ANGIOTENSIN CONVERTING ENZYME INHIBITORS/ANGIOTENSIN RECEPTOR BLOCKERS ARE ASSOCIATED WITH LOWER COLORECTAL CANCER RISK:A TERRITORY-WIDE STUDY WITH PROPENSITY SCORE ANALYSIS

Short title: ACEIs/ARBs and Post-colonoscopy CRC

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ABSTRACT

Whether angiotensin converting enzyme inhibitors and angiotensin receptor blockers modify colorectal cancer risk remains controversial. We aimed to determine association between their use and colorectal cancer risk after a negative baseline colonoscopy. This is a territory-wide retrospective cohort study recruiting patients aged ≥40 who had undergone colonoscopy between 2005 and 2013. Exclusion criteria included colorectal cancer detected <6 months of index colonoscopy, prior colorectal cancer, inflammatory bowel disease and prior colectomy. The primary outcome was colorectal cancer diagnosed between 6–36 months after index colonoscopy. Sites of colorectal cancer were categorized as proximal (proximal to splenic flexure) and distal cancer. The adjusted hazards ratio of colorectal cancer with angiotensin converting enzyme inhibitor/angiotensin receptor blocker use (≥180-day use within 5 years before index colonoscopy) was derived by propensity score regression adjustment of 23 covariates (including patient's factors, concurrent medication use and endoscopy center's performance). Of 187,897 eligible patients, 30,856 (16.4%) were angiotensin converting enzyme inhibitors/angiotensin receptor blocker users. 854 (0.45%) developed colorectal cancer between 6 and 36 months after index colonoscopy (proximal cancer:147[17.2%]). These drugs were associated with lower risk of colorectal cancer that developed <3 years after index colonoscopy (adjusted hazard ratio:0.78;95% CI:0.64–0.96), but not colorectal cancer that developed >3years (adjusted hazard ratio:1.18;95% CI 0.88–1.57); every single year increase in the drug use was associated with 5% reduction in adjusted hazard ratio risk. Angiotensin converting enzyme inhibitors/angiotensin receptor blocker were associated with a lower colorectal cancer risk in a duration-response manner.

Keywords: angiotensin converting enzyme inhibitors, angiotensin receptor blockers, renin, post-colonoscopy colorectal cancer, adenocarcinoma, interval cancer, colonoscopy

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and second leading cause of cancer death worldwide.[1] Even though its incidence and mortality can be reduced by screening colonoscopy,[2-6] a proportion of patients could develop CRC after an initial colonoscopy negative for cancer. The World Endoscopy Organization (WEO) consensus has recently proposed the term "post-colonoscopy CRC (PCCCR)" to describe CRC that develops after diagnostic colonoscopy.[7] Population-based studies estimated that up to 9% of all diagnosed CRCs are PCCRCs.[8, 9] Around 50% of PCCRCs are due to missed lesions or incomplete resection of polyps in prior colonoscopy.[8] Another possible cause of PCCRC is alternative sessile serrated pathway with rapid tumour development.[10-12]

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are commonly prescribed for patients with hypertension, congestive heart failure and proteinuira.[13] Angiotensin II receptors were showed to regulate angiogenesis, cell proliferation, and tumour progression in experimental studies.[14] Concern over possible carcinogenic effects of ACEIs/ARBs was first reported in 2003 when a post-hoc analysis of CHARM trial revealed that more fatal cancers occurred in candesartan users.[15] Since then, debates over potential carcinogenic effects of ARBs and even ACEIs on various solid organ cancer risks have been unsettled. A large cohort study of 377,649 patients showed that there was no increased risk of overall cancer.[16] Subsequently, a meta-analysis of RCTs by Sipahi I et al[17] showed that ARBs were associated with a modestly increased overall cancer risk (relative risk:1.08). A recent population-based cohort study also suggested a higher lung cancer risk among ACEI users, presumably due to accumulation of bradykinin in the lung.[18]

However, effect of ACEIs/ARBs on CRC remains controversial,[19-24] which could be accounted by the relatively small sample size or insufficient adjustment for both positive (e.g. aspirin,[25] statins[26, 27]) and negative confounding factors (e.g. comorbidities) that could bias the drug-cancer association to either direction. In this study, we aimed to determine whether baseline ACEIs/ARBs use was associated with CRC development in patients with prior colonoscopy negative for CRC (i.e. PCCRC).

MATERIALS AND METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study design and data source

We conducted a territory-wide retrospective cohort study by retrieving data from an electronic healthcare database (Clinical Data Analysis and Reporting System [CDARS]) of the Hong Kong Hospital Authority. The Hong Kong Hospital Authority is publicly funded which serves a population of 7.3 million including 90% of all primary, secondary and tertiary care services. The CDARS is a centralized electronic healthcare system which contains detailed records of patients' information including demographics, diagnoses, hospitalization including intensive care, visits to outpatient clinics and accident and emergency department, laboratory and other investigation results, endoscopic and surgical procedures, as well as drug prescription and dispensing history. The International Classification of Diseases, Ninth Revision (ICD-9) coding was used for diagnosis coding and have been shown to have a high degree of coding accuracy (> 90%) in previous territory-wide studies.[28-32]

Study subject selection

Figure 1 illustrates patient disposition process. We identified all patients (aged ≥40 years) who had undergone colonoscopy between 2005 and 2013, and excluded those with prior history of CRC, inflammatory bowel disease and colectomy. Detected CRCs diagnosed within 6 months of index colonoscopy were also excluded based on the assumption that any cancer suspected at index colonoscopy should be confirmed within this time period.[33]

Outcome definition

The primary outcome of interest was PCCRC at 3 years (PCCRC-3y), as recommended by World Endoscopy Organization (WEO) consensus, by including CRCs diagnosed between 6 and 36 months after an index colonoscopy negative for cancer.[7] The cut-off of 3 years was also commonly adopted by prior studies,[27, 33-37] as this is the estimated mean sojourn time from preclinical to clinical detectable cancer. Cancer site was categorized into proximal (from caecum to transverse colon [ICD-9 codes 153.4, 153.6, 153.0, 153.1]) and distal colon (from splenic flexure to rectum [ICD-9 codes 153.2, 153.3, 153.7, 154.0, 154.1]). Patients were observed from index colonoscopy and censored at PCCRC-3y diagnosis, death or after 3 years.

The secondary outcomes of interest were PCCRC-all (i.e. all PCCRC cases developing >6 months after index colonoscopy), and PCCRC>3y (i.e. PCCRC cases developing >36 months after index colonoscopy) (**Figure S1**). Patients were observed from index colonoscopy and censored at CRC diagnosis, death or 31 December 2017 (i.e. study end date).

We also investigated effects of ACEIs/ARBs on other solid organ cancers which were reported in previous literature (including lung, breast and prostate).[16, 18] Patients with any of these cancers developing before index colonoscopy were excluded. They were observed from index colonoscopy and censored at cancer diagnosis, death or 31 December 2017 (i.e. study end date).

Data validation

We retrieved data from our own center, the Queen Mary Hospital which is a large regional hospital, for validation. Among 137 PCCRC-3y cases, ICD-9 coding for CRC was 97.1%.

Study variables

The exposure of interest was baseline ACEI/ARB use prior to index colonoscopy. covariates taken into consideration included patient's factors and endoscopy centres' performance (annual endoscopy volume and polypectomy rate) (**Table 1**).[33, 35, 36, 38] Patient's factors included age of index colonoscopy, sex, history of colonic polyps, polypectomy at index colonoscopy, smoking status (by using ICD-9 code of V15.82 and chronic obstructive pulmonary disease [COPD] as a surrogate marker), heavy alcohol consumption (by using alcohol-related diseases as surrogate markers), comorbidities (cardiovascular, metabolic, neurological, renal and liver diseases) and concurrent medication usage (NSAIDs including aspirin,[25] cyclooxygenase [COX]-2 inhibitors[39] and statins[26, 27]). **Table S1** shows the ICD-9 codes of these covariates.

Drug prescription and dispensing records were traced up to 5 years before index colonoscopy. Medication use, including ACEIs/ARBs, was defined as exposure for at least 180 days. Dispensing duration of individual prescription for a particular drug was summed up to derive total treatment duration for individual patient. To study dose-response relationship of ACEIs/ARBs on PCCRC-3y, duration of ACEI/ARB use was categorized into three groups: (i) non-use, (ii) ≤2 years and (iii) >2 years.

We used calcium channel blockers (CCBs) (dihydropyridine and non-dihydropyridine) and diuretics (loop diuretics, thiazide diuretics, aldosterone antagonists and

potassium-sparing diuretics) as negative control exposures, as these two classes of anti-hypertensives were not reported to be associated with CRC development.[40] The relation of this exposure-outcome pair likely shared similar potential biases and confounders (both measured and unmeasured) with ACEIs/ARBs. An observed association may therefore suggest presence of residual/unmeasured confounding.

Statistical analyses

All statistical analyses were performed by the R version 3.2.5 (R Foundation for Statistical Computing) statistical software. Continuous variables were expressed as median and interquartile range (IQR). Mann-Whitney U-test was used to compare continuous variables of two groups. We adopted propensity score (PS) regression adjustment to investigate the effect of ACEIs/ARBs on PCCRC-3y risk.[37, 41] PS represented the probability of ACEIs/ARBs prescription predicted by the 23 covariates (**Table 1)** in a logistic regression model. We used Cox proportional hazards model in combination with PS regression adjustment to derive the adjusted hazard ratio (HR) of (1) primary outcome (PCCRC-3y) and (2) secondary outcomes (PCCRC>3y and PCCRC-all) with ACEIs/ARBs use.

Stratified analysis was performed according to cancer location (proximal vs distal), age, sex, history of diabetes mellitus (DM) and colonic polyps. Sensitivity analysis was performed by PS matching.[42, 43] ACEIs/ARBs users were matched to non-users in a 1:1 ratio without replacement using a greedy distance-based matching algorithm with the logit of the PS within 0.1 standard deviation. Absolute standardized difference (ASD) allows an objective assessment of the matching result. It was defined as absolute difference in means or proportions divided by pooled standard

deviation. Balance of covariates between two groups was achieved if an ASD was less than 0.20.[44] A two-sided p-value of <0.05 was used to define statistical significance.

Patient and public involvement

Our study retrieved data from electronic healthcare database and id not include patients as study participants. We will disseminate the results via general media, but not directly to patients.

RESULTS

Patient Characteristics and PCCRC-3y Risk

A total of 187,897 eligible patients who had undergone colonoscopy between 2005 and 2013 were identified (**Figure 1**), with a total of 560,306 person-years follow-up. The median age of undergoing index colonoscopy was 60.6 years (IQR:52.3–71.9), with 48.9% men. Between 6 months and 3 years after index colonoscopy, 854 PCCRC-3y cases were diagnosed including 147 (17.2%) proximal and 707 (82.8%) distal cancers, with an incidence rate of 15.2 per 10,000 person-years. The median age of patients who developed PCCRC-3 was 75.9 years (IQR:65.5–83.8), with a median time lapse of 1.2 years (IQR:0.8–1.9) from index colonoscopy.

Association between ACEIs/ARBs and PCCRC-3y

There were 30,856 ACEIs/ARBs users with median duration of 3.3 years use within the 5 years before index colonoscopy. Among the ACEIs/ARBs users, there were 169 (0.55%) PCCRC-3y cases. On univariate analysis, the crude HR of PCCRC-3y with ACEIs/ARBs use was 1.26 (95% CI:1.06–1.49;p=0.008). On PS regression adjustment, the adjusted HR of PCCRC-3y became 0.78 (95% CI:0.64–0.96) (**Table 2**). The PS adjusted absolute reduction in PCCRC-3y risk for ACEIs/ARBs users was 3.2 (95% CI:0.6–5.3) per 10,000 person-years as compared with non-users. Stratification according to cancer subsite shows that adjusted HR of PCCRC-3y with ACEI/ARB use was 0.77 (95% CI:0.61–0.97) for distal and 0.83 (95% CI:0.51–1.35) for proximal cancers, respectively.

For the two negative control exposures, adjusted HRs of PCCRC-3y were 0.86 (95% CI:0.72–1.03) for CCBs and 0.92 (95% CI:0.66–1.28) for diuretics (**Table 2**).

Duration-response between ACEIs/ARBs and PCCRC-3y

The adjusted HR of PCCRC-3y with every single year increase in ACEIs/ARBs use was 0.95 (95% CI:0.91–0.99;p=0.040). When compared with non-ACEI/ARB use, PCCRC-3y risk decreased with longer duration of ACEI/ARB use (≥2 year use–adjusted HR:0.77, 95% CI:0.60–0.97; vs <2 year use–adjusted HR:0.85, 95% CI:0.63–1.14) (**Table 3)**.

When ACEIs were considered alone, the PCCRC-3y risk also decreased with longer duration of use (≥2 year use–adjusted HR:0.75, 95% CI:0.59–0.95). On the other hand, the reduction in PCCRC-3y risk was borderline for ≥2 years ARBs use (adjusted HR:0.51, 95% CI:0.25–1.05;p=0.07).

Sensitivity analysis by PS matching

Before PS matching, some covariates were imbalanced (ASD>0.2) between ACEIs/ARBs users and non-users including age, cardiovascular risk factors and diseases, aspirin and statins. (**Table S2**). After PS matching (n=50,500 with 308 [0.6%] PCCRC-3y cases), all covariates were well balanced (ASD<0.2) between the 25,250 ACEIs/ARBs users and 25,250 non-users. The HR of PCCRC-3y risk with ACEIs/ARBs use was 0.78 (95% CI:0.62–0.98;p=0.03).

Subgroup analysis

Table 4 shows that protective effect of ACEIs/ARBs was confined to older patients (aged ≥55 years) (adjusted HR:0.79, 95% CI:0.65–0.98) and patients with history of colonic polyps (adjusted HR:0.71, 95% CI:0.52–0.97).

Association between ACEIs/ARBs and secondary outcomes (PCCRC-all and PCCRC>3y)

There were a total of 1,290 PCCRC-all cases diagnosed >6 months after index colonoscopy, including 436 PCCRC>3y that developed at a median of 5.2 years (IQR:3.7–7.2). The adjusted HR of PCCRC-all with ACEIs/ARBs use was 0.89 (95% CI:0.75–1.06;p=0.19), and that for PCCRC>3y was 1.18 (95% CI:0.88–1.57;p=0.26).

Association between ACEIs/ARBs and other solid organ tumours

On univariate analysis, ACEIs/ARBs were associated with an increased risk of lung and prostate cancer, but lower risk of breast cancer (**Table S3**). However, after PS regression adjustment, there was no association between ACEIs/ARBs and these solid organ cancers.

DISCUSSION

To our knowledge, this is the first study that specifically characterized the effect of ACEIs/ARBs in PCCRC developing within 3 years after a baseline colonoscopy negative for cancer. ACEIs/ARBs were associated with a 22% lower PCCRC-3y risk in a duration-response manner.

Our study was the largest reported study, including more than 180,000 subjects with baseline colonoscopy negative for cancer, to show a significant chemoprotective effect of ACEIs/ARBs. This is in keeping with the result of a nested case-control study of 31,086 patients using the EPIC's General Practice Research Database, in which ACEI/ARB use for ≥1 year was associated with 16% reduction of CRC risk. The CRC risk was further reduced by 25% with ACEI/ARB use for ≥5 years.[20]

Interestingly, our results showed that potential chemopreventive effect of ACEIs/ARBs was only limited to PCCRC-3y, but not PCCRC-all or PCCRC>3y. As none of prior studies stratified CRC into detected CRC and PCCRC, potential benefit of ACEIs/ARBs on PCCRC could be masked. Since adenoma-carcinoma progression could take up to decades, our results may imply that ACEIs/ARBs exert their effect by inhibiting progression of missed adenomas or cancers that develop rapidly through alternative pathway.

Angiotensin II stimulates neovascularization,[45] and hence cell proliferation, tumour formation and growth.[46, 47] It also stimulates PKC-dependent ERK activation,[48] which transduces mitogenic signals leading to DNA synthesis and cell division in intestinal epithelial cells. Hence, inhibition of angiotensin II is crucial for neovascularization[45]

and activation of protein kinase C (PKC)-dependent extracellular signal-related kinase (ERK).[48] In-vitro studies have demonstrated an inhibitory effect of ACEIs/ARBs on tumor vascularization, growth and metastasis.[14, 49, 50] Apart from reducing CRC incidence,[19, 20] clinical studies have shown that ACEIs and ARBs can reduce formation of advanced colonic polyps[23, 51] and metastasis,[52] improve tumor response to chemotherapy,[53] prolong survival and decrease tumor progression of advanced CRC.[54]

While previously reported negative studies on the association between ACEIs/ARBs and CRC were of relatively small sample size and short follow-up,[21-24] those reporting a protective effect included >30,000 patients.[19, 20] A large sample size also allowed for the investigation of duration-response relationship to strengthen causality as in our study. Another merit of our study was the territory-wide nature of electronic healthcare database with documentation of all diagnoses and drug prescription/dispensing details, hence avoiding some biases common to traditional observational studies like selection and recall biases.[25] Failure to adjust for these comorbidities, which have a negative confounding effect,[55] may bias potential beneficial effect of ACEIs/ARBs towards null or even harmful effect. This is particularly relevant as ACEI/ARB users are older with more comorbidities (**Table 1**) which were risk factors for CRC. This is well illustrated in our study with an unadjusted HR of PCCRC-3y with ACEIs/ARBs being 1.26, which became 0.78 upon PS regression adjustment for a comprehensive list of comorbidities. The importance of negative confounding (which biases an observed association towards null or even opposite direction) tends to be less emphasized as compared to positive confounding (which spuriously augments a positive association) in pharmaco-epidemiological

studies. This is also supported by analysis of ACEI/ARB effect on other solid organ tumours in this study, wherein an increased risk was only noted on univariate analysis but not on PS regression adjustment.

The validity of the observed beneficial effect was also consolidated by taking into consideration positive confounders especially aspirin[39] and statins.[26, 27] Without adjusting for these chemopreventive agents, one can argue that the apparent chemopreventive effect of ACEs/ARBs could simply arise from their close association with aspirin/statin usage linked by cardiovascular diseases. Moreover, use of negative control exposure (CCBs and diuretics) also dismissed possibility of significant biases/unmeasured confounding (e.g. indication bias, ascertainment bias) leading to spurious causal inference.[40] The causal relationship was further strengthened by demonstration of a duration-response relationship, with a 5% reduction in risk for every one year increase in ACEI/ARB use. Immortal time bias and reverse causality were circumvented by defining ACEIs/ARBs use based on baseline exposure prior to index colonoscopy with outcome of PCCRC-3y developing at a median of 1.2 years after index colonoscopy.

The controversy of ACEIs/ARBs on specific cancer risk is not limited to CRC, but also other cancers like lung cancer.[16-18] One origin of these controversies could stem from the different predefined comparator groups in these studies (placebo/non-drug use, ACEIs, ARBs or other anti-hypertensives). Comparing ACEIs with ARBs (and vice versa) instead of non-drug use or other anti-hypertensives just adds further uncertainty to this topic. Post-hoc analysis of RCTs suffers from the caveat of short follow-up and underpower,[17] which partially explain why a beneficial effect was only

observed in observational studies of longer follow-up which focused specifically on CRC and used non-ACEI/ARB exposure as comparators.

In this study, beneficial effect of ACEIs/ARBs was confined to distal cancer. This differential effect could be due to possible diverse carcinogenic mechanisms of proximal and distal cancer as well as the different embryonic origin of proximal and distal colon[50]. Further subgroup analysis finds that beneficial effect was observed among patients ≥55 years and those with a history of colonic polyps and/or polypectomy. These two factors are risk factors for higher colonic polyp burden and hence higher chance of missed polyps or incomplete resection of lesions.[56] Nevertheless, possible underpower from subgroup analysis necessitates cautious interpretation of results.

A few limitations should be acknowledged. First, data on some risk factors like family history of CRC were unavailable in the electronic health database. True prevalence of smoking and alcohol use was likely underestimated due to use of diagnostic coding only. However, it is well recognized that family history unlikely influences drug prescription in drug-cancer association research and therefore confers no confounding effect.[57] Similarly for smoking, alcohol use and obesity, balance was likely achieved in view of the highly similar proportion of COPD, alcohol-related diseases and their associated cardiovascular diseases in the matched cohort (**Table S2**). Second, drug compliance could not be ascertained. However, a unique feature of our local public health system is the simultaneous prescription and dispensing of drugs within the hospital. Moreover, non-differential misclassification, if present, would only bias drug-cancer association towards null. Third, data on some colonoscopy quality

metrics like individual endoscopist's adenoma detection rate, quality of bowel preparation, polyp characteristics (e.g. number, size, histology) were lacking. This was partly compensated by using other surrogate markers like center's colonoscopy volume and polypectomy rate, and again these factors unlikely affect choice of ACEIs/ARBs.

PERSPECTIVES

Apart from side effects and contraindications, compelling indication is another factor to be considered in the choice of a particular anti-hypertensive medication. Our study provided additional insights into the potential chemopreventive effects of ACEIs/ARBs against CRC development, apart from their known cardiovascular and renal benefits.

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NOVELTY AND SIGNIFICANCE

What is new?

- ACEIs/ARBs were associated with a 22% lower risk of colorectal cancer (CRC), in a duration-response manner.
- This beneficial effect was particularly prominent for distal CRC, and among older patients (aged ≥55 years) and those with history of colonic polyps.

What is revelant?

- While choosing ACEIs/ARBs over other anti-hypertensives, physicians may consider the chemopreventive effect of ACEIs/ARBs against CRC in addition to their cardiovascular and renoprotective effects.
- Older subjects and those with history of colonic polyps, which are known risk factors for CRC, may benefit more from the chemopreventive effect of ACEIs/ARBs

Summary

- ACEIs/ARBs were associated with a lower CRC risk in a duration-response manner, in particular distal colon. The beneifical effect was most prominent among older subjects and those with history of colonic polyps.

FIGURE LEGEND

Figure 1: Patient selection flow diagram

CRC, colorectal cancer; CLN, colonoscopy

Table 1. Characteristics of ACEIs/ARBs users and non-users

Variables	All (n=187,897)	ACEIs/ARBs users (n=30,856)	Non-users (n=157,041)
Age at index colonoscopy (years)*	60.6 (52.3 – 71.9)	70.6 (61.0 – 78.1)	58.9 (51.3 – 69.6)
Male sex (n, %)	91961 (48.9%)	16846 (54.6%)	75115 (47.8%)
History of colonic polyps (n, %)	39066 (20.8%)	8275 (26.8%)	30791 (19.6%)
Polypectomy at index colonoscopy (n, %)	28724 (15.3%)	4966 (16.1%)	23758(15.1%)
Smoking (n, %)	3874 (2.1%)	1295 (4.2%)	2579 (1.6%)
Alcohol (n, %)	1065 (0.6%)	194 (0.6%)	871 (0.6%)
DM (n, %)	17935 (9.5%)	10571 (34.3%)	7364 (4.7%)
Hypertension (n, %)	28982 (15.4%)	14271 (46.3%)	14711 (9.4%)
Dyslipidemia (n, %)	9557 (5.1%)	4562 (14.8%)	4995 (3.2%)
AF (n, %)	5673 (3.0%)	2956 (9.6%)	2717 (1.7%)
IHD (n, %)	13266 (7.1%)	7475 (24.2%)	5791 (3.7%)
CHF (n, %)	6302 (3.4%)	4455 (14.4%)	1847 (1.2%)
Stroke (n, %)	7638 (4.1%)	3549 (11.5%)	4089 (2.6%)
CRF (n, %)	3924 (2.1%)	2366 (7.7%)	1558 (1.0%)
Cirrhosis (n, %)	1250 (0.7%)	267 (0.9%)	983 (0.6%)
Dementia (n, %)	1258 (0.7%)	511 (0.6%)	747 (0.7%)
Parkinsonism (n, %)	779 (0.4%)	237 (0.8%)	542 (0.3%)
Aspirin (n, %)	26057 (13.9%)	13197 (42.8%)	12860 (8.2%)
NSAIDs (n, %)	14406 (7.7%)	2784 (9.0%)	11622 (7.4%)
COX-2 inhibitors (n,%)	209 (0.1%)	35 (0.1%)	174 (0.1%)
Statins (n,%)	23125 (12.3%)	11847 (38.4%)	11278 (7.2%)
Center endoscopy volume*	2892 (2045 – 3369)	2926 (2054 – 3369)	2892 (2045 – 3369)

Center polypectomy rate*	24.7% (21.7% - 28.4%)	25.0% (22.2% - 28.6%)	24.7% (21.7% - 28.4%)

* Age was expressed as median (years) with interquartile range

Categorical variables were expressed as number (%)

Drug use was defined as at least 180-day use

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; DM, diabetes mellitus; AF, atrial fibrillation; IHD, ischemic heart disease; CHF, congestive heart failure; CRF, chronic renal failure; NSAIDs, non-steroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2

Table 2. Association between ACEIs/ARBs use and risk of PCCRC-3y for the whole cohort and according to cancer sites (proximal and distal cancer)

Drugs	No. of patients	No. of PCCRC-3y	Person-years of follow-up	Adjusted HR*	95% CI	p-value
ACEIs/ARBs						
		All PCCRC-3y (n=187,897, PCCRC-3y=854)				
No	157,041	685	470,026	Ref	-	-
Yes	30,856	169	92,280	0.78	0.64 – 0.96	0.020
		Proximal PCCRC-3y (n=187,190, PCCRC-3y=147)				
No	156,470	114	469,229	Ref	-	-
Yes	30,720	33	92,105	0.83	0.51 – 1.35	0.456
		Distal PCCRC-3y (n=187,750, PCCRC-3y=707)				
No	156,927	571	469,865	Ref	-	-
Yes	30,823	136	92,236	0.77	0.61 – 0.97	0.027
Calcium channel blocker (Negative control exposure)						
		All PCCRC-3y (n=187,897, PCCRC-3y=854)				
No	148,387	610	444,190	Ref	-	-
Yes	39,510	244	118,116	0.86	0.72 – 1.03	0.100
		Proximal PCCRC-3y (n=187,190, PCCRC-3y=147)				
No	147,882	105	443,479	Ref	-	-
Yes	39,308	42	117,855	0.69	0.45 – 1.05	0.083
		Distal PCCRC-3y (n=187,750, PCCRC-3y=707)				
No	148,282	505	444,042	Ref	-	-
Yes	39,468	202	118,059	0.90	0.75 – 1.10	0.305
Diuretics (Negative control exposure)[#]						
		All PCCRC-3y (n=187,897, PCCRC-3y=854)				
No	180,496	813	540,177	Ref	-	-
Yes	7,401	41	22,129	0.92	0.66 – 1.28	0.618
		Proximal PCCRC-3y (n=187,190, PCCRC-3y=147)				
No	179,824	141	539,244	Ref	-	-
Yes	7,366	6	22,090	0.67	0.29 – 1.58	0.363
		Distal PCCRC-3y (n=187,750, PCCRC-3y=707)				
No	180,355	672	539,982	Ref	-	-
Yes	7,395	35	22,119	0.98	0.69 – 1.40	0.908

* Adjusted for age at which index colonoscopy was performed, sex, history of colonic polyps, polypectomy at index colonoscopy, smoking status, alcohol consumption, other comorbidities (diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation, ischemic heart disease, congestive heart failure, stroke, chronic renal failure, cirrhosis, dementia, parkinsonism) and concurrent medications (aspirin, non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, statins), annual center endoscopy volume and center polypectomy rate

[#] Diuretics included loop diuretics, thiazide diuretics, aldosterone antagonists and potassium-sparing diuretics

Abbreviations: PCCRC-3y, post-colonoscopy colorectal cancer at 3 years; HR, hazard ratio; 95% CI, 95% confidence interval; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers

Table 3. Duration-response between ACEIs/ARBs and PCCRC-3y risk

Drugs	Adjusted HR*	95% CI	p-value
ACEIs/ARBs			
Non-use	Ref	-	-
< 2 years of use	0.85	0.63 – 1.14	0.269
≥ 2 years of use	0.77	0.60 – 0.97	0.027
ACEIs			
Non-use	Ref	-	-
< 2 years of use	0.83	0.60 – 1.13	0.231
≥ 2 years of use	0.75	0.59 – 0.95	0.016
ARBs			
Non-use	Ref	-	-
< 2 years of use	0.99	0.53 – 1.87	0.974
≥ 2 years of use	0.51	0.25 – 1.05	0.066

* Adjusted for age at which index colonoscopy was performed, sex, history of colonic polyps, polypectomy at index colonoscopy, smoking status, alcohol consumption, other comorbidities (diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation, ischemic heart disease, congestive heart failure, stroke, chronic renal failure, cirrhosis, dementia, parkinsonism) and concurrent medications (aspirin, non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, statins), annual center endoscopy volume and center polypectomy rate

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; PCCRC-3y, post-colonoscopy colorectal cancer at 3 years; HR, hazard ratio; 95% CI, 95% confidence interval

Table 4. Subgroup analysis of the association between ACEIs/ARBs and PCCRC-3y risk

	Adjusted HR*	95% CI	p-value	p-interaction
Age				
≥ 55 (n=125,466, PCCRC-3y=761)	0.79	0.65 – 0.98	0.029	0.345
< 55 (n=62,431, PCCRC-3y=93)	0.86	0.26 – 2.87	0.810	
Sex				
Male (n=91,961, PCCRC-3y=513)	0.77	0.60 – 1.01	0.055	0.460
Female (n=95,936, PCCRC-3y=341)	0.79	0.56 – 1.11	0.178	
Diabetes mellitus				
Yes (n=17,935, PCCRC-3y=89)	0.73	0.46 – 1.15	0.170	0.753
No (n=169,962, PCCRC-3y=765)	0.81	0.65 – 1.02	0.073	
History of colonic polyps and/or polypectomy				
Yes (n=45,698, PCCRC-3y=326)	0.71	0.52 – 0.97	0.031	0.490
No (n=142,199, PCCRC-3y=528)	0.86	0.65 – 0.13	0.282	

* Adjusted for age at which index colonoscopy was performed, sex, history of colonic polyps, polypectomy at index colonoscopy, smoking status, alcohol consumption, other comorbidities (diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation, ischemic heart disease, congestive heart failure, stroke, chronic renal failure, cirrhosis, dementia, parkinsonism) and concurrent medications (aspirin, non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors, statins), annual center endoscopy volume and center polypectomy rate

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; PCCRC, post-colonoscopy colorectal cancer; HR, hazard ratio; 95% CI, 95% confidence interval