measured covariate at baseline (Table 1). We also adjusted for year of index-date as a proxy measure of time-varying quality of healthcare in Hong Kong. All covariates were selected based on theoretical and empirical evidence for variables known to be associated with indications of RASi prescription and outcomes.[25] Compared with the classical PS-based methods and inverse-probability of treatment weighting, overlap-weighting showed better performance with respect to target population, balance and precision.[24]

Adjustment for time-varying covariates

Discontinuation of RASi use over time can introduce substantial selection bias in RWE studies.[20,23] In the main analysis, we performed Cox-proportional hazards model with time-varying RASi exposure in the PS-OW cohort adjusted for time-varying covariates with less than 15% missingness. The latter included HbA1c, lipids, eGFR, medications and incident-CVD during the observation period for cancer events and related mortality. We checked for violation of assumption of proportional hazards using scaled Schoenfeld residual plots.[26] To estimate the absolute treatment effects and time-varying effects of RASi on the risk of outcomes, we fitted the Aalen-additive hazards model with time-varying RASi exposure adjusted for both baseline and time-varying covariates in the PS-OW cohort.[27] We tested assumptions of missing data using R '*MissMech*' package. The data was non missing completely at random (MCAR). Missing data for time-varying covariates (HbA1c, eGFR and lipids) was imputed using the chained equations with multiple imputations by age, sex and duration of diabetes.[28] This imputation method performs well for different types of misng data including non-MCAR.[29] We conducted separate analyses in the PS-OW cohorts and compared the risk associations of new-RASi versus new-CCBs use with cancer and related deaths.

Subgroup analyses

For the sex-specific and age-specific analyses, we used separate models for men, women and age-groups (<55, 55-64, and ≥65 years) to estimate the risk associations of RASi with cancer events, all-cause and cancer-specific mortality expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). For the ≥65 age-group, we further categorized them into 3 subgroups (65-69, 70-79, and ≥80 years) and compared risk associations of new-RASi versus non-RASi with cancer outcomes. Z-test was used to test for interactions.[30] We also directly

compared the risk associations with cancer between new ACEi-only and ARBs-only users in a PS-OW cohort using Cox-model adjusted for time-varying ARBs/ACEi exposures and other covariates (eFigure 2).

Sensitivity analysis

We used Cox marginal-structural-model (Cox-MSM) in new-RASi versus non-RASi users to further address competing risk of death.[31] We also included prevalent-RASi users and compared the risk associations of RASi (prevalent and new users) versus non-RASi with cancer outcomes. Since cancers may require long time to develop, we performed an additional sensitivity analysis in patients observed for longer than the median of 6.3 years and with >0.8 of the follow-up period exposed to RASi use for comparison with non-RASi users for cancer risk association.

All analyzes were implemented using R software (Version 4.0.0). A two-sided *P* value of <0.05 was considered statistically significant. Further details on statistical methods and bias consideration are provided in *Supplementary Methods*.

Role of the funding source

A.Y. was funded by the CUHK Impact Research Fellowship Scheme which did not have any role in study design, data collection, data analysis, data interpretation, or writing of this report. A.L. had full access to HKDSD-RAMP data. E.C. is the guarantor of this work with final responsibility for the decision to submit for publication.

Results

We curated a cohort of 253,491 patients with T2D from the HKDSD RAMP-DM module including 133,730 (52.8%) new-RASi users (73,596 ACEi-only users, 21,103 ARBs-only users, and 39,031 ACEi/ARBs users). For the ACEi/ARBs group, 92% were switched from ACEi to ARBs. RASi users had worse risk factors and received more medications than non-RASi users. In the PS-OW cohort, all characteristics were well-balanced between the two groups (Table 1).

The mean and median of follow-up were 6.5 (SD=3.7) years and 6.3 (IQR: 3.4-9.2) years. The mean treatment and follow-up year to death were 5.5 (SD=3.6) and 6.6 (SD=3.8) years for RASi-users. The respective figures were 6.0 (SD=3.9) and 7.4 (SD=3.6) years for ACEi-only users, and 3.3 (SD=2.2) and 3.7 (SD=2.2) for ARBs-only users. During a mean follow-up of 6.5 years, 15,030 (5.9%) and 6863 (2.7%) patients were diagnosed with all-site cancer and diabetes-related cancers. The respective crude-incidence were 9.1 and 4.1 events per-1000-person-years. A total of 24,768 (9.8%) patients died with 6590 (2.6%) deaths due to cancer and 2845 (1.1%) deaths due to diabetes-related cancer. The respective crude-incidence were 14.8, 3.9 and 1.7 events per-1000-person-years for all-cause, cancer-specifc cause, and diabetes-related cause mortality. There were 8246 (6.2%) and 6784 (5.7%) all-site cancers with respective crude-incidence of 9.2 and 9.1 events per-1000-person-years in RASi and non-RASi users (Figure 1).

RASi use and incidence of all site and site-specific cancer, and related mortality

Time-varying RASi use was associated with reduced risk of all-site cancer versus non-RASi (HR=0.76, 95% CI: 0.74-0.79, Figure 1A). The crude-incidence of diabetes-related cancers in RASi versus non-RASi users was 4.1-versus-4.2 events per-1000-person-years. Time-varying RASi use was associated with lower risk of diabetes-related cancers versus non-RASi (HR=0.79, 95% CI: 0.75-0.84). The lower risk associations were also observed in the Cox-MSM model adjusted for competing risk of death (HR=0.84, 95% CI: 0.82-0.86 for all-site cancer, and HR=0.82, 95% CI: 0.79-0.85 for diabetes-related cancers, eFigure 3). For site-specific cancers, RASi use was associated with lower risk of liver (HR=0.71, 95% CI: 0.63-0.81), lung (HR=0.64, 95% CI: 0.59-0.71), colorectal (HR=0.82, 95% CI: 0.76-0.90) and pancreas cancers (HR=0.63, 95% CI: 0.52-0.76), and neutral risk of breast (HR=0.93, 95% CI: 0.82-1.06) and prostate cancers (HR=0.86, 95% CI: 0.72-1.02). RASi use was associated with lower risk of all-cause mortality (HR=0.52, 95% CI: 0.50-0.53), cancer-specific mortality (HR=0.50, 95% CI: 0.47-0.53) and diabetes-related cancer mortality (HR=0.49, 95% CI: 0.45-0.54) (Figure 1A). In the Cox-MSM model, the reduced risk associations of cancer-related mortality in RASi users remained consistent (eFigure 3).

Absolute and cumulative effects of RASi use

Compared with non-RASi use, RASi use was associated with an absolute risk reduction of 2.6 (95% CI: 2.3, 3.0) all-site cancer, 0.7 (95% CI: 0.5, 1.0) diabetes-related cancers, 6.3 (95% CI: 5.9. 6.8) all-cause deaths, 2.2 (95% CI: 2.0, 2.5) cancer-specific deaths, and 1.0 (95% CI: 0.8, 1.2) diabetes-related cancer death per-1000-person-years (Figure 2). We observed that the treatment effect of RASi use was non time-dependent for all these main outcomes ($P_{\text{time-varying effects}}<0.001$ for all site cancer, $P_{\text{time-varying effects}}=0.003$ for diabetes-related cancers, $P_{\text{time-varying effects}}<0.001$ for all-cause mortality, $P_{\text{time-varying effects}}=0.004$ for cancer-specific mortality, and $P_{\text{time-varying effects}}=0.001$ for diabetes-related cancer mortality, suggesting that the risk reduction was independent of duration of exposure to RASi. In this cohort, all patients had at least 90 days of exposure to RASi with 75.4% (n = 100,782) persistent with the >0.8 use of RASi during the follow-up period.

Sub-group analyses by sex and age

Compared with women, men who used RASi had lower risk of all-site cancer (HR=0.71 [0.67-0.74] versus

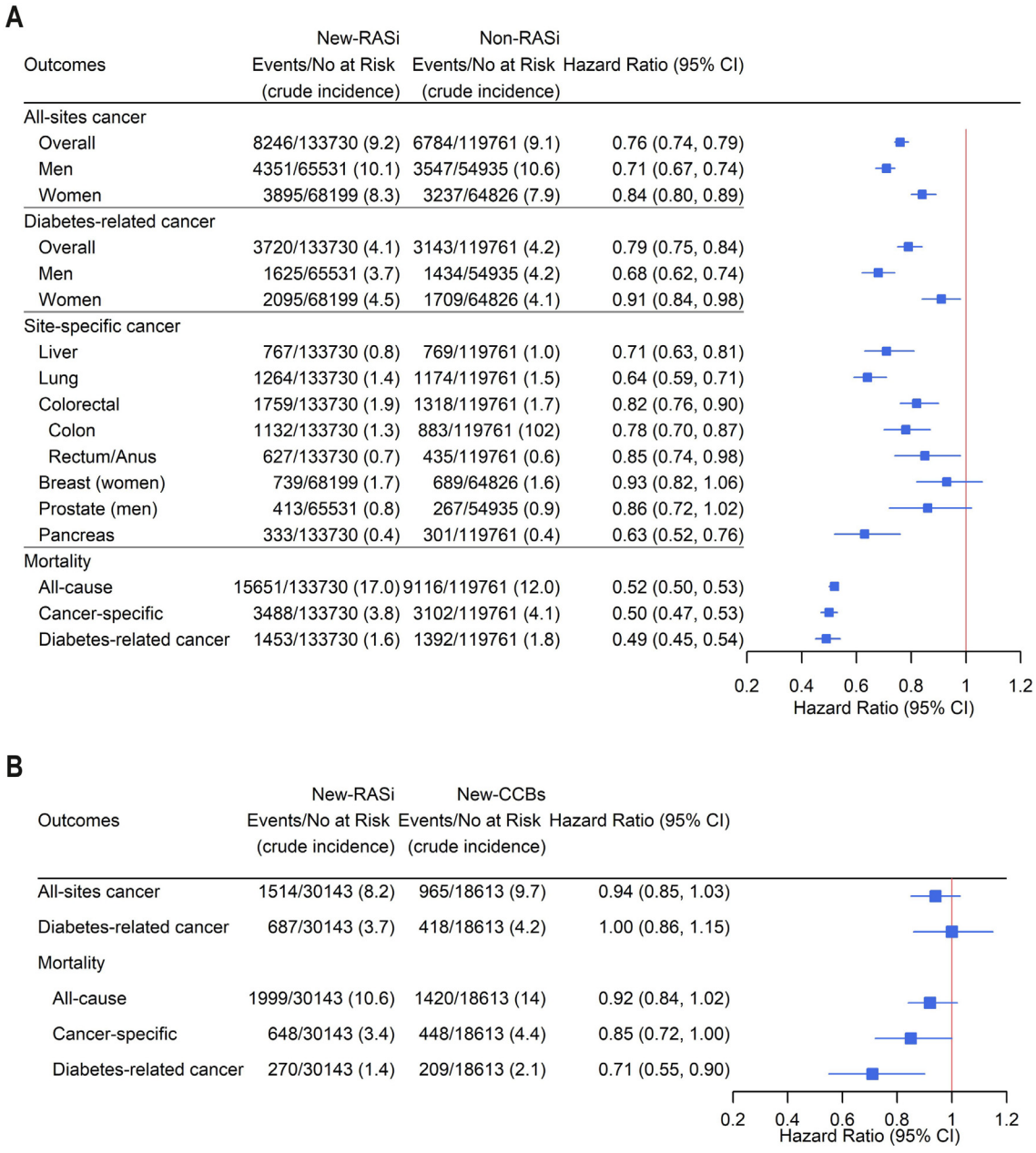

Figure 1. Risk association of new-RASi use with cancer events and related mortality compared with non-RASi (A) and new calcium-channel blockers (CCBs) (B).

Crude-incidence was expressed as events per-1000-person-years. Results of hazard ratio were yielded using time-varying renin angiotensin system inhibitors (RASi) exposure in the propensity score overlap-weighted cohort adjusted for time-varying HbA1c, lipids, estimated-glomerular filtration rate (eGFR), medications (antihypertensive, diuretics, statins and non-statins lipid-modifying drugs, beta-blockers, calcium channel blockers, alpha-blockers, insulin, metformin, and sulfonylureas), cardiovascular diseases and cancer (only for all-cause mortality).

HR=0.84 [0.80-0.89], $P_{interaction}$< 0.001) and diabetes-related cancers (HR=0.68 [0.62-0.74] versus HR=0.91 [0.84-0.98], $P_{interaction}$< 0.001, Figure 1). In diabetes-related cancers, the lower risk in men versus women was observed for liver cancer (HR=0.63, 95% CI: 0.55-0.73 versus HR=0.88, 95% CI: 0.70-1.12, $P_{interaction}$ =0.017, eTable 4). As compared with non-RASi users, RASi use was associated with similarly reduced risk of all-site cancer and cancer-related mortality across all age-groups (eFigure 4).

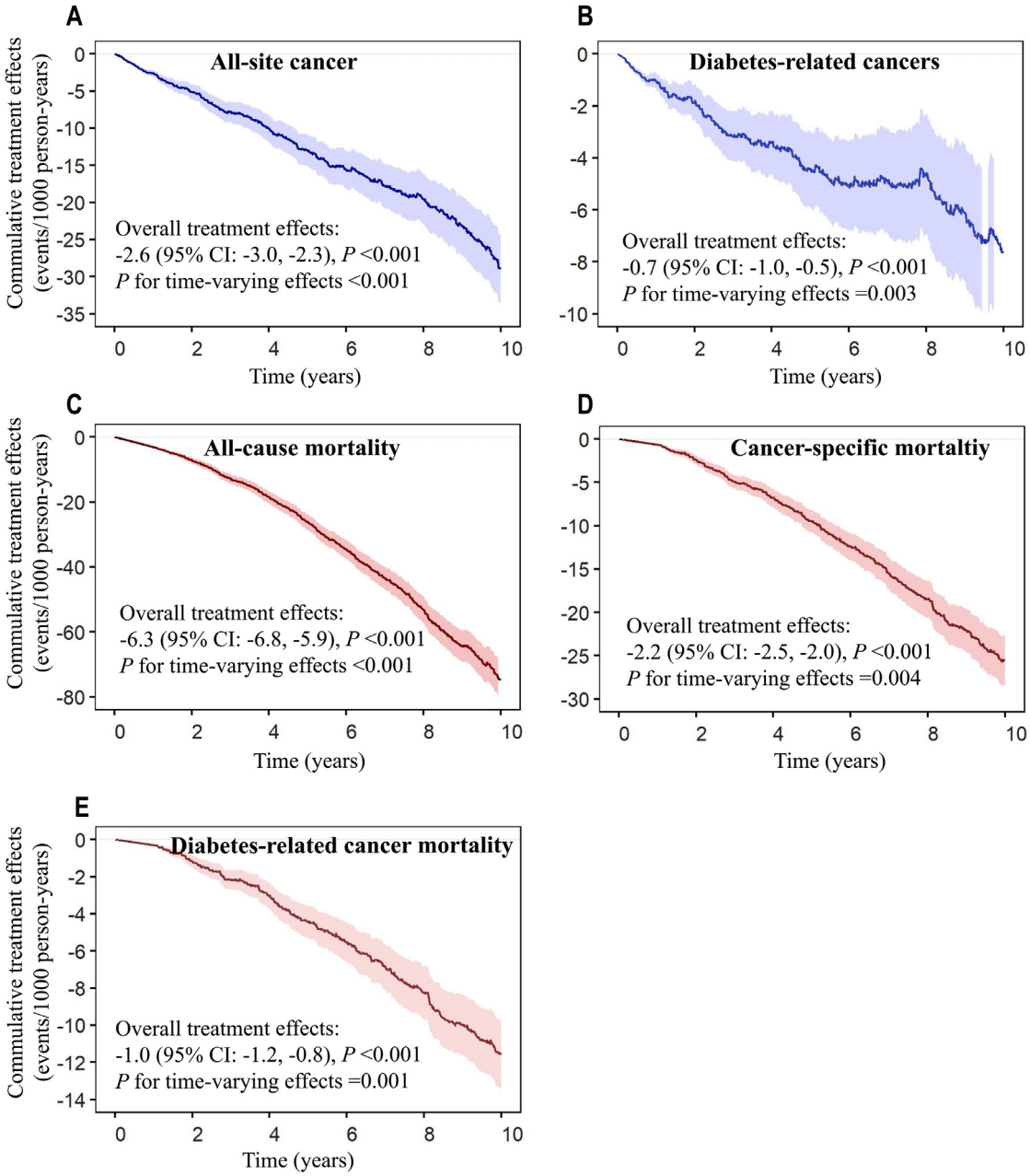

Figure 2. Cumulative treatment effects of RASi with 95% confidence intervals (CIs) in the Aalen-additive hazard model.

All-site cancer (A), diabetes-related cancers (B), all-cause mortality (C), cancer-specific mortality (D), diabetes-related cancer mortality (E). The models with time-varying renin angiotensin system inhibitors (RASi) exposure were adjusted for time-varying HbA1c, lipids, estimated-glomerular filtration rate (eGFR), medications (antihypertensive, diuretics, statins and non-statins lipids modifying drugs, beta-blockers, calcium-channel blockers, alpha-blockers, insulin, metformin, and sulfonylureas) in the propensity score overlap-weighted cohort. For all-cause mortality, we additionally adjusted for incidence of comorbidities (cardiovascular disease and cancer).

Risk associations of cancer with new-RASi versus new-CCBs users

We compared risk of cancer outcomes in 30,143 new-RASi and 18,613 new-CCBs users following balancing of baseline characteristics in PS-OW cohort (eTable 5). Over a mean 5.9 (SD=3.4) years of follow-up, there were 2479 (5.1%) all-site cancer events, 1105 (2.3%) diabetes-related cancer events, 3419 (7.0%) all-cause deaths, 1096 (2.2%) cancer-specific deaths, and 479 (1.0%) diabetes-related cancer deaths. The respective crude-

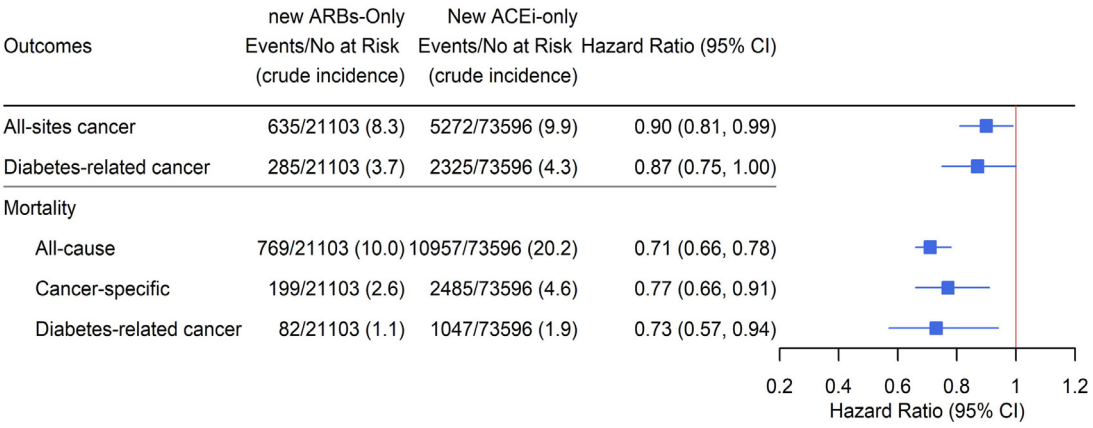

Figure 3. Comparison of risk of cancer events between new ACEi-only and ARBs-only users.

Crude-incidence was expressed as events per-1000-person-years. Results were yielded using Cox proportional hazards model with time-varying use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) in the propensity score overlap-weighted cohort adjusted for time-dependent HbA1c, lipids, eGFR, and medications (antihypertensive, diuretics, statins and non-statins lipids modifying drugs, beta-blockers, calcium-channel blockers, alpha-blockers, insulin, metformin, and sulfonylureas). For all-cause mortality, we additionally adjusted for incidence of comorbidities (CVD and cancer).

incidence rates were 8.7, 3.9, 11.8, 3.8, and 1.7 events per-1000-person-years. Compared with CCBs, time-varying RASi use was associated with neutral risk of all-site cancer (HR=0.94, 95% CI: 0.85-1.03), diabetes-related cancer (HR=1.00, 95% CI: 0.86-1.15) and all-cause mortality (HR=0.92, 95% CI: 0.84-1.02) but reduced risk of cancer-specific mortality (HR=0.85, 95% CI: 0.72-1.00) and diabetes-related cancer mortality (HR=0.71, 95% CI: 0.55-0.90) (Figure 1B). When stratified by age, reduced risk associations of RASi use with all-cause and cancer-specific mortality were most evident in the youngest age-group (18-55 years) (eTable 6).

Comparison between ACEi and ARBs

We used PS-OW to balance the baseline characteristics between 73,596 ACEi-only and 21,103 ARBs-only users (eTable 7). Compared with ACEi-only use, ARBs-only use was associated with lower risk of all-site cancer (HR=0.90, 95% CI: 0.81-0.99) all-cause mortality (HR=0.71, 95% CI: 66-0.78), cancer-specific mortality (HR=0.77, 95% CI: 66-0.91), and diabetes-related cancer mortality (HR=0.73, 95% CI: 0.57-0.94) (Figure 3).

Sensitivity analysis

We included prevalent-RASi users (n = 115,229) giving a total of 245,748 RASi users for comparison with 122,972 non-RASi users. The reduced risk associations of RASi with cancer and related mortality compared with non-RASi remained consistent (eFigure 5). Amongst 49,424 new-RASi and 54,537 non-RASi users with long follow-up year (media=9.2, IQR: 7.8-11.3), new-RASi versus had reduced risk of all-site cancer (HR=0.85, 95% CI: 0.78-0.93) and diabetes-related cancer (HR=0.77, 95% CI: 0.72-0.82) compared with non-RASi users (eFigure 6).

Discussion

Patients with T2D are frequently prescribed with RASi for lowering BP or organ protection. The increased survival had allowed the emergence of cancer as an important outcome in these patients. In this RWE study including 0.25 million Chinese patients with T2D observed for a mean period of 6.5 years, we found consistent evidence showing the attenuated risk associations of RASi versus non-RASi with all-site and diabetes-related cancer as well as cancer-specific and all-cause mortality. Amongst the RASi users, ARBs users had lower HR than ACEi users for cancer-related events. RASi use was also associated with lower HR for liver cancer and pancreatic cancer in men than women, while RASi use was associated with lower risk of all-cause and cancer-specific death compared with CCBs, especially in young-to-middle age group.

Cancer and T2D are closely related although there are few dedicated pharmacoepidemiological studies in this area.[32] To our knowledge, this is the most comprehensive RWE analysis on the risk associations of long-term RASi use with cancer events and cancer-specific death. Most meta-analyses based on RCTs and epidemiological studies showed conflicting results on the link between RASi, as a drug class, and cancer.[4,33–35] In the largest post-hoc analysis of 33 RCTs, there was also inconsistent results regarding the associations of ACEi or ARBs with cancer risk.[13] These studies, not limited to diabetes, typically captured cancer events after treatment initiation with short duration of follow-up when

the observed effects of RASi on cancer risk might become evident only with long term exposure.[4,13] In clinical trial setting, patients often received optimal care due to close monitoring with improved treatment adherence and risk factor control which could contribute to low event rates.[36] Besides, the heterogeneity in patient characteristics, study design, outcome definitions and settings might confound these associations.[4,13,34] Well-designed long term studies using RWE based on high-quality EMR data might address these knowledge gaps.[20,23] Other studies not dedicated to patients with diabetes had reported similar results as ours. In a prospective cohort of 5207 hypertensive patients from Scotland.[37] treatment with ACEi for at least 3 years was associated with 30% lower risk of cancer than non-ACEi use. In a UK cohort, cumulative use of ARBs for 1-3 years was associated with 38% reduced risk of pancreatic cancer.[38] In another study from Netherlands including 7893 patients followed up for 9.6 years, long-term high dose ACEi treatment was associated with protective effects against lung and prostate cancer, especially in those with ACE gene polymorphisms.[39]

Our study focused on patients with T2D which reduced the heterogeneity of the population. Our comprehensive analysis, prospective design, large sample size and consistent evidence on the attenuated risk of all-site, site-specific and diabetes-related cancers amongst RASi users including subgroup analyses together with the biological plausibility given the pluripotent effects of RAS increased the certainty of our results.[40]

Liver cancer is one of the leading diabetes-related cancers. We recently reported the increased risk association of liver cancer with glycemic burden in patients with T2D especially in those with obesity.[41] Chronic hyperglycemia can lead to dysregulation of metabolic, haemodynamic, growth factors/cytokines and cell signaling pathways which may be causally linked to liver and pancreatic cancers.[4,42] In this study, the crude incidence of liver cancer in patients with T2D was 2.7-fold higher than that in the general population in Hong Kong (0.8-versus-0.3 per-1000-person-years in 2018).

The attenuated cancer risk with RASi users was stronger in men than women. These subtle differences related to site-specific cancer and sex accorded with the heterogeneity of risk factors and clinical outcomes. Here, oestrogen has been shown to reduce the activity of RAS with downregulation of renin, ACE and AT-1 receptor which might contribute to the organ-protective effects of RASi in premenopausal women.[43] Other researchers had reported a more adverse proinflammatory profile in men than women with metabolic syndrome. These sex differences might contribute to the sex-related risk associations of RASi treatment with cancer.[44,45] In the main analysis, we did not find heterogeneity in the reduced cancer risk association with RASi in different age groups. However, in the comparative analysis, young patients treated with RASi had reduced risk of cancer-related mortality versus CCBs. Patients with advanced kidney disease are at higher risk of hyperkalaemia might not tolerate RASis. Thus, it remains possible that the risk differences between CCB and RASi might be confounded by indication bias although we had excluded those with ESKD at baseline and adjusted this as far as possible using PS-OW methods. Given the few event events in these young patients, large sample size with longer follow up are warranted given the increasing burden of young onset T2D.[5]

Amongst the RASi users, ARBs users had lower risk of all-cause, cancer-specific and diabetes-related cancer death than ACEi users. The differences in risk associations between ACEi and ARBs have been controversial.[46,47] In a post-hoc analysis of a RCT,[48] ACEi was associated with increased risk of lung cancer. However, in a nationwide retrospective cohort analysis of 70,000 community-dwelling adults in the United States,[49] ARBs were associated with reduced risk of lung cancer (HR=0.74, 0.67-0.83). Due to the more complete blockade of RAS with ARBs, the larger effect size with ARBs versus ACEi is plausible. Apart from directly blocking the effects of angiotensin-II on AT1 receptor, ARBs but not ACEi increases angiotensin-II level. The latter is accompanied by upregulation of ACE2 which converts angiotensin-II to angiotensin$^{1\text{-}7}$ which possesses anti-proliferative, anti-inflammatory and anti-cancer effects.[50] Besides, side effects such as cough is more common in ACEi compared with ARBs users which may lead to poorer adherence.[51] These observations may contribute to the superior effects of ARBs than ACEi. Given cancers develop over a long period, these differences in observational period between ARBs and ACEi users might be a potential bias although we have used time-dependent Cox model to address these time differences. Indeed, in our sensitivity analysis, the risk association of cancer with RASi appeared to be non-time dependent, although the majority of patients initiated on RASi remained on therapy during this 6-year follow-up period.

Apart from reduced incidence of cancer, RASi users also had reduced risk of cancer-specific death. Experimentally, activation of RAS could initiate cancer growth and promote cancer progression, while RAS inhibition reduced angiogenesis with immunomodulatory and anti-cancer effects.[52] Angiotensin-II stimulates several proangiogenic growth factors including vascular endothelial growth factor (VEGF) and angiopoetin.[53] Several clinical trials explored the anti-cancer effects of ACEi/ARBs regimens combined with platinum-based or anti-VEGF chemotherapeutic agents. In a metanalysis of seven retrospective studies, adjunctive RASi therapy with chemotherapeutic agents was associated with improved survival.[54]

The strengths of this RWE study included large number of events and long follow-up period compared

with post-hoc analyses of RCTs. This was accompanied by comprehensive documentation of baseline and time-varying factors including duration of drug exposure, treatment switching and discontinuation, cardiometabolic indices, renal function, clinical events, and use of multiple medications. We adopted new-user design, clearly defined inclusion and exclusion criteria, and robust analytic techniques to adjust for different biases. We acknowledge that the follow-up duration might not be long enough to capture slower-growing cancers. We did not capture drug adherence and could not be certain whether poor adherence to ACEi, for example, due to ACEi-related cough[51] might confound the diferential risk association for cancer between ACEi and ARBs users. The increased incidence of ACEi-related cough might also increase the likelihood of detecting lung cancer compared with ARBs. Other limitations included residual confounding by indication despite PS-based weighting of key variables associated with RASi prescription. We were unable to adjust for all medications such as non-steroidal anti-inflammatory drugs known to associated with lower risk of cancer.[55] We included data from the RAMP-DM subset of HKDSD and although they were largely similar in age, gender and frequency of HbA1c measurements, we cannot exclude the possibility that differences that may affect the generalizability of results. Despite this being one of the largest studies performed in Hong Kong Chinese patients with diabetes, our observations may not generalize to Chinese residing in Hong Kong and other settings or other ethnic groups.

In conclusion, in this RWE study of patients with T2D, use of RASi was consistently associated with reduced risk of all-site cancer and diabetes-related cancers as well as all-cause and cancer-specific death, independent of its antihypertensive effects. Amongst RASi users, ARBs had a greater effect size than ACEi for cancer-specific death. RASi use was associated with lower cancer-related death compared with CCBs. Our data support the use of RASi among individuals without cardiovascular-renal risk factors, including young-adults with T2D. In this analysis, only 30% of patients were treated with RASi at baseline with only 53% of patients put on RASi after enrolment. Given the non-time varying and cumulative nature of the reduced risk association of cancer with RASi, the economic benefits of its early use in patients with T2D might go beyond cardiovascular-renal protection.

Contributors

A.Y., E.C. and J.C. contributed to conception of the article, statistical analysis, interpretation of results, drafting, revision and approval of the manuscript. H.W., E.S.H.L., M.S., B.F. contributed to interpretation of results, revised the manuscript critically and approved the final version. A.P.S.K., R.C.W.M., and A.O.Y.L. contributed to conception of the article, revised the manuscript critically and approved the final version. E.C. is the guarantor of this work and takes responsibility for the integrity of the data, the accuracy of the data analysis, and the decision to submit the manuscript.

Data sharing statement

HKDSD welcomes collaborative research. Aggregate data may be available upon reasonable request. Proposals for future collaborations can be submitted to the HKDSD investigators (andrealuk@cuhk.edu.hk) for consideration.

Declaration of interests

J.C.N.C. has received research grants and/or honoraria for consultancy or giving lectures, from AstraZeneca, Bayer, Boehringer Ingelheim, Eli-Lilly, Hua Medicine, Lee Powder, Merck Serono, Merck Sharp & Dohme, Pfizer and Sanofi. APSK has received research grants and/or speaker honoraria from Abbott, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli-Lilly, Merck Serono, Nestle, Novo Nordisk, Pfizer and Sanofi. A.O.Y.L. has served as a member of advisory panel for Amgen, AstraZeneca, Boehringer Ingelheim and Sanofi and received research support from Amgen, Asia Diabetes Foundation, Bayer, Boehringer Ingelheim, Lee's Pharmaceutical, MSD, Novo Nordisk, Roche, Sanofi, Sugardown Ltd, Takeda. None of these relationships had any influence on the content of the present manuscript. RCWM has received research funding from AstraZeneca, Bayer, Merck Sharp & Dohme, Novo Nordisk, Pfizer and Tricida Inc. for carrying out clinical trials, and has received speaker honorarium or consultancy in advisory boards from AstraZeneca, Bayer and Boehringer Ingelheim. All proceeds have been donated to the Chinese University of Hong Kong to support diabetes research. Other authors have no conflicts of interest to disclose.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2022.104219.

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