Prescribing trends, treatment trajectory, and long-term gastrointestinal cancer safety of antihypertensive drugs

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Abstract

Antihypertensive drugs are among the most prescribed drugs worldwide, with a prevalence ranging between 8% and 35% of the adult population. There are five major classes, which include thiazide diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and beta-blockers. These classes have been approved for several years, with ARBs being the latest major class introduced in the market in 1995. Despite a long-standing prescribing history, the prescribing prevalence of antihypertensive drugs over time has not been comprehensively evaluated, and few studies have described the treatment trajectory of patients with hypertension. Additionally, there is conflicting evidence on the long-term safety of antihypertensive drugs with respect to certain gastrointestinal cancers, particularly for thiazide diuretics and dihydropyridine CCBs (dCCBs). The overall aim of this thesis was thus to describe the prescribing patterns of antihypertensive drugs in primary care practices and assess the long-term safety of thiazide diuretics and dCCBs with respect to colorectal and pancreatic cancer, respectively.

The first manuscript described the prescribing trends of antihypertensive drugs in primary care and assessed the treatment trajectory of patients with hypertension. Using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD), I estimated the period prevalence of patients with antihypertensive drug prescriptions from 1988 to 2018. To assess treatment trajectory, patients with hypertension were followed from their first- through third-line antihypertensive drug. This cohort was stratified before and after 2007, the year following important changes to UK hypertension guidelines. I showed that in a cohort of 2.7 million primary care patients, the prevalence of patients with antihypertensive drug prescriptions increased from 7.8% (1988) to 21.9% (2018) and was observed for all major classes except thiazide diuretics.

Most patients with hypertension initiated thiazide diuretics (36.8%) and beta-blockers (23.6%) as first-line drugs before 2007, and ACE inhibitors (39.9%) and CCBs (31.8%) after 2007. After 2007, 17.3% of patients were not prescribed guideline-recommended first-line agents, potentially leading to suboptimal cardiovascular outcomes.

The second manuscript assessed whether thiazide diuretics were associated with an increased risk of incident colorectal cancer compared with dCCBs. I assembled a population-based, new-user, active comparator cohort study of 742,084 patients using the CPRD. I estimated hazard ratios (HRs) with 95% confidence intervals (CIs) of incident colorectal cancer using Cox proportional hazard models. Models were weighted using standardized morbidity ratio weights generated from calendar time-specific propensity scores. I showed that thiazide diuretics were not associated with an increased risk of colorectal cancer compared with dCCBs (weighted HR 0.97, 95% CI 0.90-1.04).

In the third manuscript, I investigated the comparative safety of dCCBs and thiazide diuretics with respect to incident pancreatic cancer. Using the CPRD, I assembled a population-based, new-user, active comparator cohort of 702,448 patients. Cox proportional hazards models were used to estimate HRs with 95% CIs for pancreatic cancer, comparing dCCBs with thiazide diuretics. Models were weighted using standardized morbidity ratio weights based on calendar time-specific propensity scores. I found that dCCBs were not associated with an increased risk of pancreatic cancer compared with thiazide diuretics (weighted HR 0.93, 95% CI 0.80-1.09).

This thesis fills important knowledge gaps in the prescribing patterns and long-term gastrointestinal cancer safety of antihypertensive drugs. It provides a comprehensive description of the antihypertensive drug classes prescribed in primary care over a 31-year period. In addition, findings from the comparative safety studies suggest that thiazide diuretics and dCCBs appear safe

with respect to colorectal and pancreatic cancer outcomes, providing reassurance to patients and physicians. This is particularly important given the high prevalence of these drugs and their long-term use in the clinical population.

Résumé

Les antihypertenseurs sont l'un des groupes de médicaments les plus prescrits au monde, avec une prévalence allant de 8 à 35% de la population adulte. Il existe cinq grandes classes, incluant les diurétiques thiazidiques, les inhibiteurs calciques, les inhibiteurs de l'enzyme de conversion de l'angiotensine, les antagonistes de récepteurs de l'angiotensine, et les bétabloquants. Ces groupes de médicaments ont été approuvés il y a plusieurs années, avec les antagonistes de récepteur de l'angiotensine ayant été le dernier groupe approuvé en 1995. Malgré le fait que ces antihypertenseurs soient prescrits depuis plusieurs années, la prévalence des prescriptions à travers le temps n'a pas été évaluée de façon compréhensive, et seulement quelques études ont décrites la trajectoire de traitement des patients ayant un diagnostic d'hypertension. De plus, les études portant sur la sécurité des médicaments à long terme ont fourni des résultats contradictoires, particulièrement pour les diurétiques thiazidiques et les inhibiteurs calciques. L'objectif global de cette thèse est donc de déterminer les tendances temporelles de prescription d'antihypertenseurs en soins primaires et d'évaluer la sécurité des diurétiques thiazidiques et des inhibiteurs calciques en termes de cancer colorectal et du pancréas, respectivement.

Le premier manuscrit décrit les tendances de prescriptions d'antihypertenseurs en soins primaire et évalue la trajectoire de traitement des patients ayant un diagnostic d'hypertension. Avec la banque de données du Clinical Practice Research Datalink (CPRD) du Royaume-Uni, j'ai estimé la prévalence des prescriptions d'antihypertenseurs de 1988 à 2018. Pour estimer la trajectoire de traitement, j'ai suivi les patients avec un diagnostic d'hypertension dès la prescription d'un antihypertenseur de première ligne jusqu'à la troisième ligne. Cette cohorte a été stratifiée avant et après 2007, l'année suivant des changements majeurs dans les lignes directrices sur l'hypertension au Royaume-Uni. J'ai démontré que dans une cohorte de 2,7 millions de patients

en soins primaires, la prévalence des patients ayant une prescription pour un antihypertenseur est passé de 7,8% en 1988 à 21,9% en 2018 et a été observé pour quatre classes majeures d'antihypertenseurs sauf les diurétiques thiazidiques. La majorité des patients ont débuté les diurétiques thiazidiques (36,8%) et les bétabloquants (23,6%) comme antihypertenseur de première ligne avant 2007. Après 2007, ce sont les inhibiteurs de l'enzyme de conversion de l'angiotensine (39,9%) et les inhibiteurs calciques (31,8%) qui ont été débuté les plus fréquemment. Après 2007, 17,3% des patients se sont vus prescrire des antihypertenseurs de première ligne non-recommandés par les lignes directives sur l'hypertension, pouvant potentiellement porter à des issues cardiovasculaires cliniques sous-optimales.

Dans le deuxième manuscrit, j'ai évalué si les diurétiques thiazidiques, comparés aux inhibiteurs calciques, étaient associés à une augmentation du risque de cancer colorectal. Avec l'aide du CPRD, j'ai mené une étude de cohorte populationnelle rétrospective de 742,084 patients nouvellement prescrit des diurétiques thiazidiques, en incluant comme groupe comparateur les inhibiteurs calciques dihydropyridiques. J'ai utilisé le modèle de risques proportionnels de Cox afin d'estimer le rapport de risque instantané (RRI) ainsi que les intervalles de confiance de l'incidence du cancer colorectal selon le ratio de mortalité standardisé pondéré. J'ai démontré que les diurétiques thiazidiques n'étaient pas associés à une augmentation du risque de cancer colorectal, comparés au inhibiteurs calciques dihydropyridiques (RRI pondéré : 0,97, 95% IC 0,90-1,04).

Dans le troisième manuscrit, j'ai évalué la sécurité comparative des inhibiteurs calciques dihydropyridiques et les diurétiques thiazidiques selon le risque d'augmentation du cancer du pancréas. En utilisant le CPRD, j'ai mené une étude de cohorte populationnelle rétrospective de 702,448 patients nouvellement prescrit des inhibiteurs calciques dihydropyridiques, en incluant

comme groupe comparateur les diurétiques thiazidiques. J'ai utilisé le modèle de risques proportionnels de Cox afin d'estimer le RRI ainsi que les intervalles de confiance de l'incidence du cancer du pancréas selon le ratio de mortalité standardisé pondéré. J'ai rapporté que les inhibiteurs calciques dihydropyridiques n'étaient pas associés à une augmentation du risque de cancer du pancréas, comparé au diurétiques thiazidiques (RRI pondéré 0,93, 95% IC 0,80-1,09).

Cette thèse comble d'importantes lacunes dans le savoir de la recherche sur les tendances temporelles de prescription d'antihypertenseurs et la sécurité à long terme de ces médicaments en rapport aux cancers gastrointestinaux. Elle apporte une description compréhensive des classes d'antihypertenseurs prescrit en soins primaires sur une période de 31 ans. De plus, les résultats des analyses de sécurité comparative suggèrent que les diurétiques thiazidiques ainsi que les inhibiteurs calciques dihydropyridiques semblent sécuritaire en termes de risque de cancer colorectal et du pancréas, rassurant les médecins ainsi que leurs patients. Ceci est particulièrement important étant donné la prévalence de ces médicaments et la durée de leur utilisation dans la population clinique.

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Contributions of authors

Manuscript 1: Treatment and prescribing trends of antihypertensive drugs in 2.7 million UK primary care patients over 31 years: a population-based cohort study

Published in BMJ Open

For this objective, I developed the research question with guidance from Dr. Azoulay. I drafted the protocol to obtain research data from the United Kingdom Clinical Practice Research Datalink Independent Scientific Advisory Committee and ethics approval from the Jewish General Hospital. I was responsible for data management, data analysis, interpretation of results, and manuscript writing. All co-authors (EGM, TS, JB, LA) contributed to the study design, interpretation of results, and review of the manuscript.

Manuscript 2: Thiazide diuretics and risk of colorectal cancer: a population-based cohort study

Under revisions at American Journal of Epidemiology

For this objective, I conceptualized the research question with Dr. Azoulay. I drafted the protocol to obtain research data from the United Kingdom Clinical Practice Research Datalink Independent Scientific Advisory Committee and ethics approval from the Jewish General Hospital. I was responsible for data management, data analysis, and manuscript writing. All co-authors (EGM, TS, IM, JB, LA) contributed to the study design, interpretation of results, and review of the manuscript.

Manuscript 3: Dihydropyridine calcium channel blockers and risk of pancreatic cancer: a population-based cohort study

Under revisions at Journal of American Heart Association

For this objective, I conceptualized the research question in collaboration with Dr. Azoulay. I drafted the protocol for submission to the United Kingdom Clinical Practice Research Datalink Research Data Governance (formerly Independent Scientific Advisory Committee) and to obtain ethics approval from the Jewish General Hospital. I was responsible for data management, data analysis, and manuscript writing. All co-authors (EGM, TS, JB, LA) contributed to the study design, interpretation of results, and review of the manuscript.

Statement of originality

The research presented in this thesis represents original scholarship, which advances knowledge in the field of prescribing trends and long-term cancer safety of antihypertensive drugs.

Thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, and beta-blockers are drugs with a long-standing prescribing history. Clinical guidelines for hypertension have recommended, either in the past or currently, these five classes of drugs for the management of hypertension. However, there is limited information on the prescribing practices of these antihypertensive drugs over time and on the primary care population being prescribed these drugs. In Manuscript 1, we addressed these gaps by comprehensively describing trends in the prescribing of antihypertensive drugs in the primary care setting, as well as trends in the treatment of patients with hypertension from first-line to third-line treatments. Our findings showed that nearly one-quarter of patients were prescribed antihypertensive drugs in the primary care setting. Additionally, most patients with hypertension initiated guideline-recommended first-line agents. However, not all patients were prescribed recommended antihypertensive drugs, potentially leading to suboptimal cardiovascular outcomes.

In Manuscript 2 and Manuscript 3, we investigated the safety of thiazide diuretics and dihydropyridine calcium channel blockers with respect to gastrointestinal cancers. As thiazide diuretics and dihydropyridine calcium channel blockers are first-line drugs for the treatment of hypertension, it was essential to address the limited evidence available on their long-term cancer safety and the methodological limitations of previous studies.

Previous studies have associated thiazide diuretics with an elevated risk of colorectal cancer. While this association is biologically plausible, these studies had important, conclusion-altering methodological biases. In Manuscript 2, we aimed to determine whether thiazide diuretics

were associated with an increased risk of colorectal cancer compared with dihydropyridine calcium channel blockers. We found that thiazide diuretics were not associated with an increased risk of colorectal cancer, even after more than ten years of cumulative duration of use. However, we observed effect modification among patients with inflammatory bowel disease and potentially with a history of polyps.

Recent studies have reported that dihydropyridine calcium channel blockers may increase the risk of pancreatic cancer, but these studies had significant methodological limitations. In Manuscript 3, we aimed to investigate whether dihydropyridine calcium channel blockers were associated with an increased risk of pancreatic cancer compared with thiazide diuretics. Our findings showed that dihydropyridine calcium channel blockers were not associated with an increased risk of pancreatic cancer.

Overall, this thesis provides important evidence on the prescribing of antihypertensive drugs in primary care practices, the pharmacological management of patients with hypertension, and the long-term gastrointestinal cancer safety of thiazide diuretics and dihydropyridine calcium channel blockers. This evidence helps better understand the prescribing practices of primary care physicians and the prescription burden in primary care populations while providing reassurance to clinicians and their patients on the long-term cancer safety of their treatments.

I declare that I have received guidance from my supervisor, Dr. Laurent Azoulay, on my thesis objectives. I declare that I have received methodological and clinical guidance from my thesis committee members, Dr. Tibor Schuster, Dr. James M. Brophy, and Dr. Emily G. McDonald. The conception, execution, and drafting of the three manuscripts and the thesis were entirely my own.

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List of acronyms and abbreviations

ACE	Angiotensin-converting enzyme
ARB	Angiotensin II receptor blocker
BMI	Body mass index
BNF	British National Formulary
CCB	Calcium channel blocker
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
dCCB	Dihydropyridine calcium channel blocker
GOLD	Gp OnLine Data
HR	Hazard ratio
IPCW	Inverse probability of censoring weighting
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
RAAS	Renin-angiotensin-aldosterone enzyme system
RCT	Randomized controlled trial
RR	Risk ratio
RRI	Rapport de risque instantané
UK	United Kingdom

CHAPTER 1. INTRODUCTION

1.1 Overview

It is estimated that approximately 1.3 billion adults between the ages of 30-79 have hypertension.[1] In Canada, 6 million adults have hypertension, representing 22.6% of the adult population, with an increasing prevalence over time.[2] Canada, along with South Korea and Iceland, have the highest treatment rates globally, with over 70% of patients with hypertension receiving treatment.[1]

Antihypertensive drugs are among the most commonly prescribed drugs worldwide, with a prevalence between 8% and 35% of the adult population.[3-8] There are five major classes, composed of thiazide diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and beta-blockers. These classes have been recommended for the management of hypertension for several years, with ARBs being the latest major class having received approval in 1995.[9] Currently, the American College of Cardiology/American Heart Association, Hypertension Canada, National Institute for Health and Care Excellence/British and Irish Hypertension Society, the European Society of Cardiology/European Society of Hypertension, and the International Society of Hypertension guidelines recommend initiating treatment for hypertension with any of the five major antihypertensive drug classes.[10-14] These classes have been found to produce similar reductions in blood pressure and to be equally effective in the primary prevention of cardiovascular disease.[15-21] In addition, three of those guidelines (the American College of Cardiology/American Heart Association, Hypertension Canada, and the International Society of Hypertension) more specifically recommend dihydropyridine CCBs (dCCBs) over non-dihydropyridine CCBs (non-dCCBs) as a first-line treatment due to the more potent vasodilatory effect of dCCBs.[10,12,13] Despite

their high prevalence of use, however, there is a lack of studies documenting the prescribing patterns of antihypertensive drugs.[3] While some of the studies are now outdated, other studies have been either limited in scope, restricted to a short calendar time period, or have been wide-ranging, rendering unclear the contributions of each class to the overall prescribing landscape.[3,22-24] While these studies add valuable contributions, there is still a need to better understand prescription patterns more comprehensively.

Thiazide diuretics and dCCBs represent two of the first drug classes indicated for use in hypertension. Thiazide diuretics are a prevalent class of antihypertensive drugs with over sixty years of prescribing history, prescribed to nearly 10% of the adult population.[3,25] Similarly, dCCBs have been approved for more than three decades and remain a first-line choice for hypertension.[26,27] As long-term pharmacological management of hypertension is common,[28] three large meta-analyses of randomized controlled trials (RCTs) have investigated the safety of antihypertensive drugs with respect to cancer outcomes.[29-31] One meta-analysis reported an odds ratio (OR) of 1.06 (95% confidence interval (CI): 1.01-1.12) with dCCBs for any cancer,[30] while one meta-analysis reported a hazard ratio (HR) of 1.06 (95% CI: 1.01-1.11) with CCBs (including dCCBs and non-dCCBs) for any cancer.[31] Both meta-analyses concluded that excess risk for dCCBs and other CCBs could not be ruled out.[30,31] Additionally, only one of the three meta-analyses investigated site-specific cancers, which included colorectal, breast, lung, prostate, and skin cancers.[31] This meta-analysis reported a numerically elevated HR for colorectal cancer with thiazide diuretics compared with other antihypertensive drugs (HR: 1.17, 95% CI: 0.96-1.41), although with a CI crossing the null value.[31]

Important pharmacoepidemiologic questions remain in light of these findings. First, the increased risk of any cancer for dCCBs reported in meta-analyses generates important concerns

about the cancer safety of this drug class and highlights the need to investigate whether this increased risk is attributed to a specific cancer site.[30,31] Second, only one meta-analysis of RCTs reported site-specific cancers, which was limited to five cancer sites.[31] Therefore, there remains critical evidence gaps in the long-term cancer safety of dCCBs, along with a need to specifically investigate the numerically elevated effect estimate reported for thiazide diuretics and colorectal cancer.

Indeed, observational studies investigating the association between antihypertensive drugs and risk of cancer have generated conflicting findings. Studies assessing the association between thiazide diuretics and colorectal cancer have reported either protective,[32] null,[32-37] or elevated effect estimates.[33,35,38,39] Recent studies also reported an increased risk of pancreatic cancer associated with CCBs (dCCBs and non-dCCBs), with effect estimates ranging between 1.10-2.07,[40-42] although these studies combined dCCBs with non-dCCBs together as one group. Overall, most of these observational studies included non-users as the comparator group, rendering their clinical utility challenging as hypertension often requires pharmacologic treatment.[1] Additionally, using non-users as the comparator group can introduce important confounding by indication, and when possible, the use of an active comparator group is recommended.[43] Some of these studies also had important methodological limitations such as immortal time bias, the inclusion of prevalent users, recall bias, and latency bias, limiting the conclusions drawn from the findings. Therefore, despite the long-standing prescribing history of thiazide diuretics and dCCBs, strong evidence of their long-term cancer safety is largely lacking, especially for gastrointestinal cancers such as colorectal cancer and pancreatic cancer.

1.2 Research objectives

The overall purpose of this thesis was to address some of the knowledge gaps in the prescribing patterns of antihypertensive drugs and generate new evidence on the long-term gastrointestinal cancer safety of thiazide diuretics and dCCBs. Three objectives were specifically defined to achieve this goal:

1. To describe the treatment and prescribing trends of antihypertensive drugs in primary care practices over time (Chapter 4).
2. To evaluate the association between thiazide diuretics and the risk of colorectal cancer, when compared with dCCBs (Chapter 5).
3. To assess the association between dCCBs and the risk of pancreatic cancer, when compared with thiazide diuretics (Chapter 6).

1.3 Thesis organization

This is a manuscript-based thesis organized around nine chapters. Chapter 2 introduces the background relating to antihypertensive drugs and gastrointestinal cancers. Chapter 3 provides an overview of the data source used for this thesis, the United Kingdom (UK) Clinical Practice Research Datalink (CPRD) Gp OnLine Data (GOLD), and provides further details of the methodology employed in the three manuscripts. Chapter 4 presents a population-based cohort study on the treatment and prescribing trends of antihypertensive drugs in UK primary care patients over a 31-year period (Manuscript 1). Chapter 5 presents a population-based cohort study examining the association between thiazide diuretics and the risk of colorectal cancer compared with dCCBs (Manuscript 2). Chapter 6 presents a population-based cohort study investigating the

association between dCCBs and the risk of pancreatic cancer compared with thiazide diuretics (Manuscript 3). Chapter 7 provides an overview of the findings, a discussion on the strengths and limitations of the research, implications of the findings, and future directions. Chapter 8 provides a reference list for Chapters 1 to 3 and 7, while references for Chapters 4 to 6 are provided within their corresponding manuscripts. Chapter 9 contains the ethics approval certificates.

CHAPTER 2. BACKGROUND

2.1. Overview of hypertension

2.1.1 Epidemiology of hypertension

Hypertension, or high blood pressure, is the leading contributor to disability-adjusted life years in the world in women and the second leading contributor in men.[44] It is estimated that approximately 1.3 billion adults between the ages of 30-79 have hypertension.[1] Indeed, a large pooled analysis of 104 million primary care patients found that the age-standardized prevalence of hypertension doubled between 1990 and 2019 in primary care patients aged 30-79.[1] Countries such as Canada, Peru, and the UK (in women only) reported the lowest prevalence of hypertension, with less than 25% of its primary care population.[1] In Canada, approximately 6 million adults have hypertension, representing 22.6% of the adult population, with increasing prevalence over time.[2] Non-modifiable risk factors for hypertension include age, sex, family history, ethnicity, and comorbidities such as diabetes and chronic kidney disease.[45,46] Modifiable risk factors include a diet high in salt/sugar/fat, physical inactivity, smoking, high alcohol consumption, and obesity.[45-47]

2.1.2 Diagnosis and management of hypertension

Blood pressure measurement includes systolic and diastolic blood pressure readings. Generally, a diagnosis of hypertension involves a systolic blood pressure reading equal to or greater than 140 mmHg and/or a diastolic blood pressure reading equal to or greater than 90 mmHg, although variations exist in the thresholds across different patient populations, countries, and time periods. Since 1999 in the UK, the National Institute for Health and Care Excellence/British and Irish Hypertension Society has determined high blood pressure to represent

a threshold of 140/90 mmHg.[11,48-51] Prior to that decision, thresholds were 160 mmHg and 100 mmHg for systolic and diastolic blood pressure, respectively.[52,53] In 2017, the American College of Cardiology/American Heart Association changed thresholds for stage 1 hypertension from 140/90 mmHg to 130/80 mmHg.[12] Similarly, Hypertension Canada lowered the high blood pressure thresholds to 130/80 mmHg from 140/90 mmHg in 2020.[10]

In patients with documented hypertension, changes in health behaviours are first recommended as disease management through increased physical activity, healthier diet, weight reduction, and smoking cessation.[10-12] Pharmacological management of hypertension through the use of antihypertensive drugs is recommended when blood pressure cannot be reduced through these lifestyle interventions.[10-12]

2.2 Overview of major antihypertensive drug classes

There are five major classes of antihypertensive drugs, which include thiazide diuretics, CCBs, renin-angiotensin-aldosterone system (RAAS) inhibitors primarily composed of ACE inhibitors and ARBs, and beta-blockers.[54] Although there exist some differences in the recommended pharmacological management of hypertension, guidelines from the American College of Cardiology/American Heart Association, Hypertension Canada, National Institute for Health and Care Excellence/British and Irish Hypertension Society, the European Society of Cardiology/European Society of Hypertension, and the International Society of Hypertension recommend initiating any of those five antihypertensive drug classes (guidelines from Hypertension Canada in **Figure 2.1**).[10-14] Other antihypertensive drugs also exist, which include diuretics other than thiazide diuretics (i.e., loop diuretics, potassium-sparing diuretics, and mineralocorticoid-receptor antagonists), direct renin inhibitors (i.e., aliskiren, a newer class of

RAAS inhibitors),[55] alpha-1 blockers, centrally acting alpha agonists (i.e., clonidine), direct-acting vasodilators (i.e., hydralazine, minoxidil), and ganglion-blocking agents, although these classes are not commonly prescribed as first-line treatment for the management of hypertension.[46,54]

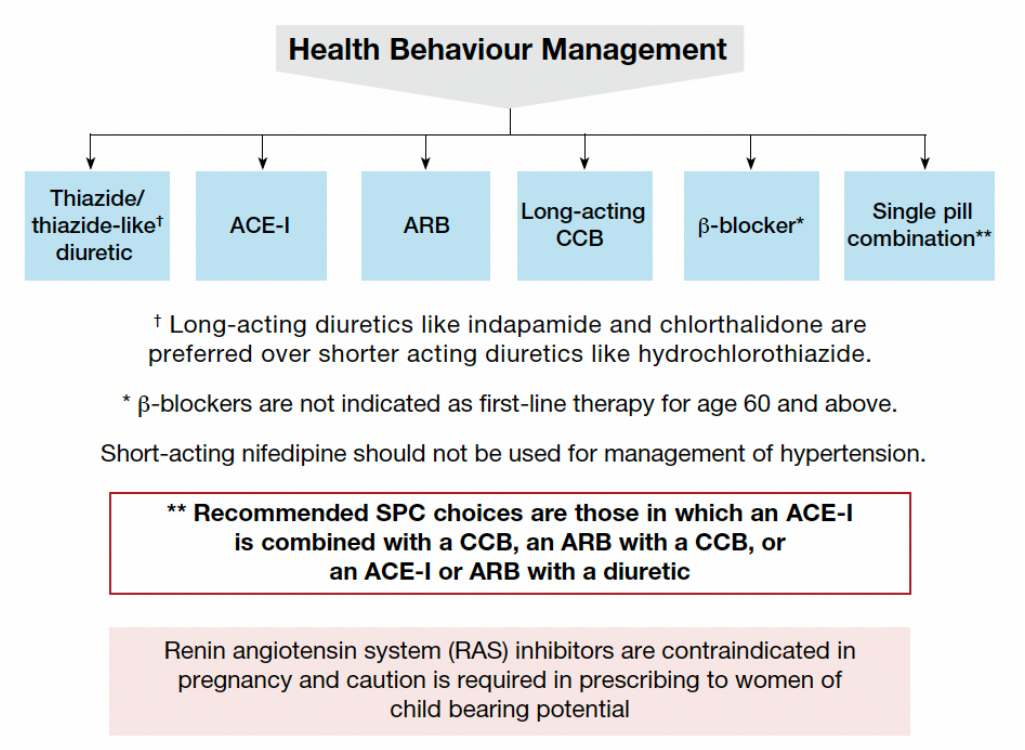

Figure 2.1 Hypertension Canada guidelines for first line treatment of adults with systolic/diastolic hypertension without other compelling indications.[10,56]

2.2.1. Thiazide diuretics

The nephron is the functional unit of the kidney that contains the glomerulus and the renal tubule. The renal tubule is divided into the proximal tubule, the loop of Henle, the distal convoluted tubule, and the collecting duct.[57] Each component is responsible for a portion of sodium reabsorption.[57] Approximately 5% of sodium reabsorption occurs in the distal convoluted tubule through the sodium-chloride cotransporter, which is responsible for sodium transport from the lumen to the interstitium through the activation of the ATP-dependent sodium-potassium

pump.[58,59] The macula densa is a group of specialized epithelial cells that plays a role in regulating the glomerular filtration rate through the tubuloglomerular feedback mechanism.[58] The distal convoluted tubule, being located after the macula densa on the nephron, constitutes the first segment of the nephron where the rate of sodium reabsorption is not regulated by the feedback mechanism.[58] As a portion of sodium reabsorption is mediated by the distal convoluted tubule, any inhibition of sodium transport would impact the concentration of urinary sodium, fluid losses, and arterial blood pressure.[58] Thiazide diuretics are diuretics that directly act in the distal convoluted tubule by blocking the sodium-chloride cotransporter, thus inhibiting sodium reabsorption (**Figure 2.2**).[59,60] The initial mechanism of action of thiazide diuretics is therefore to cause volume depletion through increased urinary sodium concentration and decreased cardiac preload and output.[58,59,61] However, the mechanism by which thiazide diuretics have a persistent impact on blood pressure is still not fully understood despite being prescribed for more than sixty years.[25,59,61] It has been suggested that the persistent reduction in blood pressure might be exerted through either a distinct direct vasodilatory effect rather than a diuretic effect or through an indirect action consequent to the chronic decrease in plasma volume and cardiac output, leading to a vasodilatory adaptation by the blood vessels.[59,61]

Thiazide diuretics can be divided into two groups depending on their chemical properties. Thiazide-type and thiazide-like diuretics are both thiazide diuretics, although thiazide-like diuretics lack the benzothiadiazine molecular structure.[62] Thiazide-type diuretics include hydrochlorothiazide, chlorothiazide, bendroflumethiazide, trichlormethiazide, methyclothiazide, polythiazide, quinethazone, benzthiazide, hydroflumethiazide, and cyclopenthiazide, whereas thiazide-like diuretics include mefruside, indapamide, chlorthalidone, clopamide, xipamide and metolazone. Both groups have the same mechanism of action and are indicated as first-, second-,

and third-line drugs for the management of hypertension.[10-13,62] In addition to hypertension, thiazide diuretics are indicated for the management of oedema due to conditions such as chronic heart failure, chronic kidney disease, nephrotic syndrome, acute glomerulonephritis, and hepatic cirrhosis, or medications such as estrogen therapy and corticosteroids.[60] Additionally, thiazide diuretics are used in the management of nephrolithiasis due to idiopathic hypercalciuria, osteoporosis, and nephrogenic diabetes insipidus.[60,63]

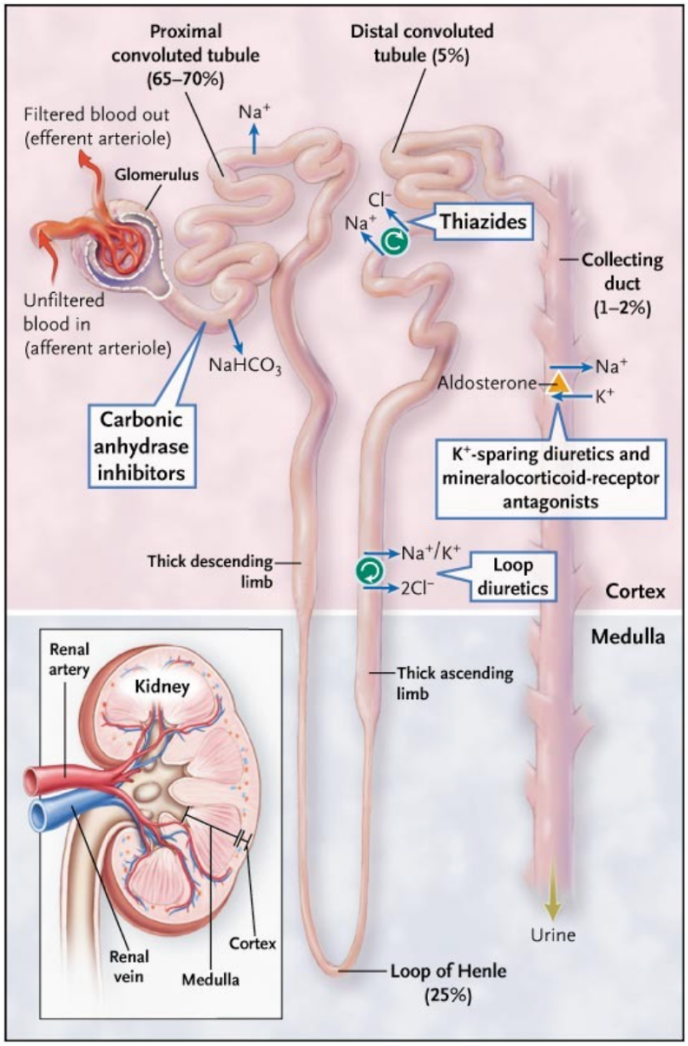

Figure 2.2 Site of action of thiazide diuretics and other diuretics in the nephron, with the percentage of sodium reabsorption in parentheses. Reproduced with permission from Ernst (2009).[59] Copyright Massachusetts Medical Society.

2.2.2. Calcium channel blockers

Intracellular calcium is a necessary element for the regulation of cardiac muscular contraction.[64] In the myocardium (i.e., the muscle layer of the heart or cardiac muscle) and vascular smooth muscles, L-type calcium channels are the predominant calcium channels, which are transmembrane voltage-gated protein complexes that regulate the entry of calcium ions into the cell.[64] L-type calcium channels are also present in the brain, skeletal muscle, and pancreas.[65,66] Calcium thus enters the cardiac muscle cell membrane (i.e., cardiomyocyte) through these L-type calcium channels.[64] CCBs act by binding to the L-type voltage-gated calcium channels,[65] which reduces the amount of calcium passing through the cell membrane. This creates vasodilation, which increases oxygenated blood and decreases blood pressure. Some CCBs also cause negative inotropic effects by blocking calcium entry into the conducting cells of the heart, slowing the heart rate. CCBs are classified as either dihydropyridine calcium channel blockers (dCCBs) or non-dihydropyridine calcium channel blockers (non-dCCBs), depending on their physiologic effect.[65] dCCBs are vascular selective in which they primarily cause peripheral vasodilation.[65] In contrast, non-dCCBs are mainly myocardial selective and have anti-arrhythmic properties, causing the inhibition of the sinoatrial and atrioventricular nodes to reduce heart rate.[65]

The first CCBs were approved over thirty years ago, starting with the non-dCCB verapamil in 1982 and the dCCB amlodipine in 1987.[67-69] dCCBs include amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, and nisoldipine. dCCBs are primarily indicated for the management of hypertension and chronic stable angina, and are also used in Raynaud's disease and post-subarachnoid hemorrhage.[65] Non-dCCBs include verapamil and diltiazem and are indicated for the management of hypertension, chronic stable angina, and cardiac arrhythmias due to their effect on heart function.[65] Although both dCCB and non-dCCBs

are indicated for the management of hypertension, dCCBs are preferred over non-dCCBs due to their more potent vasodilatory effect.[10,12,13]

2.2.3. Renin-angiotensin-aldosterone system inhibitors

Renin-angiotensin-aldosterone system (RAAS) inhibitors are a group of drugs that have an inhibitory effect on RAAS, composed of ACE inhibitors, ARBs, and direct renin inhibitors.[54] Renin is an enzyme responsible for regulating blood pressure and secreted by the juxtaglomerular kidney cells.[70] It is responsible for converting angiotensinogen to angiotensin I, which is converted to angiotensin II by the angiotensin-converting enzyme.[55] Angiotensin II binds to the angiotensin I receptor type, a receptor responsible for vasoconstriction, aldosterone synthesis and secretion, and vasopressin secretion.[55] ACE inhibitors act by inhibiting the angiotensin-converting enzyme, causing a reduction in the production of angiotensin II, and by inhibiting the degradation of bradykinin, a peptide vasodilator, thus lowering blood pressure.[71] The mechanism of action of ARBs differs from ACE inhibitors. ARBs use competitive antagonism of the angiotensin II receptors by selectively blocking the binding of angiotensin II to the angiotensin I receptor type, thus inhibiting the effect of angiotensin II.[72] In contrast to ACE inhibitors, ARBs do not affect the degradation of bradykinin. Finally, direct renin inhibitors block the conversion of angiotensinogen to angiotensin I, causing a decrease in the formation of angiotensin II.[55]

ACE inhibitors have been used for the treatment of hypertension since the 1980s.[73] ACE inhibitors include captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril. ARBs were approved in 1995,[74] and include candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan. Direct renin inhibitors include only one agent, aliskiren, which was approved in 2007.[55] Both ACE inhibitors

and ARBs are indicated in the treatment of hypertension (especially in diabetic patients to prevent diabetic nephropathy), heart failure, chronic kidney disease, left ventricular dysfunction, and ST-elevation myocardial infarction.[54] Although aliskiren is approved for the management of hypertension, it is currently mainly used as an add-on therapy.[55]

2.2.4. Beta-blockers

There are two types of beta receptors relevant to the mechanism of action of beta-blockers. These include beta-1 receptors, which are located primarily in the myocardium and mediate cardiac activity, and beta-2 receptors in the vascular smooth muscles and regulate vasodilation.[75] Beta-blockers act by inhibiting norepinephrine and epinephrine from binding to the beta 1 and beta 2 receptors.[75] Beta-blockers are thus categorized into two groups depending on their receptor-specific effect: cardio-selective beta-blockers, which include atenolol, bisoprolol, metoprolol, and esmolol, bind to the beta-1 receptors, thus inducing arterial vasodilation and decreased heart rate, whereas non-cardioselective beta-blockers, which include propranolol, carvedilol, sotalol, and labetalol, bind to both beta-1 and beta-2 receptors.[75]

Beta-blockers have been used for over sixty years and have been a mainstay drug for treating cardiac arrhythmias.[76] Although this class of drug is indicated for the management of hypertension, beta-blockers are only currently recommended as first-line agents in patients aged 60 and younger and with specific indications such as heart failure and myocardial infarction.[10,46,77] They are also used for the treatment of ischemic heart disease, migraine, and anxiety.[76]

2.3. Epidemiology of antihypertensive drugs

Antihypertensive drugs are among the most commonly prescribed drugs worldwide, with a prevalence ranging between 8% and 35% of the adult population.[3-8] In a large pooled analysis of 104 million primary care individuals, Canada, South Korea and Iceland represented countries with the highest treatment rates in the world, with over 70% of patients with hypertension receiving treatment and over 50% having their hypertension controlled (i.e., adequately treated).[1] Despite the high prevalence of antihypertensive drugs, however, there is a lack of studies documenting the prescribing patterns of these drugs.[3] The few studies that have described prescription trends of antihypertensive drugs have been limited to defining trends within a specific region, clinical population, or time period, have been either very specific (e.g., with a focus on one class) or broad in scope (e.g., trends in antihypertensive drugs overall), or are currently outdated.[3,22-24] While these studies add value to the prescription patterns landscape, there is still a need to better understand prescription patterns at a larger scale and more comprehensively.

In the UK, previous studies have described prescribing trends of antihypertensive drugs in primary care practices, although these trends were reported for specific patient populations, indications, drug classes, or over short calendar time periods.[9,23,78-91] One study examining prescription trends over a 6-year period reported that prescriptions for thiazide diuretics decreased between 2006 and 2012, while prescriptions for ACE inhibitors and CCBs increased.[23] Similarly, a previous UK study showed a decrease in the number of thiazide prescriptions between 2010 and 2016/2017.[79] Changes in UK hypertension treatment guidelines, notably in 2004 when ACE inhibitors and CCBs were newly recommended as first-line treatment for hypertension along with thiazide diuretics and beta-blockers,[49] may have contributed to this decline. The first guideline, published by the British Hypertension Society in 1989, recommended thiazide diuretics and beta-

blockers as first-line treatments.[52] Similar recommendations were made in subsequent guidelines,[48,53] although ACE inhibitors, CCBs, and later ARBs were considered potential options. As more evidence became available from RCTs and hypertension treatment became more complex,[92-109] the National Institute for Health and Care Excellence/British and Irish Hypertension Society published four new guidelines and updates (2004, 2006, 2011, 2019) recommending ACE inhibitors, ARBs, and CCBs as first-line agents and introducing treatment choice based on age and ethnicity.[49-51,110] However, no studies have comprehensively described the changes in prescribing practices over extended time periods that allow for an overview of the changing prescription landscape between the publication of the first hypertension guideline in 1989 to today.

In Canada, a study of three population-based cross-sectional surveys of adults with hypertension reported an increase in hypertension treatment from 34.6% (95% CI: 29.2%-40.0%) in 1986 to 79.0% (95% CI: 71.3%-86.7%) in 2009.[111] An Ontario study reported that antihypertensive prescriptions rose by 58% between 1998-2003, with an increase for thiazide diuretics, CCBs, and beta-blockers after 1999.[112] Two longitudinal studies using the Intercontinental Medical Statistics Health database, which contains prescriptions data through retail pharmacies, found that prescriptions for antihypertensive drugs increased by 106.2% from 1996 to 2006,[113] with an increase by 4,054% for ARBs, 127% for thiazide diuretics, 108% for ACE inhibitors, 55% for CCBs, and 87% for beta-blockers.[114] Another 2016 study using the Intercontinental Medical Statistics Health database showed that the number of prescriptions dispensed increased between 2007 and 2014 in Canada, from 68 million prescriptions to 87 million.[2] A 2022 cross-sectional study of Canadian adults aged 20-79 reported that 23.2% (95% CI: 22.1%-24.4%) had hypertension, and 79.1% (95% CI: 76.4%-81.8%) were treated with at least one antihypertensive drug.[115] Among those treated, RAAS inhibitors and thiazide diuretics were

the most commonly prescribed classes, with 75.3% (95% CI: 73.1%-77.5%) using RAAS inhibitors, 42.0% (95% CI: 39.6%-44.5%) using diuretics, 25.8% (95% CI: 23.7%-27.9%) using CCBs, 24.6% (95% CI: 22.6%-26.6%) using beta-blockers, and 8.9% (95% CI: 7.3%-10.4%) using other antihypertensive drugs.[115] Similarly, a cross-sectional study using primary care data reported a prescription prevalence of 24.2% among primary care patients.[8] Prescription patterns were similar in the United States, with previous studies reporting an increase in the prescription rates of ACE inhibitors over time, and thiazide diuretics representing the second most commonly prescribed class of antihypertensive drugs (30% of all prescriptions).[3,116] Thiazide and thiazide-like diuretics were also reported to be the most commonly prescribed class of diuretic prescriptions.[3,117]

As prescribing practices in primary care settings continually change in light of new guidelines, approval of new antihypertensive drugs, and introduction of new policies, reporting the prescription patterns of antihypertensive drugs represents an important contribution to the understanding of antihypertensive treatments. Despite the prevalence of antihypertensive drugs, however, few studies have described the prescribing trends of these drugs over time. Thus, an updated and comprehensive evaluation of the prescription patterns of antihypertensive drugs is critically needed to address these current knowledge gaps.

2.4. Efficacy, effectiveness, and safety of antihypertensive drugs

2.4.1 Efficacy and effectiveness of antihypertensive drugs

Overall, most guidelines recommend initiating treatment for hypertension with any of the major antihypertensive drug classes, including thiazide diuretics, CCBs, ACE inhibitors, ARBs, and beta-blockers.[10-14] Additionally, the American College of Cardiology/American Heart

Association, Hypertension Canada, and the International Society of Hypertension guidelines more specifically recommend the use of dCCBs over non-dCCBs as a first-line treatment due to their more potent vasodilatory effect.[10,12,13] In meta-analyses of RCTs, these five classes have been found to produce similar reductions in blood pressure and to be equally effective in the primary prevention of cardiovascular disease.[15-21]

Outside of RCTs, there have been contemporary efforts to investigate the comparative effectiveness of antihypertensive drugs from population-based studies, notably through the development of LEGEND-HTN, a large-scale partnership including a network of databases from multiple countries to generate evidence on the effectiveness and safety of antihypertensive drugs.[118,119] One LEGEND-HTN study of 4.9 million patients assessed the comparative effectiveness of new users of thiazide diuretics, dCCBs, non-dCCBs, ACE inhibitors, and ARBs with respect to acute myocardial infarction, hospitalization for heart failure, and stroke (**Figure 2.3**).[118] Similarly to RCTs, the study reported no overall difference in effectiveness between classes, although there was some evidence of cardiovascular benefits for thiazide diuretics over ACE inhibitors.[118] Importantly, non-dCCBs were significantly inferior than dCCBs, thiazide diuretics, ACE inhibitors, and ARBs for myocardial infarction, heart failure, and stroke, further suggesting that when CCBs are indicated, dCCBs should be the preferred choice over non-dCCBs.[118] Another large LEGEND-HTN study of 2.9 million patients found no statistically significant differences between first-line new-users of ACE inhibitors and ARBs with respect to outcomes of myocardial infarction, heart failure, and stroke.[119]

	Comparator	Acute myocardial infarction	Hospitalisation for heart failure	Stroke
THZ	ACEi	0·84 (0·75–0·95), 0·01	0·83 (0·74–0·95), 0·01	0·83 (0·74–0·95), 0·01
THZ	ARB	0·93 (0·81–1·11), 0·41	0·90 (0·79–1·06), 0·19	0·93 (0·80–1·11), 0·41
THZ	dCCB	0·90 (0·81–1·02), 0·14	0·90 (0·80–1·04), 0·18	0·89 (0·79–1·03), 0·14
THZ	ndCCB	0·70 (0·59–0·84), <0·01	0·58 (0·52–0·65), <0·01	0·78 (0·71–0·87) 0·01
ACEi	ARB	1·11 (0·95–1·32), 0·20	1·05 (0·88–1·26), 0·60	1·07 (0·92–1·27), 0·38
ACEi	dCCB	1·08 (0·96–1·22), 0·18	1·08 (0·94–1·25), 0·24	1·05 (0·93–1·21), 0·38
ACEi	ndCCB	0·87 (0·77–1·00), 0·04	0·68 (0·60–0·78), <0·01	0·89 (0·82–0·98), 0·02
ARB	dCCB	0·95 (0·80–1·14), 0·69	1·04 (0·86–1·26), 0·66	0·99 (0·83–1·19), 0·93
ARB	ndCCB	0·78 (0·69–0·91), 0·01	0·71 (0·64–0·80), <0·01	0·84 (0·73–0·97), 0·05
dCCB	ndCCB	0·84 (0·76–0·93), <0·01	0·73 (0·68–0·78), <0·01	0·87 (0·79–0·96), 0·01

Data are HR (95% CI), p value. Estimates were calibrated to reduce residual bias and report the HR for patients in the target cohort relative to comparator cohort. HRs of less than 1 favour target. THZ=thiazide or thiazide-like diuretics. ACEi=angiotensin-converting enzyme inhibitors. ARB=angiotensin receptor blockers. dCCB=dihydropyridine calcium channel blockers. ndCCB=non-dihydropyridine calcium channel blockers. HR=hazard ratio.

Table 3: **Meta-analytic HR estimates and their 95% CIs comparing the relative risk of highlighted cardiovascular efficacy outcomes between target and comparator in new users of first-line antihypertensive drug classes**

Figure 2.3 Meta-analytic hazard ratios and 95% confidence intervals comparing the exposed group (first column) with the comparator group (second column) in initiators of antihypertensive drugs. Reprinted from Suchard (2019)[118] with permission from Elsevier. Copyright Elsevier 2022.

2.4.2 Short-term safety of antihypertensive drugs

Several RCTs have assessed the safety of antihypertensive drugs as part of their efficacy protocol. Indeed, large meta-analysis of 58 RCTs reported that compared with placebo, antihypertensive drugs were not associated with an increased risk of falls (summary risk ratio (RR): 1.05, 95% CI: 0.89-1.24), but were associated with an increased risk of acute kidney injury (summary RR: 1.18, 95% CI: 1.01-1.39), hyperkalemia (summary RR: 1.89, 95% CI 1.56-2.30), hypotension (summary RR: 1.97, 95% CI: 1.67-2.32), and syncope (summary RR: 1.28, 95% CI: 1.03-1.59).[120]

In observational studies, a population-based cohort study of 4.9 million new users of antihypertensive drugs reported that thiazide diuretics were associated with a higher risk of hypokalemia and hyponatremia compared with ACE inhibitors, ARBs, dCCBs, and non-dCCBs, with HRs ranging from 1.8-2.9.[118] ACE inhibitors have been shown in meta-analyses of RCTs to induce cough and angioedema.[102,121] In a large population-based cohort study, ACE inhibitors were also associated with an increased risk of acute pancreatitis, compared with dCCBs (HR: 1.45, 95% CI: 1.15-1.83).[122]

2.4.3 Long-term cancer safety of antihypertensive drugs

To date, three large meta-analyses of RCTs have also assessed the safety of antihypertensive drugs with respect to cancer outcomes.[29-31] The first meta-analysis, which included 27 RCTs with a placebo comparison group, reported no association between thiazide diuretics, CCBs, ACE inhibitors, ARBs, beta-blockers and risk of cancer, with odd ratios (ORs) ranging between 0.94-1.12.[29] Similarly, a meta-analysis identified 70 RCTs of antihypertensive drugs and placebo, and reported no association between the five classes of drugs and risk of cancer (ORs ranging between 0.97-1.05) or cancer mortality (ORs ranging between 0.93-1.08), although a 15% increased risk of any cancer for the ACE inhibitor and ARBs combination was reported (OR: 1.15, 95% CI: 1.02-1.28), as well as a 6% increased risk for dCCBs (OR: 1.06, 95% CI: 1.01-1.12).[30] More recently, a meta-analysis including 33 trials with long-term follow-up investigated the association between antihypertensive drugs and risk of cancer. Findings showed no association between ACE inhibitors, ARBs, beta-blockers and risk of any cancer, with HRs ranging between of 0.95-1.01, except for CCBs (HR: 1.06, 95% CI: 1.01-1.11). Both meta-analyses concluded that an excess risk for CCBs, particularly for the dCCB class, could not be ruled out.[30,31] Of the three

meta-analyses that have investigated the association between antihypertensive drugs and cancer, only one reported site-specific cancers (breast, colorectal, lung, prostate, and skin cancer).[31] This meta-analysis reported a numerically elevated effect estimate for colorectal cancer when comparing thiazide diuretics with other antihypertensive drugs, although the CI crossed the null value (HR: 1.17, 95% CI: 0.96-1.41).[31]

While the findings of these meta-analyses of RCTs are informative, it is important to note that they have important limitations. First, none of the RCTs included in the three meta-analyses were designed to assess cancer safety outcomes.[29-31] Second, only one RCT captured site-specific cancers, and few patients were included in RCTs.[31] Third, the reported duration of follow-up was relatively short, with 75% of RCTs having a follow-up of less than five years in the site-specific meta-analysis.[31] Finally, interpretation of the findings to the real-world population is difficult considering the careful selection and monitoring of patients included in those RCTs.

Additional questions remain. First, two of the three meta-analyses reported an increased risk for any cancer in CCBs, particularly for dCCBs, generating concerns on the long-term safety of this drug class with respect to cancer. This further highlights the need for specific investigations to determine whether an association exist between dCCBs and risk of cancer. Importantly, studies specifically designed to assess potential site-specific cancer risk should be prioritized.[30,31] Second, only one meta-analysis of RCTs reported site-specific cancers, which only included five cancer sites.[31] Therefore, there remains critical evidence gaps in the long-term cancer safety of dCCBs, along with a need to specifically investigate the numerically elevated effect estimate reported for thiazide diuretics and colorectal cancer.

To date, population-based studies that have examined the safety of thiazide diuretic with respect to colorectal cancer generated conflicting findings, yielding either protective,[32] null,[32-37] or

elevated effect estimates.[33,35,38,39] Recently, observational studies investigating the association between antihypertensive drugs and risk of cancer have reported a possible association between CCBs (overall) and an increased risk of pancreatic cancer, with effect estimates ranging between 1.10-2.07.[40-42] These studies will be described in greater detail in **Section 2.6.1 Thiazide diuretics and risk of colorectal cancer**, and in **Section 2.6.2 Dihydropyridine calcium channel blockers and risk of pancreatic cancer**. Overall, several of these studies lacked an active comparator group, potentially introducing confounding by indication and rendering the clinical utility of those studies challenging as hypertension often requires pharmacologic treatment.[1] Further, potentially important methodological biases were present in some of these studies, including immortal time bias, prevalent user bias, and latency bias.

Thus, despite the long-standing prescribing history of thiazide diuretics and dCCBs, strong evidence of their long-term cancer safety is largely lacking, especially for gastrointestinal cancers such as colorectal cancer and pancreatic cancer. As such, there is a need for stronger evidence from specifically designed, large population-based studies with new-user, active comparator design to determine whether specific antihypertensive drug classes are associated with an increased risk of cancer, particularly with respect to colorectal and pancreatic cancers.

2.5 Epidemiology of gastrointestinal cancers

Large meta-analyses of RCTs reported that thiazide diuretics were associated with a numerically elevated risk of colorectal cancer, and that CCBs, particularly dCCBs, were associated with an increased risk of any cancer.[30,31] Although pancreatic cancer was not captured in those meta-analyses, previous observational studies investigating the association between antihypertensive drugs and site-specific cancers reported an elevated risk specifically for

pancreatic cancer in users of CCBs (overall).[40-42] The association between those two antihypertensive drug classes and those specific gastrointestinal cancers thus warrant further investigation.

Gastrointestinal cancer refers to malignancies of the gastrointestinal tract and major organs of the digestive system, which include the esophagus, stomach, liver, biliary system (gallbladder and bile duct), pancreas, colon, and rectum.[123] In 2018, there were an estimated 4.8 million incident cases of gastrointestinal cancers and 3.4 million death from gastrointestinal cancers worldwide, representing 26% of all new cancer cases and 35% of cancer-related deaths, respectively.[124]

2.5.1 Colorectal cancer

The large intestine is the last segment of the gastrointestinal tract and includes the cecum, colon, rectum, and anal canal. Colorectal cancer is an adenocarcinoma originating from the epithelial lining of the colon and rectum.[125] Colorectal cancer is the third most common cancer worldwide, accounting for 1.9 million incident cases in 2020, or 10% of new cancer cases.[126] In men, it is the third most common cancer, behind lung and prostate cancer, and the second most common cancer in women, behind breast cancer.[126] In Canada and the UK, colorectal cancer is the third most common cancer behind prostate/breast and lung cancer, accounting for 12% of new cases in men and 10% of new cases in women.[127,128] It has an age-standardized incidence rate of 54.9 cases per 100,00 population in Canada and 69.3 cases per 100,000 population in the UK.[127,128] Reassuringly, however, the incidence of colorectal cancer has decreased by 4% since 2013 in Canada and by 6% since 2006 in the UK, in part due to colorectal cancer screening.[127,128] In terms of cancer mortality, colorectal cancer is the second most common cause of cancer deaths worldwide behind lung cancer, accounting for 9.4% of all cancer-related deaths, or 940,000

deaths.[126] Similarly, it is the second leading cause of cancer mortality in Canada (11% of all cancer deaths) and the UK (10% of all cancer deaths).[127,128] The five-year relative survival varies between 10%-92% depending on cancer stage.[128]

Non-modifiable risk factors for colorectal cancer include age[129] as well as hereditary and genetic factors including familial adenomatous polyposis, Lynch syndrome, Peutz-Jeghers syndrome, Li Fraumeni syndrome, juvenile polyposis syndrome, hereditary mixed polyposis syndrome, Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and cystic fibrosis.[130-134] History of polyps and inflammatory bowel disease are also important risk factors for colorectal cancer.[135,136] Modifiable risk factors include physical inactivity, obesity, high alcohol intake, smoking, consumption of processed and red meat, and radiation (X-rays and gamma rays).[125,137-139] In contrast, previous use of aspirin has been inversely associated with colorectal cancer risk.[140]

2.5.2 Pancreatic cancer

The pancreas is an organ located in the upper abdomen, playing an important role in digestion and blood glucose regulation. Pancreatic cancer originates from pancreatic duct cells, with pancreatic ductal adenocarcinoma accounting for more than 90% of pancreatic cancer cases.[141,142] The incidence of pancreatic cancer sharply increases after 40 years of age, from 0.8 case per 100,000 population in adults aged 35-39 to 2.3 cases per 100,000 population in adults aged 40-44.[127,143] It also varies widely between regions, with Europe, North America, Australia, and New Zealand having the highest incidence, ranging between 5.6-9.9 per 100,000 population.[126] Although pancreatic cancer accounts for only 3% of all cancer cases worldwide, it is an aggressive cancer with poor prognosis and a mortality nearly equal to its incidence.[126,127,143] It is the seventh leading cause of cancer mortality globally, and is expected to become the third leading cause of

cancer deaths in 2021 in Canada.[126,127] Only 25% of patients diagnosed with pancreatic cancer survive their first year after diagnosis, and the five-year survival rate recently reached nearly 10% for the first time in over 35 years.[127,142] As such, studies suggesting potential associations between prescription drugs and increased risk of pancreatic cancer,[40-42] as discussed in **2.4.3 Long-term cancer safety of antihypertensive drugs,** must be urgently and specifically investigated.

Non-modifiable risk factors for pancreatic cancer include age and sex.[144,145] Some genetic conditions have previously been associated with an elevated incidence of pancreatic cancer, including Lynch syndrome, hereditary pancreatitis, Peutz-Jeghers syndrome, familial atypical multiple mole and melanoma syndrome, ataxia-telangiectasia, hereditary breast and ovarian cancer syndrome, multiple endocrine neoplasia type 1, von Hippel Lindau syndrome, neurofibromatosis type 1, and cystic fibrosis.[146-149] Some diagnoses have also been associated with elevated incidence, such as chronic pancreatitis and diabetes.[145,150,151] There are also several modifiable risk factors for pancreatic cancer, with smoking having the strongest association with pancreatic cancer, followed by obesity, excessive alcohol consumption, and a diet high in fat and processed meats.[142,145,152,153]

2.6 Antihypertensive drugs and gastrointestinal cancers

2.6.1 Thiazide diuretics and risk of colorectal cancer

Although limited, there is some evidence that thiazide diuretics might play a role in colorectal cancer carcinogenesis. From a biological standpoint, previous studies have suggested that thiazide diuretics inhibit the human apical sodium-dependent transporter, whose primary role is in the intestinal reabsorption of secondary bile acids in the colon.[154,155] Bile acids are steroid acids synthesized in the gastrointestinal tract and are essential for the digestion and absorption of

fats and fat-soluble vitamins.[156] It has been suggested that impairing the intestinal reabsorption of bile acids through repeated exposure may lead to high concentration of bile acids in the colon, subsequently leading bile acids to induce DNA damage in epithelial cells, increasing apoptosis resistance in the mucosa, and promoting colorectal cancer.[156,157] As long-term pharmacological management of hypertension is common,[28] thiazide diuretics might thus play a role in colorectal cancer.[154,156,157]

However, despite more than six decades of prescribing history of diuretics and thiazide diuretics,[25] only eight observational studies have examined their safety with respect to colorectal cancer. A summary of all eight observational studies can be found in **Table 2.1**. The eight observational studies examining a possible association generated conflicting findings, yielding either protective,[32] null,[32-37] or elevated effect estimates.[33,35,38,39] A 2001 subgroup analysis of patients participating in a myocardial infarction prevention trial reported a near doubling of the risk of colorectal cancer associated with diuretics compared with non-use (HR: 1.96, 95% CI:1.21-3.17). When comparing patients using hydrochlorothiazide with non-users, the HR was 2.12 although with a wide CI crossing the null value (95% CI: 0.85-5.26).[39] A 2008 case-control study reported an OR of 1.00 (95% CI: 0.70-1.44) for colorectal cancer in ever-users of diuretics compared with non-users, and analyses by cancer type (colon, rectum) and duration of use (< 2 years, ≥ 2 years) did not show evidence of an association although confidence intervals were wide.[33] In contrast, when compared with diuretics and beta-blockers, a 2012 nested case-control study reported a decreased risk of colorectal cancer for ACE inhibitors (RR: 0.87, 95% CI: 0.81-0.93), ARBs (RR: 0.89, 95% CI 0.81-0.98), and CCBs (RR: 0.90, 95% CI: 0.84-0.97), potentially suggesting an increased risk for the diuretics/beta-blockers group rather than a decreased risk for ACE inhibitors, ARBs, and CCBs.[38] In a 2014 nested case-control study, Makar et al reported ORs

of 1.00 (95% CI 0.92-1.09) for colorectal cancer in individuals with less than three years of thiazide diuretic use, 0.93 (CI% 0.80-1.09) with three to five years of use, and 0.85 (95% CI 0.70-1.05) with more than five years of use, compared with non-use.[32] When the analysis was repeated with only users of any antihypertensive drugs as the comparator group, the OR ranged between 1.01-1.03 with confidence intervals crossing the null value. More recently, a cohort study found a HR of 0.92 (0.66-1.28) for post-colonoscopy colorectal cancer events in users of diuretics compared with non-users.[34] However, using post-colonoscopy as the start of follow-up rather than initiation of diuretics could have introduced immortal time bias and induced prevalent user bias.[158,159] Finally, a 2021 Women's Health Initiative cohort study reported elevated point estimates for colorectal cancer in users of ACE inhibitors, ARBs, and diuretics together compared with normotensive non-users (HR: 1.14, 95% CI: 0.90-1.44), compared with hypertensive non-users (HR: 1.15, 95% CI: 0.87-1.50), and compared with hypertensive users of any antihypertensive drugs (HR: 1.10, 95% CI: 0.87-1.39).[35]

Only two of the eight observational studies examined the colorectal cancer safety of thiazide diuretics using an active comparator and distinguishing between thiazide diuretics and all diuretics.[36,37] Of those, only one investigated whether the association varied with duration of use,[36] and none reported associations by individual agents within the thiazide diuretic class. One nested case-control study examining the long-term use of antihypertensive drugs and risk of colorectal cancer reported an OR of 0.87 (95% CI: 0.72-1.06) for thiazide diuretics when compared with CCBs, and an OR of 0.80 (95% CI: 0.54-1.20) after more than 7.5 years of use.[36] The second study found a HR of 1.00 (95% CI: 0.80-1.30) for RAAS inhibitors, which included both ACE inhibitors and ARBs, when compared with thiazide diuretics.[37] However, the median follow-up was only 2.2

years and important information was missing on strong risk factors for colorectal cancer such as smoking, obesity, and alcohol use.

Importantly, five of these eight observational studies combined users of different types of diuretics (thiazide diuretics, loop diuretics, potassium-sparing diuretics, and other diuretics),[33-35,38,39] which have different mechanisms of action, wide indications, and distinct patient populations.[160] These studies reported conflicting findings, with effect estimates ranging between 0.92-1.96 for colorectal cancer although most with wide CIs crossing the null value.[33-35,39] Further, five of these eight studies included non-users as the comparator group.[32-35,39] As no clear comparator groups were defined in such studies, it is difficult to assess the comparative safety of these drugs. Using non-users as the comparator group can introduce confounding by indication and when possible, the use of an active comparator group is recommended.[43] Additionally, some of these studies had important methodological limitations such as immortal time bias, inclusion of prevalent users, recall bias, confounding by indication, and latency bias, which limits the conclusion drawn from the findings.[158,159,161] Although three meta-analyses including those observational studies have recently been conducted, it is difficult to assess the reported pooled estimates given the important methodological limitations of the included studies, as discussed above.[162-164] Further, these meta-analyses only included studies with non-users as the comparator group, rendering a clinical comparison difficult.

To date, three large meta-analyses of RCTs examined the use of antihypertensive drugs and risk of cancer.[29-31] Only one meta-analysis included site-specific cancers however, which reported a 17% increased risk of colorectal cancer for thiazide diuretics compared with other antihypertensive drugs, with confidence intervals crossing the null value (95% CI: 0.96-1.41).[31] However, these meta-analyses of RCTs contained important limitations in the assessment of cancer

safety. First, none of the RCTs included in the three meta-analyses were designed to assess cancer safety outcomes.[29-31] Second, few RCTs provided a breakdown of site-specific cancers, limiting the sample size available to detect these outcomes.[31] Third, the reported duration of follow-up was relatively short, with 75% of RCTs having a follow-up of less than five years in the site-specific meta-analysis.[31] Finally, interpretation of the findings to the real-world population is difficult considering the careful selection and monitoring of patients included in those RCTs.

The association between thiazide diuretics and colorectal cancer has been understudied and warrants further investigation. This is particularly important given that colorectal cancer has the third highest incidence among all cancers.[165] Previous studies included important, conclusion-altering limitations such as short duration of follow-up, immortal time bias, prevalent user bias, confounding by indication, recall bias, and latency bias. Further, none of the studies were specifically designed to investigate the association between thiazide diuretics and risk of colorectal cancer using a clinically relevant, active comparator group. As such, there is a need to address those important knowledge gaps in the long-term safety of thiazide diuretics with respect to colorectal cancer while addressing the key limitations in previous studies.

Table 2.1 Observational studies of diuretics and risk of colorectal cancer

First Author (Year)	Study design	Study size	Exposure	Comparator	Outcome	Estimate (95% CI)	Main limitation
Tenenbaum (2001)	Cohort	12,370	Hydrochlorothiazide	Non-use	Colorectal cancer	HR: 2.12 (0.85-5.20)	Immortal time bias, Confounding by indication
		14,166	Diuretics	Non-use		HR: 1.96 (1.21-3.17)	
Assimes (2008)	Nested case-control	9,370	Thiazide diuretics	CCBs	Colorectal cancer	OR: 0.87 (0.72-1.06) >7.5 years of use: OR: 0.80 (0.54-1.20)	Few colorectal cancer events for comparator group, No adjustment for important risk factors (smoking, obesity, alcohol)
Boudreau (2008)	Case-control	1,330	Diuretics	Non-use	Colorectal cancer	OR: 1.00 (0.70-1.44) Colon: OR: 1.00 (0.68-1.48) Rectum: OR: 1.06 (0.42-2.70) <2 years of use: 1.13 (0.71-1.80) <2 years of use, colon: 1.08 (0.65-1.81) <2 years of use, rectum: 1.39 (0.44-4.33) >2 years of use: 0.91 (0.60-1.40) >2 years of use, colon: 0.95 (0.60-1.50) >2 years of use, rectum: 0.77 (0.23-2.60)	Confounding by indication, Latency bias
Azoulay (2012)	Nested case-control	86,636	CCBs	Diuretics + beta-blockers	Colorectal cancer	RR: 0.90 (0.84-0.97)	Difficult to distinguish effect of diuretics vs beta-blockers
Makar (2014)	Nested case-control	33,933	Thiazide diuretics	Non-use	Colorectal cancer	<3 years of use: OR: 1.00 (0.92-1.09) 3-5 years of use: OR: 0.93 (0.80-1.09) >5 years of use: OR: 0.85 (0.70-1.05)	Confounding by indication, Latency bias
		25,292		Use of any other		<3 years of use: OR: 1.03 (0.94-1.13)	

				antihypertensive drugs		3-5 years of use: OR: 1.01 (0.86-1.18) >5 years of use: OR: 1.01 (0.82-1.24)	
Htoo (2019)	Cohort	141,093	ACE inhibitors + ARBs	Thiazide diuretics	Colorectal cancer	HR: 1.00 (0.80-1.30)	Short follow-up, No adjustment for important risk factors (smoking, obesity, alcohol)
Cheung (2020)	Cohort	187,897	Diuretics	Non-use	Colorectal cancer	HR: 0.92 (0.66-1.28) Proximal colon HR: 0.67 (0.29-1.58) Distal colon HR: 0.98 (0.69-1.40)	Immortal time bias, Prevalent user bias, Confounding by indication
Brasky (2021)	Cohort	78,108	ACE inhibitors + ARBs + Diuretics	Non-use, normotensive individuals	Colorectal cancer	HR: 1.14 (0.90-1.44)	Confounding by indication, Prevalent user bias, Recall bias, Difficult to distinguish effect of diuretics vs ACE inhibitor/ARB
		20,286		Non-use, hypertensive individuals		HR: 1.15 (0.87-1.50)	
		31,340		Use of any antihypertensive drugs, hypertensive individuals		HR: 1.10 (0.87-1.39	

Abbreviations: ACE, angiotensin-converting enzyme; ARB; angiotensin II receptor blocker; CCBs, calcium channel blockers; CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, rate ratio

2.6.2. Dihydropyridine calcium channel blockers and risk of pancreatic cancer

The biological mechanisms behind a possible association between dCCBs and pancreatic cancer are limited and conflicting. It has been suggested that dCCBs may improve prognosis and survival in patients diagnosed with pancreatic cancer.[166] Indeed, high levels of soluble receptor for advanced glycation end products (sRAGE) might play a protective role in pancreatic cancer progression, and previous studies have shown that some CCBs increase sRAGE concentrations, thus inhibiting the pro-inflammatory RAGE signalling pathway.[167,168] In contrast, sRAGE levels have been reported to be significantly lower in users of some CCBs compared with users of other antihypertensive drugs and non-users.[40] Some studies have also suggested that dCCBs may inhibit apoptosis and promote tumor growth through the inhibition of DNA fragmentation.[169,170]

Although dCCBs have been approved for over thirty years,[26] only six observational studies to date have investigated a possible association between CCBs, including dCCBs and non-dCCBs, and pancreatic cancer.[40-42,171-173] Further, most studies did not distinguish between dCCBs and non-dCCBs. This is important because the American College of Cardiology/American Heart Association, Hypertension Canada, and the International Society of Hypertension guidelines more specifically recommend dCCBs over non-dCCBs as a first-line treatment for hypertension due to their more potent vasodilatory effects.[10,12,13] A summary of all six observational studies can be found in **Table 2.2**. Two earlier cohort studies assessing the incidence rate of pancreatic cancer in users of any CCBs (i.e., dCCBs and/or non-dCCBs) compared with the general Danish population reported standardized incidence rates of 1.20 (95% CI: 0.70-1.20) and 0.86 (95% CI: 0.57-1.25), respectively.[172,173] However, important risk factors for pancreatic cancer such as smoking and body mass index (BMI) could not be captured. In a case-control study, the use of any CCBs was not associated with an increased risk of pancreatic cancer (RR: 1.10, 95% CI: 0.70-1.80) compared

with non-users.[171] A higher point estimate was observed in patients who used any CCBs for >5 years (RR 1.80, 95% CI: 0.80-4.00), however, with wide CI crossing the null value.[171] More recently, a Women's Health Initiative cohort study of 145,551 menopausal women reported a HR of 1.20 (95% CI: 0.94-1.56) for pancreatic cancer in users of any CCBs compared with non-users, and a HR of 1.40 (95% CI: 1.10-1.78) when compared with users of other antihypertensive drugs.[40] When stratifying by duration of action (long-acting CCBs versus short-acting CCBs), users of short-acting CCBs had an increased risk of pancreatic cancer compared with users of other antihypertensive drugs (HR 1.66, 95% CI: 1.20-2.28), with a HR of 2.07 (95% CI: 1.42-3.02) associated with more than three years of short-acting CCBs use, with dCCBs representing the majority of short-acting CCBs in that study.[40] A 2019 cohort study of 8,311 patients with chronic pancreatitis reported a HR of 1.56 (95% CI: 0.76-3.22) in any CCB users compared with non-users, although few pancreatic cancer events occurred in the patient population during the study period.[41] Finally, a 2021 cohort study of 70,549 patients reported a HR of 1.32 (95% CI: 0.79-2.20) in any CCB users compared with non-users.[42]

Importantly, only two of the six observational studies to date were specifically designed to investigate pancreatic cancer.[40,41] Of those, one study included only patients with chronic pancreatitis.[41] Although chronic pancreatitis is an important risk factor for pancreatic cancer, it represents a specific and small subset of the patient population using antihypertensive drugs.[150] Further, only one of those studies assessed a potential association by duration of use, which found an increased risk of pancreatic cancer, and none reported analyses by individual molecules.[40] Additionally, most studies did not distinguish between dCCBs and non-dCCBs. There is thus an important knowledge gap in understanding the association between dCCBs and pancreatic cancer. In addition, the observational studies had important, conclusion-altering biases that precluded from

drawing further conclusions, such as prevalent user bias, recall bias, latency bias, and confounding by indication through the use of non-users or the general population as the comparator group.[43,174] Using a clinically relevant, active comparator group constitutes an important study design feature in order to adequately assess the comparative safety of dCCBs.[43]

Another five observational studies investigating associations between CCBs (including dCCBs and non-dCCBs) and cancer have grouped pancreatic cancer with other cancers, such as smoking-related cancers or gastrointestinal cancers.[36,175-178] Combining different cancer sites into one category to form a composite outcome, similarly to composite endpoints in RCTs, may provide a statistical advantage through an increase in the number of events for that composite outcome, and statistical efficiency and precision around the reported effect estimate, especially if the cancer sites grouped together are uncommon.[179] However, it renders the interpretation of an association difficult, while still not providing clear evidence regarding potential associations between dCCBs and pancreatic cancer or any of the specific cancer sites. Among the five observational studies with composite cancer outcome that included pancreatic cancer, one study reported a RR of 1.68 (95% CI: 1.06-2.54) for smoking-related cancers which included lung, pancreatic, kidney, and bladder cancers,[176] while the other four studies had elevated effect estimates ranging from 1.01-2.50 with wide CIs crossing the null value.[36,175,177,178] Finally, one nested case-control study investigated the association between ACE inhibitors and ARBs and the risk of pancreatic cancer.[180] However, the comparator group included any other antihypertensive drug classes, including CCBs, limiting the conclusions drawn from this study with respect to dCCBs specifically.

Three large meta-analyses of RCTs to date have investigated the safety of antihypertensive drugs with respect to cancer outcomes.[29-31] One meta-analysis reported an OR of 1.06 (95% CI: 1.01-1.12) with dCCBs for any cancer,[30] while one recent meta-analysis reported a HR of 1.06

(95% CI: 1.01-1.11).[31] Both meta-analyses concluded that excess risk for CCBs, particularly for dCCBs, could not be ruled out, and that the risk of cancer for this drug class needed to be further investigated.[30,31] However, only one of the three meta-analyses investigated site-specific cancers, which included five cancer sites (colorectal, breast, lung, prostate, and skin) but not pancreatic cancer.[31] To date, no meta-analyses of RCTs have included pancreatic cancer. These meta-analyses of RCTs also contain important limitations in the assessment of cancer safety, as described in detail in **Section 2.4.3 Long-term cancer safety of antihypertensive drugs.**

Therefore, given the findings of an elevated risk of pancreatic cancer from observational studies and the lack of evidence from meta-analyses of RCTs, stronger evidence is needed to elucidate whether an association exists between dCCBs and pancreatic cancer. This is particularly important given that pancreatic cancer is the seventh leading cause of cancer death and dCCBs are commonly prescribed first-line antihypertensive drugs for the management of hypertension.[3,27,165] No studies to date have been specifically designed to assess the comparative safety of dCCBs and the risk of pancreatic cancer, or has used a clinically relevant comparator group to minimize confounding by indication. Further, as defined in **Section 2.2.2 Calcium channel blockers**, the use of dCCBs rather than any CCBs provides a more clinically relevant exposure group. Previous studies also had important limitations such as immortal time bias, prevalent user bias, and recall bias. Given the limited evidence available to date, there are still important gaps in our understanding of the long-term pancreatic cancer safety of dCCBs.

Table 2.2 Observational studies of calcium channel blockers and risk of pancreatic cancer

Studies including pancreatic cancer as a separate outcome							
First Author (Year)	**Study design**	**Study size**	**Exposure**	**Comparator**	**Outcome**	**Estimate (95% CI)**	**Main limitation**
Olsen (1997)	Cohort	17,911	CCBs	General population	Pancreatic cancer	SIR: 1.20 (0.70-1.20)	Confounding by indication, Missing important risk factors (smoking, obesity), Latency bias
Rosenberg (1998)	Case-control	16,005	CCBs	Non-use	Pancreatic cancer	RR: 1.10 (0.70-1.80) >5 years of use: RR: 1.80 (0.80-4.00)	Few pancreatic cancer events, Recall bias, Exposure misclassification
Sorensen (2000)	Cohort	23,167	CCBs	General population	Pancreatic cancer	SIR: 0.86 (0.57-1.25)	Confounding by indication, Missing important risk factors (smoking, obesity), Latency bias
Wang (2018)	Cohort	145,551	CCBs	Non-use	Pancreatic cancer	HR: 1.20 (0.94-1.56)	Confounding by indication, Recall bias, Exposure misclassification, Prevalent user bias, Latency bias
				Other antihypertensive drugs		HR: 1.40 (1.10-1.78)	
			Long-acting CCBs	Other antihypertensive drugs		Ever use: HR: 1.12 (0.85-1.46) <3 years of use: HR: 1.14 (0.79-1.63) >3 years of use: HR: 1.10 (0.77-1.58)	
			Short-acting CCBs	Other antihypertensive drugs		Ever use: HR: 1.66 (1.20-2.28) <3 years of use: HR: 1.15 (0.67-1.97) >3 years of use: HR: 2.07 (1.42-3.02)	
Kirkegard (2019)	Cohort	8,311	CCBs	Non-use	Pancreatic cancer	HR: 1.56 (0.76-3.22)	Confounding by indication, Few pancreatic cancer events
Cho (2021)	Cohort	70,549	CCBs	Non-use	Pancreatic cancer	HR: 1.32 (0.79-2.20)	Confounding by indication, Latency bias

Abbreviations: ACE, angiotensin-converting enzyme; ARB; angiotensin II receptor blocker; CCBs, calcium channel blockers; CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, rate ratio; SIR, standardized incidence ratio

CHAPTER 3. DATA SOURCE AND METHODOLOGY

The data source used for Manuscripts 1-3 is the UK CPRD GOLD database, described in detail below.

3.1 Overview of the Clinical Practice Research Datalink

Citizens residing in the UK have access to free and comprehensive healthcare services provided by the UK National Health Service (NHS).[181] More than 98% of the UK population are registered with a primary care practice, and as such general practitioners are the primary point of contact for individuals seeking non-urgent care and act as the referral point for specialist treatment.[181] Specialists also inform general practitioners of diagnoses about their patients.

The CPRD was established in 1987 and is one of the largest primary care databases in the world.[181] As of March 2022, the CPRD GOLD contained complete anonymized electronic medical records for more than 20.9 million patients enrolled in over 985 general practices in England, Wales, Scotland, and Northern Ireland.[182] A total of 3.1 million patients are currently enrolled, representing 6.4% of the UK population, with a median follow-up time of 13.0 years (interquartile range: 4.6-25.9).[182] The patient population included in the CPRD has been demonstrated to be representative of the UK population in terms of age, sex, ethnicity, and BMI distribution.[181,183,184] Further, the Quality and Outcomes Framework, an incentive payment program for general practitioners established in 2004 to better capture the recording of key lifestyle factors, resulted in an increase in the completeness of recorded variables such as smoking, blood pressure measurements, BMI, and alcohol intake over time, with those variables reaching 75%-98% completeness in the CPRD database.[181]

Data is collected daily as part of routine clinical care and entered into the Vision® general practice patient management software, with participating general practices providing anonymized, patient-level data to the CPRD monthly.[181] Every patient is assigned a unique NHS identifier. The CPRD contains demographic characteristics, anthropometric data such as BMI, lifestyle variables such as smoking and alcohol use, laboratory tests, medical diagnoses and symptoms, procedures, prescription information, vaccination history, referrals to secondary care and hospital, and death information.[182] For lifestyle variables, symptoms, medical history, medical diagnoses, and procedures such as blood pressure measurements, the CPRD uses the Read code classification which is a standardized clinical terminology system used since 1986 in UK primary care practices.[181] Prescriptions issued include product name, British National Formulary (BNF) code, quantity, and dosage information, recorded using a coded drug dictionary based on the UK Prescription Pricing Authority Dictionary.[181] Results of laboratory tests ordered by the general practitioner are electronically linked to the patients' records. Data quality in the primary care practices is assured through two main quality assurance metrics to ensure the use of research-quality data: patient acceptability, which is a patient-level consistency metric based on registration date, age, gender, and valid record of healthcare episodes, and up-to-standard dates, which is a practice-level consistency metric based on the continuity of research-quality recording data and accurate reporting of deaths. Diagnoses in the CPRD have also been shown to be highly valid; a systematic review of 212 studies assessing the validity of 183 diagnoses in the CPRD confirmed the validity of 89% of those diagnoses.[185] For cancer specifically, colorectal cancer diagnoses have been validated in the CPRD, with a positive predictive value of 98%, sensitivity of 92%, and specificity of 99% when compared with the National Cancer Data Repository.[186,187] Pancreatic

cancer is also well recorded, with a positive predictive value of 96% and sensitivity of 92% when compared with pancreatic cancer diagnoses reported in the National Cancer Data Repository.[186,188]

3.2 Methodology

3.2.1 Study populations

We used the CPRD to construct the study cohorts in Manuscripts 1-3. For Manuscript 1, we identified three cohorts. In all three cohorts, we identified all patients aged 18 years and over and registered with a general practice between January 1, 1988 and December 31, 2018. We defined cohort entry as the start of registration with the general practice, the date the general practice met data quality standards, or January 1, 1988, whichever came later. In the first cohort, we identified patients with a prescription for at least one antihypertensive drug during the study period (i.e., prevalent users and initiators). These drugs included thiazide and thiazide-like diuretics, CCBs, ACE inhibitors, ARBs, beta-blockers, other diuretics (loop diuretics, potassium-sparing diuretics, other diuretics), and other agents (alpha blockers, alpha agonists, direct-acting vasodilators, centrally-acting agents, ganglion-blocking agents, direct renin inhibitors, and combination pills) and were identified using 2,849 product codes included in 34 BNF codes **(BNF codes listed in Table 3.1)**. In the second cohort, we identified all patients aged 18 years and older with a first-ever prescription for an antihypertensive drug (listed above and in **Table 3.1**) during the study period. Cohort entry corresponded to the date of the first-ever antihypertensive drug prescription in monotherapy in the patient's medical record. For this cohort, all patients were required to have at least one year of medical history in the CPRD before cohort entry. This was necessary to ascertain first-ever status and to have a sufficient look-back period to capture clinically relevant characteristics. In the third cohort assessing the treatment trajectory of patients

with hypertension, we identified all patients with evidence of hypertension before cohort entry and initiating a first-line antihypertensive drug (listed above and in **Table 3.1**) during the study period. The date of the first-line drug prescription was the date of cohort entry.

For Manuscript 2, we assembled a new-user, active comparator cohort of patients aged 18 years and older. Cohort entry was defined as the date of the first prescription for either a thiazide diuretic or dCCB between January 1, 1990 and March 31, 2018. We selected patients with a minimum of one year of medical history in the CPRD before cohort entry, which was used as a washout period to ensure that only new users of either study drug were included in the cohort. When assessing the effect of a drug, using drug initiation (i.e., the inclusion of new users) as a starting point is important,[158] as it minimizes left truncation. The inclusion of prevalent users would introduce left truncation of the exposed time period prior to cohort entry, thus introducing exposure misclassification and providing potentially incorrect estimates dependent on the proportion of prevalent users included in the cohort.[174,189] Patients with concomitant use of thiazide diuretics and dCCB at cohort entry were excluded. At any time before cohort entry, we excluded patients with rare genetic conditions that have known associations with early-onset colorectal cancer,[130-134] as well as previous solid organ transplantation, as this is a rare intervention with a possible association with colorectal cancer,[190] and patients previously diagnosed with colorectal cancer. Finally, patients were required to have a minimum of one-year of follow-up after cohort entry to allow for a biologically plausible latency period and ensure the inclusion of incident events during follow-up. This lag period is essential in studies of cancer outcomes due to the natural progression of cancer as a disease. Generally, cancer have a long induction period (i.e., time between a component cause and initiation of cancer) and latency period (i.e., time between disease initiation and detection), representing several months to years between a potential exposure and

the detection of disease.[191] Thus, lagging exposures represent a study design method to account for cancer latency.[174] Lagging exposure also minimizes detection bias, as patients newly initiating prescription drugs are generally seen more closely by their general practitioners in the weeks/months after treatment initiation. Additionally, it minimizes the detection of prevalent cancer cases, because events detected shortly after drug initiation cannot be attributed to the exposure of interest and should be counted as unexposed person-time. However, because the true induction and latency periods are often unknown, sensitivity analyses using different lag periods are usually recommended.[174]

For Manuscript 3, we identified a new-user, active comparator cohort of primary care patients initiating either a dCCB or a thiazide diuretic between January 1, 1990 and March 31, 2018. Cohort entry was defined as the date of the first of either dCCB or thiazide diuretic prescription during the study period. Patients were required to be at least 40 years of age and have a minimum of one year of medical history in the CPRD before cohort entry. Our decision to include patients aged 40 and older was due to the sharp increase in the incidence of pancreatic cancer after 40 years of age, from 0.8 case per 100,000 population in adults aged 35-39 to 2.3 cases per 100,000 population in adults aged 40-44 (see **Section 2.5.2 Pancreatic cancer**).[127,143] We excluded patients with concomitant prescriptions for both study drugs at cohort entry, as well as those previously diagnosed with rare genetic conditions or interventions that have been associated with an elevated incidence of pancreatic cancer at any time before cohort entry.[146-149] To identify incident events during follow-up, we excluded patients with a previous diagnosis of pancreatic cancer or total pancreatectomy at any time before cohort entry. Finally, patients were required to have at least one year of follow-up after cohort entry to allow for a minimum cancer latency period and minimize

the detection of prevalent pancreatic cancers. More details on the study populations are provided in Chapters 4-6.

3.2.2 Exposure definitions

In Manuscript 1, in each calendar year of the study period, we considered primary care patients to be exposed to an antihypertensive drug if at least one prescription was recorded during the calendar year. End of follow-up was defined as the end of registration with the general practice, death from any cause, or December 31, 2018, whichever came first. In the third cohort evaluating the treatment trajectory of patients with hypertension, patients were considered exposed from their first-ever antihypertensive drug until the last prescription date on record, end of registration with the general practice, death from any cause, or December 31, 2018, whichever came first.

Figure 3.1 presents a schematic of the exposure definition for Manuscript 2 and Manuscript 3. In Manuscript 2, patients were considered continually exposed to their cohort entry drug (i.e., their first prescription for either a thiazide diuretic or a dCCB, whichever came first) one year after cohort entry until a diagnosis of colorectal cancer, one year after switching to the other study drug (i.e., consistent with the one-year lag period at cohort entry, patients who switched from a dCCB to a thiazide diuretic were considered exposed to dCCBs for one year after switching and censored thereafter, with person-time at risk during the one-year lag period attributed to dCCBs) or censored on death from any cause, end of registration with the general practice, or end of study period (March 31, 2019), whichever occurred first.

Similar to Manuscript 2, in Manuscript 3, patients were followed one year after the date of the new prescription for a dCCB or a thiazide diuretic until the first of the following events: an incident diagnosis of pancreatic cancer, one year after switching to the other study drug, censored

on death from any cause, end of registration with the general practice, or end of study period (March 31, 2019).

We used a modified intention-to-treat exposure as the primary exposure definition in Manuscripts 2 and 3, and an intention-to-treat exposure in sensitivity analyses. An intention-to-treat exposure assumes that the patient remains continuously exposed to the initial study drug, ignoring treatment discontinuation and switches, until the end of follow-up.[192] A modified intention-to-treat exposure definition assumes that the patient remains continuously exposed until the end of follow-up, although the patient is censored when switching to the other study drug occurs. Both of these exposure definitions are more commonly used in studies of drug safety with cancer outcomes, where the effect of the exposure is considered irreversible. This definition aligns with the hypothesized biological mechanisms discussed in **Section 2.6.1 Thiazide diuretics and risk of colorectal cancer** and in **Section 2.6.2 Dihydropyridine calcium channel blockers and risk of pancreatic cancer,** which assume a permanent effect of thiazide diuretics and dCCBs on the development of colorectal cancer and pancreatic cancer, respectively, which would persist beyond treatment discontinuation. An on-treatment exposure is another exposure definition option in studies of drug safety, where it considers a patient exposed from the initial drug exposure until drug discontinuation,[192] generally with a grace period added after the date of discontinuation to take into account short-lasting residual effect of the drug. This exposure definition is best suited for acute outcomes and thus would be rarely appropriate in studies of cancer outcomes due to their long latency period.

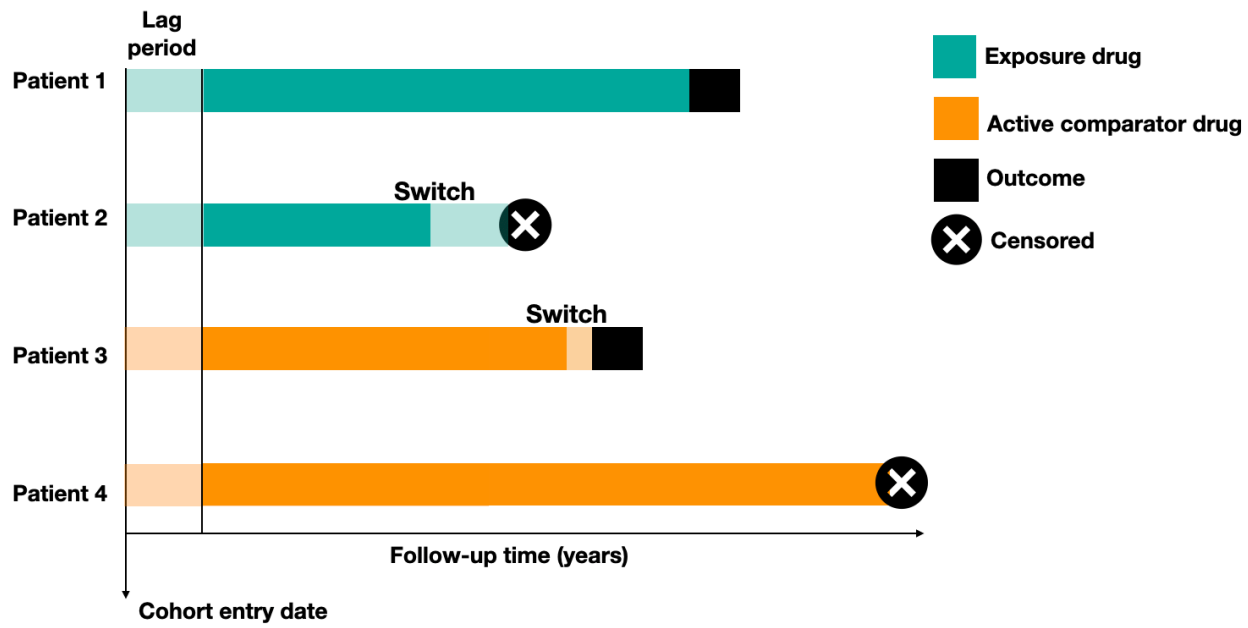

Figure 3.1 Schematic of the exposure definition. This depicts the modified intention-to-treat exposure definition used in Manuscript 2 and Manuscript 3. Cohort entry date is the date of the first prescription for either study drug i.e., the first of either thiazide diuretic or dCCB. All patients were required to have a minimum of one year of follow-up after cohort entry (lag period, considered as unexposed person-time). Therefore, the follow-up started one year after cohort entry for all patients (i.e., start of person-time at risk or exposed person-time). Patient 1 initiated the exposure drug and was considered exposed starting one year after cohort entry. Follow-up ended on the date of the outcome, depicted by a black square. Similarly, patient 2 initiated the exposure drug and was considered exposed starting one year after cohort entry. Once the patient switched to the active comparator drug, a one-year period was applied whereas an outcome occurring during that one-year period would be attributed to the initial exposure drug. After the one-year period has elapsed, the patient is censored. Patient 3 initiated the active comparator drug and subsequently switched to the exposure drug. The patient had an outcome during the one-year period after the

switch which was attributed to the active comparator drug. Patient 4 initiated the active comparator drug and was subsequently censored at the end of the study period.

3.2.3 Outcome definitions

For Manuscript 1, we assessed the period prevalence of each antihypertensive drug. In the cohort describing treatment trajectory, patients were followed from their initial first-line treatment to subsequent treatment lines up to the third line. A change in treatment line was defined by a patient switching one drug class to a new drug class or adding on a new drug class. At each treatment line, we captured the new drug class and calculated the median number of days between each treatment change (from the date of the first prescription of the first-line treatment to the date of the first prescription of the second-line treatment, and so on).

In Manuscript 2, we identified colorectal cancer events using Read codes (**Table 3.2**). Colorectal cancer diagnoses have been validated in the CPRD, with a positive predictive value of 98%, sensitivity of 92%, and specificity of 99% when compared with the National Cancer Data Repository.[186,187]

In Manuscript 3, we identified pancreatic cancer events using Read codes (**Table 3.3**). Pancreatic cancer is well recorded in the CPRD, with a positive predictive value of 96% and sensitivity of 92% when compared with pancreatic cancer diagnoses reported in the National Cancer Data Repository.[186,188]

Given that colorectal cancer and pancreatic cancer had been previously validated in the CPRD, which reported high positive predictive values, sensitivity, and specificity, (i.e., 92% and above), with the National Cancer Data Repository would offer only marginal benefits. Of the primary care practices contributing data to the CPRD, only primary care practices in England and

75% of those English practices agreed for linkage to the National Cancer Data Repository. Linkage would thus lead to a potentially significant decrease in the available sample population for our two population-based cohort studies. Therefore, our choice not to link the CPRD to the National Cancer Data Repository was based on optimizing sample size, while preserving a high validity for colorectal and pancreatic cancer diagnoses.

3.2.4 Baseline characteristics and potential confounders

Details of the covariate definitions and assessment windows are presented in **Table 3.4**. In Manuscript 1, for the second and third cohorts, we captured the following characteristics: age, sex, BMI, smoking status, systolic and diastolic blood pressure, diagnoses of hypertension, heart failure, coronary heart disease, peripheral vascular disease, stroke, arrhythmias, atrial fibrillation, stable angina, myocardial infarction, diabetes, and chronic kidney disease.

In Manuscript 2 and Manuscript 3, we captured the following potential confounders: age, sex, BMI, smoking status, alcohol-related disorders, hypertension, coronary heart disease, heart failure, peripheral vascular disease, stroke, atrial fibrillation, stable angina, myocardial infarction, chronic obstructive pulmonary disease, end-stage renal disease, ulcerative colitis, Crohn's disease, other inflammatory bowel disease, cholecystectomy, previous cancer diagnoses other than nonmelanoma skin cancer, statins, aspirin, other non-steroidal anti-inflammatory drugs, antidiabetic medications (insulin, metformin, sulfonylureas, incretin-based drugs, sodium-glucose cotransporter-2 inhibitors, and other antidiabetic drugs), antihypertensive drugs (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, non-dCCBs, diuretics other than thiazide diuretics, and other antihypertensive drugs), proton pump inhibitors, and vitamin D supplements, screening for breast cancer (through mammography), colorectal

cancer (through a fecal occult blood test or participation in the national bowel screening programme), and prostate cancer (through prostate-specific antigen testing), as well as records of influenza vaccination.

Additionally, we captured history of polyps, hormone replacement therapy, bisphosphonates, and calcium supplements in Manuscript 2, and diagnoses of chronic pancreatitis, cirrhosis of the liver, helicobacter pylori infection, hepatitis B infection, and selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors in Manuscript 3.

3.2.5 Calendar-time specific propensity scores and standardized mortality ratio weighting

For Manuscript 2 and Manuscript 3, we used calendar-time specific propensity scores to re-weigh our study population and allow for balance between the "treated" and "reference" groups on the prespecified covariates described in **Section 3.2.4 Baseline characteristics and potential confounders**. For Manuscript 2, the treated population was new users of thiazide diuretics and the reference population was new users of dCCBs, whereas for Manuscript 3, the treated population was new users of dCCBs and the reference population was new users of thiazide diuretics.

We used propensity scores for confounding adjustment in the two new-users, active comparator cohort studies described in Manuscript 2 and Manuscript 3. The use of propensity scores in this context is conceptually equivalent to RCTs, where the goal is to emulate a target trial to achieve exchangeability between the treated and reference populations on measured covariates.[193,194] RCTs would be an unethical study design choice to investigate the effect of a drug exposure on cancer outcomes, as it would require very large patient populations (at least 100,000 patients) and require long durations of follow-up (at least 5 years) given the long disease latency of some cancers.[195] As such, population-based studies using propensity scores represent good

design choices to provide key evidence on the long-term cancer safety of commonly prescribed drugs. Propensity score methods also have the advantages of allowing a clear definition of the target of inference (estimand) and excluding atypical patients with very low probability of receiving the drug of interest.[196]

The propensity score is an estimate of a patient's probability of receiving a drug conditional on their observed baseline covariates.[193,194] First, we constructed a propensity score model with the treated group as the dependent variable and the prespecified covariates described in **Section 3.2.4 Baseline characteristics and potential confounders** as independent variables. In the multivariable logistic regression model, we estimated the propensity score within five-year calendar band at cohort entry. The use of calendar year was primarily informed by Manuscript 1 to account for changes in the prescription prevalence of antihypertensive drugs over the study period. It was also used to account for variations in the incidence of colorectal and pancreatic cancer over time,[127,128,143] and for heterogeneity in the recording of covariates in the CPRD over the study period, as described in **Section 3.1 Overview of the Clinical Practice Research Datalink**.[181] Second, we evaluated the distributional overlap between the treated and reference groups by plotting the estimated density function, and propensity scores in the non-overlapping regions were trimmed. Third, we selected the average treatment effect among the treated population as our target of inference so that the covariate distribution in new users of the reference group would be similar to the distribution observed in new users of the treated group. To align with our selected target of inference, we selected the standardized morbidity ratio weighting approach.[196] By using the propensity score to re-weight the population, weighting approaches create a pseudo-population with the goal of achieving balance between the observed covariates in the weighted pseudo-population.[196] Other weighting approaches are available, although some with

different targets of inference such as the average treatment effect.[196] Propensity score methods other than weighting approaches also exist, which include matching, stratification, and direct adjustment, with matching representing the most commonly used propensity score method.[197-199] Our choice to use standardized morbidity ratio weighting rather than matching is due to the key disadvantage of the matching approach to discard unmatched observations, resulting in a decreased sample size and which reduces the precision of the effect estimate. Indeed, a recent review of 306 cardiovascular studies using propensity score methods found that 18% of studies using matching discarded more than half of unmatched treated individuals.[198] In contrast, few observations are discarded when using propensity score weighting.

For the standardized morbidity ratio weights, patients in the treated group were given a weight of 1 while patients in the reference group were given a weight of the odds of treatment probability, calculated as propensity score/1- propensity score.[196,200] Extreme weights were truncated at 0.1 or 10. As a diagnostic step, we evaluated covariate balance for each exposure group using absolute standardized differences, with pre-defined differences lower than 0.10 indicative of an achieved balance,[201] and to provide further assurance that the propensity score had not been mis-specified. Finally, weighted Cox proportional hazard models stratified on five-year calendar bands of cohort entry were fit to estimate HR and 95% CIs of cancer using robust variance estimators. Robust variance estimators are recommended to account for the adjustments to the size of the pseudo-population.[196]

Table 3.1 British National Formulary codes for antihypertensive drugs

BNF code	BNF header
2020100	Thiazides And Related Diuretics
2020200	Loop Diuretics
2020300	Potassium-sparing Diuretics And Aldosterone Antagonists
2020400	Potassium-sparing Diuretics With Other Diuretics
2020500	Osmotic Diuretics
2020600	Mercurial Diuretics
2020800	Diuretics With Potassium
2040000	Beta-adrenoceptor Blocking Drugs
2040100	Beta-adrenoceptor Blocking Drugs With Diuretic
2050100	Vasodilator Antihypertensive Drugs
2050200	Centrally Acting Antihypertensive Drugs
2050501	Angiotensin-converting Enzyme Inhibitors
2050502	Angiotensin-ii Receptor Antagonists
2050503	Renin Inhibitors
2050504	Angiotensin-ii Receptor Antagonists With Diuretic
2060200	Calcium-channel Blockers
2050400	Alpha-adrenoceptor Blocking Drugs
02020100/02040000	Thiazides And Related Diuretics/Beta-adrenoceptor Blocking Drugs
02020100/02050501	Thiazides And Related Diuretics/Angiotensin-Converting Enzyme Inhibitors
02020100/09050102	Thiazides And Related Diuretics/Hypercalcaemia And Hypercalciuria
02020700/11065300	Carbonic Anhydrase Inhibitors/Carbonic Anhydrase Inhibitors
02030200/02040000	Drugs For Arrhythmias/Beta-Adrenoceptor Blocking Drugs
02030201/02040000	Supraventricular & Ventricular Arrhythmias/Beta-Adrenoceptor Blockers
02030202/02060200	Supraventricular Arrhythmias/Calcium-Channel Blockers
02040000/02050000	Beta-Adrenoceptor Blocking Drugs/Hypertension And Heart Failure
02040000/02060200	Beta-Adrenoceptor Blocking Drugs/Calcium-Channel Blockers
02040000/02090000	Beta-adrenoceptor Blocking Drugs/Antiplatelet Drugs
02040000/04070402	Beta-Adrenoceptor Blocking Drugs/Prophylaxis Of Migraine
02050200/04070402	Centrally Acting Antihypertensive Drugs/Prophylaxis Of Migraine/Oestrogens and HRT
02050200/04070402/06040101	Centrally Acting Antihypertensive Drugs/Prophylaxis Of Migraine/Oestrogens And HRT
02050502/02050600	Angiotensin-ii Receptor Antagonists/Other Antihypertensives
04070402/06040101	Prophylaxis Of Migraine/Oestrogens And HT

Table 3.2 Read codes for colorectal cancer

Read code	Read term
B13..00	Malignant neoplasm of colon
B141.00	Malignant neoplasm of rectum
B133.00	Malignant neoplasm of sigmoid colon
B134.00	Malignant neoplasm of caecum
B141.12	Rectal carcinoma
B131.00	Malignant neoplasm of transverse colon
B141.11	Carcinoma of rectum
B130.00	Malignant neoplasm of hepatic flexure of colon
B13z.11	Colonic cancer
B132.00	Malignant neoplasm of descending colon
B136.00	Malignant neoplasm of ascending colon
B902500	Neoplasm of uncertain behaviour of rectum
B137.00	Malignant neoplasm of splenic flexure of colon
B902400	Neoplasm of uncertain behaviour of colon
B134.11	Carcinoma of caecum
B140.00	Malignant neoplasm of rectosigmoid junction
B13z.00	Malignant neoplasm of colon NOS
B14..00	Malignant neoplasm of rectum, rectosigmoid junction and anus
B13y.00	Malignant neoplasm of other specified sites of colon
B14z.00	Malignant neoplasm rectum, rectosigmoid junction and anus NOS
B14y.00	Malignant neoplasm other site rectum, rectosigmoid junction and anus
B138.00	Malignant neoplasm, overlapping lesion of colon
B1z0.11	Cancer of bowel

Table 3.3 Read codes for pancreatic cancer

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

Table 3.4 Covariate definition and assessment window

	Variable type	Covariate assessment window (definition)	Source
Baseline covariates			
Age	Continuous	At cohort entry (cohort entry minus mid-year of year of birth)	-
Sex	Male/Female	At cohort entry	-
BMI	Categorical (4 categories)	Most recent measurement before/at cohort entry	-
Smoking status	Categorical (3 categories)	Most recent measurement before/at cohort entry	Product codes and Read codes
Alcohol-related disorders	Yes/No	Defined as presence of a diagnosis of alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and hepatic failure at any time before cohort entry	Read codes
Comorbidities			
Hypertension	Yes/No	Defined as either a diagnosis of hypertension at or ever before cohort entry or by the presence of at least three elevated systolic (≥140mmHg) or diastolic (≥90mmHg) blood pressure measurements[202] at or in the year before cohort entry	Read codes (diagnosis only)
Coronary heart disease	Yes/No	Any time before cohort entry	Read codes
Heart failure	Yes/No	Any time before cohort entry	Read codes
PVD	Yes/No	Any time before cohort entry	Read codes
Stroke	Yes/No	Any time before cohort entry	Read codes
Atrial fibrillation	Yes/No	Any time before cohort entry	Read codes
Stable angina	Yes/No	Any time before cohort entry	Read codes
Myocardial infarction	Yes/No	Any time before cohort entry	Read codes
COPD	Yes/No	Any time before cohort entry	Read codes
End-stage renal disease	Yes/No	Any time before cohort entry	Read codes
Ulcerative colitis	Yes/No	Any time before cohort entry	Read codes
Crohn's disease	Yes/No	Any time before cohort entry	Read codes
Other IBD	Yes/No	Any time before cohort entry	Read codes
History of polyps	Yes/No	Any time before cohort entry	Read codes
Cholecystectomy	Yes/No	Any time before cohort entry	Read codes
Previous cancer	Yes/No	Any time before cohort entry	Read codes
Chronic pancreatitis	Yes/No	Any time before cohort entry	Read codes
Cirrhosis of the liver	Yes/No	Any time before cohort entry	Read codes
Helicobacter pylori infection	Yes/No	Any time before cohort entry	Read codes
Hepatitis B infection	Yes/No	Any time before cohort entry	Read codes
Medications	Yes/No		
HRT	Yes/No	Any time before cohort entry	Product codes and Read codes
Bisphosphonates	Yes/No	Any time before cohort entry	Product codes

Statins	Yes/No	Any time before cohort entry	Product codes
Aspirin	Yes/No	Any time before cohort entry	Product codes
Other NSAIDs	Yes/No	Any time before cohort entry	Product codes
Antidiabetic drugs			
Insulin	Yes/No	Any time before cohort entry	Product codes
Metformin	Yes/No	Any time before cohort entry	Product codes
Sulphonylureas	Yes/No	Any time before cohort entry	Product codes
Incretin-based drugs	Yes/No	Any time before cohort entry	Product codes
SGLT-2 inhibitors	Yes/No	Any time before cohort entry	Product codes
Other antidiabetic drugs	Yes/No	Any time before cohort entry	Product codes
Antihypertensive drugs			
ACE inhibitors	Yes/No	Any time before cohort entry	Product codes
ARBs	Yes/No	Any time before cohort entry	Product codes
Beta-blockers	Yes/No	Any time before cohort entry	Product codes
Non-dihydropyridine CCBs	Yes/No	Any time before cohort entry	Product codes
Other diuretics	Yes/No	Any time before cohort entry	Product codes
Other antihypertensive drugs	Yes/No	Any time before cohort entry	Product codes
PPIs	Yes/No	Any time before cohort entry	Product codes
Calcium supplement	Yes/No	Any time before cohort entry	Product codes
Vitamin D supplement	Yes/No	Any time before cohort entry	Product codes
SSRIs/SNRIs	Yes/No	Any time before cohort entry	Product codes
Screening and other health behaviours			
Mammography	Yes/No	Year before cohort entry	Read codes
Fecal occult blood test	Yes/No	Year before cohort entry	Read codes
PSA test	Yes/No	Year before cohort entry	Read codes
Influenza vaccination	Yes/No	Year before cohort entry	Read codes

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ASD, absolute standardized difference; BMI, body mass index; COPD, chronic obstructive pulmonary disease; dCCB, dihydropyridine calcium channel blocker; IBD, inflammatory bowel disease; HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drugs; SGLT-2, sodium-glucose cotransporter-2; PVD, peripheral vascular disease; PPI, proton pump inhibitors; PS, propensity score; PSA, prostate-specific antigen; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors

CHAPTER 4. MANUSCRIPT 1: Treatment and prescribing trends of antihypertensive drugs in 2.7 million UK primary care patients over 31 years: a population-based cohort study

4.1 Preface

Antihypertensive drugs have a long-standing prescribing history, with several classes of drugs available for the pharmacological management of hypertension over time. Few studies however have comprehensively described the prescribing trends of antihypertensive drugs in primary care settings. This gap in the literature is important because updated treatment guidelines, approval of new drugs, and introduction of policies may impact prescribing practices. Further, there is a need to better understand the patient populations being prescribed these drugs to inform both clinical practice and the design of comparative effectiveness and safety studies.

The following chapter addressed this gap through three aims. The first aim describes the long-term prescribing trends of antihypertensive drugs in primary care patients. Between 1988 and 2018, we assessed the period prevalence of patient with antihypertensive drug prescriptions and the period prevalence by patient subgroups including sex, age, and indication (hypertension, heart failure, coronary heart disease, diabetes, and chronic kidney disease). The second aim describes the patient population with first-ever antihypertensive drug prescriptions. The third aim assesses the trajectory of antihypertensive drug prescriptions, from first- to third-line, in primary care patients with hypertension. For this analysis, we followed patients from their initial first-line treatment to subsequent treatment lines up to the third line.

This manuscript provides the rationale for the choice of study design, study population, and exposure definition in Manuscript 2 and Manuscript 3. Manuscript 1 is under review at *BMJ Open*.

Treatment and prescribing trends of antihypertensive drugs in 2.7 million UK primary care patients over 31 years: a population-based cohort study

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ABSTRACT

Objectives: To describe the prescribing trends of antihypertensive drugs in primary care patients and assess the trajectory of antihypertensive drug prescriptions, from first- to third-line, in patients with hypertension according to changes to the United Kingdom (UK) hypertension management guidelines.

Design: Population-based cohort study.

Setting and Participants: We used the UK Clinical Practice Research Datalink, an electronic primary care database representative of the UK population. Between 1988 and 2018, we identified all adult patients with at least one prescription for thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, or calcium channel blockers (CCBs).

Primary and Secondary Outcome Measures: We estimated the period prevalence of patients with antihypertensive prescriptions for each calendar year over a 31-year period. Treatment trajectory was assessed by identifying patients with hypertension newly initiating an antihypertensive drug, and treatment changes were defined by a switch or add-on of a new class. This cohort was stratified before and after 2007, the year following important changes to UK hypertension management guidelines.

Results: The cohort included 2,709,241 patients. The prevalence of primary care patients with antihypertensive drug prescriptions increased from 7.8% (1988) to 21.9% (2018) and was observed for all major classes except thiazide diuretics. Patients with hypertension initiated thiazide diuretics (36.8%) and beta-blockers (23.6%) as first-line drugs before 2007, and ACE inhibitors (39.9%) and CCBs (31.8%) after 2007. After 2007, 17.3% were not prescribed guideline-recommended first-line agents. Overall, patients were prescribed a median of 2 classes (interquartile range 1-2) after first-line treatment.

Conclusion: Nearly one-quarter of primary care patients were prescribed antihypertensive drugs by the end of the study period. Most patients with hypertension initiated guideline-recommended first-line agents. Not all patients, particularly females, were prescribed recommended agents however, potentially leading to suboptimal cardiovascular outcomes. Future research should aim to better understand the implication of this finding.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Most comprehensive study to date on the prescribing trends of antihypertensive drugs by sex, age group, and patient population.
- The extended follow-up captures major changes in UK hypertension treatment guidelines over time.
- The database captures prescriptions issued by general practitioners rather than dispensing information.

INTRODUCTION

Antihypertensive drugs are commonly prescribed drugs, used by 15-26% of the adult population.[1,2] There are five major classes, composed of thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, and calcium channel blockers (CCBs). These classes have been approved for several years, with ARBs being the latest class introduced in the market in 1995.[3]

Despite a long-standing prescribing history, the prescription prevalence of antihypertensive drugs over time has not been comprehensively evaluated. Further, evidence suggest that sex differences may exist in the prescriptions of different antihypertensive drug classes in primary care settings[4], and changes to hypertension management over time have led to earlier treatment initiation in the disease course and in younger patients.[5] The addition of large country-specific studies describing the different patient subgroups being prescribed these drugs and the changes in treatment intensity over time would thus help better understand these issues.

Additionally, although guidelines have been published on the pharmacological treatment of patients with hypertension, few studies have investigated the application of these guidelines in real-world clinical practice. This gap in the literature is important because early guidelines originally recommended thiazide diuretics and beta-blockers as first-line treatment, which were gradually replaced by ACE inhibitors, ARBs and CCBs in later guidelines.[6-11] Further, in the UK, more specific antihypertensive drug classes became recommended over time as the initial treatment of choice and for subsequent treatment lines. As such, an assessment of the pharmacological management of patients for hypertension, from first- to third-line, is needed to identify the treatment trajectory of these patients over time and the potential gaps and inequities in best practice management of hypertension.

Thus, the objectives of this population-based study were to describe the long-term prescribing trends of antihypertensive drugs in UK primary care patients and define the trajectory of antihypertensive drug prescriptions, from first- to third-line, in primary care patients with hypertension.

METHODS

Data source

This study was conducted using the UK Clinical Practice Research Datalink (CPRD) GOLD, a large primary care database of electronic medical records representative of the UK population.[12,13] The CPRD contains demographic information, anthropometric data such as body mass index, and lifestyle variables such as smoking. Medical diagnoses, laboratory test results, procedures, and specialist referrals are recorded using Read codes, and prescriptions details are recorded using the British National Formulary (BNF) dictionary.[13]

Patient records provided by the general practices are assessed for quality through data quality checks through the Quality and Outcomes Framework, with lifestyle variables such as smoking, blood pressure, body mass index (BMI), and alcohol intake having over 70% completeness in the CPRD.[14] The CPRD has also been shown to be representative of the UK population for age, sex, ethnicity, and BMI distribution,[13] and diagnoses have been shown to have high sensitivity and specificity.[15]

Study population

Using the CPRD, we first identified a cohort of patients at least 18 years of age and registered with a general practice between January 1, 1988 and December 31, 2018. Cohort entry was defined as the patient's start of registration with the general practice, the date the general practice met data quality standards, or January 1, 1988, whichever came later. End of follow-up was defined as the patient's end of registration with the general practice, death from any cause, or December 31, 2018, whichever came first. Within this cohort, we identified patients who received at least one antihypertensive drug prescription during the study period, with no restrictions on

specific comorbidities as these drugs can be prescribed for different indications. These drugs consisted of all those available in the UK during the study period and included thiazide and thiazide-like diuretics, ACE inhibitors, ARBs, beta-blockers, CCBs, other diuretics (loop diuretics, potassium-sparing diuretics, other diuretics), and other agents (alpha blockers, alpha agonists, direct-acting vasodilators, centrally-acting agents, ganglion-blocking agents, direct renin inhibitors, and combination pills) (BNF codes in **Supplementary Table 1**).

Statistical analyses

Period prevalence of patients with antihypertensive drug prescriptions

We first estimated the period prevalence of primary care patients prescribed antihypertensive drugs, overall and stratified by antihypertensive drug class, in each calendar year of the study period. Period prevalence was calculated by dividing the number of patients who were prescribed an antihypertensive drug by the total number of patients in the CPRD in each calendar year during the study period. Second, we assessed the period prevalence among patient subgroups, including by sex and age (18-39, 40-59, 60-79, ≥80 years), and by indications of use (hypertension, heart failure, coronary heart disease, diabetes, and chronic kidney disease). The latter was calculated by dividing the number of patients with a given indication prescribed antihypertensive drugs by the total number of patients prescribed any antihypertensive drug with that indication. This analysis was conducted to describe the patient population with these specific conditions. Finally, we estimated the number of antihypertensive drug classes prescribed to primary care patients over the study period overall, by sex, and by age group, to better understand changes in treatment intensity over time in primary care.

Characteristics of patients initiating a first-ever antihypertensive drug

To better understand the patient population initiating antihypertensive drugs, we identified all patients aged 18 and above with a first prescription for an antihypertensive drug between January 1, 1988 and December 31, 2018. Cohort entry corresponded to the date of the first-ever antihypertensive drug prescription in monotherapy in the patient's medical record. For this analysis, all patients were required to have at least one year of medical history in the CPRD before cohort entry. This was necessary to ascertain first-ever status and to have a sufficient look-back period to capture clinically relevant characteristics. Patient characteristics were described overall (1988-2018) and by decades (1988-1999, 2000-2009, 2010-2018). The following characteristics were captured at cohort entry: age, sex, body mass index, smoking status, systolic and diastolic blood pressure (last measurement before cohort entry); and measured ever before: diagnoses of hypertension, heart failure, coronary heart disease, peripheral vascular disease, stroke, arrhythmias, atrial fibrillation, stable angina, myocardial infarction, diabetes, and chronic kidney disease.

Because recent evidence has shown an increase in beta-blockers prescriptions for non-cardiovascular conditions over time, we described the distribution of this drug class in patients with a first-ever and ever prescription.

Treatment trajectory

We also assessed the treatment trajectory among patients initiating a first-line antihypertensive drug in monotherapy before and after January 1, 2007. This dichotomization was based on the June 2006 pharmacological update of the 2004 National Institute for Health and Care Excellence (NICE) guidelines on hypertension in primary care.[9,10] These guidelines newly

recommended ACE inhibitors (or ARBs if ACE inhibitors are not well tolerated) as the preferred initial first-line treatment in younger patients rather than beta-blockers.

For this analysis, we identified patient initiating a first-line antihypertensive drug with evidence of hypertension before cohort entry. Evidence of hypertension was defined by either a diagnosis of hypertension before cohort entry or by at least three elevated systolic (≥140mmHg) or diastolic (≥90mmHg) blood pressure measurements at or in the year before cohort entry.[16] Patients were followed from their initial first-line treatment to subsequent treatment lines up to the third line. A change in treatment line was defined by a patient switching one drug class to a new drug class or adding on a new drug class. End of follow-up was defined as the last prescription date on record. At each treatment line, we captured the new drug class and calculated the median number of days between each treatment change (from the date of the first prescription of the first-line treatment to the date of the first prescription of the second-line treatment, and so on). Finally, to describe treatment intensity, we calculated the number of antihypertensive drug classes prescribed after failure on first-line monotherapy treatment over the study period. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 19_153A) and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Patient and public involvement

Patients and the public were not involved in the design and implementation of the study, as study participants (as this study involved the use of secondary data), or in dissemination plans.

RESULTS

Period prevalence of patients with antihypertensive drug prescriptions

Within a cohort of 11,417,758 primary care patients, 2,709,241 patients were prescribed at least one antihypertensive drug during the study period. Overall, the prevalence of patients with antihypertensive drug prescriptions increased from 7.8% in 1988 to 21.9% in 2018, but has remained relatively steady since 2006 (**Figure 1**). By the end of the study period, 51.0% were prescribed two or more antihypertensive drug classes.

Figure 2 presents the period prevalence for each antihypertensive drug class during the study period. Between 1988 and 2018, the prevalence increased for ACE inhibitors (0.4% *vs* 9.3%), CCBs (1.4% *vs* 8.7%), and beta-blockers (2.6% *vs* 8.6%). The prevalence of patients prescribed ARBs modestly increased from 0% in 1995 (the year ARBs entered the UK market) to 4.0% in 2018. For thiazide diuretics, the prevalence decreased from a peak of 7.3% in 2005 to 3.8% in 2018. In 2018, ACE inhibitors represented 24.5% of all antihypertensive drug prescriptions, followed by CCBs (22.9%), beta-blockers (22.5%), ARBs (10.4%), thiazide diuretics (9.9%), other diuretics (8.3%), and other antihypertensive drugs (1.4%). Treatment intensity increased during the study period (**Supplementary Figure 1**), with patients being prescribed a median of 1 drug class (interquartile range 1-2, maximum 7) in 1988 to 2 (interquartile range 1-2, maximum 7) in 2018. During the study period, female patients were more likely than male patients to be prescribed only one class (52.5% *vs* 45.3% in 2018, respectively) (**Supplementary Figures 2A-B**). Patients aged 60 and over were increasingly more likely to be prescribed 2 or more classes (**Supplementary Figures 3A-D**).

Supplementary Figures 4A-D present the period prevalence for males and females by age groups. Female patients were consistently more likely to be prescribed thiazide diuretics compared

with male patients throughout the study period. In contrast, more male patients were prescribed ACE inhibitors than females, across all age groups. Similarly, more males were prescribed CCBs during the study period, except for the youngest (18-39 years old) and oldest (80+) age groups. For beta-blockers, the prevalence of patients aged 18-39 years increased from 0.3% in 1988 to 1.9% for males and 4.0% for females in 2018.

Supplementary Figures 5-9 show the prevalence of antihypertensive drugs for patients with hypertension, heart failure, coronary heart disease, diabetes, and chronic kidney disease, respectively, to describe the patient population with these conditions. In hypertension, the prevalence of patients with beta-blocker and thiazide diuretic prescriptions was highest from 1988 until 2005-2006, when the 2004 guideline and the 2006 pharmacological update began primarily recommending ACE inhibitors and CCBs for the management of hypertension (**Supplementary Figure 5**).[9,10] In patients with heart failure, the most prevalent drug classes were diuretics (since 1988), ACE inhibitors (since 1992) and beta-blockers (since 2003) (**Supplementary Figure 6**). Beta-blockers were contraindicated for chronic heart failure until the publication of guidelines in 1997[17] after which the prevalence rose rapidly, becoming the most prevalent by the end of the study period. Patients with coronary heart disease and type 2 diabetes showed a similar pattern, with the highest prevalence for ACE inhibitors, beta-blockers, and CCBs, particularly after 2000 (**Supplementary Figures 7-8**). Finally, among patients with chronic kidney disease, the prevalence of patients with ACE inhibitors, CCBs, beta-blockers, and loop diuretics was highest for most of the study period, however with a sharp decline for loop diuretics in 2006, the publication year of the Quality and Outcomes Framework for chronic kidney disease in England and UK chronic kidney disease management guidelines (**Supplementary Figure 9**).

Characteristics of patients initiating a first-ever antihypertensive drug

There were 1,425,542 patients with a first-ever antihypertensive drug prescription in monotherapy during the study period (**Supplementary Figure 10**); 44.6% of those were males, and the mean age was 55.4 years (standard deviation (SD): 17.2).

Table 1 describes the characteristics of patients initiating first-ever antihypertensive drugs, overall and by drug class, during the study period. Beta-blockers represented the most commonly initiated drugs (36.4%), followed by ACE inhibitors (17.5%). Males were more likely to receive ACE inhibitors, ARBs, and CCBs (62.7%, 60.0%, and 52.7%, respectively), while females were more likely to receive thiazide diuretics, beta-blockers, other diuretics, and other antihypertensive drugs (62.9%, 59.9%, 61.6%, 89.8%, respectively). The majority of prescriptions in the "Other antihypertensive drugs" category (71.3%) were for clonidine hydrochloride 0.025mg tablets.

Most patients initiating a thiazide diuretic, ACE inhibitor, ARB, and CCB had hypertension (71.2%, 76.4%, 76.6%, and 67.9%, respectively). In contrast, patients initiating a beta-blocker, other diuretics, and other antihypertensive drugs were less likely to have hypertension (22.9%, 14.1%, 21.6%, respectively). The majority of first-ever beta-blocker prescriptions were for propranolol (**Supplementary Table 2).**[18]

Supplementary Tables 3-5 describe the characteristics of patients initiating a first-ever antihypertensive drug by decade (1988-1999, 2000-2009, 2010-2018). Between the first and the third decades, there was an overall increase in the proportion of patients diagnosed with diabetes (8.9% *vs* 21.3%) and chronic kidney disease (0.3% *vs* 3.6%), as well as hypertension for ACE inhibitors (71.4% *vs* 78.2%), CCBs (44.2% *vs* 73.8%), and other diuretics (10.6% *vs* 16.8%).

Treatment trajectory

The trajectory analysis included 317,210 patients with hypertension initiating a first-line antihypertensive drug in the pre-2007 cohort and 302,774 patients in the post-2007 cohort. **Supplementary Tables 6-7** present the baseline characteristics of these patients. Patients in the pre-2007 cohort were slightly older than the post-2007 cohort (60.5 years, SD: 18.3) *vs* 58.1 years, SD: 14.0) and had a higher pre-treatment mean systolic (166.2 mmHg, SD: 17.9 *vs* 161.1 mmHg, SD: 16.5) and diastolic blood pressure (94.9 mmHg, SD: 10.6 *vs* 93.4 mmHg, SD: 10.7). In the pre-2007 cohort, 79.4% of patients switched to or added-on a new antihypertensive drug in contrast to 53.2% of patients in the post-2007 cohort (**Supplementary Table 8**). In the post-2007 cohort, female patients were less likely to be prescribed a guideline-recommended first-line agent.

Figure 3 presents the treatment trajectory of patients initiating an antihypertensive drug before January 1, 2007. In this cohort, thiazide diuretics (36.8%) and beta-blockers (23.6%) were the most common first-line drugs. Among patients with first-line thiazide diuretic prescriptions, ACE inhibitors and beta-blockers were the most common second-line treatment (26.9% and 25.6%, respectively). Among patients with first-line beta-blocker prescriptions, thiazide diuretics and ACE inhibitors were the most common second-line treatment (23.7% and 22.6%, respectively). Treatment trajectory details for ARBs and "Others" are in **Supplementary Figure 11**. The median number of days between treatment changes for first-line thiazide diuretics was 186 days (interquartile range 47-870) and 319 days (interquartile range 59-1211) for first-line beta-blockers (**Supplementary Figure 12**).

Figure 4 presents the treatment trajectory after January 1, 2007. The most common first-line drugs were ACE inhibitors (39.9%) and CCBs (31.8%). A total of 17.3% of patients were not prescribed a guideline-recommended first-line agent. Among patients with first-line ACE inhibitor

prescriptions, CCBs were the most common second-line drugs (25.5%). Similarly, among patients with first-line CCB prescriptions, ACE inhibitors were the most common second-line drugs (30.9%). Treatment trajectory details for ARBs and "Others" are in **Supplementary Figure 13**. The median number of days before starting second-line treatment was 182 days (interquartile range 63-654) for ACE inhibitors and 114 days (interquartile range 39-468) for CCBs (**Supplementary Figure 14**).

The median number of antihypertensive drug classes prescribed after failure on first-line treatment was 2 (interquartile range 1-2, maximum 7). Over time, the percentage of patients prescribed two classes after failure on first-line treatment increased from 35.9% in 1989 to 45.8% in 2018. Similarly, patients with 3 classes increased from 9.8% in 1990 to 16.2% in 2018. (**Supplementary Figure 15**).

DISCUSSION

Principal findings

In this large population-based study, the prevalence of patients prescribed antihypertensive drugs increased during the study period but has remained relatively steady since 2006, with 21.9% of primary care patients receiving antihypertensive drugs by the end of the study period. The prescription prevalence was highest for ACE inhibitors (24.5%), CCBs (22.9%) and beta-blockers (22.5%). Beta-blockers were most prevalent in females and in youngest and oldest patients. Most patients with hypertension initiated guideline-recommended first-line agents, with thiazide diuretics and beta-blockers representing the most common first-line drugs before 2007 (36.8% and 23.6%, respectively) and ACE inhibitors and CCBs after 2007 (39.9% and 31.8%, respectively). Fewer females initiated recommended first-line agents.

Comparison with previous studies

Although previous studies have described prescribing trends of antihypertensive drugs in UK primary care practices, these trends were reported for specific patient populations, indications, drug classes, or over short time periods.[3,19-33] As such, there was a gap in the literature for a comprehensive assessment of the prescribing practices in primary care over time. In our study, 8% of adult primary care patients were prescribed antihypertensive drugs in 1988, which increased to 22% by the end of the study period. Other countries and jurisdictions have reported an overall prevalence in adult populations ranging between 8%-35%, with an increase over time.[1,2,34-37] A large pooled analysis of 104 million primary care individuals found that age-standardized prevalence of hypertension doubled between 1990 and 2019 in primary care patients aged 30-79, although countries such as Canada, Peru, and the UK (in women only) reported the lowest

prevalence of hypertension diagnosis with less than <25% of its primary care population.[38] In terms of hypertension treatment, the age-standardized prevalence was above 70% in Canada, South Korea, and Iceland, but reported to be only 47% in the UK.

The prevalence of patients with ACE inhibitor and CCB prescriptions has increased steadily over the last three decades, while it has decreased sharply for thiazide diuretics since 2005. Similarly, a previous UK study showed a decrease in the number of thiazide prescriptions between 2010 and 2016/2017.[20] Changes in UK hypertension treatment guidelines, notably in 2004 when ACE inhibitors and CCBs were newly recommended as first-line treatment for hypertension along with thiazide diuretics and beta-blockers,[9] may have contributed to this decline. This decreasing trend was also seen in our findings specific to patients with hypertension. As thiazide diuretics have been associated with lower treatment adherence than ACE inhibitors, ARBs, and CCBs,[39-41] this could have led clinicians to favour other classes with higher adherence. We also observed a shorter number of days between treatment changes in patients with thiazide diuretic prescriptions for hypertension than for other drugs. These faster treatment changes might have been due to the well-known side effects associated with thiazide diuretics.[42] Concerningly, as we consistently observed more female patients being prescribed thiazide diuretics throughout the study period, lower treatment adherence could lead to suboptimal blood pressure control in women.

A large 2020 systematic review and meta-analysis of sex differences in cardiovascular medication prescriptions in primary care patients found that women were 27% more likely to be prescribed thiazide diuretics but less likely to be prescribed ACE inhibitors (pooled prevalence ratio 0.83%, 95% CI 0.78-0.89).[4] Our study consistently showed a higher prevalence of female patients with thiazide diuretic prescriptions and a lower prevalence ACE inhibitor prescriptions than male patients over the study period, similar to previous large studies of primary care

patients.[43,44] This sex difference may perhaps be explained by dissimilar presentations of cardiovascular symptoms, or different reporting of adverse events in men compared with women[45,46] A 2019 systematic review of adverse drug reactions to heart failure drugs showed that cough and angioedema were reported more frequently in women treated with ACE inhibitors than men.[47] These factors may in turn be reflected in the clinical decisions leading to prescribing practices. Nonetheless, further research should focus on better understanding these sex differences in prescribing practices.

Our results also showed an age and sex difference in beta-blockers prescriptions. Beta-blockers were the first-ever drug class for 36.4% of the cohort and were predominantly prescribed in the youngest patients, primarily females, and without hypertension or other cardiovascular indications. After 2010, when beta-blockers were no longer recommended as first-line therapy for hypertension,[10] beta-blocker still constituted nearly 41% of patients with first-ever drugs. Notably, the prevalence of patients aged 18-39 with a beta-blocker prescription increased over time, most markedly since 2007. Similarly, between 1999-2000 and 2011-2012, a US study found a nearly eight-fold increase in the prevalence of adults aged 20-39 with non-cardioselective beta-blocker prescriptions.[1] Our study also showed that the majority of those first-ever prescriptions were for propranolol. Similarly, a recent study found a 2.5-fold increase in the prevalence of propranolol prescriptions for anxiety in UK primary care practices between 2003 and 2018, with a higher incidence for female patients and patients aged <45 years old.[18] This increase in prescriptions may correspond to the increase in the recording of anxiety symptoms and diagnoses in female and younger patients in recent years.[48] Although propranolol is licensed for use in anxiety symptoms management,[49] there is currently limited evidence of their long-term effectiveness and safety[50,51] and no specific recommendations exist from NICE regarding its use in anxiety.[52] Further, the UK

Healthcare Safety Investigation Branch recently informed of a potential risk of propranolol toxicity in overdose, reporting a 33% increase in deaths potentially associated with propranolol overdose between 2012 and 2017.[52] Additionally, our study found a sharp increase in patients aged 80 and over with beta-blockers prescriptions, representing the largest age group with prescriptions for this class. Beta-blockers, and specifically non-cardioselective beta-blockers such as propranolol, have been associated with increased risk of fall in the elderly.[53] Together, these findings warrant further investigation to understand the benefits and safety of beta-blockers, especially propranolol.

National guidelines recommend select first-line agents for antihypertensive treatment. Published by the British Hypertension Society in 1989, the first guideline recommended thiazide diuretics and beta-blockers as first-line treatments.[6] At that time, ACE inhibitors and CCBs were new agents with limited evidence of their efficacy. Similar recommendations were made in subsequent guidelines,[7,8] although ACE inhibitors, CCBs, alpha-blockers, and later, ARBs could be considered potential options. As more evidence became available from randomized controlled trials and hypertension treatment became more complex,[54-71] NICE and the British Hypertension Society published four new guidelines and updates (2004, 2006, 2011, 2019) recommending ACE inhibitors and CCBs as first-line agents and introducing treatment choice based on age and ethnicity.[9-11,72] Our findings showed that patients treated after 2007 were younger and had a lower mean blood pressure measurements than those treated before 2007. This is consistent with recent improvements in hypertension management which have led to the earlier treatment of patients, those younger in age, and those with lower initial blood pressure. However, much remains to be done. Previous studies showed that patients initiating an ACE inhibitor or a CCB had similar reductions in blood pressure, regardless of age,[73,74] suggesting that treatment choice based on indications rather than age might be more important.

The treatment trajectories in our study relatively reflected the UK hypertension management guidelines published during the study period, with thiazide diuretics and beta-blockers being the most common first-line agents in the pre-2007 cohort and ACE inhibitors and CCBs in the post-2007 cohort. Similarly, one UK study found that diuretics and beta-blockers were prescribed in 54% of patients between 1993-1997.[19] More recently, another UK study found that 69.7% of patients initiated an ACE inhibitor or CCB between 2006 and 2014.[75] In our study however, 17.3% of patients were not prescribed a guideline-recommended first-line agents after 2007 and female patients were less likely to be prescribed an ACE inhibitor, ARB, or a CCB, which are the currently guideline-recommended first-line agents. Further, 19.5% of patients were prescribed three or more antihypertensive drug class after failure on first-line monotherapy, with some patients being prescribed up to seven classes. These findings show that some patients may be less likely to receive first-line agents and more likely to be overprescribed antihypertensive drugs, potentially leading to less effective treatment and higher risk of adverse effects. These gaps and inequities in best practice management of hypertension should be further investigated. Further, studies should investigate which specific treatment trajectory optimizes cardiovascular outcomes in patients with hypertension.

Strengths and limitations of the study

Our study has several strengths. First, with the inclusion of 2.7 million patients, it is the largest and most comprehensive study to date on the prescribing trends of antihypertensive drugs, which presents trends by drug class, sex, age group, and comorbidities. Second, the 31-year study period provides the most extended follow-up to date and captures major changes in UK treatment guidelines over time. Third, this study describes the treatment trajectory of antihypertensive drugs

from first- through third-line, which provide a detailed picture of the treatment lines used in the management of patients with hypertension and the duration of each of these treatment lines. Finally, the CPRD has been shown to be representative of the UK population and undergoes regular data quality checks to ensure its validity.[13]

Our study also has limitations. First, as the CPRD represents prescriptions issued by general practitioners, prescriptions from specialists are not captured in the database. However, in the UK, most patients treated with antihypertensive drugs are managed by general practitioners.[76,77] Second, the CPRD captures prescriptions rather than dispensing information. Therefore, it is possible that some patients may not fill a prescription or adhere to the prescription. However, our study focused on the prescription rather than use of antihypertensive drugs. Third, for the treatment trajectory cohort, the analysis was limited to patients with a recorded diagnosis of hypertension through a robust algorithm. However, it is possible that some patients were not captured by this definition, leading to an underestimation of the number of patients included in the cohort. However, there is no evidence suggesting that these patients would differ by type of antihypertensive drug class. Fourth, it is possible that antihypertensive drugs may have been prescribed for other indications than hypertension. However, we captured the first-ever antihypertensive prescription after a diagnosis of hypertension, therefore minimizing the likelihood that the prescriptions were indicated for other comorbidities. Lastly, it is possible that we might not have captured the first-ever prescriptions for some patients.

In summary, nearly one-quarter of primary care patients were prescribed antihypertensive drugs by the end of the study period, with half of those concomitantly receiving two or more classes. Beta-blockers were most prevalent in females and in both the youngest and oldest patients, although this class is associated with adverse events. Most patients with hypertension initiated a

thiazide diuretic or beta-blocker before 2007 and an ACE inhibitor or CCB after 2007. These prescribing patterns relatively mirror the changes in hypertension management guidelines during the study period. However, fewer females initiated recommended first-line agents, potentially leading to suboptimal cardiovascular outcomes. Future studies should investigate these gaps and inequities, as well as which specific treatment trajectory optimizes cardiovascular outcomes in patients with hypertension.

CONTRIBUTORSHIP STATEMENT

All authors (JR, EGM, TS, JMB, and LA) conceived and designed the study, interpreted the data, critically revised the manuscript for important intellectual content, read and approved the final version of the manuscript, and are responsible for its content. LA acquired the data. JR conducted the analyses. JR drafted the manuscript. LA attests that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted.

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COMPETING INTERESTS

JR received consulting fees for work unrelated to this study from Biogen. LA received consulting fees from Janssen and Pfizer for work unrelated to this study. JB, TS, and EGM have no conflicts to disclose.

DATA SHARING STATEMENT

No data are available.

ETHICS STATEMENT

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 19_153A) and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

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Table 1. Baseline characteristics of primary care patients with a first-ever antihypertensive drug prescription between January 1, 1988 and December 31, 2018

	Thiazide diuretics	ACE inhibitors	ARBs	Beta-blockers	CCBs	Other diuretics	Other [a]	Total
Total	202,856 (14.9)	237,923 (17.5)	17,846 (1.3)	494,333 (36.4)	196,485 (14.5)	157,994 (11.6)	52,632 (3.9)	1,360,069
Males, n (%)	75,317 (37.1)	149,293 (62.7)	10,731 (60.0)	201,755 (40.1)	103,536 (52.7)	60,632 (38.4)	5,353 (10.2)	606,617 (44.6)
Mean age, years (SD)	63.2 (14.5)	55.3 (13.0)	57.0 (13.4)	45.9 (16.7)	61.5 (14.1)	65.9 (17.7)	53.5 (12.0)	55.4 (17.2)
Mean BMI, kg/m^2 (SD)	27.7 (5.4)	29.4 (6.0)	28.8 (5.8)	26.2 (5.4)	27.5 (5.4)	27.6 (6.8)	26.8 (5.3)	27.4 (5.8)
Smoking status								
Current	54,949 (27.1)	58,332 (24.5)	4,212 (23.6)	155,440 (31.4)	46,474 (23.6)	43,226 (27.4)	15,851 (30.1)	378,484 (27.8)
Never	94,945 (46.8)	114,852 (48.3)	8,808 (49.4)	227,370 (46.0)	94,175 (47.9)	64,733 (41.0)	23,968 (45.5)	628,851 (45.2)
Past	32,981 (16.3)	57,318 (24.0)	3,830 (21.5)	74,052 (15.0)	46,490 (23.6)	28,990 (18.3)	7,668 (14.6)	251,329 (18.5)
Unknown	19,981 (9.8)	7,421 (3.1)	996 (5.6)	37,471 (7.6)	9,346 (4.8)	21,045 (13.3)	5,145 (9.8)	101,405 (7.5)
Mean blood pressure, mmHg (SD)								
Systolic	160.9 (22.9)	156.6 (20.0)	157.1 (20.9)	133.5 (22.0)	157.4 (23.5)	136.4 (19.4)	133.0 (20.1)	146.0 (24.8)
Diastolic	91.3 (12.2)	92.3 (12.3)	92.2 (12.1)	80.7 (12.2)	89.9 (13.0)	79.2 (10.1)	80.4 (10.9)	85.7 (13.3)
Hypertension [b]	144,530 (71.2)	181,752 (76.4)	13,668 (76.6)	113,052 (22.9)	133,362 (67.9)	22,232 (14.1)	11,388 (21.6)	619,984 (45.6)
Year of initiation, n (%)								
1988-1993	10,748 (5.3)	2,683 (1.1)	0	20,137 (4.1)	6,182 (3.1)	11,944 (7.6)	5,463 (10.4)	57,157 (4.2)
1994-1999	37,126 (18.3)	11,124 (4.7)	588 (3.3)	60,356 (12.2)	16,230 (8.3)	28,427 (18.0)	7,424 (14.1)	161,275 (11.9)
2000-2005	105,496 (52.0)	51,364 (21.6)	7,514 (42.1)	142,009 (28.7)	32,484 (16.5)	46,137 (29.2)	15,888 (30.2)	400,892 (29.5)
2006-2011	41,214 (20.3)	107,238 (45.1)	6,174 (34.6)	131,472 (26.6)	68,823 (35.0)	41,638 (26.4)	14,726 (28.0)	411,285 (30.2)
2012-2018	8,272 (4.1)	65,514 (27.5)	3,570 (20.0)	140,359 (28.4)	72,766 (37.0)	29,848 (18.9)	9,131 (17.3)	329,460 (24.2)
Medical history, n (%) [c]								
Heart failure	1,107 (0.5)	3,024 (1.3)	100 (0.6)	1,234 (0.2)	403 (0.2)	9,852 (6.2)	269 (0.5)	15,989 (1.2)
Coronary heart disease [d]	19,310 (9.5)	25,597 (10.8)	1,457 (8.2)	46,243 (9.4)	24,899 (12.7)	17,680 (11.2)	2,344 (4.5)	137,530 (10.1)
Peripheral vascular disease	4,233 (2.1)	5,751 (2.4)	316 (1.8)	3,877 (0.8)	6,913 (3.5)	5,781 (3.7)	482 (0.9)	27,353 (2.0)
Stroke	5,090 (2.5)	8,577 (3.6)	396 (2.2)	4,395 (0.9)	5,079 (2.6)	5,766 (3.6)	449 (0.9)	29,752 (2.2)
Arrythmias	3,768 (1.9)	5,343 (2.2)	379 (2.1)	27,442 (5.6)	6,756 (3.4)	9,326 (5.9)	512 (1.0)	53,526 (3.9)
Atrial fibrillation	2,676 (1.3)	3,916 (1.6)	271 (1.5)	19,669 (4.0)	4,214 (2.1)	7,977 (5.0)	292 (0.6)	39,015 (2.9)
Stable angina	3,246 (1.6)	5,233 (2.2)	279 (1.6)	19,313 (3.9)	8,912 (4.5)	4,627 (2.9)	412 (0.8)	42,022 (3.1)
Myocardial infarction	1,446 (0.7)	6,873 (2.9)	262 (1.5)	11,846 (2.4)	2,930 (1.5)	3,755 (2.4)	175 (0.3)	27,287 (2.0)
Diabetes	21,707 (10.7)	80,306 (33.8)	4,503 (25.2)	59,012 (11.9)	32,154 (16.4)	20,901 (13.2)	7,221 (13.7)	225,813 (16.6)
Chronic kidney disease	1,991 (1.0)	11,522 (4.8)	686 (3.8)	4,707 (1.0)	6,018 (3.1)	4,428 (2.8)	444 (0.8)	29,796 (2.2)

Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; SD, standard deviation; BMI, body mass index

[a] Other antihypertensive drugs

[b] Defined as a recorded diagnosis of hypertension or at least three elevated systolic (≥140) or diastolic (≥90) blood pressure readings in the year before cohort entry

[c] Non mutually exclusive categories

[d] Includes stable ischemic heart disease (chronic coronary syndrome), carotid artery disease (carotid stenosis), and peripheral arterial disease

FIGURE LEGENDS

Figure 1 Overall period prevalence of primary care patients with antihypertensive drug prescriptions

Figure 2 Period prevalence of primary care patients with antihypertensive drug prescriptions, stratified by drug class

Figure 3 Treatment trajectory of primary care patients with hypertension with a first-ever antihypertensive drug prescription before January 1, 2007

Figure 4 Treatment trajectory of primary care patients with hypertension with a first-ever antihypertensive drug prescription after January 1, 2007

Figure 1. Overall period prevalence of primary care patients with antihypertensive drug prescriptions

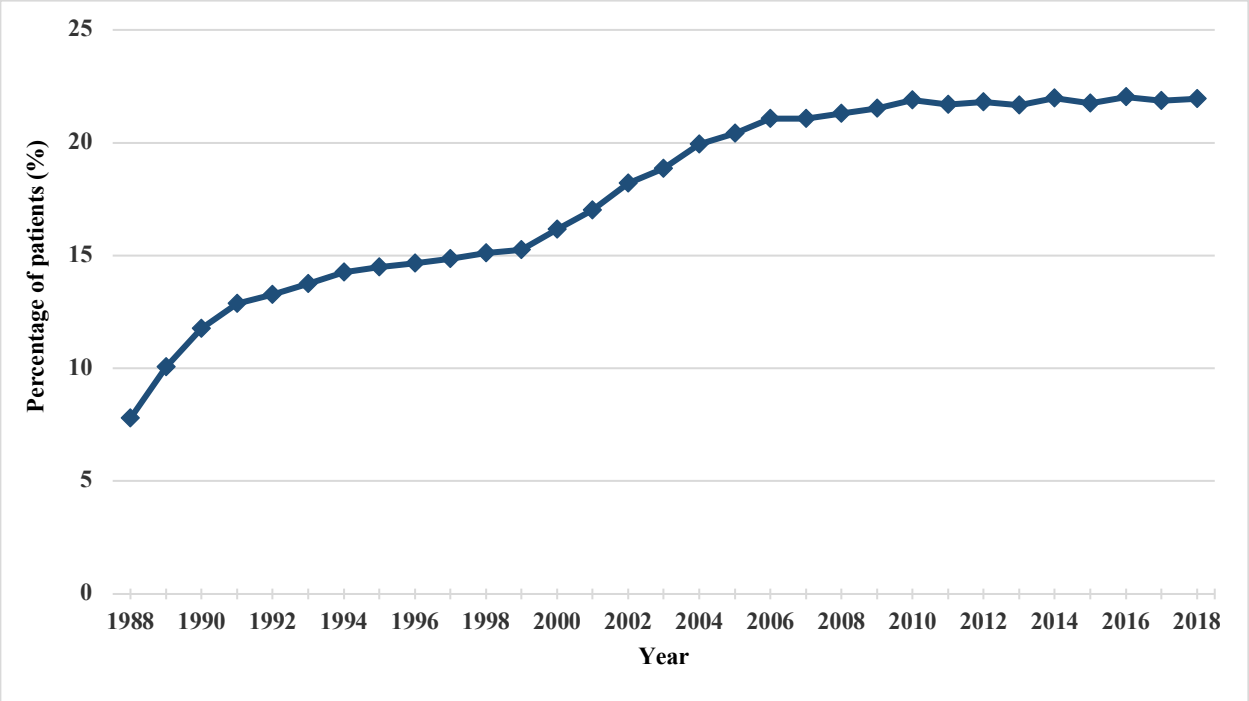


Figure 2. Period prevalence of primary care patients with antihypertensive drug prescriptions, stratified by drug class

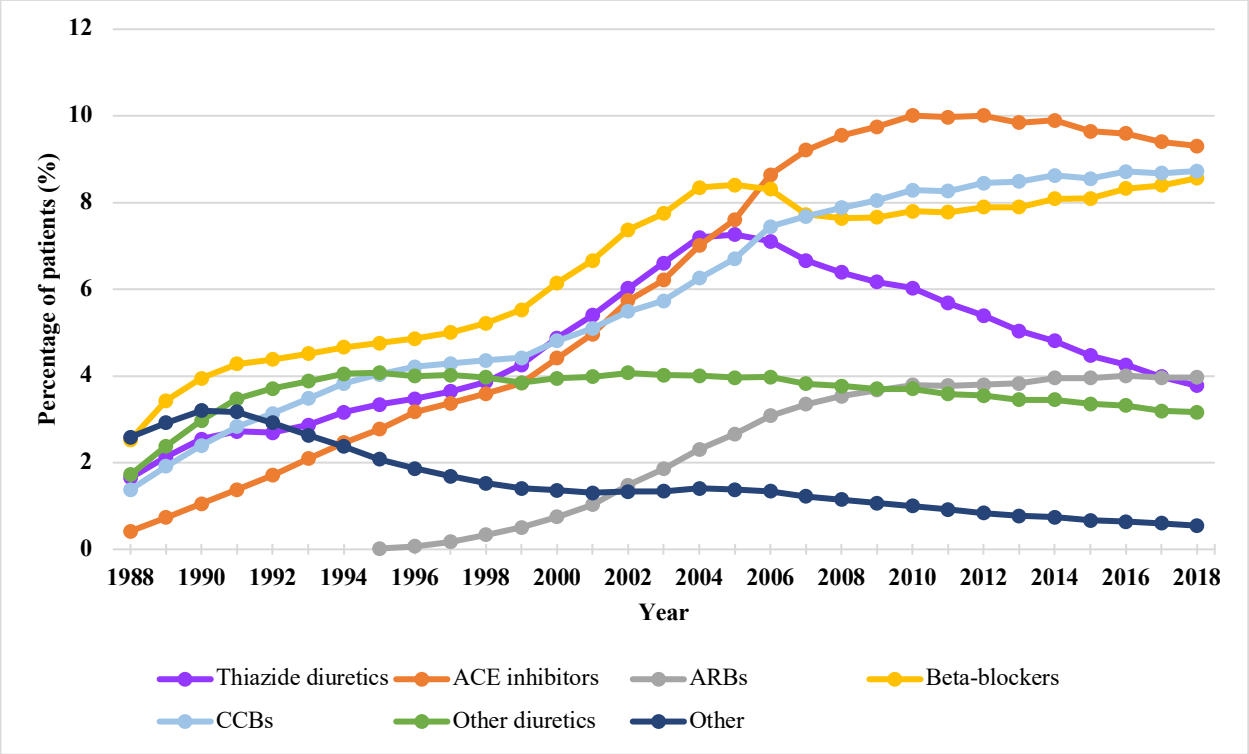
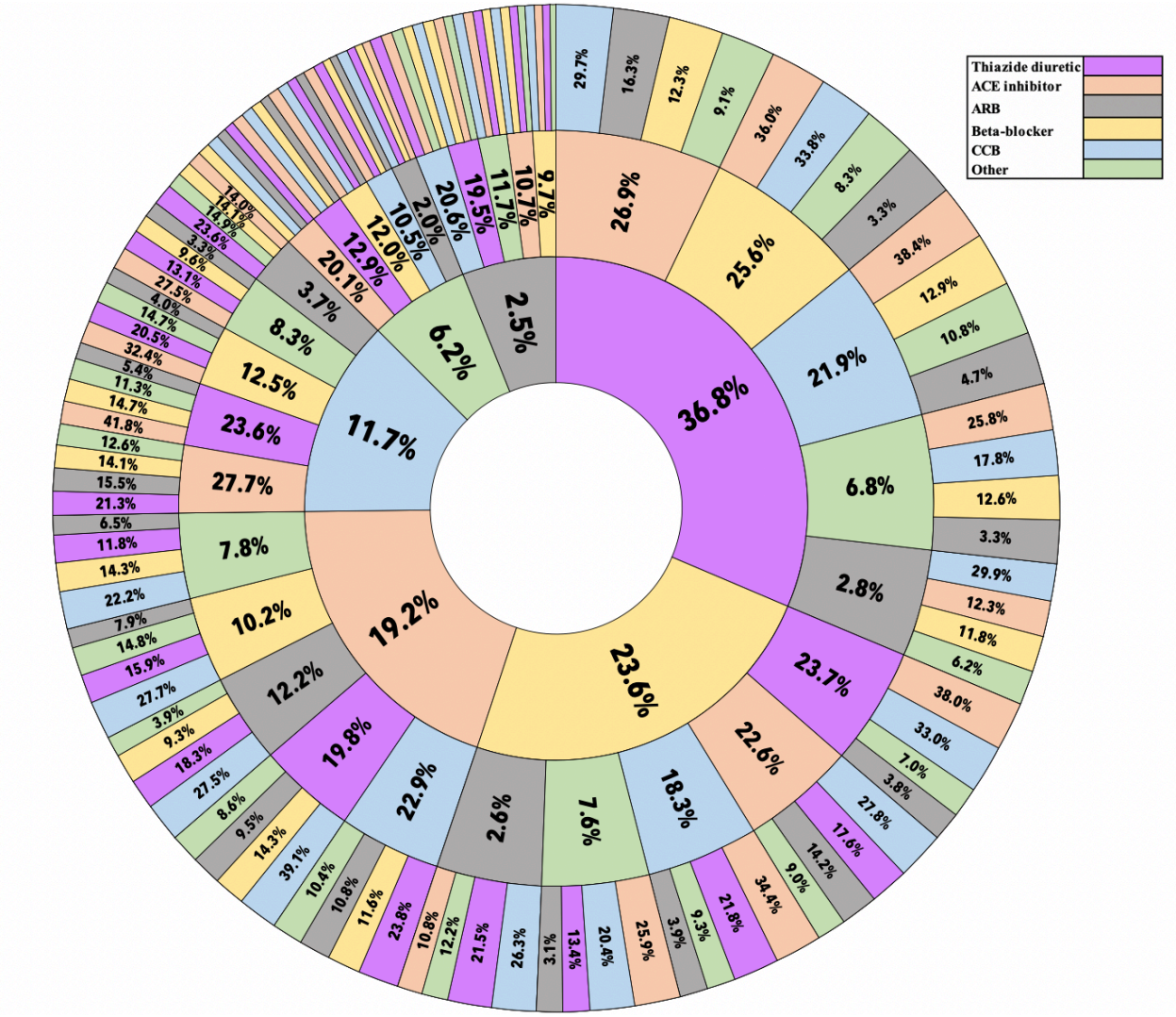


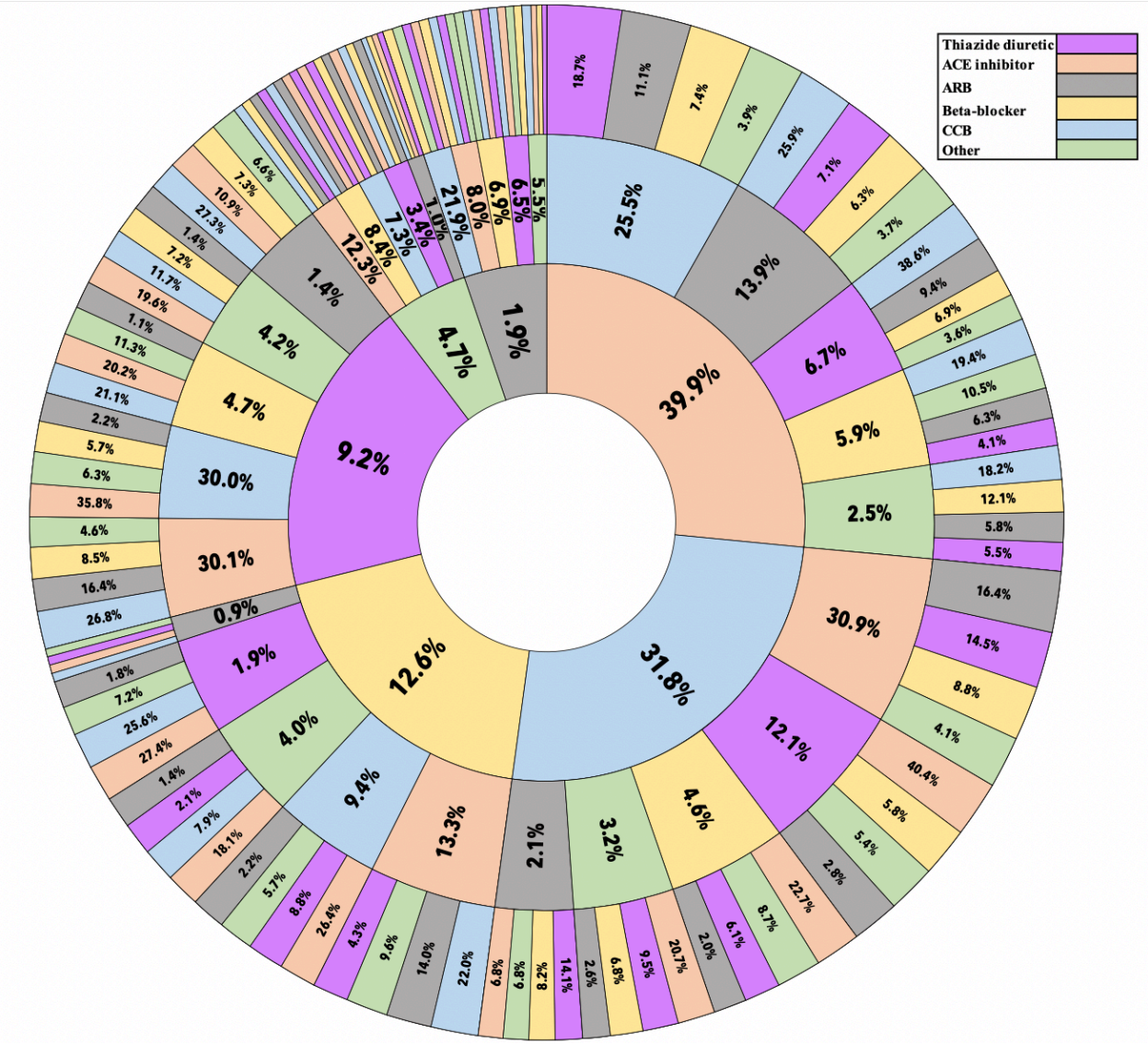
Figure 3. Treatment trajectory of primary care patients with hypertension with a first-ever antihypertensive drug prescription before January 1, 2007 [a]



Abbreviation: angiotensin-converting enzyme inhibitor, ACE inhibitor; angiotensin II receptor blocker, ARB; calcium channel blocker, CCB.

[a] Each concentric circle represents a treatment line. Percentages do not reach 100% as only patients who switched to or added-on a new drug class are included. Fewer patients were prescribed first-line ARBs and other antihypertensive drugs, resulting in thinner slices for these two classes. As such, details of third-line results for ARB and Other are in **Supplementary Figure 15** to better visualize the results**.**

Figure 4. Treatment trajectory of primary care patients with hypertension with a first-ever antihypertensive drug prescription after January 1, 2007 [a]



Abbreviation: angiotensin-converting enzyme inhibitor, ACE inhibitor; angiotensin II receptor blocker, ARB; calcium channel blocker, CCB.

[a] Each concentric circle represents a treatment line. Percentages do not reach 100% as only patients who switched to or added-on a new drug class are included. Fewer patients were prescribed first-line ARBs and other antihypertensive drugs, resulting in thinner slices for these two classes. As such, details of third-line results for ARB and Other are in **Supplementary Figure 16** to better visualize the results.

SUPPLEMENTARY MATERIAL

Treatment and prescribing trends of antihypertensive drugs in 2.7 million UK primary care patients over 31 years: a population-based cohort study

Figures: Treatment trajectory

Supplementary Table 1. British National Formulary codes for antihypertensive drugs

BNF code	BNF header
2020100	Thiazides And Related Diuretics
2020200	Loop Diuretics
2020300	Potassium-sparing Diuretics And Aldosterone Antagonists
2020400	Potassium-sparing Diuretics With Other Diuretics
2020500	Osmotic Diuretics
2020600	Mercurial Diuretics
2020800	Diuretics With Potassium
2040000	Beta-adrenoceptor Blocking Drugs
2040100	Beta-adrenoceptor Blocking Drugs With Diuretic
2050100	Vasodilator Antihypertensive Drugs
2050200	Centrally Acting Antihypertensive Drugs
2050501	Angiotensin-converting Enzyme Inhibitors
2050502	Angiotensin-ii Receptor Antagonists
2050503	Renin Inhibitors
2050504	Angiotensin-ii Receptor Antagonists With Diuretic
2060200	Calcium-channel Blockers
2050400	Alpha-adrenoceptor Blocking Drugs
02020100/02040000	Thiazides And Related Diuretics/Beta-adrenoceptor Blocking Drugs
02020100/02050501	Thiazides And Related Diuretics/Angiotensin-Converting Enzyme Inh
02020100/09050102	Thiazides And Related Diuretics/Hypercalcaemia And Hypercalciuria
02020700/11065300	Carbonic Anhydrase Inhibitors/Carbonic Anhydrase Inhibitors And S
02030200/02040000	Drugs For Arrhythmias/Beta-Adrenoceptor Blocking Drugs
02030201/02040000	Supraventricular & Ventricular Arrhythmias/Beta-Adrenoceptor Bloc
02030202/02060200	Supraventricular Arrhythmias/Calcium-Channel Blockers
02040000/02050000	Beta-Adrenoceptor Blocking Drugs/Hypertension And Heart Failure
02040000/02060200	Beta-Adrenoceptor Blocking Drugs/Calcium-Channel Blockers
02040000/02090000	Beta-adrenoceptor Blocking Drugs/Antiplatelet Drugs
02040000/04070402	Beta-Adrenoceptor Blocking Drugs/Prophylaxis Of Migraine/Drugs Fo
02050200/04070402	Centrally Acting Antihypertensive Drugs/Prophylaxis Of Migraine/O
02050200/04070402/06040101	Centrally Acting Antihypertensive Drugs/Prophylaxis Of Migraine/Oestrogens And Hrt
02050502/02050600	Angiotensin-ii Receptor Antagonists/Other Antihypertensives
04070402/06040101	Prophylaxis Of Migraine/Oestrogens And Hrt

Supplementary Table 2. Distribution of beta-blockers prescriptions among patients with a first-ever and ever prescription

Type of beta-blocker	Number of patients with first-ever prescription (%)[a]	Number of patients with ever prescription (%)[b]
Propranolol 40mg	118,129 (23.9)	221,444 (16.0)
Propranolol 80mg	94,042 (19.0)	195,533 (14.0)
Propranolol 10mg	91,899 (18.6)	175,639 (12.7)
Atenolol 50mg	61,051 (12.4)	390,754 (28.2)
Atenolol 25mg	44,143 (8.9)	289,576 (20.9)
Bisoprolol 2.5mg	25,367 (5.1)	248,670 (18.0)
Bisoprolol 1.25mg	15,345 (3.1)	164,137 (11.8)
Bisoprolol 5mg	9,035 (1.8)	165,388 (12.0)
Metoprolol 50mg	5,149 (1.0)	38,252 (2.8)
Sotalol 40mg	4,802 (1.0)	28,457 (2.1)
Atenolol 100mg	3,758 (0.8)	112,497 (8.1)
Labetalol 100mg	4,168 (0.8)	11,279 (0.8)
Labetalol 200mg	3,143 (0.6)	8,860 (0.6)
Propranolol 160mg	957 (0.2)	19,425 (1.4)
Sotalol 80mg	1,443 (0.3)	17,439 (1.3)
Nebivolol 5mg	1,130 (0.2)	18,169 (1.3)
Bisoprolol 10mg	876 (0.2)	58,102 (4.2)

[a] Other agents included carvedilol, celiprolol, oxprenolol, timolol, acebutolol, pindolol (n=9,886, 2.0%)
[b] Non mutually exclusive categories

Supplementary Table 3. Baseline characteristics of primary care patients with a first-ever antihypertensive drug prescription between January 1, 1988 and December 31, 1999

	Thiazide diuretics	ACE inhibitors	ARBs	Beta-blockers	CCBs	Other diuretics	Other[a]	Total
Total	47,874 (21.9)	13,807 (6.3)	588 (0.3)	80,493 (36.9)	22,412 (10.3)	40,371 (18.5)	12,887 (5.9)	218,432
Males, n (%)	14,305 (29.9)	8,207 (59.4)	351 (59.7)	34,141 (42.4)	11,683 (52.1)	15,865 (39.3)	2,279 (17.7)	86,831 (39.8)
Mean age, years (SD)	62.4 (15.8)	69.8 (13.3)	59.3 (12.7)	48.5 (15.9)	61.5 (14.4)	68.3 (17.1)	56.2 (15.9)	57.7 (17.6)
Mean BMI, kg/m^2 (SD)	27.0 (5.1)	28.0 (5.2)	27.6 (5.0)	25.6 (4.7)	26.5 (4.9)	26.4 (5.5)	26.4 (5.1)	26.4 (5.0)
Smoking status								
Current	10,857 (22.7)	3,362 (24.4)	160 (27.2)	22,935 (28.5)	5,500 (24.5)	8,807 (21.8)	2,870 (22.3)	54,491 (25.0)
Never	23,748 (49.6)	6,712 (48.6)	269 (45.8)	35,541 (44.1)	9,921 (44.3)	15,951 (39.5)	5,623 (43.6)	97,765 (44.8)
Past	3,547 (7.4)	1,195 (8.7)	49 (8.3)	5,225 (6.5)	2,089 (9.3)	3,023 (7.5)	766 (5.9)	15,894 (7.3)
Unknown	9,722 (21.9)	2,538 (18.4)	110 (18.7)	16,792 (20.8)	4,902 (21.9)	12,590 (31.2)	3,628 (28.2)	50,282 (23.0)
Mean blood pressure, mmHg (SD)								
Systolic	158.4 (26.5)	162.4 (23.1)	162.9 (21.1)	139.2 (25.2)	152.5 (25.6)	143.0 (21.9)	139.0 (23.8)	147.2 (26.3)
Diastolic	91.0 (13.3)	94.2 (12.9)	94.1 (11.9)	83.4 (13.5)	87.9 (13.5)	81.5 (10.4)	82.4 (12.1)	86.0 (13.5)
Hypertension [b]	26,714 (55.8)	9,865 (71.4)	424 (72.1)	21,827 (27.1)	9,906 (44.2)	4,271 (10.6)	2,883 (22.4)	75,980 (34.8)
Medical history, n (%) [c]								
Heart failure	773 (1.6)	552 (4.0)	8 (1.4)	87 (0.1)	101 (0.5)	5,950 (14.7)	231 (1.8)	7,702 (3.5)
Coronary heart disease [d]	5,462 (11.4)	2,788 (20.2)	78 (13.3)	12,592 (15.6)	7,624 (34.0)	6,499 (16.1)	914 (7.1)	35,957 (16.5)
Peripheral vascular disease	1,098 (2.3)	475 (3.4)	14 (2.4)	848 (1.1)	1,770 (7.9)	1,821 (4.5)	214 (1.7)	6,240 (2.9)
Stroke	1,274 (2.7)	392 (2.8)	16 (2.7)	718 (0.9)	811 (3.6)	1,584 (3.9)	154 (1.2)	4,949 (2.3)
Arrythmias	1,038 (2.2)	543 (3.9)	19 (3.2)	2,422 (3.0)	1,128 (5.0)	2,834 (7.0)	246 (1.9)	8,230 (3.8)
Atrial fibrillation	761 (1.6)	427 (3.1)	14 (2.4)	1,273 (1.6)	622 (2.8)	2,426 (6.0)	181 (1.4)	5,704 (2.6)
Stable angina	1,261 (2.6)	743 (5.4)	19 (3.2)	5,624 (7.0)	4,568 (20.4)	2,214 (5.5)	240 (1.9)	14,669 (6.7)
Myocardial infarction	596 (1.2)	1,080 (7.8)	8 (1.4)	4,180 (5.2)	1,506 (6.7)	1,918 (4.8)	120 (0.9)	9,408 (4.3)
Diabetes	3,199 (6.7)	4,159 (30.1)	101 (17.2)	5,005 (6.2)	2,631 (11.7)	3,573 (8.9)	757 (5.9)	19,425 (8.9)
Chronic kidney disease	92 (0.2)	96 (0.7)	S[e]	172 (0.2)	125 (0.6)	104 (0.3)	15 (0.1)	607 (0.3)

Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; SD, standard deviation; BMI, body mass index

[a] Other antihypertensive drugs

[b] Defined as a recorded diagnosis of hypertension or at least three elevated systolic (≥120) or diastolic (≥90) blood pressure readings in the year before cohort entry

[c] Non mutually exclusive categories

[d] Includes stable ischemic heart disease (chronic coronary syndrome), carotid artery disease (carotid stenosis), and peripheral arterial disease

[e] Cell <5 patients are suppressed as per Clinical Practice Research Datalink policy

Supplementary Table 4. Baseline characteristics of primary care patients with a first-ever antihypertensive drug prescription between January 1, 2000 and December 31, 2009

	Thiazide diuretics	ACE inhibitors	ARBs	Beta-blockers	CCBs	Other diuretics	Other[a]	Total
Total	137,473 (20.1)	127,627 (18.6)	12,566 (1.8)	228,382 (33.3)	78,206 (11.4)	75,147 (11.0)	26,194 (3.8)	685,595
Males, n (%)	54,697 (39.8)	80,708 (63.2)	7,673 (61.1)	98,018 (42.9)	41,642 (53.3)	28,596 (38.1)	2,552 (9.7)	313,886 (45.8)
Mean age, years (SD)	63.4 (14.0)	57.8 (13.2)	57.7 (13.3)	47.8 (16.6)	61.7 (14.5)	65.8 (17.9)	53.2 (11.0)	56.7 (16.7)
Mean BMI, kg/m^2 (SD)	27.7 (5.4)	29.1 (5.8)	28.7 (5.6)	26.2 (5.2)	27.2 (5.3)	27.5 (6.6)	26.6 (5.2)	27.4 (5.7)
Smoking status								
Current	40,738 (29.6)	33,921 (26.6)	3,219 (25.6)	81,013 (35.5)	21,753 (27.8)	23,869 (31.8)	9,061 (34.6)	213,574 (31.2)
Never	61,901 (45.0)	58,448 (45.8)	5,889 (46.9)	96,980 (42.5)	34,710 (44.4)	29,333 (39.0)	11,696 (44.7)	298,957 (43.6)
Past	24,672 (18.0)	30,762 (24.1)	2,604 (20.7)	32,253 (14.1)	17,890 (22.9)	13,805(18.4)	3,959 (15.1)	125,945 (18.4)
Unknown	10,162 (7.4)	4,496 (3.5)	854 (6.8)	18,136 (7.9)	3,853 (4.9)	8,140 (10.8)	1,478 (5.6)	47,119 (6.8)
Mean blood pressure, mmHg (SD)								
Systolic	162.5 (21.5)	157.0 (20.2)	159.3 (20.4)	137.0 (23.4)	158.0 (24.1)	136.3 (18.8)	133.2 (19.8)	148.6 (24.8)
Diastolic	91.9 (11.7)	91.8 (12.4)	93.0 (11.9)	82.3 (12.8)	89.9 (13.1)	79.1 (9.9)	80.4 (10.8)	86.7 (13.2)
Hypertension [b]	105,944 (77.1)	96,472 (75.6)	9,977 (79.4)	64,283 (28.1)	52,662 (67.3)	10,836 (14.4)	6,087 (23.2)	346,261 (50.5)
Medical history, n (%) [c]								
Heart failure	314 (0.2)	1,491 (1.2)	57 (0.5)	532 (0.2)	162 (0.2)	3,058 (4.1)	32 (0.1)	5,646 (0.8)
Coronary heart disease [d]	12,698 (9.2)	14,997 (11.8)	1,075 (8.6)	24,108 (10.6)	10,374 (13.3)	7,777 (10.3)	1,124 (4.3)	72,153 (10.5)
Peripheral vascular disease	2,771 (2.0)	3,453 (2.7)	234 (1.9)	1,948 (0.9)	2,952 (3.8)	2,655 (3.5)	195 (0.7)	14,208 (2.1)
Stroke	3,253 (2.4)	5,181 (4.1)	264 (2.1)	2,016 (0.9)	1,798 (2.3)	2,645 (3.5)	208 (0.8)	15,365 (2.2)
Arrythmias	2,408 (1.8)	3,199 (2.5)	272 (2.2)	12,125 (5.3)	3,125 (4.0)	4,509 (6.0)	196 (0.7)	25,834 (3.8)
Atrial fibrillation	1,694 (1.2)	2,466 (1.9)	191 (1.5)	8,618 (3.8)	2,060 (2.6)	3,940 (5.2)	96 (0.4)	19,065 (2.8)
Stable angina	1,882 (1.4)	3,164 (2.5)	204 (1.6)	10,202 (4.5)	3,366 (4.3)	1,833 (2.4)	152 (0.6)	20,803 (3.0)
Myocardial infarction	801 (0.6)	3,762 (3.0)	171 (1.4)	5,456 (2.4)	1,066 (1.4)	1,363 (1.8)	52 (0.2)	12,671 (1.8)
Diabetes	15,296 (11.1)	44,128 (34.6)	3,076 (24.5)	23,804 (10.4)	10,267 (13.1)	9,142 (12.2)	3,392 (12.9)	109,105 (15.9)
Chronic kidney disease	1,141 (0.8)	6,190 (4.9)	408 (3.2)	1,522 (0.7)	1,764 (2.3)	1,569 (2.1)	175 (0.7)	12,769 (1.9)

Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; SD, standard deviation; BMI, body mass index

[a] Other antihypertensive drugs

[b] Defined as a recorded diagnosis of hypertension or at least three elevated systolic (≥140) or diastolic (≥90) blood pressure readings in the year before cohort entry

[c] Non mutually exclusive categories

[d] Includes stable ischemic heart disease (chronic coronary syndrome), carotid artery disease (carotid stenosis), and peripheral arterial disease

Supplementary Table 5. Baseline characteristics of primary care patients with a first-ever antihypertensive drug prescription between January 1, 2010 and December 31, 2018

	Thiazide diuretics	ACE inhibitors	ARBs	Beta-blockers	CCBs	Other diuretics	Other[a]	Total
Total	17,509 (3.8)	96,489 (21.2)	4,692 (1.0)	185,458 (40.7)	95,867 (21.0)	42,476 (9.3)	13,551 (3.0)	456,042
Males, n (%)	6,315 (36.1)	60,378 (62.6)	2,707 (57.7)	69,596 (37.5)	50,211 (52.4)	16,171 (38.1)	522 (3.9)	205,900 (45.2)
Mean age, years (SD)	63.9 (14.5)	54.5 (12.3)	54.8 (13.5)	42.5 (16.7)	61.4 (13.7)	63.8 (17.8)	51.4 (8.6)	52.2 (17.4)
Mean BMI, kg/m^2 (SD)	28.5 (6.0)	30.0 (6.2)	29.4 (6.2)	26.5 (5.8)	27.9 (5.5)	28.7 (7.6)	27.3 (5.6)	27.9 (6.2)
Smoking status								
Current	3,354 (19.2)	21,049 (21.8)	833 (17.8)	51,492 (27.8)	19,221 (20.1)	10,550 (24.8)	3,920 (28.9)	110,419 (24.2)
Never	9,296 (53.1)	49,692 (51.5)	2,650 (56.5)	94,849 (51.2)	49,544 (51.7)	19,449 (45.8)	6,649 (49.1)	232,129 (50.9)
Past	4,762 (27.2)	25,361 (26.3)	1,177 (25.1)	36,574 (19.7)	26,511 (27.7)	12,162 (28.6)	2,943 (21.7)	109,490 (24.0)
Unknown	97 (0.6)	387 (0.4)	32 (0.7)	2,543 (1.4)	591 (0.6)	315 (0.7)	39 (0.3)	4,004 (0.9)
Mean blood pressure, mmHg (SD)								
Systolic	154.6 (22.1)	155.4 (19.1)	150.7 (20.8)	127.0 (16.5)	157.9 (22.5)	131.7 (16.6)	127.9 (15.6)	141.6 (23.6)
Diastolic	87.5 (11.9)	92.8 (12.0)	89.7 (12.4)	77.7 (10.3)	90.2 (12.7)	77.5 (9.6)	78.4 (9.6)	84.1 (13.1)
Hypertension [b]	11,872 (67.8)	75,415 (78.2)	3,267 (69.6)	26,942 (14.5)	70,794 (73.8)	7,125 (16.8)	2,418 (17.8)	197,833 (43.4)
Medical history, n (%) [c]								
Heart failure	20 (0.1)	981 (1.0)	35 (0.7)	615 (0.3)	140 (0.1)	844 (2.0)	6 (0.0)	2,241 (0.5)
Coronary heart disease [d]	1,150 (6.6)	7,812 (8.1)	304 (6.5)	9,543 (5.1)	6,901 (7.2)	3,404 (8.0)	306 (2.3)	29,420 (6.5)
Peripheral vascular disease	364 (2.1)	1,823 (1.9)	68 (1.4)	1,081 (0.6)	2,191 (2.3)	1,305 (3.1)	73 (0.5)	6,905 (1.5)
Stroke	563 (3.2)	3,004 (3.1)	116 (2.5)	1,661 (0.9)	2,470 (2.6)	1,537 (3.6)	87 (0.6)	9,438 (2.1)
Arrythmias	322 (1.8)	1,601 (1.7)	88 (1.9)	12,895 (7.0)	2,503 (2.6)	1,983 (4.7)	70 (0.5)	19,462 (4.3)
Atrial fibrillation	221 (1.3)	1,023 (1.0)	66 (1.4)	9,778 (5.3)	1,532 (1.6)	1,611 (3.8)	15 (0.1)	14,246 (3.1)
Stable angina	103 (0.6)	1,326 (1.4)	56 (1.2)	3,487 (1.9)	978 (1.0)	580 (1.4)	20 (0.1)	6,550 (1.4)
Myocardial infarction	49 (0.3)	2,031 (2.1)	83 (1.8)	2,210 (1.2)	358 (0.4)	474 (1.1)	S[e]	5,208 (1.1)
Diabetes	3,212 (18.3)	32,019 (33.2)	1,326 (28.3)	30,203 (16.2)	19,256 (20.1)	8,195 (19.3)	3,072 (22.7)	97,283 (21.3)
Chronic kidney disease	758 (4.3)	5,236 (5.4)	275 (5.9)	3,013 (1.6)	4,129 (4.3)	2,755 (6.5)	254 (1.9)	16,420 (3.6)

Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; SD, standard deviation; BMI, body mass index

[a] Other antihypertensive drugs

[b] Defined as a recorded diagnosis of hypertension or at least three elevated systolic (≥140) or diastolic (≥90) blood pressure readings in the year before cohort entry

[c] Non mutually exclusive categories

[d] Includes stable ischemic heart disease (chronic coronary syndrome), carotid artery disease (carotid stenosis), and peripheral arterial disease

[e] Cell <5 patients are suppressed as per Clinical Practice Research Datalink policy

Supplementary Table 6. Baseline characteristics of hypertensive primary care patients with a first-line antihypertensive drug prescription before January 1, 2007

	Thiazide diuretics	ACE inhibitors	ARBs	Beta-blockers	CCBs	Other diuretics	Other[a]	Total
Total	116,749 (36.8)	60,929 (19.2)	7,922 (2.5)	74,917 (23.6)	37,230 (11.7)	11,907 (3.8)	7,556 (2.4)	317,210
Males, n (%)	47,592 (40.8)	38,033 (62.4)	4,851 (61.2)	36,452 (48.7)	20,299 (54.5)	4,471 (37.6)	1,949 (25.8)	153,647 (48.4)
Mean age, years (SD)	63.8 (12.9)	58.1 (12.7)	57.7 (12.8)	55.4 (14.0)	63.2 (13.0)	67.3 (16.2)	57.8 (14.2)	60.5 (13.8)
Mean body mass index, kg/m^2 (SD)	27.6 (5.2)	29.0 (5.6)	28.7 (5.5)	27.4 (5.1)	27.6 (5.2)	28.1 (6.4)	27.7 (5.5)	27.9 (5.4)
Smoking status								
Current	34,296 (29.4)	17,348 (28.5)	2,151 (27.2)	24,422 (32.6)	10,322 (27.7)	3,437 (28.9)	2,034 (26.9)	94,010 (29.6)
Never	54,632 (46.8)	27,748 (45.5)	3,710 (46.8)	34,271 (45.8)	16,630 (44.7)	5,188 (43.6)	3,607 (47.7)	145,786 (46.0)
Past	17,776 (15.2)	12,132 (19.9)	1,497 (18.9)	9,579 (12.8)	7,009 (18.8)	1,905 (16.0)	875 (11.6)	50,773 (16.0)
Unknown	10,045 (8.6)	3,701 (6.1)	564 (7.1)	6,645 (8.9)	3,269 (8.8)	1,377 (11.6)	1,040 (13.8)	26,641 (8.4)
Mean blood pressure, mmHg (SD)								
Systolic	168.7 (16.9)	163.5 (17.2)	164.1 (17.5)	164.8 (18.9)	168.2 (18.2)	153.4 (17.5)	160.0 (20.8)	166.2 (17.9)
Diastolic	95.1 (10.0)	94.8 (10.9)	95.4 (10.5)	96.1 (10.9)	94.3 (11.3)	85.7 (10.2)	93.0 (11.2)	94.9 (10.6)
Medical history, n (%) [b]								
Heart failure	262 (0.2)	493 (0.8)	21 (0.3)	122 (0.2)	103 (0.3)	1,110 (9.3)	41 (0.5)	2,152 (0.7)
Coronary heart disease [c]	13,123 (11.2)	7,359 (12.1)	702 (8.9)	10,717 (14.3)	6,047 (16.2)	2,267 (19.0)	672 (8.9)	20,887 (6.6)
Peripheral vascular disease	2,431 (2.1)	1,737 (2.9)	141 (1.8)	874 (1.2)	1,739 (4.7)	574 (4.8)	102 (1.3)	7,598 (2.4)
Stroke	2,597 (2.2)	1,921 (3.2)	140 (1.8)	1,067 (1.4)	1,133 (3.0)	612 (5.1)	125 (1.7)	7,595 (2.4)
Arrythmias	2,009 (1.7)	1,318 (2.2)	155 (2.0)	2,410 (3.2)	1,125 (3.0)	1,023 (8.6)	125 (1.7)	8,165 (2.6)
Atrial fibrillation	1,395 (1.2)	984 (1.6)	103 (1.3)	1,650 (2.2)	765 (2.1)	882 (7.4)	83 (1.1)	5,862 (1.8)
Stable angina	2,093 (1.8)	1,583 (2.6)	126 (1.6)	3,933 (5.2)	2,137 (5.7)	718 (6.0)	139 (1.8)	10,729 (3.4)
Myocardial infarction	799 (0.7)	1,203 (2.0)	76 (1.0)	1,908 (2.5)	724 (1.9)	446 (3.7)	53 (0.7)	5,209 (1.6)
Diabetes	12,048 (10.3)	22,004 (36.1)	1,773 (22.4)	9,258 (12.4)	5,149 (13.8)	2,240 (18.8)	1,090 (14.4)	53,562 (16.9)
Chronic kidney disease	356 (0.3)	937 (1.5)	98 (1.2)	294 (0.4)	392 (1.1)	97 (0.8)	32 (0.4)	2,206 (0.7)

Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; SD, standard deviation; BMI, body mass index

[a] Other antihypertensive drugs

[b] Non mutually exclusive categories

[c] Includes stable ischemic heart disease (chronic coronary syndrome), carotid artery disease (carotid stenosis), and peripheral arterial disease

Supplementary Table 7. Baseline characteristics of hypertensive primary care patients with a first-line antihypertensive drug prescription after January 1, 2007

	Thiazide diuretics	ACE inhibitors	ARBs	Beta-blockers	CCBs	Other diuretics	Other[a]	Total
Total	27,781 (9.2)	120,823 (39.9)	5,746 (1.9)	38,135 (12.6)	96,132 (31.8)	10,325 (3.4)	3,832 (1.3)	302,774
Males, n (%)	11,172 (40.2)	74,394 (61.6)	3,448 (60.0)	13,662 (35.8)	52,042 (54.1)	3,751 (36.3)	368 (9.6)	158,839 (52.5)
Mean age, years (SD)	66.2 (12.4)	54.4 (11.9)	55.8 (12.7)	49.7 (16.3)	63.8 (11.9)	66.1 (17.2)	51.1 (10.6)	58.1 (14.0)
Mean body mass index, kg/m^2 (SD)	28.1 (5.6)	30.0 (6.1)	29.3 (6.0)	27.6 (5.9)	28.2 (5.4)	29.4 (7.7)	28.4 (6.0)	28.9 (6.0)
Smoking status								
Current	5,037 (18.1)	25,466 (21.1)	1,102 (19.2)	8,238 (21.6)	18,427 (19.2)	2,200 (21.3)	950 (24.8)	61,420 (20.3)
Never	14,713 (53.0)	62,859 (52.0)	3,080 (53.6)	20,641 (54.1)	49,482 (51.5)	4,945 (47.9)	2,011 (52.5)	157,731 (52.1)
Past	7,844 (28.2)	31,884 (26.4)	1,505 (26.2)	9,072 (23.8)	27,632 (28.7)	3,118 (30.2)	858 (22.4)	81,913 (27.1)
Unknown	187 (0.7)	614 (0.5)	59 (1.0)	184 (0.5)	591 (0.6)	62 (0.6)	13 (0.3)	1,710 (0.6)
Mean blood pressure, mmHg (SD)								
Systolic	164.4 (15.3)	160.0 (15.6)	160.3 (16.7)	150.8 (17.0)	164.6 (16.4)	147.7 (15.1)	148.8 (17.0)	161.1 (16.5)
Diastolic	91.4 (10.3)	95.2 (10.1)	94.2 (10.2)	89.4 (11.0)	92.9 (10.8)	83.2 (9.8)	89.4 (10.5)	93.4 (10.7)
Medical history, n (%) [b]								
Heart failure	23 (0.1)	416 (0.3)	21 (0.4)	187 (0.5)	15 (0.0)	278 (2.7)	S[d]	1,042 (0.3)
Coronary heart disease [c]	2,125 (7.6)	7,822 (6.5)	349 (6.1)	3,479 (9.1)	7,071 (7.4)	1,239 (12.0)	155 (4.0)	22,240 (7.3)
Peripheral vascular disease	576 (2.1)	1,829 (1.5)	86 (1.5)	345 (0.9)	2,090 (2.2)	374 (3.6)	25 (0.7)	5,325 (1.8)
Stroke	688 (2.5)	2,512 (2.1)	103 (1.8)	543 (1.4)	1,997 (2.1)	559 (5.4)	32 (0.9)	6,434 (2.1)
Arrythmias	495 (1.8)	1,557 (1.3)	93 (1.6)	3,402 (8.9)	1,796 (1.9)	687 (6.7)	22 (0.6)	8,052 (2.7)
Atrial fibrillation	328 (1.2)	938 (0.8)	66 (1.1)	2,619 (6.9)	1,146 (1.2)	577 (5.6)	8 (0.2)	5,682 (1.9)
Stable angina	206 (0.7)	843 (0.7)	40 (0.7)	1,252 (3.3)	778 (0.8)	236 (2.3)	10 (0.3)	3,355 (1.1)
Myocardial infarction	81 (0.3)	762 (0.6)	39 (0.7)	575 (1.5)	291 (0.3)	156 (1.5)	S[d]	1,906 (0.6)
Diabetes	4,487 (16.2)	35,055 (29.0)	1,427 (24.8)	10,847 (28.4)	18,746 (19.5)	2,812 (27.2)	1,222 (31.9)	74,596 (24.6)
Chronic kidney disease	1,134 (4.1)	6,195 (5.1)	335 (5.8)	1,097 (2.9)	4,237 (4.4)	892 (8.6)	91 (2.4)	14,071 (4.6)

Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; SD, standard deviation; BMI, body mass index

[a] Other antihypertensive drugs

[b] Non mutually exclusive categories

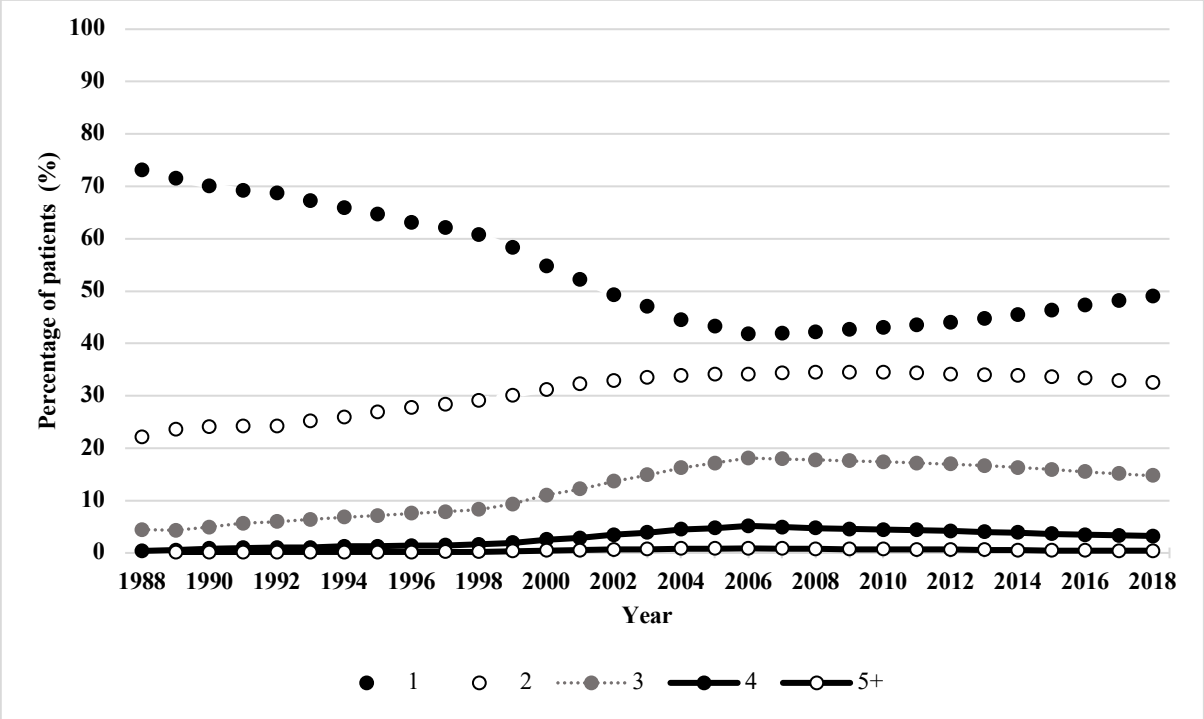
[c] Includes stable ischemic heart disease (chronic coronary syndrome), carotid artery disease (carotid stenosis), and peripheral arterial disease

[d] Cell <5 patients are suppressed as per Clinical Practice Research Datalink policy

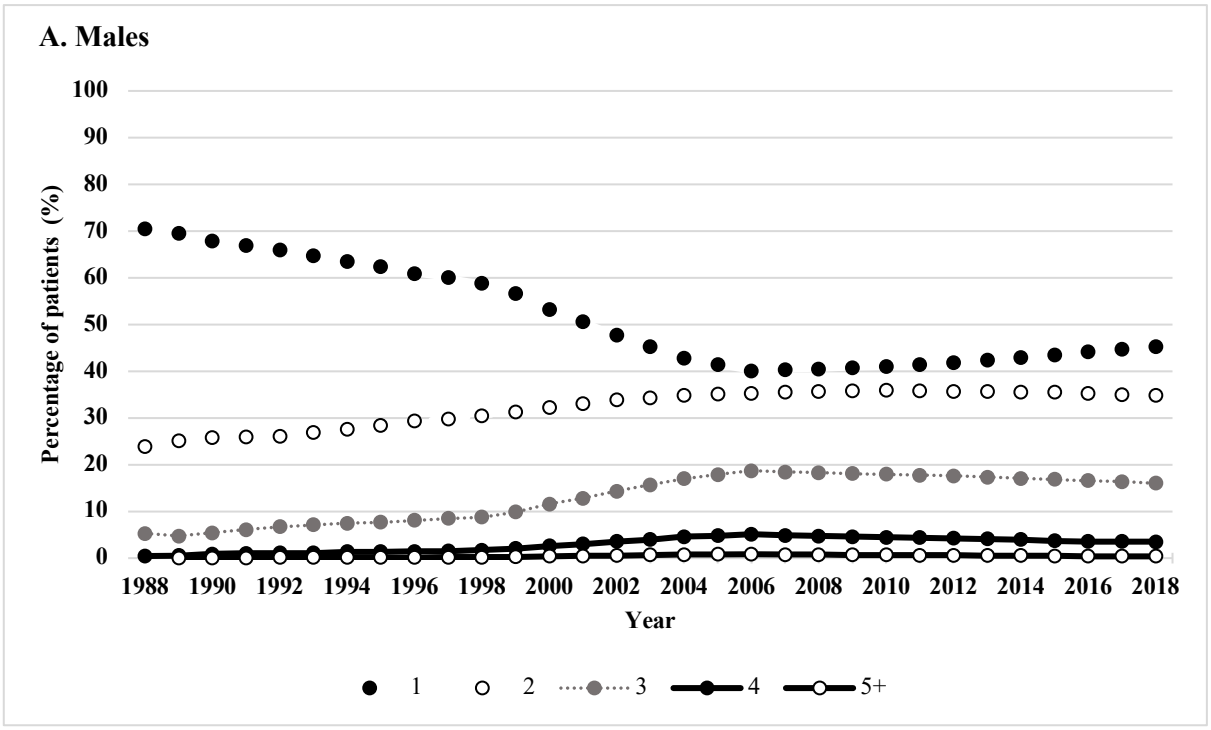
Supplementary Table 8. Percentage of patients with switches or add-ons and median number of days of prescription before treatment change

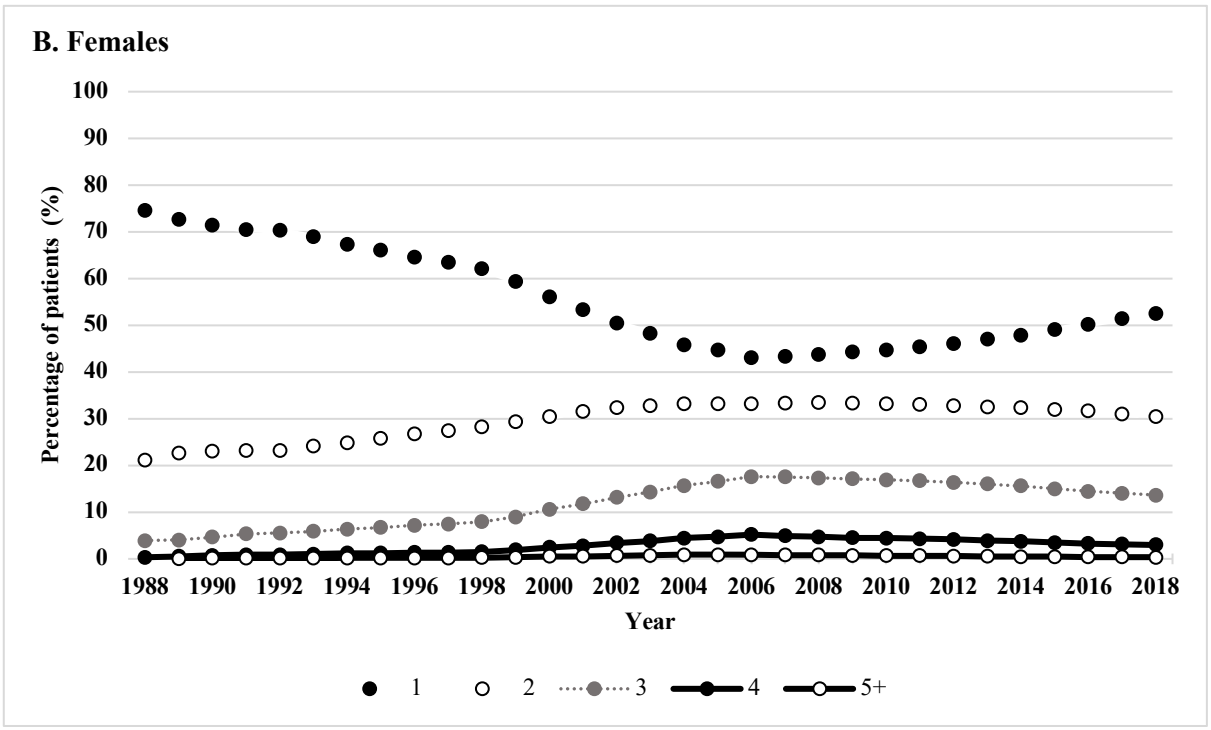
Number of switches or add-ons	Pre-2007 cohort		Post-2007 cohort	
	n (%)	Median number of days of prescription (interquartile range)	n (%)	Median number of days of prescription (interquartile range)
0	65,323 (20.6)	801 (64-2678)	141,587 (46.8)	580 (83-1535)
1	71,726 (22.6)	1232 (252-2849)	83,870 (27.7)	704 (154-1618)
2	71,614 (22.6)	1188 (250-2676)	46,737 (15.4)	625 (124-1492)
3	56,959 (18.0)	1048 (191-2470)	20,933 (6.9)	519 (83-1331)
4	33,559 (11.0)	847 (132-2138)	7,302 (2.4)	442 (53-1183)
≥5	18,029 (5.7)	710 (102-1922)	2,345 (0.8)	319 (26-1025)

Supplementary Figure 1. Percentage of primary care patients with antihypertensive drug prescriptions, stratified by treatment intensity (number of classes prescribed)

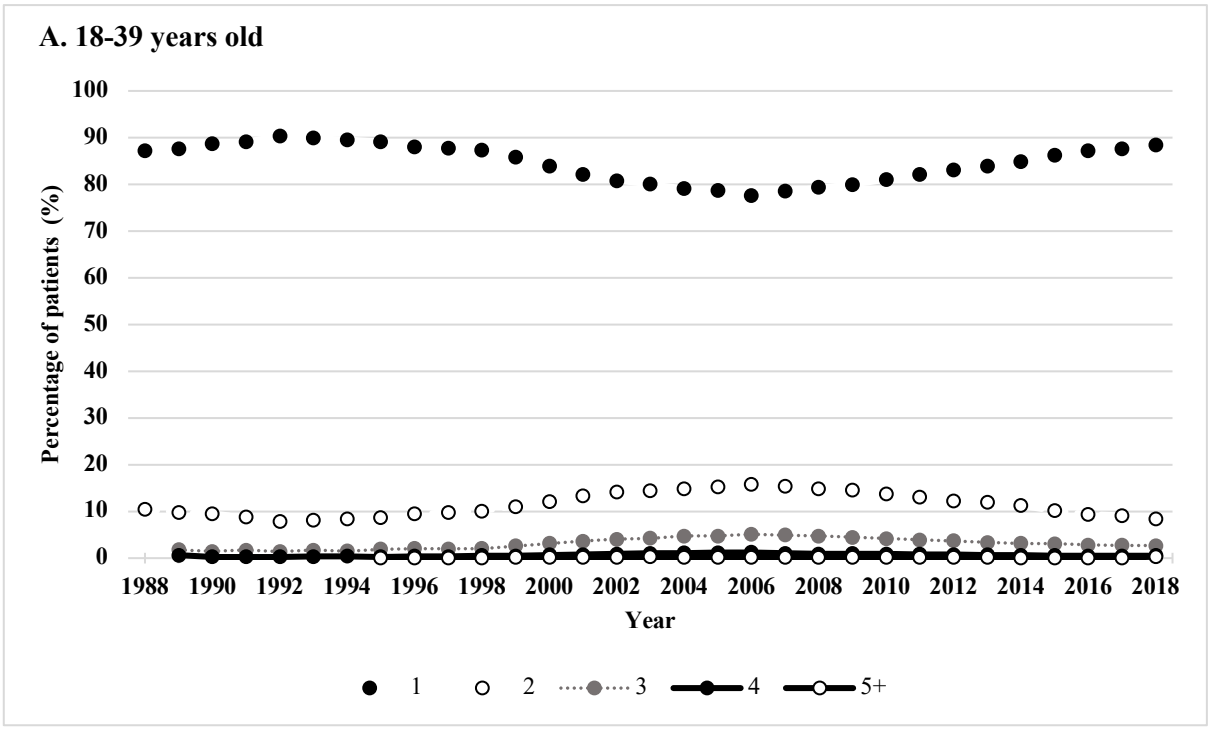


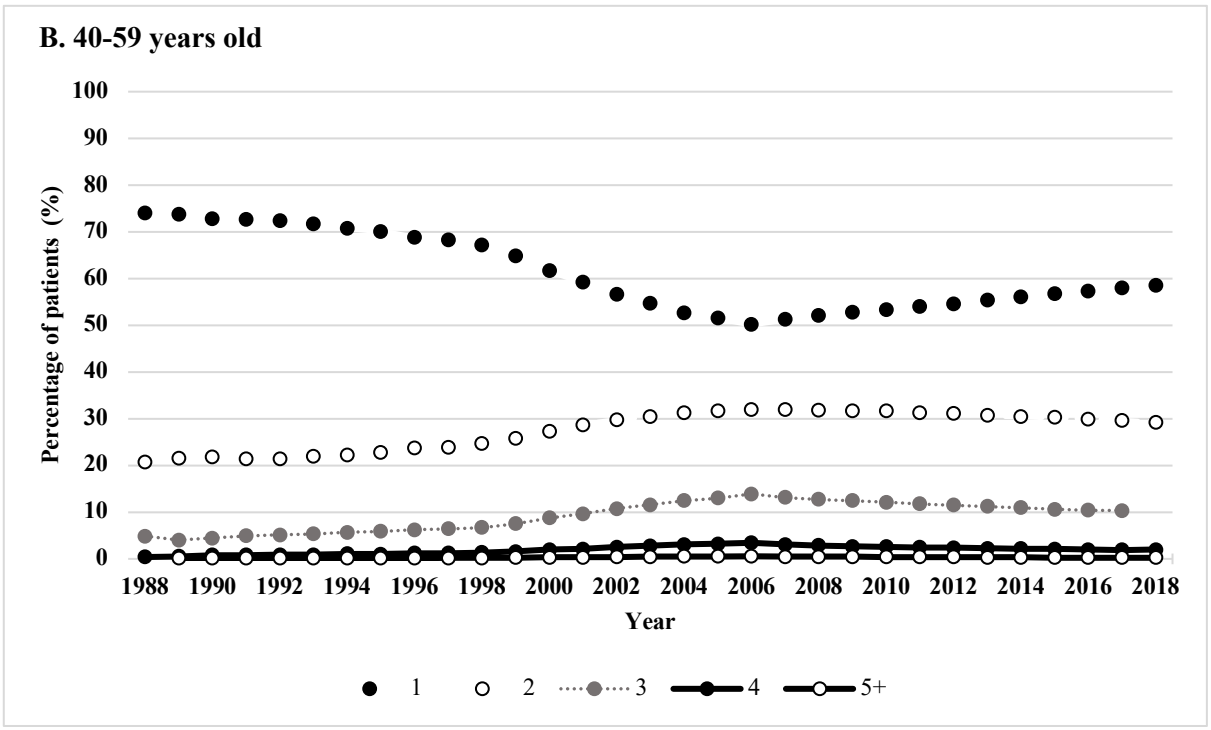
Supplementary Figures 2AB. Percentage of male and female primary care patients with antihypertensive drug prescriptions, stratified by treatment intensity (number of classes prescribed)



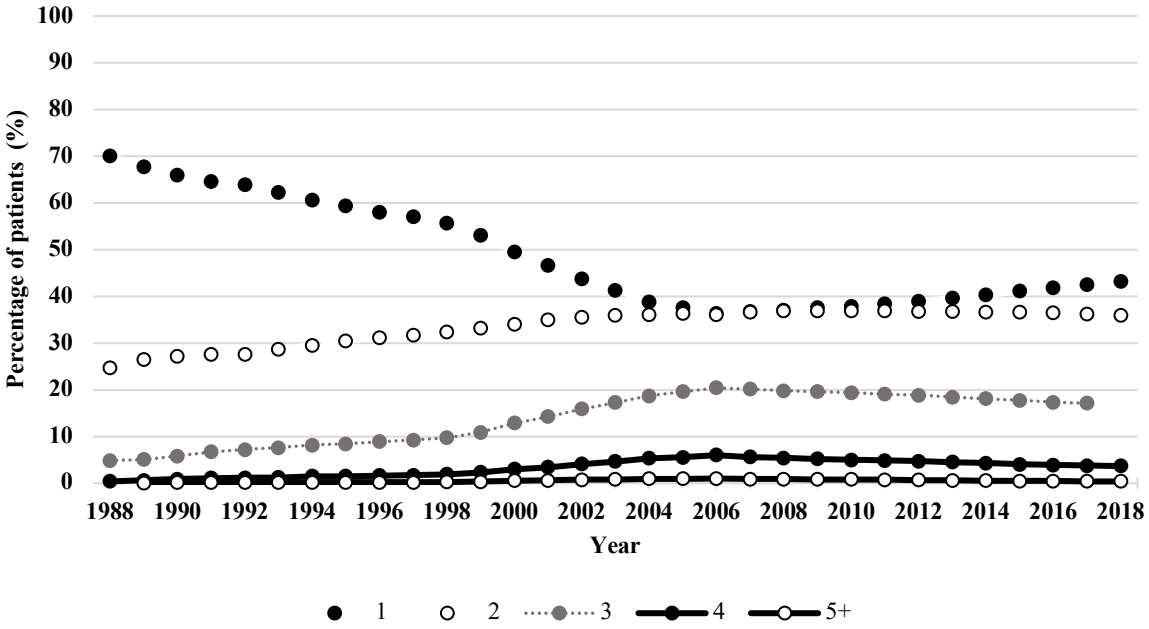


Supplementary Figures 3A-D. Percentage of primary care patients with antihypertensive drug prescriptions for each age group, stratified by treatment intensity (number of classes prescribed)

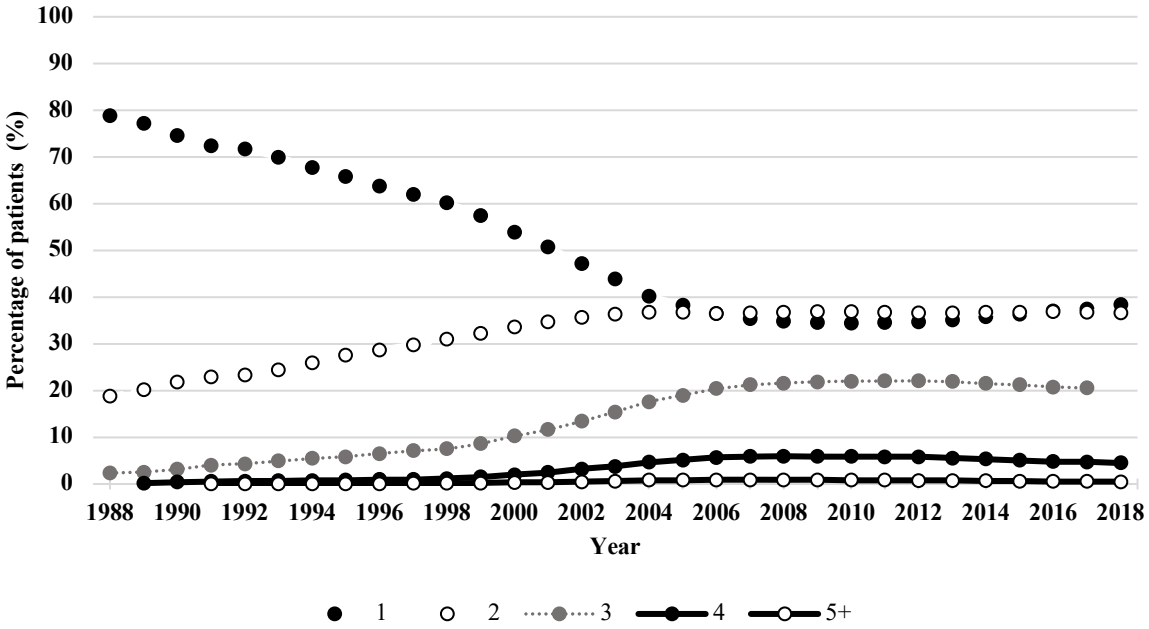




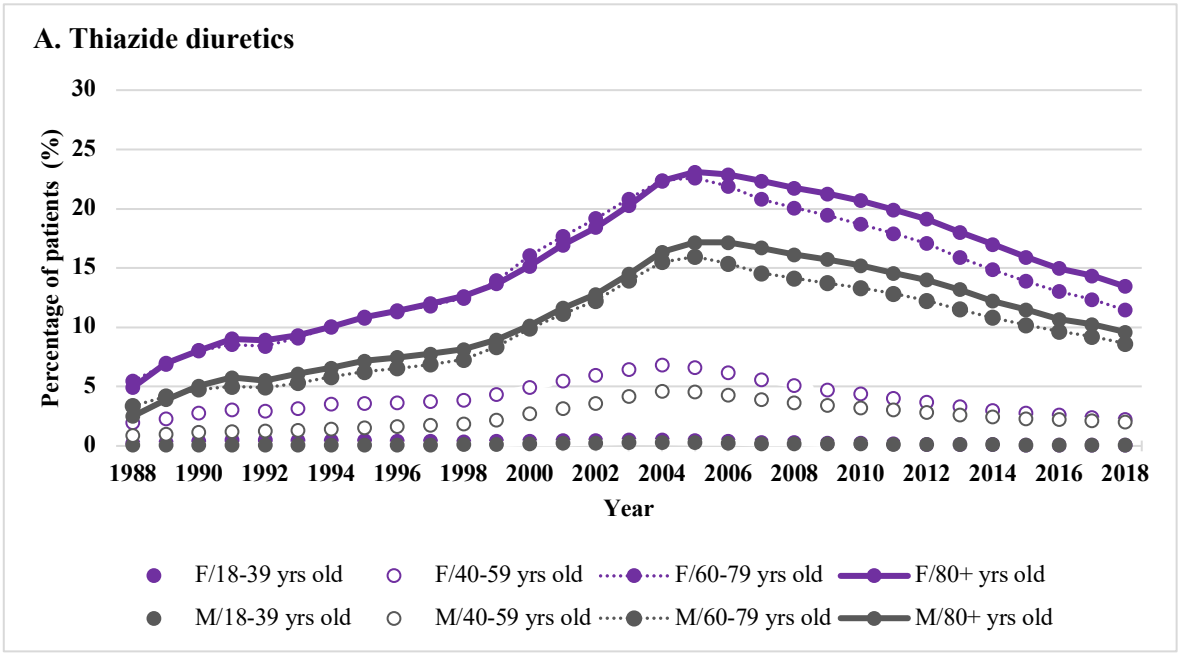
C. 60-79 years old

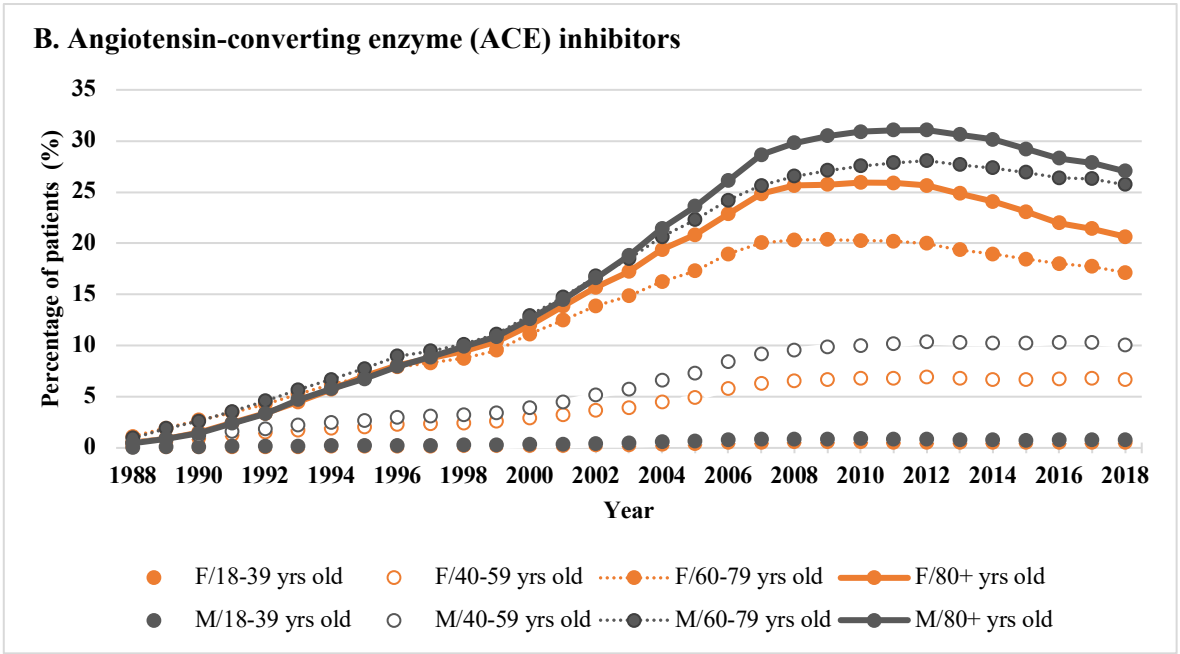


D. 80+ years old

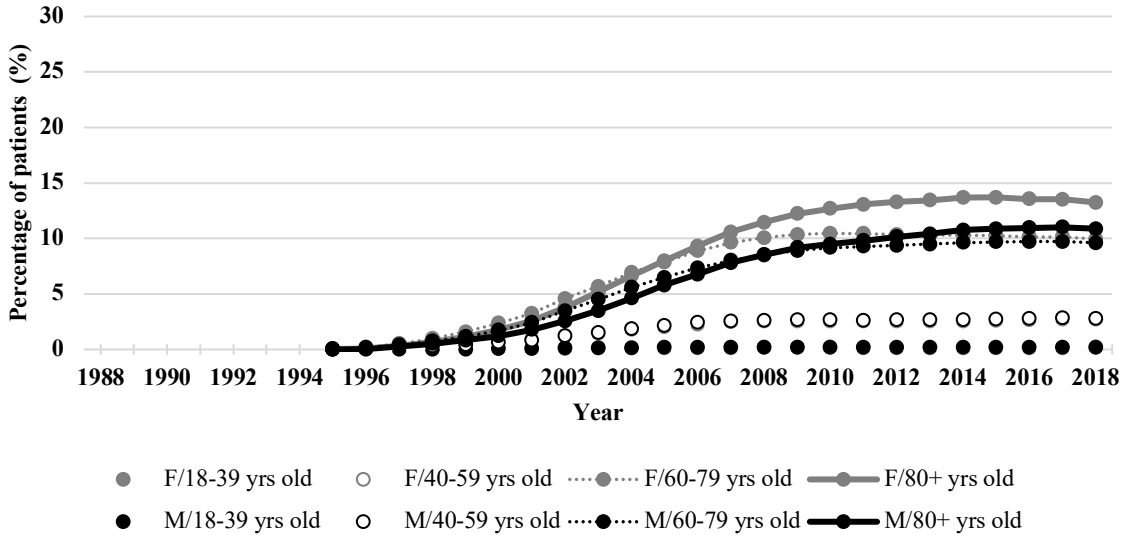


Supplementary Figures 4A-G. Period prevalence of primary care patients for each antihypertensive drug class, stratified by sex and age

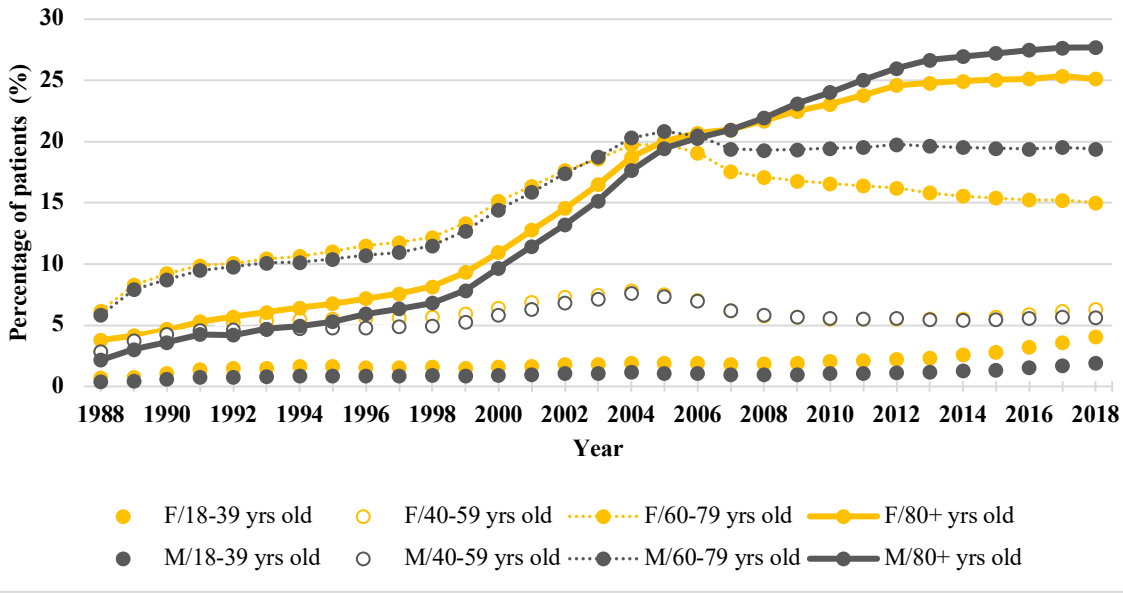




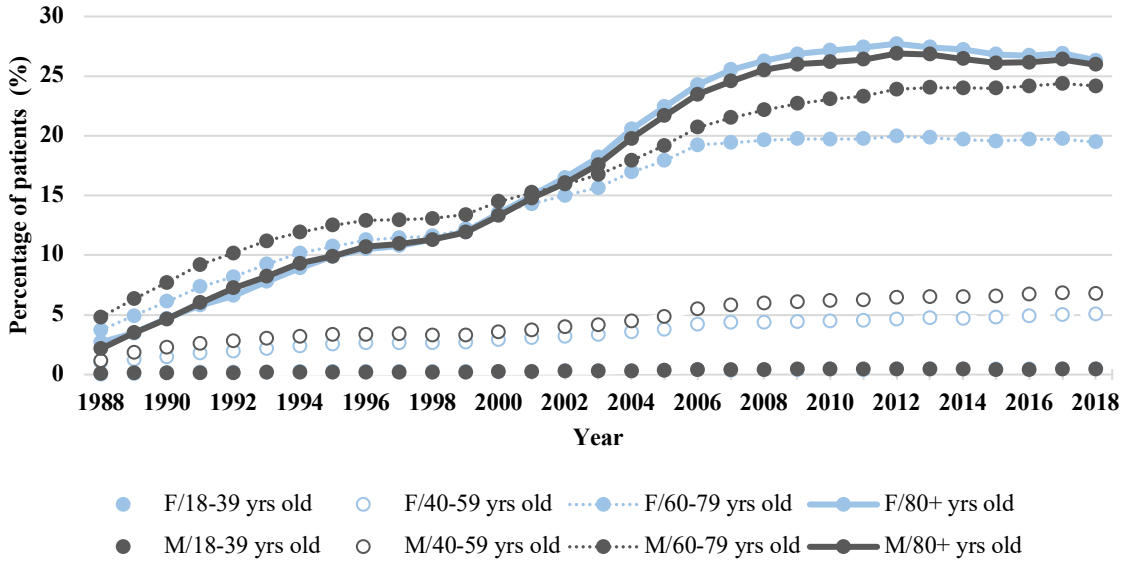
C. Angiotensin II receptor blockers (ARBs)



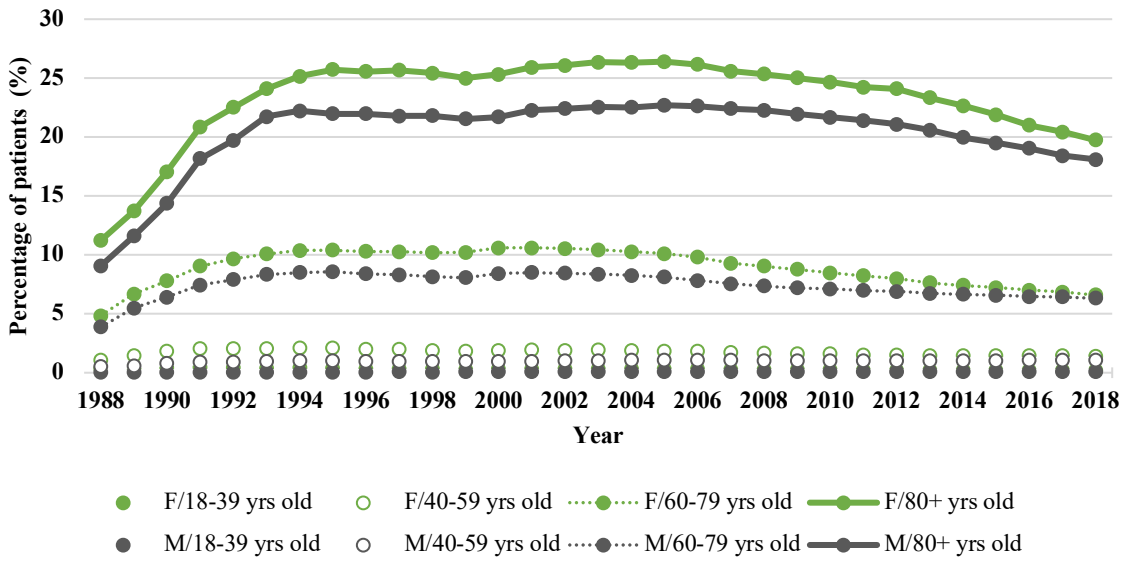
D. Beta-blockers



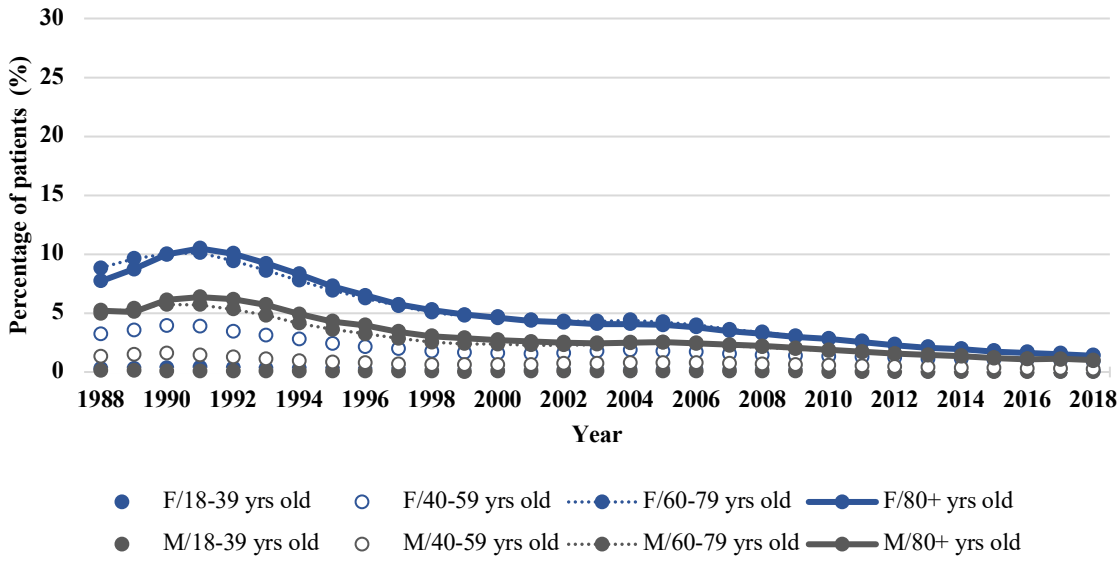
E. Calcium channel blockers (CCBs)



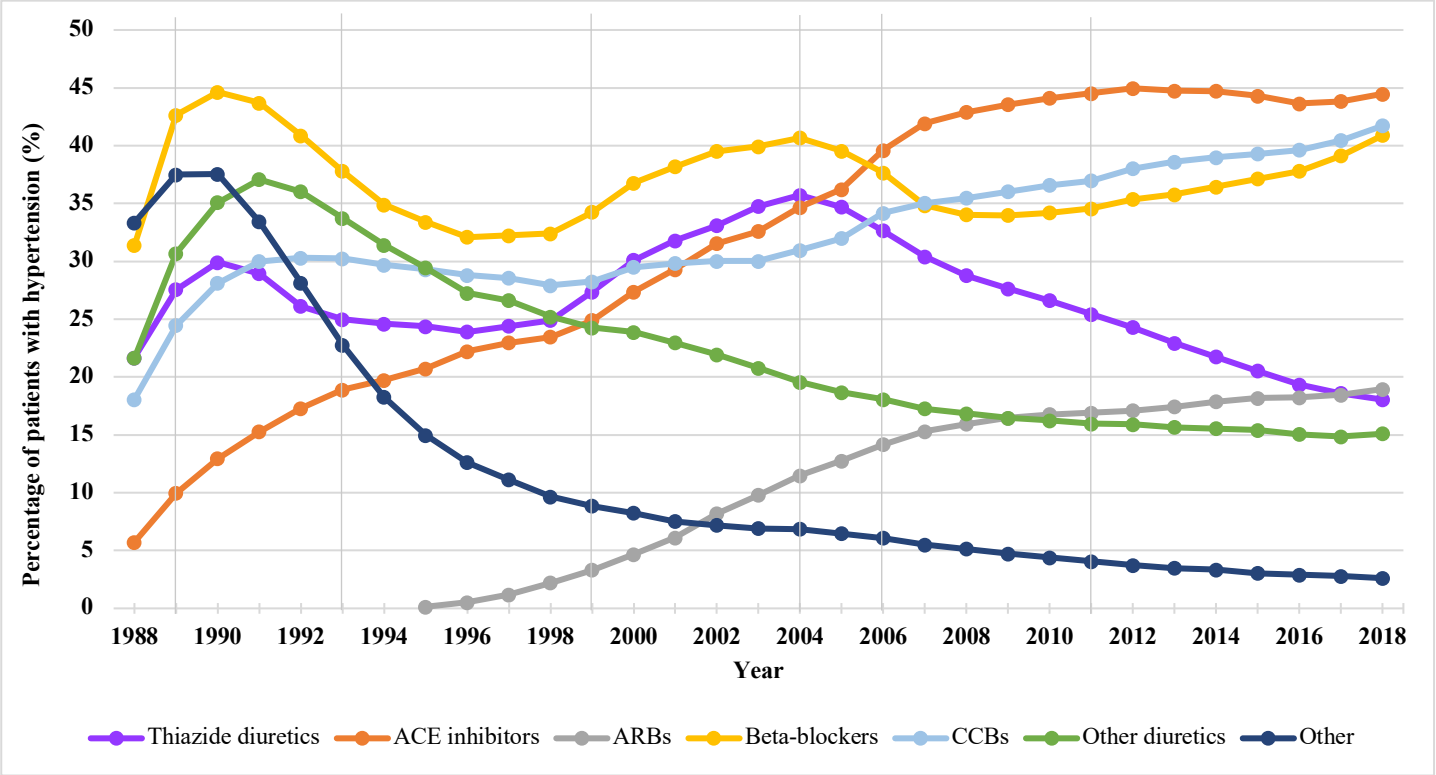
F. Other diuretics



G. Other antihypertensives



Supplementary Figure 5. Period prevalence of primary care patients with hypertension and with antihypertensive drug prescriptions, stratified by antihypertensive drug class [a]



[a] The vertical grey bars denote the year of publication of hypertension management guidelines or guideline updates by the British Hypertension Society (BHS)[1-3] and the National Institute for Health and Care Excellence (NICE), in collaboration with BHS.[4-5]

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4. National Institute for Clinical Excellence. *Clinical guideline 18. Hypertension - management of hypertension in adults in primary care.* NICE, London, 2004.
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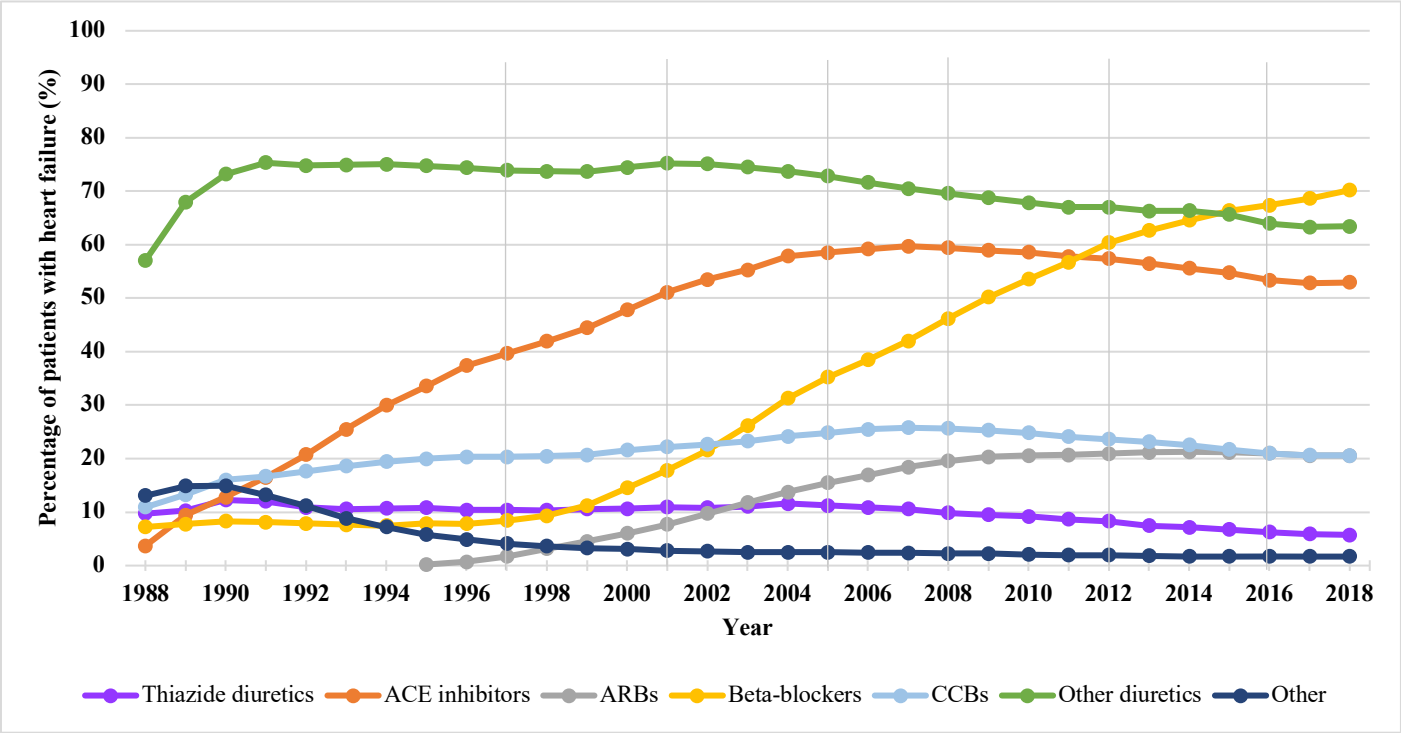
6. National Institute for Health and Clinical Excellence. *Hypertension: clinical management of primary hypertension in adults (update) (Clinical guideline 127).* 2011.

Supplementary Figure 6. Period prevalence of primary care patients with heart failure and with antihypertensive drug prescriptions, stratified by antihypertensive drug class [a]



[a] The vertical grey bars denote the year of publication of heart failure management guidelines or guideline updates by the European Society of Cardiology (ESC).

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1. Remme WJ, Cleland JGF, Task Force of the Working Group on Heart Failure of the European Society of Cardiology. The treatment of heart failure. Eur Heart J 1997; 18: 736-53.
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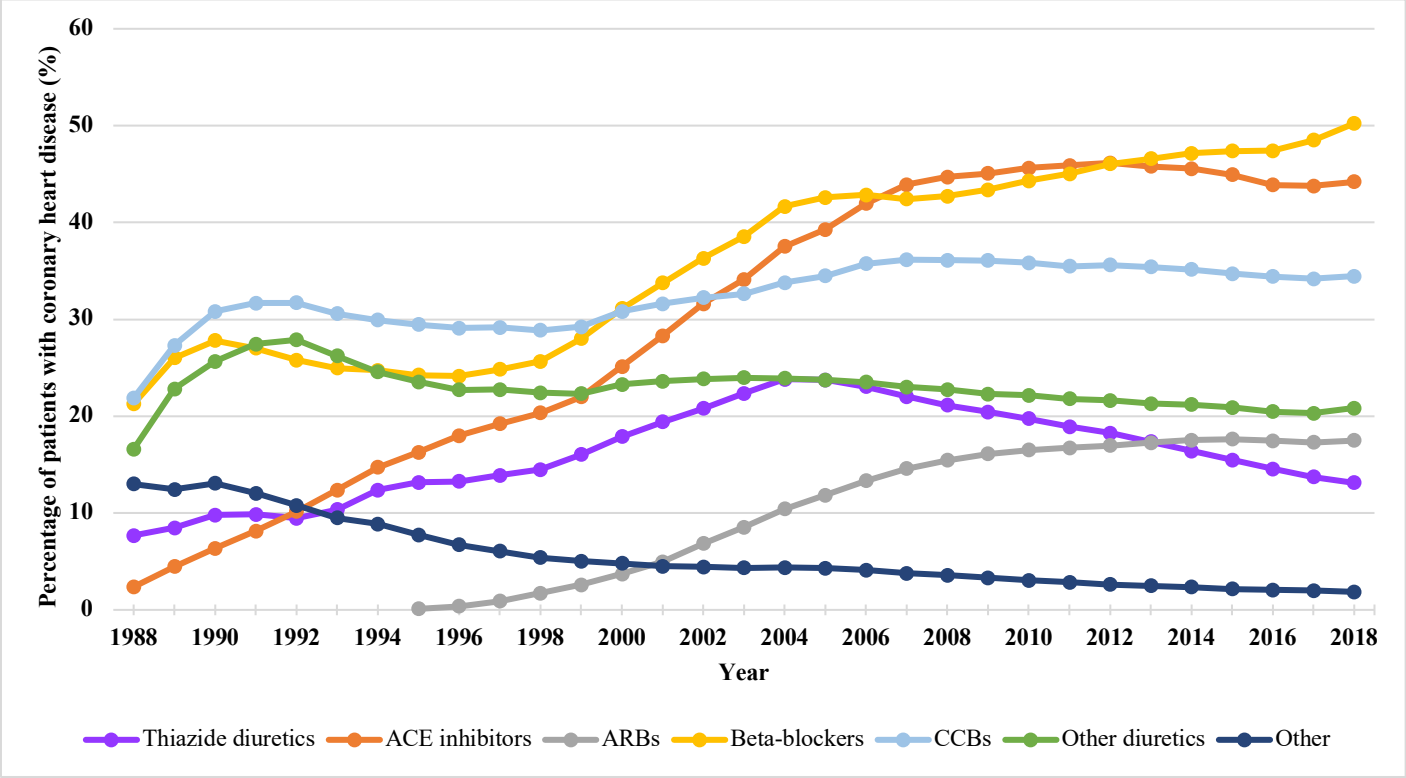
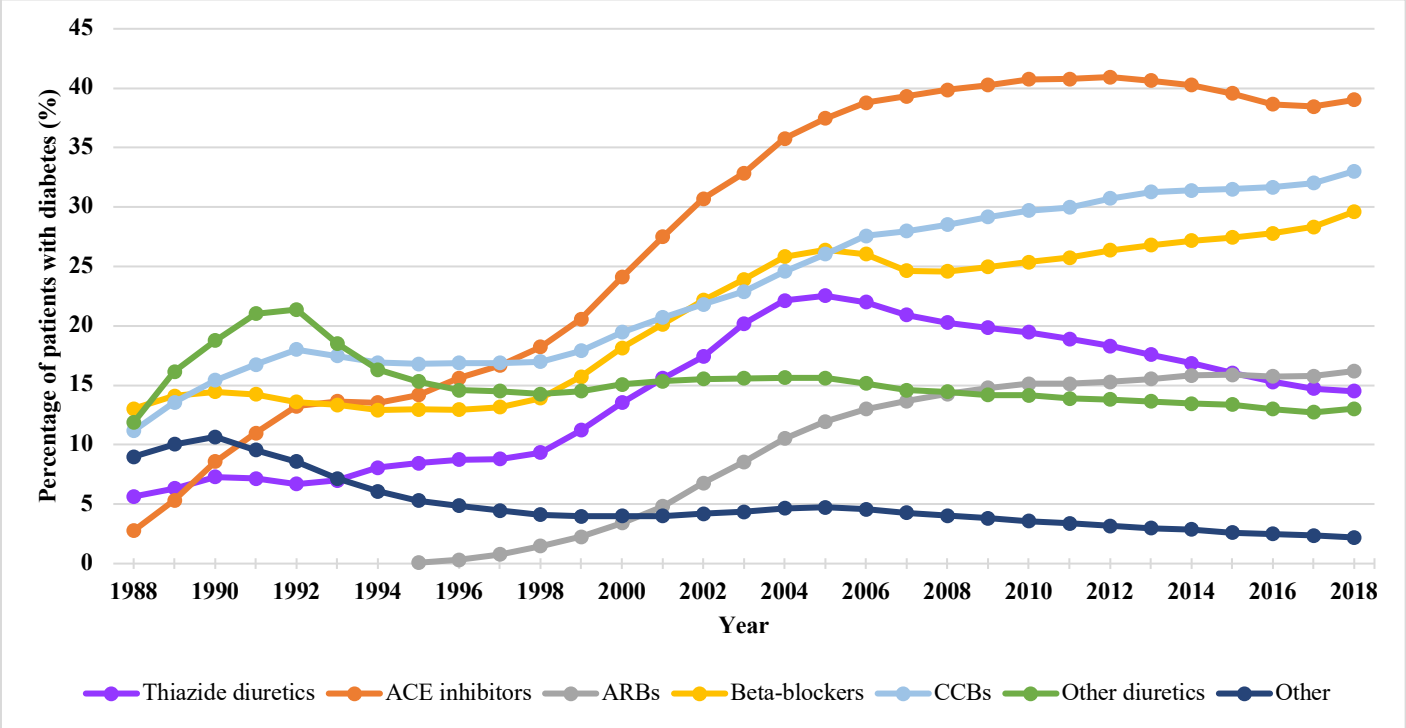
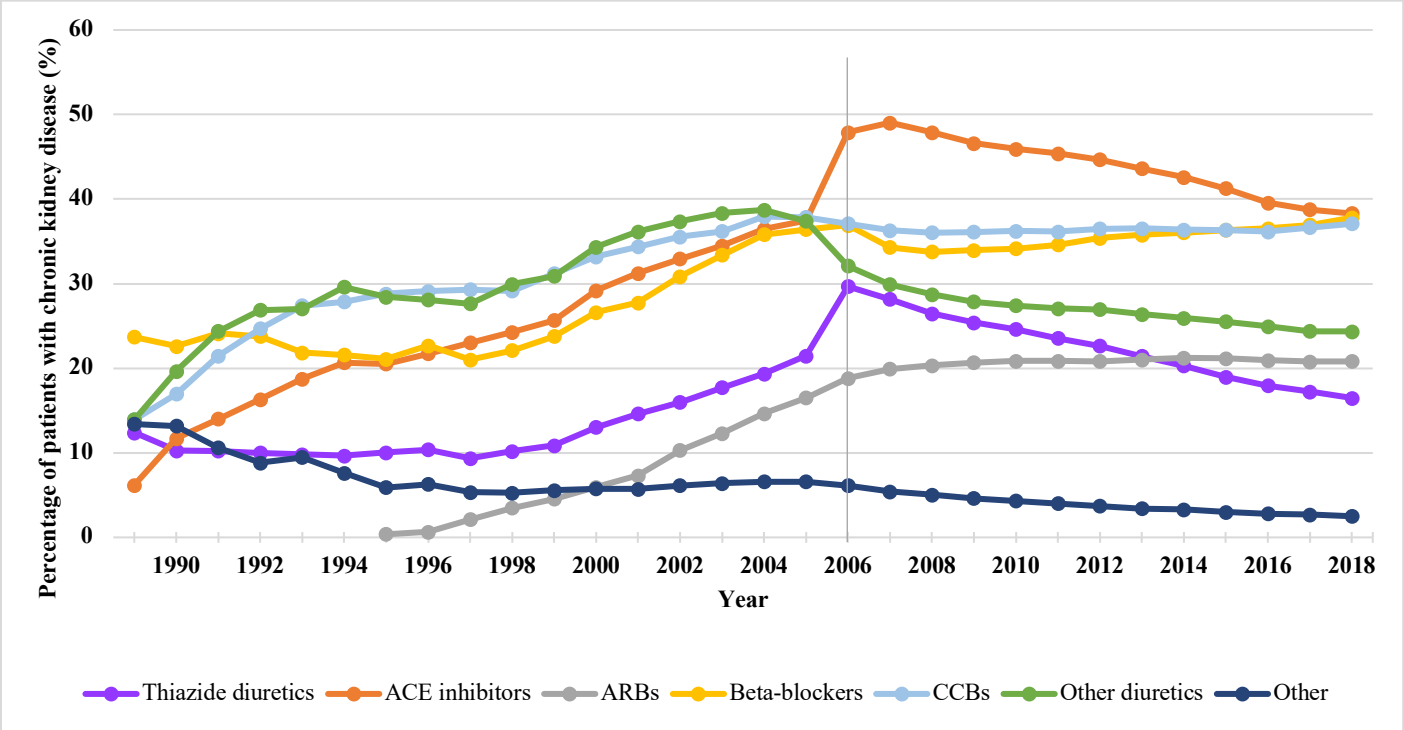
Supplementary Figure 7. Period prevalence of primary care patients with coronary heart disease and with antihypertensive drug prescriptions, stratified by antihypertensive drug class



Supplementary Figure 8. Period prevalence of primary care patients with diabetes and with antihypertensive drug prescriptions, stratified by antihypertensive drug class



Supplementary Figure 9. Period prevalence of primary care patients with chronic kidney disease and antihypertensive drug prescriptions, stratified by antihypertensive drug class [a,b]



[a] Year 1988 was suppressed due to small cell count (<5 patients) as per Clinical Practice Research Datalink policy

[b] The vertical grey bar marks the introduction of the Quality and Outcomes Framework for chronic kidney disease (CKD) in England in February 2006, which contained indicators of care to enhance the management of CKD. One incentivized indicator of care included the percentage of patients in the CKD register with a prescription for ACE inhibitors or ARBs.[1] Further, UK guidelines for CKD management were published in March 2006 by the Royal College of Physicians, the Royal College of General Practitioners and the Renal Association.

References

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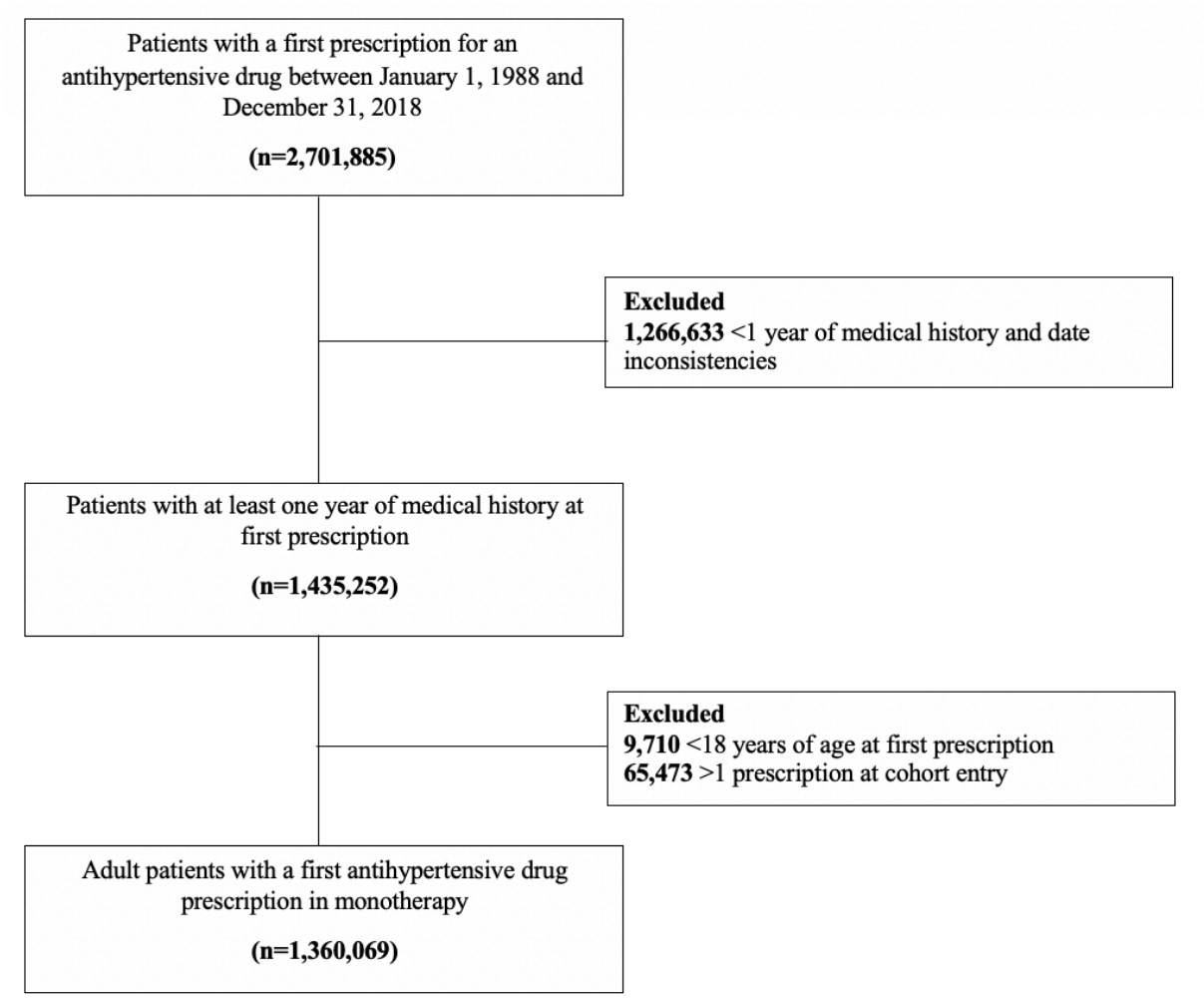
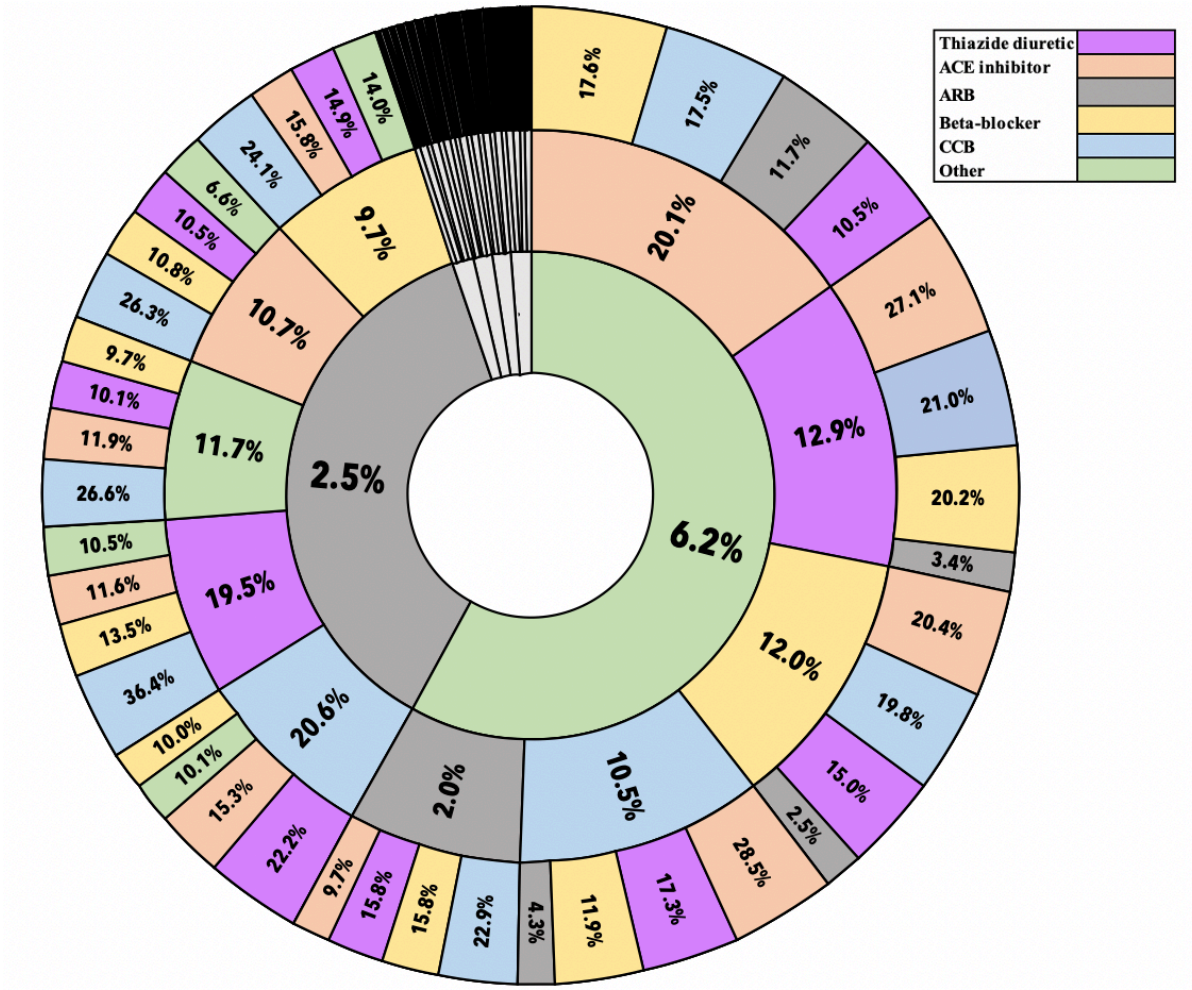
Supplementary Figure 10. Study flow chart of patients with a first-ever antihypertensive drug prescription in monotherapy



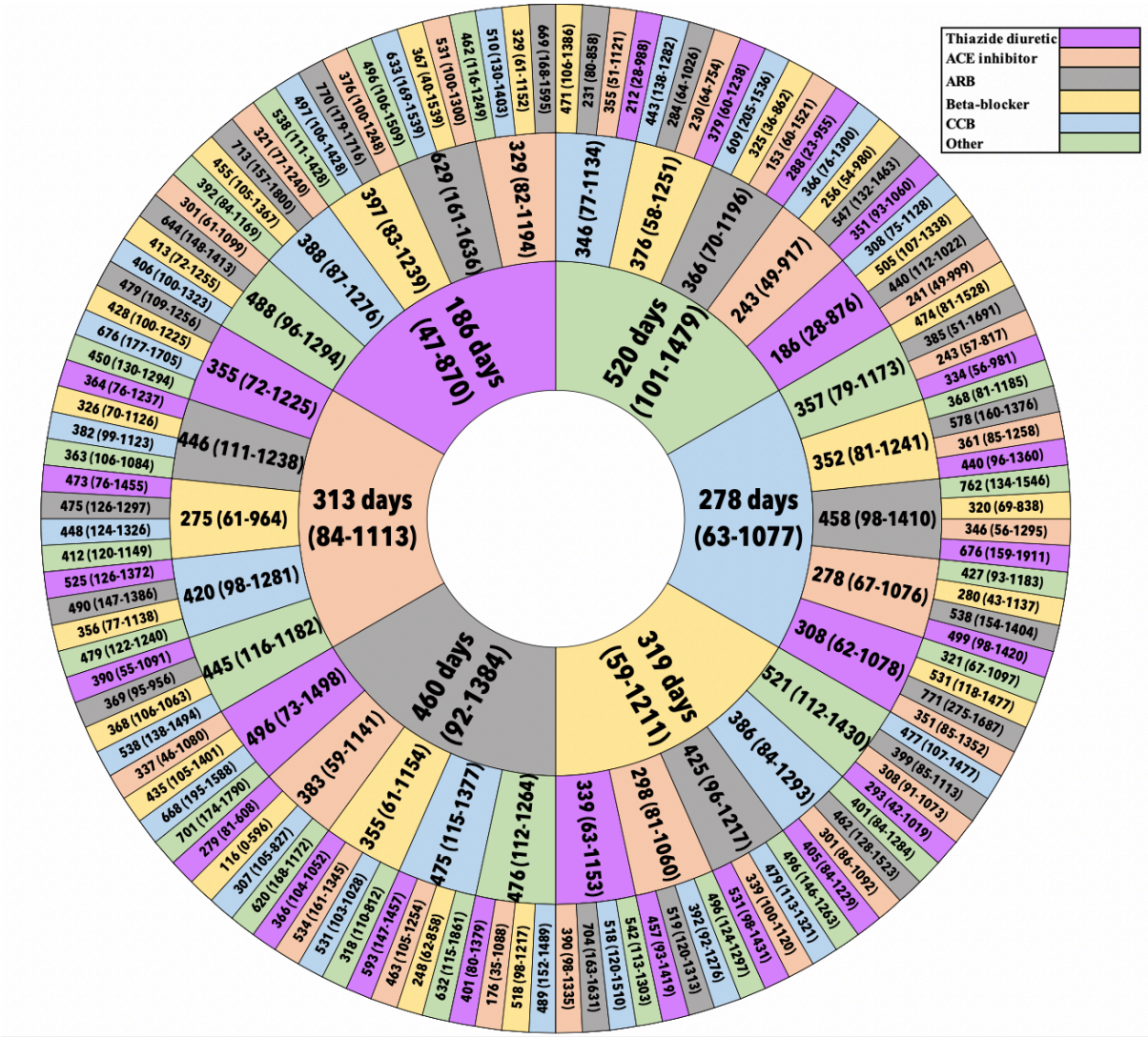
Supplementary Figure 11. Treatment trajectory of primary care patients with hypertension and a first-ever ARB or Other antihypertensive drug before January 1, 2007 [a]



Abbreviation: angiotensin-converting enzyme inhibitor, ACE inhibitor; angiotensin II receptor blocker, ARB; calcium channel blocker, CCB.

[a] Each concentric circle represents a treatment line. Percentages do not include patients who did not switch or added-on a new drug class.

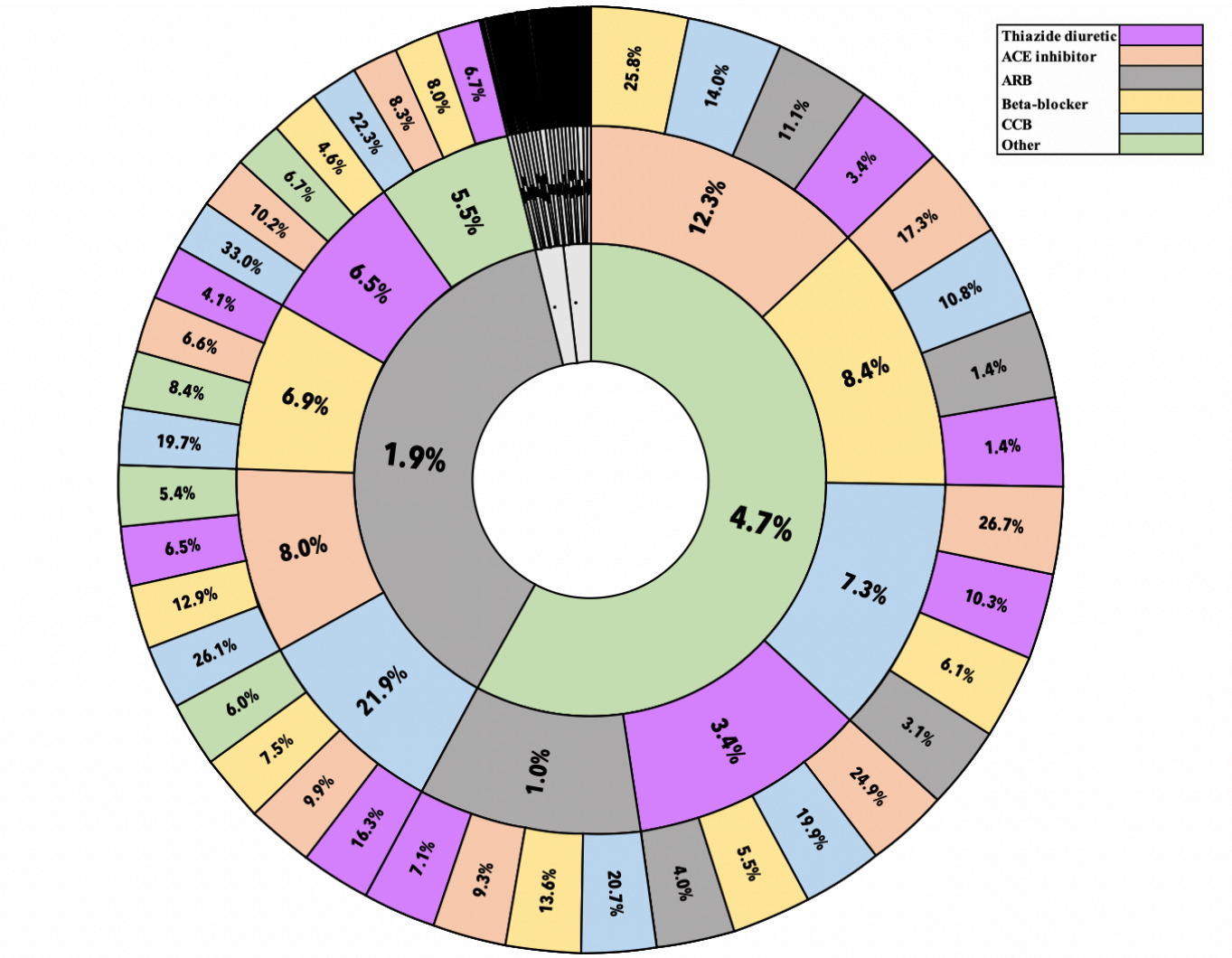
Supplementary Figure 12. Median number of days (interquartile range) of each treatment line for primary care patients with hypertension with a first-ever antihypertensive drug prescription before January 1, 2007 [a]



Abbreviation: angiotensin-converting enzyme inhibitor, ACE inhibitor; angiotensin II receptor blocker, ARB; calcium channel blocker, CCB.

[a] Each concentric circle represents a treatment line.

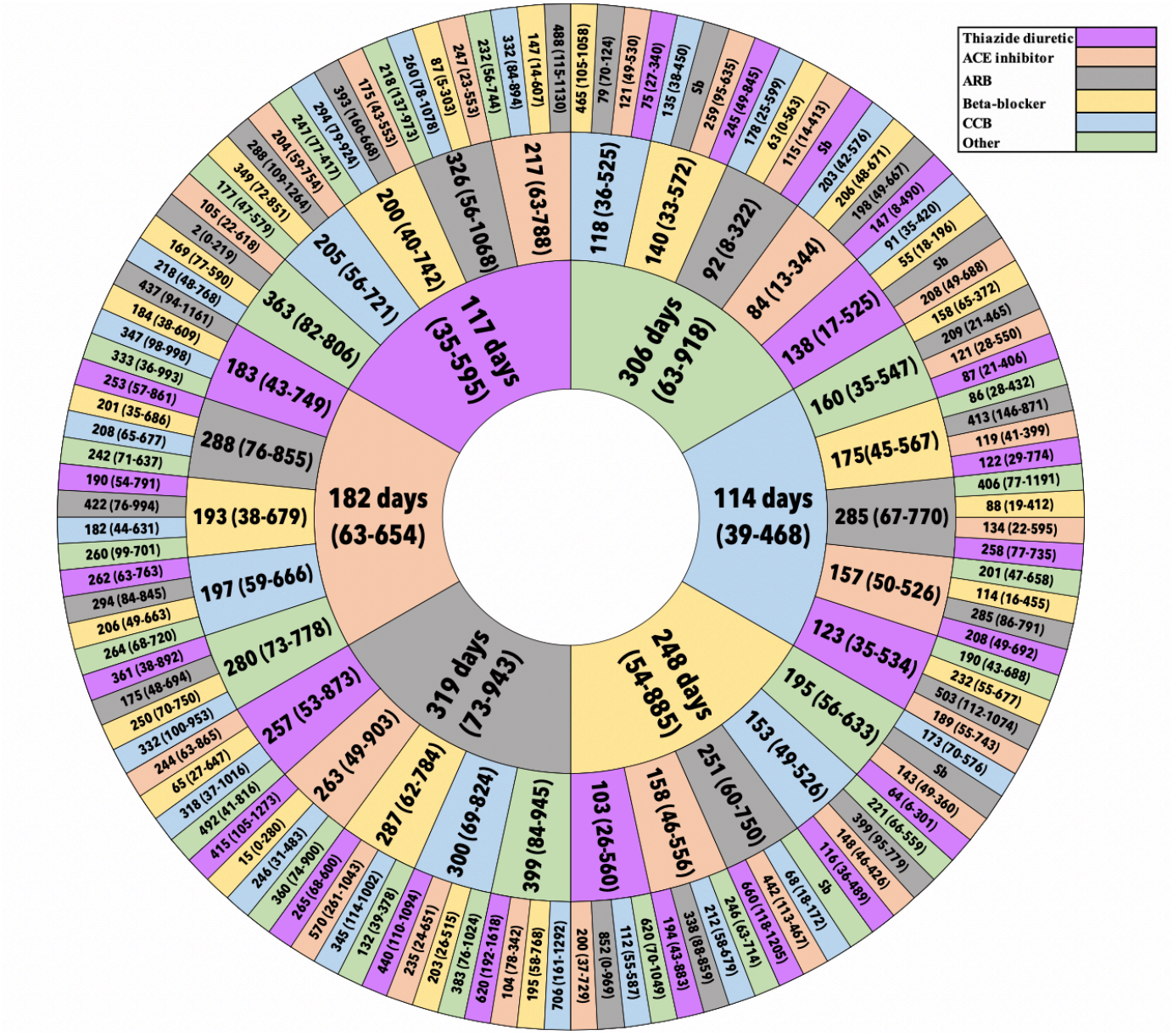
Supplementary Figure 13. Treatment trajectory of primary care patients with hypertension and a first-ever ARB or Other antihypertensive drug after January 1, 2007 [a]



Abbreviation: angiotensin-converting enzyme inhibitor, ACE inhibitor; angiotensin II receptor blocker, ARB; calcium channel blocker, CCB.

[a] Each concentric circle represents a treatment line. Percentages do not include patients who did not switch or added-on a new drug class.

Supplementary Figure 14. Median number of days (interquartile range) of each treatment line for primary care patients with hypertension with a first-ever antihypertensive drug prescription after January 1, 2007 [a]

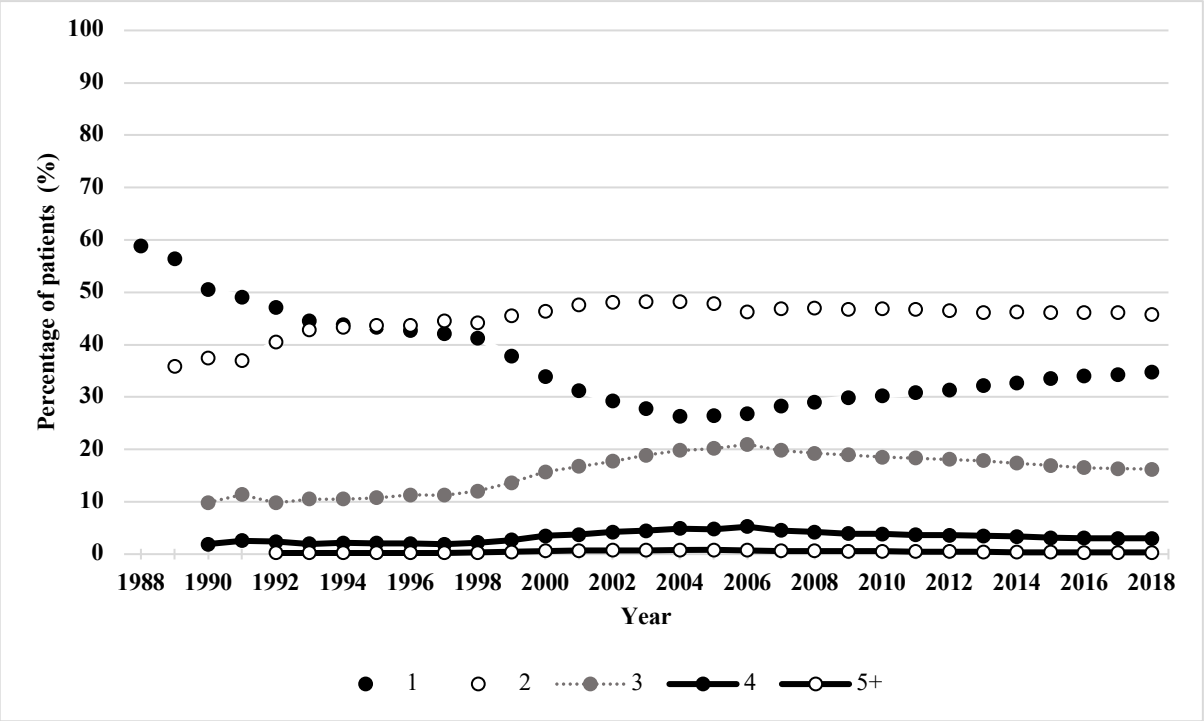


Abbreviation: angiotensin-converting enzyme inhibitor, ACE inhibitor; angiotensin II receptor blocker, ARB; calcium channel blocker, CCB.

[a] Each concentric circle represents a treatment line.

[b] Cells <5 patients are suppressed as per Clinical Practice Research Datalink policy

Supplementary Figure 15. Percentage of primary care patients with hypertension and antihypertensive drug prescriptions, stratified by number of antihypertensive drug classes prescribed after failure on first-line monotherapy [a]



[a] Some years were suppressed due to small cell count (<5 patients) as per Clinical Practice Research Datalink policy

CHAPTER 5. MANUSCRIPT 2: Thiazide diuretics and risk of colorectal cancer: a population-based cohort study

5.1 Preface

In Chapter 4, we found that the prevalence of patients with antihypertensive drug prescriptions increased during the study period, with nearly one-quarter of all primary care patients receiving prescriptions by the end of the study period. We also found that thiazide diuretics and CCBs were two of the most commonly prescribed classes during the study period, and that most patients received prescriptions for several years. Therefore, investigating the long-term safety of these drugs is important to better understand the risk-benefit profile of these classes.

In recent years, several studies have investigated the association between antihypertensive drugs and cancer risk. Eight observational studies investigating the association between thiazide diuretics and the risk of colorectal cancer reported conflicting findings, including protective, null, or elevated effect estimates.[32-39] While this association is biologically plausible, some of these studies had important, conclusion-altering biases such as prevalent user bias and confounding by indication.[43,158] Importantly, none of the studies were specifically designed to address this potential safety concern. Additionally, there remains limited evidence on whether an association between thiazide diuretics and colorectal cancer exists with long duration of use, in specific patient subgroups, or with specific thiazide diuretic agents. Therefore, this question warrants further consideration while addressing the limitations of previous studies. Chapter 5 aimed to address these gaps by investigating whether thiazide diuretics are associated with an increased risk of colorectal cancer compared with dCCBs, a clinically relevant comparator. Manuscript 2 has been submitted to *European Heart Journal.*

Thiazide diuretics and risk of colorectal cancer: a population-based cohort study

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ONE-SENTENCE SUMMARY

In this large population-based cohort study of 742,084 patients, thiazide diuretics were not associated with an increased risk of colorectal cancer compared with dihydropyridine calcium channel blockers, a clinically relevant comparator.

ABSTRACT

Background and aims: Previous studies have associated thiazide diuretics with an elevated risk of colorectal cancer. While this association is biologically plausible, these studies had important methodological limitations. We thus aimed to determine whether thiazide diuretics are associated with an increased risk of colorectal cancer compared with dihydropyridine calcium channel blockers (dCCBs).

Methods: We assembled a population-based, new-user, active comparator cohort using the United Kingdom Clinical Practice Research Datalink. Initiators of thiazide diuretics were compared with initiators of dCCBs between 1990 and 2018. We estimated hazard ratios (HR) with 95% confidence intervals (CIs) of incident colorectal cancer using Cox proportional hazard models. Models were weighted using standardized morbidity ratio weights generated from calendar time-specific propensity scores. Secondary analyses investigated associations with cumulative duration of use, time since initiation, individual molecules, cancer type, and effect modification with age, sex, aspirin use, inflammatory bowel disease, and history of polyps.

Results: The cohort included 377,784 initiators of thiazide diuretics and 364,300 initiators of dCCBs, generating 3,619,291 person-years of follow-up. After a median follow-up of 4.6 years, thiazide diuretics were not associated with an increased risk of colorectal cancer compared with dCCBs (weighted HR 0.97, 95% CI 0.90-1.04). Secondary analyses yielded similar results, although an increased risk was observed among patients with inflammatory bowel disease (weighted HR 2.46, 95% CI 1.13-5.36) and potentially among those with a history of polyps (weighted HR: 1.46, 95% CI 0.93-2.31).

Conclusions: This large population-based cohort study of 742,084 patients suggest that thiazide diuretics are not associated with an overall increased risk of colorectal cancer when compared with

dCCBs. While these findings provide some reassurance, additional research is needed to corroborate these findings and the elevated risks observed among patients with inflammatory bowel disease and a history of polyps.

Keywords: antihypertensive drugs, thiazide diuretics, calcium channel blockers, cancer, colorectal cancer, cohort, propensity score

Non-standard abbreviations and acronyms: ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; dCCBs, dihydropyridine calcium channel blockers; CPRD, Clinical Practice Research Datalink; CI, confidence interval; GOLD, Gp OnLine Data; HR, Hazard ratio; RCT, randomized controlled trial; UK, United Kingdom

INTRODUCTION

Thiazide diuretics are commonly prescribed antihypertensive drugs used in up to 42% of patients with hypertension.[1,2] While randomized controlled trials (RCTs) have shown that these drugs effectively reduce cardiovascular morbidity in patients with hypertension,[3-5] there is some evidence that this drug class may be associated with an increased risk of colorectal cancer. Indeed, in vitro studies have suggested that thiazide diuretics inhibit the human apical sodium-dependent transporter, which plays a primary role in the intestinal reabsorption of secondary bile acids.[6] At high concentrations and with repeated exposures, it has been shown that secondary bile acids induce DNA damage in colonic epithelial cells and increase apoptosis resistance in the colonic mucosa, which can eventually lead to colorectal cancer.[7]

To date, observational studies reporting on this possible association generated conflicting findings. These studies have reported either protective,[8,9] null,[8-13] or elevated effect estimates.[10,13-15] Importantly, none of these studies were specifically designed to investigate the association between thiazide diuretics and colorectal cancer, and few compared thiazide diuretics with a clinically-relevant comparator.[16] Additionally, several of these studies had conclusion-altering biases, such as the inclusion of prevalent users and time-related biases.[17] Recently, a meta-analysis of RCTs reported a modest increased risk of colorectal cancer associated with thiazide diuretics compared with other antihypertensive drugs, although the confidence interval (CI) included the null value (hazard ratio [HR]: 1.17, 95% CI: 0.96-1.41).[18]

Due to the conflicting evidence to date, we conducted a large, population-based, new-user, active comparator cohort study to assess whether thiazide diuretics are associated with an increased risk of colorectal cancer compared with dihydropyridine calcium channel blockers (dCCBs), another commonly prescribed antihypertensive drug class.

METHODS

Data Source

This population-based cohort study was conducted using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD). The CPRD is a large database of electronic primary care records representative of the UK population.[19,20] It includes patient characteristics, anthropometric and lifestyle information (e.g., body mass index (BMI), smoking status, alcohol use), diagnoses classified using Read codes, and prescription details recorded using the British National Formulary dictionary.[20] Colorectal cancer diagnoses recorded in the CPRD have been validated, with a positive predictive value of 98%, sensitivity of 92%, and specificity of 99% when compared with the UK National Cancer Data Repository.[21,22]

Study Population

We conducted a new-user, active comparator cohort study comparing initiators of thiazide diuretics with initiators of dCCBs. Cohort entry date was defined as the first prescription for either a thiazide diuretic or a dCCB between 1 January 1990 and 31 March 2018. We selected dCCBs as the active comparator group to minimize confounding by indication as both thiazide diuretics and dCCBs are guideline-recommended first-line drugs in the management of hypertension.[23-29] Furthermore, dCCBs have not previously been associated with an increased risk of colorectal cancer.[18,30,31] Thiazide diuretics included hydrochlorothiazide, chlorothiazide, bendroflumethiazide, trichlormethiazide, methyclothiazide, polythiazide, quinethazone, benzthiazide, hydroflumethiazide, cyclopenthiazide, mefruside, indapamide, chlorthalidone, clopamide, xipamide and metolazone, alone or in combination with other antihypertensive drugs except dCCBs. dCCBs included amlodipine, felodipine, isradipine, lacidipine, lercanidipine,

nicardipine, nifedipine, nimodipine, and nisoldipine, alone or in combination with other antihypertensive drugs except thiazide diuretics. British National Formulary codes are listed in **Supplementary Tables 1-2**.

To be included in the cohort, patients were required to be at least 18 years of age and have a minimum of one year of medical history in the CPRD before cohort entry. The latter was used as a washout period to identify new users. Patients with concomitant use of thiazide diuretics and dCCB at cohort entry were excluded. We also excluded patients with rare genetic conditions that have known associations with early-onset colorectal cancer, which included familial adenomatous polyposis, Lynch syndrome, Peutz-Jeghers syndrome, Li Fraumeni syndrome, juvenile polyposis syndrome, hereditary mixed polyposis syndrome, Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and cystic fibrosis at any time before cohort entry.[32-36] We excluded patients with previous solid organ transplantation at any time before cohort entry, as this is a rare intervention with a possible association with colorectal cancer,[37] and patients previously diagnosed with colorectal cancer at any time before cohort entry. Finally, due to the latency period between disease initiation and colorectal cancer diagnosis, patients were required to have a minimum of a one-year follow-up period after cohort entry. This lag period was to allow for a biologically plausible latency period and ensure the inclusion of incident events during follow-up, while minimizing possible detection bias around the time of treatment initiation.

Exposure Definition

Patients were considered exposed starting one year after cohort entry (i.e., person-time at risk) until a diagnosis of colorectal cancer (Read codes listed in **Supplementary Table 3**), one year after switching to one of the study drugs, death from any cause, end of registration with the

general practice, or end of the study period (31 March 2019), whichever occurred first (see **Supplementary Figure 1** for a schematic of the exposure definition)**.**

Potential Confounders

We considered a wide range of potential confounders measured before or at cohort entry. These covariates included age (modeled flexibly as a continuous variable using restricted cubic spline), sex, BMI, and smoking status (ever, never, unknown). We also considered the following variables measured at any time before cohort entry: alcohol-related disorders (including alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and hepatic failure), hypertension (defined as either a diagnosis of hypertension at or ever before cohort entry or by the presence of at least three elevated systolic (≥140mmHg) or diastolic (≥90mmHg) blood pressure measurements at or in the year before cohort entry),[38] coronary heart disease, heart failure, peripheral vascular disease, stroke, atrial fibrillation, stable angina, myocardial infarction, chronic obstructive pulmonary disease, end-stage renal disease, ulcerative colitis, Crohn's disease, other inflammatory bowel disease, history of polyps, cholecystectomy, and previous cancer diagnoses other than nonmelanoma skin cancer. We included drugs that have been previously associated with the incidence of colorectal cancer, measured at any time before cohort entry: hormone replacement therapy, bisphosphonates, statins, aspirin, other non-steroidal anti-inflammatory drugs, antidiabetic medications (insulin, metformin, sulfonylureas, incretin-based drugs, sodium-glucose cotransporter-2 inhibitors, and other antidiabetic drugs, separately), antihypertensive drugs (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, non-dCCBs, diuretics other than thiazide diuretics, and other antihypertensive drugs, separately), proton pump inhibitors, calcium supplements, and vitamin D supplements. We also included

variables capturing recent screening behaviors, measured in the year before cohort entry: screening for breast cancer (through mammography), colorectal cancer (through a fecal occult blood test or participation in the national bowel screening programme), and prostate cancer (through prostate-specific antigen testing), as well as records of influenza vaccination.

Statistical Analyses

We used calendar time-specific propensity scores to account for changes in the prescribing of antihypertensive drugs over the study period[39] and in the incidence of colorectal cancer over time (i.e., propensity scores were estimated within 5-year calendar bands at year of cohort entry).[40] We used multivariable logistic regression to estimate the predicted probability of receiving a thiazide diuretic versus a dCCB conditional on the covariates listed above. We evaluated the propensity score distributional overlap between the two exposure groups and trimmed the non-overlapping regions of the propensity score distributions. We used the propensity scores to assign treatment weights using the standardized morbidity ratio weighting approach.[41] Patients initiating a thiazide diuretic were given a weight of 1, while patients initiating a dCCB were given a weight of the odds of treatment probability, calculated as propensity score/(1-propensity score). We used descriptive statistics to summarize the characteristics of the two groups before and after weighting and assessed covariate balance using absolute standardized differences, with differences less than 0.10 indicative of good balance.[42] We targeted the average treatment effect in the treated population.

For each exposure group, we calculated weighted incidence rates of colorectal cancer with CIs based on the Poisson distribution and constructed weighted Kaplan-Meier curves to present the cumulative incidence during follow-up. Weighted Cox proportional hazards regression models,

stratified on calendar year of cohort entry, were fit to estimate hazard ratios (HRs) with 95% CIs using robust variance estimators.

Secondary Analyses

We conducted five secondary analyses. First, we assessed the presence of a duration-response relation according to three cumulative duration of use categories (<5 years, 5-10 years, >10 years), calculated as the sum of all prescription durations from cohort entry until the risk set date. For this analysis, the use of thiazide diuretics and dCCBs was modelled as a time-varying variable, updated at each person-day of follow-up. Second, we assessed the presence of an association according to time since initiation (<5 years, 5-10 years, and >10 years), defined as the time from cohort entry until the risk set date. Third, we assessed whether the association varied with individual thiazide diuretic molecules (bendroflumethiazide, indapamide, hydrochlorothiazide, chlorthalidone, metolazone, cyclopenthiazide, and other thiazide diuretics). Fourth, to assess the presence of an association according to colorectal cancer type, we separated colorectal cancer events by colon cancer and rectal cancer. Finally, we assessed the presence of effect modification by including a product term in the primary analysis for the exposure and potential effect modifier. These analyses were conducted by sex and age, as there are age and sex differences in the incidence of colorectal cancer,[43] previous use of aspirin, which has been inversely associated with colorectal cancer risk,[44] as well as history of polyps and inflammatory bowel disease, which are important risk factors for colorectal cancer.[45,46]

Sensitivity Analyses

We conducted three sensitivity analyses. First, we increased the length of the lag period from one year to three, five, and ten years. Second, we repeated the primary analysis in which we ignored switching between the study drugs during the follow-up period (analogous to a classic intention-to-treat exposure definition). Third, we assessed the impact of potential informative censoring due to 1) non-random switching between the exposure groups and 2) competing risk due to death, using stabilized inverse probability of censoring weights (**Supplementary Method 1**). All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC) and R (version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The cohort included 377,784 initiators of thiazide diuretics and 364,300 initiators of dCCBs (**Figure 1**). The cohort was followed for a median 4.6 years (interquartile range 2.1-8.5), including the one-year lag period, representing 5.1 years (interquartile range 2.3-9.5) for initiators of thiazide diuretics and 4.1 years (interquartile range 2.0-7.4) for initiators of dCCBs. There were 5,011 colorectal cancer events during the study period, generating a weighted incidence rate of 139.6 (95% CI 136.0-143.2) per 100,000 person-years. During the follow-up period, more thiazide diuretic initiators switched to a dCCB (41.7%) compared to dCCB initiators switching to a thiazide diuretic (24.3%).

Table 1 presents the baseline patient characteristics before and after weighting. Before weighting, the two study groups were similar on most baseline characteristics, although initiators of thiazide diuretics were more likely to be female and less likely to have been prescribed statins, ACE inhibitors, and proton pump inhibitors. After weighting, all characteristics were well balanced between the exposure groups, with no standardized differences above 0.03.

In the primary analysis, thiazide diuretics were not associated with an overall increased risk of colorectal cancer compared with dCCBs, for a weighted incidence rate of 136.8 (95% CI 131.8-141.9) per 100,000 person-years for thiazide diuretics, 142.4 (95% CI 134.7-146.5) per 100,000 person-years for dCCBs, and a weighted HR of 0.97, 95% CI 0.90-1.04 (**Table 2**). The weighted cumulative incidence curves did not significantly diverge over time (**Supplementary Figure 2**).

In the secondary analysis assessing duration-response, the HRs did not increase with increasing cumulative duration of use, yielding a weighted HR of 0.97 (95% CI 0.82-1.14) after five to ten years of use and 0.82 (95% CI 0.59-1.13) after more than ten years of use (**Table 2**).

Similarly, there was no evidence of an association according to time since initiation, with a weighted HR of 0.96 (95% CI 0.77-1.21) after more than ten years since initiating treatment with thiazide diuretics (**Table 2**). Analysis by individual thiazide diuretic molecules did not show evidence of associations (**Supplementary Table 4**). Similarly, there was no evidence of an association by colorectal cancer type for both colon and rectal cancer (**Supplementary Table 5**). Furthermore, there was no evidence of effect measure modification by sex, age, and history of aspirin use (**Supplementary Tables 6-8**). The HR was moderately elevated for history of polyps, although the CI included the null (weighted HR 1.46, 95% CI 0.93-2.31, **Supplementary Figure 9**). There was presence of effect modification for history of inflammatory bowel disease, with a weighted HR of 2.46 (95% CI 1.13-5.36, **Supplementary Figure 10**).

The sensitivity analyses yielded results consistent with the primary analysis (**Figure 2**). Results from the analyses using a three-, five-, and ten-year lag period were consistent with the primary analysis, with weighted HRs ranging between 0.93-0.96 (**Supplementary Table 11**). The analysis using an intention-to-treat exposure definition yielded a weighted HR of 0.99 (95% CI 0.93-1.05) (**Supplementary Table 12**). Similarly, the marginal HR was 1.01 (95% CI 0.93-1.09) in the inverse probability of censoring weighting analysis, accounting for switching/adding on the other study drug and competing risk of death (**Supplementary Table 13**).

DISCUSSION

In this population-based, new-user, active comparator cohort study of 742,084 primary care patients, the use of thiazide diuretics was not associated with an overall increased risk of colorectal cancer compared with dCCBs. There was no evidence of an association by cumulative duration of use, including among patients with over ten years of thiazide diuretic use, by time since initiation of thiazide diuretics, and by cancer type (colon, rectal cancer). No individual thiazide diuretic molecules were found to be associated with incident colorectal cancer. Overall, the sensitivity analyses using a different lag period (three, five, and ten years), an intention-to-treat exposure definition, and an inverse probability of censoring weighting approach generated results consistent with the primary analysis. However, thiazide diuretics were associated with an increased risk of colorectal cancer among patients with inflammatory bowel disease and potentially among patients with a history of polyps.

Despite the long-standing prescribing history of thiazide diuretics, only two observational studies have investigated their comparative safety with respect to colorectal cancer.[8,11] Of those, only one reported a duration analysis, and none reported analyses by individual agents. One nested case-control study reported an odds ratio of 0.87 (95% CI: 0.72-1.06) for thiazide diuretics compared with CCBs and 0.80 (95% CI: 0.54-1.20) after more than 7.5 years of use.[8] The other study found a hazard ratio of 1.00 (95% CI: 0.80-1.30) for renin-angiotensin-aldosterone-system inhibitors compared with thiazide diuretics, although the median follow-up was only 2.2 years.[11] Other observational studies combined users of different types of diuretics (thiazide diuretics, loop diuretics, and potassium-sparing diuretics), which have different biological effects, wide indications, and typically prescribed to distinct patient populations.[10,12-15] These studies reported conflicting findings, with effect estimates ranging between 0.92-1.96 for colorectal cancer,

although most with wide CIs crossing the null value.[10,12,13,15] Finally, some studies included non-users as the comparator group.[9,10,12,13,15] However, no clear comparator groups being defined in such studies renders the assessment of the comparative safety of diuretics difficult. Using non-users as the comparator group can introduce important confounding by indication, and when possible, the use of an active comparator group is recommended.[16] Additionally, these studies had other important methodological limitations such as immortal time bias, inclusion of prevalent users, and recall bias, all of which limits the conclusions drawn from previous findings.[17,47] Lastly, although three meta-analyses of observational studies on antihypertensive drugs and colorectal cancer have recently been conducted, it is difficult to interpret the reported pooled estimates given the methodological limitations of the included studies.[31,48,49] Once again, these meta-analyses only included studies with non-users as the comparator group, rendering the clinical utility challenging as hypertension often requires pharmacologic treatment.[50] Finally, to date, only three large meta-analyses of RCTs have examined the use of antihypertensive drugs and the risk of cancer.[18,51,52] Only one included site-specific cancers, however, which reported a 17% increased risk of colorectal cancer for thiazide diuretics compared with other antihypertensive drugs, although the CIs were wide and crossed the null value.[18]

From a biological standpoint, it has been suggested that thiazide diuretics inhibit the human apical sodium-dependent transporter, which impacts the intestinal reabsorption of secondary bile acids.[6] At repeated exposure and high concentrations in the colon, this subsequently leads secondary bile acids to potentially induce DNA damage in epithelial cells with increased apoptosis resistance in the mucosa, promoting colorectal cancer.[7] While the use of thiazide diuretics was not associated with an overall increased risk of colorectal cancer, we did observe an increased risk among patients with inflammatory bowel disease and potentially among those with a history of

polyps. While these conditions are known risk factors for colorectal cancer,[45,46] additional research will be needed to corroborate these findings and determine whether patients with these conditions represent susceptible individuals.

This study has several strengths. First, we identified new users of thiazide diuretics and dCCBs which minimized left truncation (i.e., a time period during which exposure occurs, but is not captured by the study as it occurs before the chosen cohort entry date) and allowed us to properly assess the colorectal cancer risk with cumulative duration of use and time since initiation. Second, using an active comparator minimized confounding by indication while offering a comparator drug for which there is clinical equipoise according to current and past hypertension management guidelines.[23-29] Thus, these design choices, together with defining the initiation of treatment as the start of person-time at risk, eliminated immortal time bias which can be an important and potentially conclusion-altering bias.[47,53] Third, the use of calendar time specific propensity scores helped account for temporal variations in colorectal cancer incidence and prescription prevalence of antihypertensive drugs, while taking advantage of the key benefits of propensity scores (e.g., allowing for a defined target population and appropriate inclusion of patients).[41] Fourth, the use of the CPRD allowed for the adjustment of potentially important confounders and risk factors for colorectal cancer, such as smoking status and BMI. Finally, we were able to follow some patients for extended time periods, with a maximum follow-up of nearly 28 years in our study.

This study also has some limitations. First, the CPRD contains only prescriptions issued by general practitioners rather than specialists, potentially introducing some exposure misclassification. However, it is well documented that most patients treated with antihypertensive drugs in the UK are managed by general practitioners, thus minimizing the impact of this

misclassification.[54,55] Second, treatment non-adherence could have led to exposure misclassification. However, repeated prescriptions are likely indicative of some treatment adherence, and our cumulative duration analysis showed results consistent with our primary analysis. Third, misclassification of the outcome is possible, although validation studies reported that colorectal cancer was well recorded in the CPRD when compared with the National Cancer Data Repository.[21,22] Fourth, it was not possible to stratify colorectal cancer by cancer stage or site, as these details are not available in the CPRD. However, we conducted a secondary analysis stratifying by type (colon, rectal), which provided findings consistent with our primary analysis. Finally, residual confounding is possible, as the CPRD does not contain information on diet or physical activity. However, our choice of an active comparator design and inclusion of health-related behaviour variables aimed at reducing the potential impact of unmeasured confounding.

CONCLUSIONS

Findings from this large population-based, new users, active comparator study suggest that thiazide diuretics are not associated with an overall increased risk of colorectal cancer compared with dCCBs. Overall, this study provides reassurance to physicians and patients regarding the long-term gastrointestinal safety of thiazide diuretics with respect to colorectal cancer. However, additional research will be needed to corroborate the increased risk observed among patients with inflammatory bowel disease and potentially among patients with a history of polyps.

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DETAILS OF ETHICAL APPROVAL

The study protocol was approved by the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink (protocol number 19_121A) and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

CONFLICT OF INTEREST DISCLOSURES

JR received consulting fees for work unrelated to this study from Biogen. LA received consulting fees from Janssen and Pfizer for work unrelated to this study. EGM, TS, IM, and JMB have no conflicts to disclose.

AUTHOR RESPONSIBILITY INFORMATION

JR and LA conceived the study. JR, EGM, TS, IM, JMB, and LA designed the study, interpreted the data, critically revised the manuscript for important intellectual content, and approved the final version of the manuscript. LA acquired the data. JR conducted the analyses. JR drafted the manuscript. LA attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. JR, EGM, TS, IM, JMB, and LA agree to be accountable for all aspect of the work.

DATA AND CODE AVAILABILITY

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

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FIGURE LEGENDS

Figure 1 Study flow diagram of patients initiating thiazide diuretics and dihydropyridine calcium channel blockers in the Clinical Practice Research Datalink between January 1, 1990 and March 31, 2018

Figure 2 Forest plot summarizing the results of the primary analysis and sensitivity analyses. Weighted hazard ratios and confidence intervals are presented for the association between thiazide diuretics and colorectal cancer compared with dihydropyridine calcium channel blockers

Table 1. Baseline characteristics of thiazide diuretic initiators and dihydropyridine calcium channel blocker initiators, before and after weighting

	Before weighting			After weighting [a]		
Characteristics	**Thiazide diuretic**	**dCCB**	**ASD**	**Thiazide diuretic**	**dCCB**	**ASD**
Total	377,784	364,300		377,784	375,270	
Mean age, years (SD)	62.8 (13.9)	61.7 (13.4)	0.08	62.8 (13.9)	63.1 (14.0)	0.01
Male, n (%)	148,692 (39.3)	194,906 (53.5)	0.28	148,692 (39.3)	150,144 (40.0)	0.01
BMI, n (%)						
<25 kg/m^2	95,103 (25.2)	91,467 (25.1)	0.00	95,103 (25.2)	94,470 (25.2)	0.00
25-29.9 kg/m^2	124,367 (32.9)	126,365 (34.7)	0.03	124,367 (32.9)	123,432 (32.8)	0.00
≥30 kg/m^2	97,525 (25.8)	106,075 (29.1)	0.07	97,525 (25.8)	97,166 (25.8)	0.00
Unknown	60,789 (16.1)	40,393 (11.1)	0.14	60,789 (16.1)	60,200 (16.1)	0.00
Alcohol-related disorders, n (%)	10,923 (2.9)	17,962 (4.9)	0.10	10,923 (2.9)	11,089 (3.0)	0.00
Smoking status, n (%)						
Ever	166,421 (44.0)	174,575 (47.9)	0.07	166,421 (44.0)	165,955 (44.2)	0.00
Never	178,263 (47.2)	175,242 (48.1)	0.01	178,263 (47.2)	176,947 (47.1)	0.00
Unknown	33,100 (8.7)	14,483 (4.0)	0.19	33,100 (8.7)	32,367 (8.6)	0.00
Medical history, n (%) [b]						
Hypertension	290,242 (76.8)	289,755 (79.5)	0.06	290,242 (76.8)	293,425 (78.1)	0.03
Coronary heart disease	58,451 (15.4)	74,824 (20.6)	0.13	58,451 (15.4)	58,267 (15.5)	0.00
Heart failure	7,473 (2.0)	7,378 (2.0)	0.00	7,473 (2.0)	8,414 (2.2)	0.01
PVD	9,910 (2.6)	14,650 (4.0)	0.07	9,910 (2.6)	10,516 (2.8)	0.01
Stroke	12,894 (3.4)	12,373 (3.4)	0.00	12,894 (3.4)	13,947 (3.7)	0.01
Atrial fibrillation	11,107 (2.9)	11,184 (3.0)	0.00	11,107 (2.9)	11,887 (3.1)	0.01
Stable angina	18,830 (5.0)	33,119 (9.1)	0.16	18,830 (5.0)	19,204 (5.1)	0.00
Myocardial infarction	10,212 (2.7)	17,760 (4.9)	0.11	10,212 (2.7)	10,624 (2.8)	0.00
COPD	36,629 (9.7)	32,085 (8.8)	0.03	36,629 (9.7)	36,931 (9.8)	0.00
End-stage renal disease	519 (0.1)	1,891 (0.5)	0.06	519 (0.1)	559 (0.1)	0.00
Ulcerative colitis	1,969 (0.5)	2,263 (0.6)	0.01	1,969 (0.5)	1,938 (0.5)	0.00
Crohn's disease	1,050 (0.3)	1,261 (0.3)	0.01	1,050 (0.3)	1,054 (0.3)	0.00
Other IBD	430 (0.1)	646 (0.2)	0.01	430 (0.1)	441 (0.1)	0.00
History of polyps	4,785 (1.2)	6,850 (1.9)	0.04	4,785 (1.2)	4,728 (1.2)	0.00
Cholecystectomy	14,684 (3.8)	14,000 (3.8)	0.00	14,684 (3.8)	14,657 (3.9)	0.00
Previous cancer	18,405 (4.8)	19,719 (5.4)	0.02	18,405 (4.8)	18,524 (4.9)	0.00
Medications, n (%)						
HRT	57,721 (15.3)	44,031 (12.1)	0.09	57,721 (15.3)	56,218 (15.0)	0.00
Bisphosphonates	10,453 (2.7)	14,103 (3.9)	0.06	10,453 (2.7)	10,579 (2.8)	0.00
Statins	65,576 (17.3)	116,046 (31.9)	0.34	65,576 (17.3)	66,965 (17.8)	0.01
Aspirin	74,074 (19.6)	95,653 (26.3)	0.15	74,074 (19.6)	75,364 (20.0)	0.01
Other NSAIDs	221,129 (58.5)	229,436 (63.0)	0.09	221,129 (58.5)	219,693 (58.5)	0.00
Insulin	5,613 (1.4)	9,856 (2.7)	0.08	5,613 (1.4)	6,154 (1.6)	0.01
Metformin	14,509 (3.8)	28,030 (7.7)	0.16	14,509 (3.8)	15,574 (4.1)	0.01
Sulfonylureas	11,283 (3.0)	18,645 (5.1)	0.10	11,283 (3.0)	12,277 (3.3)	0.01
Incretin-based drugs	645 (0.2)	2,836 (0.8)	0.08	645 (0.2)	663 (0.2)	0.00
SGLT-2 inhibitors	59 (0.0)	322 (0.1)	0.03	59 (0.0)	60 (0.0)	0.00
Other antidiabetic drugs	3,583 (0.9)	6,500 (1.8)	0.07	3,583 (0.9)	3,795 (1.0)	0.00
ACE inhibitors	76,455 (20.2)	122,443 (33.6)	0.30	76,455 (20.2)	80,787 (21.5)	0.03
ARBs	18,704 (5.0)	26,982 (7.4)	0.10	18,704 (5.0)	19,833 (5.3)	0.01
Beta-blockers	98,105 (26.0)	110,013 (30.2)	0.09	98,105 (26.0)	99,636 (26.5)	0.01
Non-dihydropyridine CCBs	12,763 (3.4)	11,806 (3.2)	0.00	12,763 (3.4)	13,918 (3.7)	0.01
Other diuretics	35,497 (9.4)	36,154 (9.9)	0.01	35,497 (9.4)	37,577 (10.0)	0.02
Other antihypertensive drugs	9,646 (2.5)	9,594 (2.6)	0.00	9,646 (2.5)	9,547 (2.5)	0.00
PPIs	83,865 (22.2)	130,908 (35.9)	0.30	83,865 (22.2)	84,489 (22.5)	0.00
Calcium supplement	55,556 (14.7)	56,854 (15.6)	0.02	55,556 (14.7)	55,713 (14.8)	0.00

Vitamin D supplement	18,156 (4.8)	26,708 (7.3)	0.10	18,156 (4.8)	18,474 (4.9)	0.00
Screening and other health behaviours, n (%)						
Mammography	26,047 (6.9)	23,717 (6.5)	0.01	26,047 (6.9)	25,545 (6.8)	0.00
Fecal occult blood test	3,565 (0.9)	11,665 (3.2)	0.15	3,565 (0.9)	3,659 (1.0)	0.00
PSA test	11,351 (3.0)	20,499 (5.6)	0.12	11,351 (3.0)	11,672 (3.1)	0.00
Influenza vaccination	130,398 (34.5)	106,427 (29.2)	0.11	130,398 (34.5)	132,185 (35.2)	0.01
Cohort entry year, n (%)						
1990-1993	19,174 (5.1)	8,990 (2.5)	0.13	19,174 (5.1)	18,500 (5.0)	0.00
1994-1998	46,341 (12.3)	21,694 (6.0)	0.21	46,341 (12.3)	45,914 (12.2)	0.00
1999-2003	135,971 (36.0)	44,012 (12.1)	0.58	135,971 (36.0)	134,058 (35.7)	0.01
2004-2008	122,747 (32.5)	104,805 (28.7)	0.08	122,747 (32.5)	122,491 (32.6)	0.00
2009-2013	43,689 (11.6)	115,524 (31.7)	0.50	43,689 (11.6)	43,758 (11.6)	0.00
2014-2018	9,862 (2.6)	69,275 (19.0)	0.54	9,862 (2.6)	10,546 (2.8)	0.01

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ASD, absolute standardized difference; BMI, body mass index; COPD, chronic obstructive pulmonary disease; dCCB, dihydropyridine calcium channel blocker; IBD, inflammatory bowel disease; HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drugs; SGLT-2, sodium-glucose cotransporter-2; PVD, peripheral vascular disease; PPI, proton pump inhibitors; PS, propensity score; PSA, prostate-specific antigen; SD, standard deviation

[a] Characteristics weighted using standardized morbidity ratio weighting. [b] Not mutually exclusive. [c] Participation in the national bowel screening programme was also included

Table 2. Crude and adjusted hazard ratios for colorectal cancer comparing thiazide diuretics with dihydropyridine calcium channel blockers

Exposure	Events	Person years	Weighted incidence rate (95% CI) [a,b]	Crude hazard ratio	Weighted hazard ratio (95% CI) [b,c]
Primary analysis					
dCCBs	2,199	1,564,616	142.4 (137.2-147.7)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	2,812	2,055,305	136.8 (131.8-141.9)	0.96	0.97 (0.90-1.04)
Cumulative duration < 5 years [d]					
dCCBs	1720	1,291,404	132.2 (126.6-138.0)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	2138	1,657,416	128.9 (123.3-134.5)	0.96	0.98 (0.90-1.07)
Cumulative duration 5-10 years [d]					
dCCBs	392	231,522	174.3 (160.5-188.9)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	550	324,935	169.2 (155.4-184.0)	0.99	0.97 (0.82-1.14)
Cumulative duration >10 years [d]					
dCCBs	87	41,690	206.1 (176.7-239.0)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	124	72,954	169.9 (141.3-202.6)	0.80	0.82 (0.59-1.13)
Time since initiation < 5 years					
dCCBs	1412	1,071,549	132.2 (125.9-139.0)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	1613	1,223,421	131.8 (125.4-138.4)	0.99	1.00 (0.91-1.10)
Time since initiation 5-10 years [e]					
dCCBs	587	374,042	151.2 (141.2-161.7)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	815	575,605	141.5 (132.0-151.6)	0.90	0.94 (0.81-1.08)
Time since initiation >10 years [e]					
dCCBs	200	119,000	153.0 (138.1-169.0)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	383	256,269	149.4 (134.8-165.1)	0.89	0.96 (0.77-1.21)

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

[a] Per 100,000 person-years. [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands. [d] Cumulative duration was modeled in a time-varying fashion. [e] Propensity score was re-estimated and weights were re-calculated for these categories.

Figure 1. Study flow diagram of patients initiating thiazide diuretics and dihydropyridine calcium channel blockers in the Clinical Practice Research Datalink between January 1, 1990 and March 31, 2018

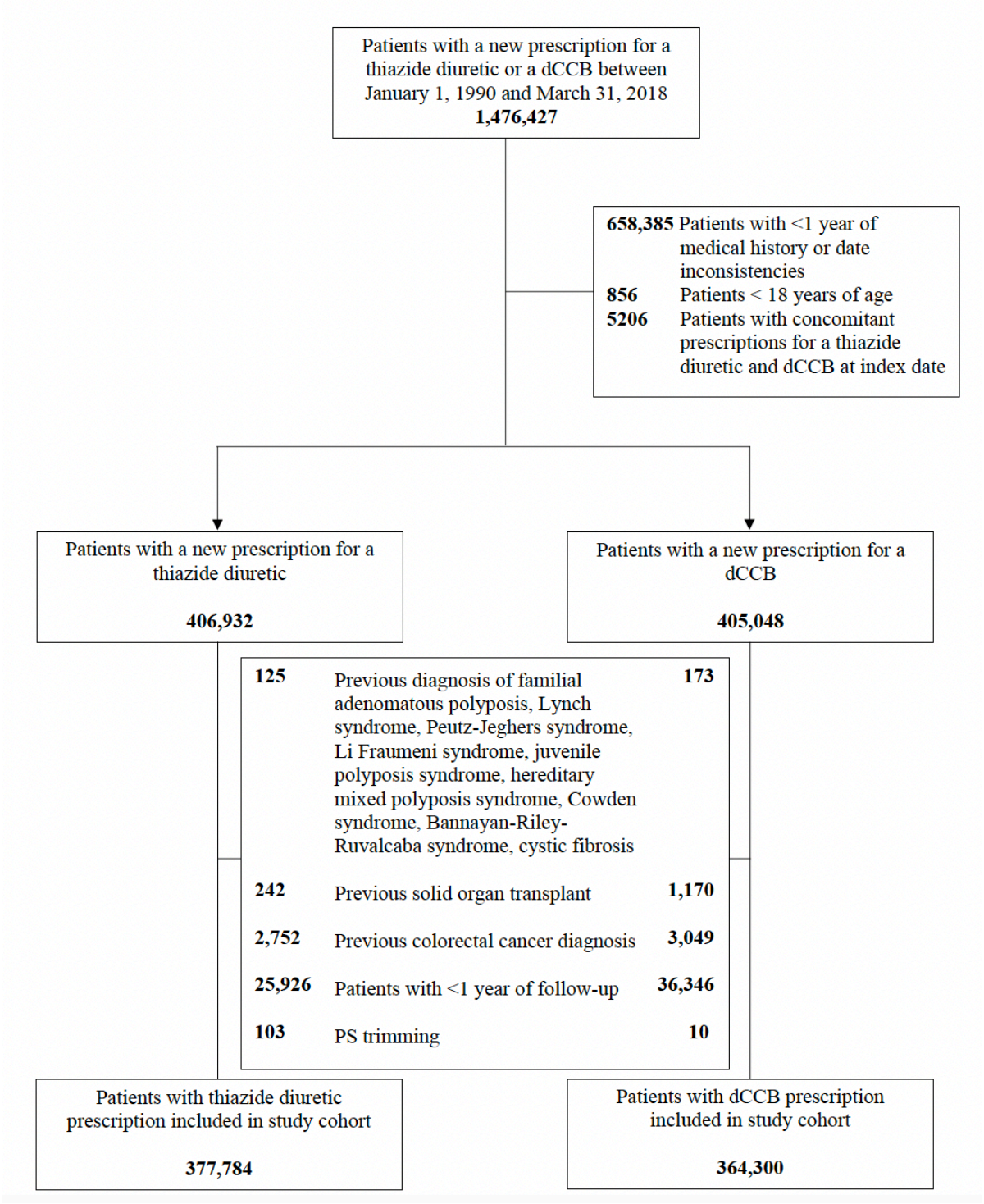
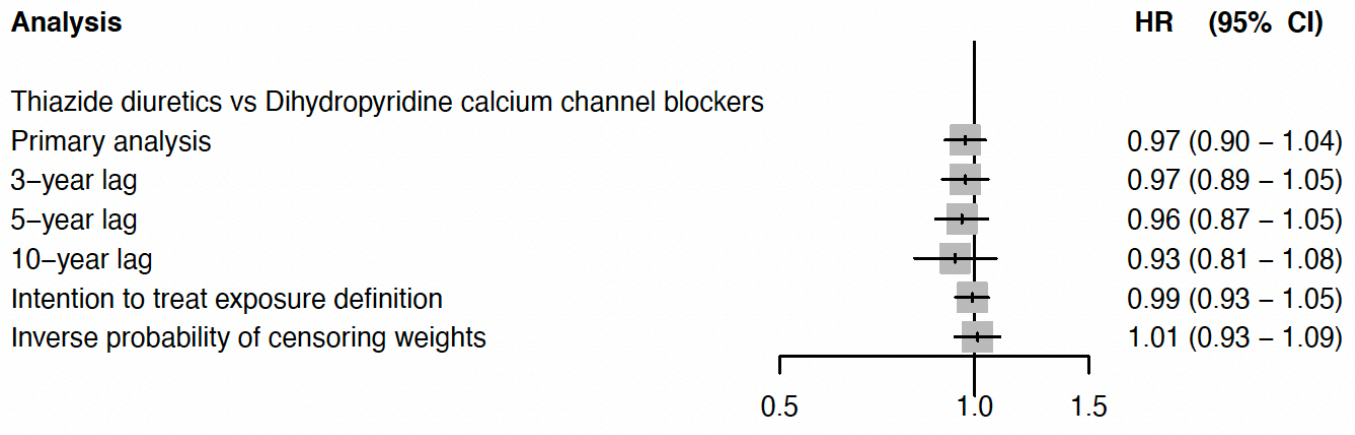


Figure 2. Forest plot summarizing the results of the primary analysis and sensitivity analyses. Weighted hazard ratios and confidence intervals are presented for the association between thiazide diuretics and colorectal cancer compared with dihydropyridine calcium channel blockers



SUPPLEMENTARY MATERIAL

Thiazide diuretics and risk of colorectal cancer: a population-based cohort study

Supplementary Table 1. British National Formulary codes for thiazide diuretics

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

Supplementary Table 2. British National Formulary codes for dihydropyridine calcium channel blockers

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

Supplementary Table 3. Read codes for colorectal cancer

Read code	Read term
Colon	
B13..00	Malignant neoplasm of colon
B130.00	Malignant neoplasm of hepatic flexure of colon
B131.00	Malignant neoplasm of transverse colon
B132.00	Malignant neoplasm of descending colon
B133.00	Malignant neoplasm of sigmoid colon
B134.00	Malignant neoplasm of caecum
B134.11	Carcinoma of caecum
B135.00	Malignant neoplasm of appendix
B136.00	Malignant neoplasm of ascending colon
B137.00	Malignant neoplasm of splenic flexure of colon
B138.00	Malignant neoplasm, overlapping lesion of colon
B13y.00	Malignant neoplasm of other specified sites of colon
B13z.00	Malignant neoplasm of colon NOS
B13z.11	Colonic cancer
B180200	Malignant neoplasm of retrocaecal tissue
B1z..00	Malig neop oth/ill-defined sites digestive tract/peritoneum
B1z0.00	Malignant neoplasm of intestinal tract, part unspecified
B1z0.11	Cancer of bowel
B902400	Neoplasm of uncertain behaviour of colon
BB5N100	[M] Adenocarcinoma in adenomatous polposis coli
BB5L100	[M] Adenocarcinoma in adenomatous polyp
BB5L300	[M] Adenocarcinoma in multiple adenomatous polyps
Rectum	
B14..00	Malignant neoplasm of rectum, rectosigmoid junction and anus
B140.00	Malignant neoplasm of rectosigmoid junction
B141.00	Malignant neoplasm of rectum
B141.11	Carcinoma of rectum
B141.12	Rectal carcinoma
B14y.00	Malignant neoplasm other site rectum, rectosigmoid junction and anus
B14z.00	Malignant neoplasm rectum, rectosigmoid junction and anus NOS
B18y200	Malignant neoplasm of mesorectum
B902500	Neoplasm of uncertain behaviour of rectum

Supplementary Table 4. Crude and adjusted hazard ratios for colorectal cancer comparing individual thiazide diuretic molecules with dihydropyridine calcium channel blockers

	Events	Person years	Weighted incidence rate (95% CI) [a,b]	Crude hazard ratio	Weighted hazard ratio (95% CI) [b,c]
Primary analysis					
dCCBs	2,199	1,564,616	142.4 (137.2-147.7)	1.00 [Reference]	1.00 [Reference]
Individual thiazide diuretic molecule					
Bendroflumethiazide	2471	1,789,704	138.0 (132.6-143.6)	0.96	0.97 (0.90-1.04)
Indapamide	131	86,807	150.9 (126.1-179.0)	1.07	1.05 (0.88-1.26)
Hydrochlorothiazide	130	109,655	118.5 (99.0-140.7)	0.82	0.87 (0.72-1.05)
Chlorthalidone	53	43,445	121.9 (91.3-159.5)	0.85	0.88 (0.66-1.16)
Metolazone	12	7,306	164.2 (84.8-286.9)	1.18	1.20 (0.67-2.12)
Cyclopenthiazide	S[e]	13,052	84.2 (42.0-150.7)	0.58	0.65 (0.36-1.18)
Other[d]	S[e]	5,336	74.9 (20.4-191.9)	0.51	0.58 (0.21-1.54)

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

[a] Per 100,000 person-years, [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands. [d] Other include chlorothiazide, hydroflumethiazide, mefruside, polythiazide, benzthiazide, methyclothiazide, xipamide, and clopamide. [e] Cells with less than 5 observations are suppressed as per the confidentiality policy of the Clinical Practice Research Datalink. One adjacent cell must also be suppressed to prevent secondary deduction.

Supplementary Table 5. Crude and adjusted hazard ratios for colorectal cancer comparing thiazide diuretics with dihydropyridine calcium channel blockers, stratified by cancer type

	Events	Person years	Weighted incidence rate (95% CI) [a,b]	Crude hazard ratio	Weighted hazard ratio (95% CI) [b,c]
Primary analysis					
dCCBs	2,199	1,564,616	142.4 (137.2-147.7)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	2,812	2,055,305	136.8 (131.8-141.9)		0.97 (0.90-1.04)
Cancer type [d]					
Colon					
dCCBs	1,674	1,564,616	108.4 (103.9-113.1)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	2,174	2,055,305	105.7 (101.3-110.3)	0.97	0.98 (0.90-1.07)
Rectum					
dCCBs	508	1,564,616	33.1 (30.6-35.7)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	613	2,055,305	29.8 (27.5-32.2)	0.90	0.90 (0.77-1.04)

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

[a] Per 100,000 person-years. [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands. [d] Other cancer types not otherwise specified generated 42 events

Supplementary Table 6. Crude and adjusted hazard ratios for colorectal cancer comparing thiazide diuretics with dihydropyridine calcium channel blockers (effect modification by sex)

	Male	Female
Events	2,786	2,225
Person-years	1,595,057	2,024,864
Weighted incidence rate (95% CI) [a,b]	180.6 (174.0-187.4)	114.1 (110.0-118.4)
Crude hazard ratio		
dCCBs	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	1.05	1.05
Weighted hazard ratio (95% CI) [b,c]		
dCCBs	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	1.01 (0.92-1.10)	0.97 (0.86-1.09)

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

[a] Per 100,000 person-years, [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands

Supplementary Table 7. Crude and adjusted hazard ratios for colorectal cancer comparing thiazide diuretics with dihydropyridine calcium channel blockers (effect modification by age)

	Age ≤ 55	**Age > 55**
Events	513	4,498
Person-years	1,259,191	2,360,730
Weighted incidence rate (95% CI) [a,b]	41.1 (37.8-44.5)	193.1 (187.9-198.5)
Crude hazard ratio		
dCCBs	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	0.95	0.99
Weighted hazard ratio (95% CI) [b,c]		
dCCBs	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	0.98 (0.78-1.22)	0.99 (0.92-1.07)

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

[a] Per 100,000 person-years. [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands

Supplementary Table 8. Crude and adjusted hazard ratios for colorectal cancer comparing thiazide diuretics with dihydropyridine calcium channel blockers (effect modification by history of aspirin use)

	No history of aspirin use	History of aspirin use
Events	3,557	1,454
Person-years	2,846,256	773,665
Weighted incidence rate (95% CI) [a,b]	128.2 (124.3-132.0)	193.0 (182.9-203.4)
Crude hazard ratio		
dCCBs	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	0.97	1.09
Weighted hazard ratio (95% CI) [b,c]		
dCCBs	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	0.95 (0.87-1.04)	1.05 (0.93-1.19)

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

[a] Per 100,000 person-years. [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands

Supplementary Table 9. Crude and adjusted hazard ratios for colorectal cancer comparing thiazide diuretics with dihydropyridine calcium channel blockers (effect modification by history of polyps)

	No history of polyps	History of polyps
Events	4,908	103
Person-years	3,574,584	45,337
Weighted incidence rate (95% CI) [a,b]	138.8 (135.2-142.5)	212.5 (171.3-260.6)
Crude hazard ratio		
dCCBs	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	0.95	1.21
Weighted hazard ratio (95% CI) [b,c]		
dCCBs	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	0.96 (0.89-1.03)	1.46 (0.93-2.31)

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

[a] Per 100,000 person-years. [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands

Supplementary Table 10. Crude and adjusted hazard ratios for colorectal cancer comparing thiazide diuretics with dihydropyridine calcium channel blockers (effect modification by history of inflammatory bowel disease)

	No history of inflammatory bowel disease	History of inflammatory bowel disease
Events	4,977	34
Person-years	3,588,638	31,283
Weighted incidence rate (95% CI) [a,b]	140.0 (136.4-143.7)	85.5 (57.1-123.0)
Crude hazard ratio		
dCCBs	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	0.95	1.29
Weighted hazard ratio (95% CI) [b,c]		
dCCBs	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	0.96 (0.89-1.03)	2.46 (1.13-5.36)

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

[a] Per 100,000 person-years. [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands

Supplementary Table 11. Crude and adjusted hazard ratios for colorectal cancer comparing thiazide diuretics with dihydropyridine calcium channel blockers (different lag periods)

	Events	Person years	Weighted incidence rate (95% CI) [a,b]	Crude hazard ratio	Weighted hazard ratio (95% CI) [b,c]
Primary analysis					
dCCBs	2,199	1,564,616	142.4 (137.2-147.7)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	2,812	2,055,305	136.8 (131.8-141.9)	0.96	0.97 (0.90-1.04)
3-year lag period					
dCCBs	1,633	1,084,458	149.0 (143.1-155.2)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	2,354	1,638,474	143.6 (137.9-149.5)	0.94	0.96 (0.89-1.05)
5-year lag period					
dCCBs	1,171	727,750	157.8 (150.7-165.1)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	1,907	1,266,658	150.5 (143.8-157.4)	0.93	0.95 (0.87-1.04)
10-year lag period					
dCCBs	408	223,018	171.4 (159.9-183.5)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	861	535,904	160.6 (150.1-171.7)	0.87	0.93 (0.80-1.07)

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

[a] Per 100,000 person-years. [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands

Supplementary Table 12. Crude and adjusted hazard ratios for the association between thiazide diuretics and risk of colorectal cancer (intention-to-treat exposure definition)

	Events	Person years	Weighted incidence rate (95% CI) [a,b]	Crude hazard ratio	Weighted hazard ratio (95% CI) [b,c]
Primary analysis					
dCCBs	2,199	1,564,616	142.4 (137.2-147.7)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	2,812	2,055,305	136.8 (131.8-141.9)	0.96	0.97 (0.90-1.04)
Intention-to-treat exposure definition					
dCCBs	3,037	2,063,762	149.7 (145.3-154.2)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	4,615	3,100,437	148.8 (144.5-153.2)	0.97	0.99 (0.93-1.05)

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

[a] Per 100,000 person-years. [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands

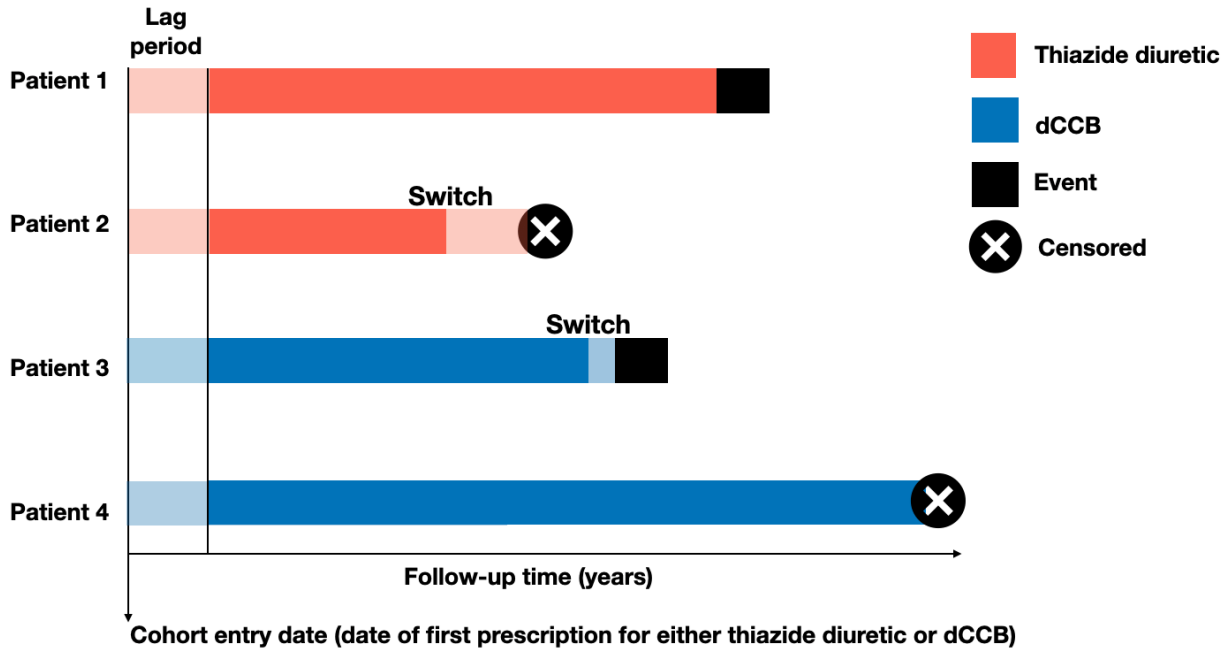
Supplementary Table 13. Crude and adjusted hazard ratios for the association between thiazide diuretics and risk of colorectal cancer (inverse probability of censoring weighting)

	Events	Person years	Weighted incidence rate (95% CI) [a,b]	Crude hazard ratio	Weighted hazard ratio (95% CI) [b,c]
Primary analysis					
dCCBs	2,199	1,564,616	142.4 (137.2-147.7)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	2,812	2,055,305	136.8 (131.8-141.9)	0.96	0.97 (0.90-1.04)
Inverse probability of censoring weighting					
dCCBs	2,199	1,762,259	138.6 (134.0-143.2)	1.00 [Reference]	1.00 [Reference]
Thiazide diuretics	2,812	2,257,740	138.8 (134.0-143.7)	0.98	1.01 (0.93-1.09)

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

[a] Per 100,000 person-years. [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands

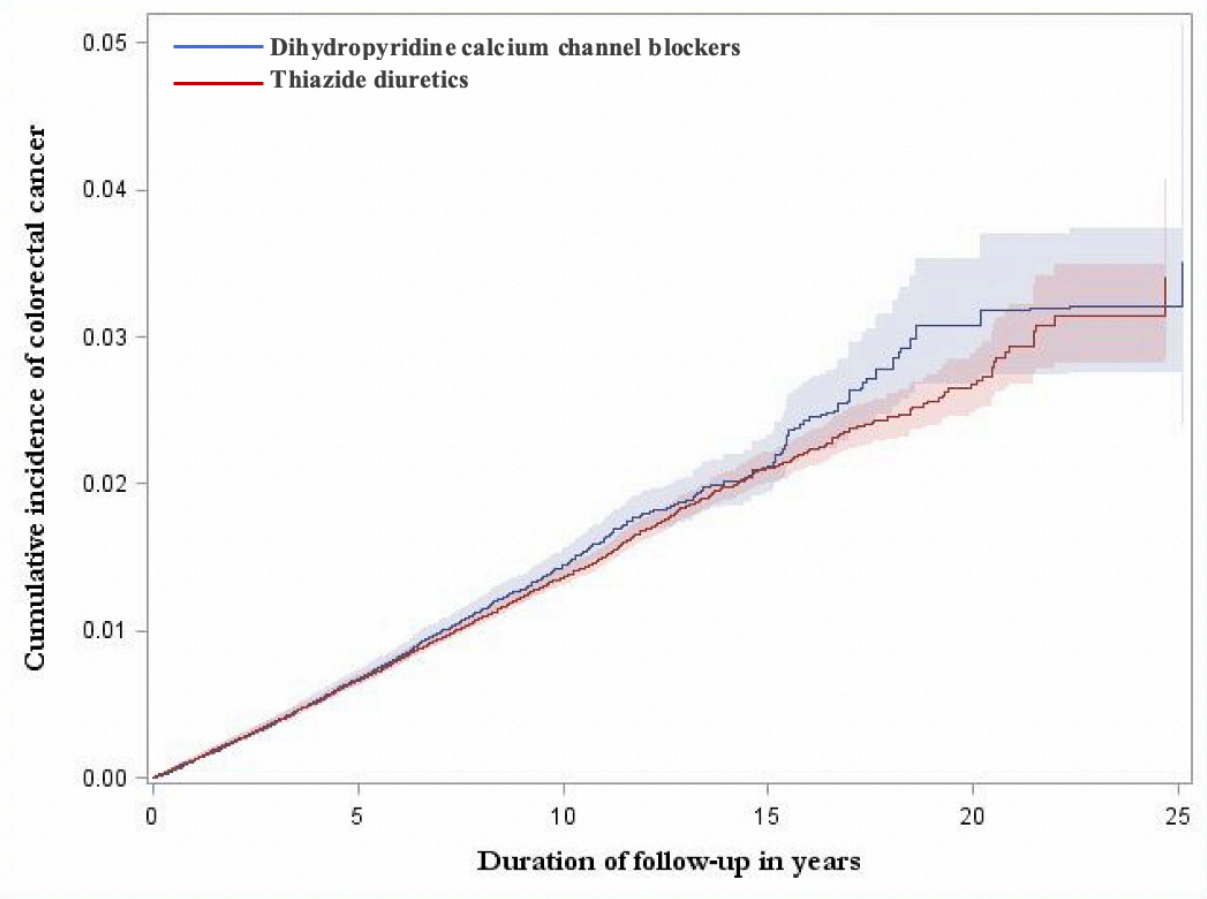
Supplementary Figure 1. Exposure definition



Abbreviations: dCCBs; dihydropyridine calcium channel blockers

All patients were required to have a minimum of one year of follow-up after cohort entry (lag period). Therefore, the follow-up started one year after cohort entry for all patients (start of person-time at risk or start of exposed person-time). Patient 1 initiated a thiazide diuretic, then was considered exposed one year after cohort entry. Follow-up ended on the date of an event (colorectal cancer). Similarly, patient 2 initiated a thiazide diuretic, then was considered exposed one year after cohort entry. Once the patient switched to a dCCB, a one-year period was applied whereas any event occurring during that one-year period would be attributed to thiazide diuretic. The patient was censored after the one-year period had elapsed. Patient 3 initiated a dCCB then switched to a thiazide diuretic. The patient had an event during the one-year period after the switch which was attributed to the dCCB group. Patient 4 initiated a dCCB then was censored at the end of the study period.

Supplementary Figure 2. Weighted Kaplan-Meier curve for the cumulative incidence of colorectal cancer [a,b]



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

Supplementary Method 1. Inverse probability of censoring weighting

Inverse probability of censoring weighting (IPCW) was used to account for potential informative censoring due to switching to (or adding on) the other study drug (i.e., a thiazide diuretic user switching to a dCCB, or a dCCB user adding on a thiazide diuretic) and assess the presence of competing risk of death from any cause. We conducted this analysis by applying two weights: one weight for switching to (or adding on) one of the two drug classes under study and one weight for mortality to account for death as competing risk.

First, we subdivided each patient' follow-up period by 1-year intervals, and updated the covariates at each interval based on the previous interval. The covariates included age (modeled flexibly as a continuous variable using restricted cubic spline), sex, body mass index, smoking status, alcohol-related disorders, hypertension, coronary heart disease, heart failure, peripheral vascular disease, stroke, atrial fibrillation, stable angina, myocardial infarction, chronic obstructive pulmonary disease, end-stage renal disease, inflammatory bowel disease, history of polyps, cholecystectomy, previous cancer diagnoses other than nonmelanoma skin cancer, hormone replacement therapy in women, bisphosphonates, statins, aspirin, other non-steroidal anti-inflammatory drugs, antidiabetic medications, antihypertensive drugs, proton pump inhibitors, calcium supplements, and vitamin D supplements, screening for breast cancer, colorectal cancer, and prostate cancer, and records of influenza vaccination.

Second, we estimated the probability of not being censored due to switching, separately for the thiazide diuretic cohort and the dCCB cohort. For each cohort, at each one-year interval, we generated the probability by fitting a multivariable logistic regression model stratified by 5-year calendar bands, conditional on the covariates described above.

Third, we estimated the probability of not being censored due to death from any cause, separately for the thiazide diuretic cohort and the dCCB cohort. Similar to the first model, for each cohort, at each one-year interval, we generated the probability by fitting a multivariable logistic regression model stratified by 5-year calendar bands, conditional on the covariates described above.

Finally, we used the conditional probabilities to generate weights at every interval for each patient (i.e., the probability of not being censored in the current interval is conditioned on the patient not being censored in the previous interval). We used the conditional probabilities from intercept-only model in the numerator to stabilize the two IPCWs. Extreme weights were truncated at the 1st and 99th interval. For each patient, we took the product of the two stabilized weights and the standardized morbidity ratio weight to obtain a final weight to re-weight the cohort. Finally, we used weighted Cox proportional hazard models to estimate marginal hazard ratios and confidence intervals of colorectal cancer associated with thiazide diuretics compared with dCCBs, using robust variance estimators.

CHAPTER 6. MANUSCRIPT 3: Dihydropyridine calcium channel blockers and risk of pancreatic cancer: a population-based cohort study

6.1 Preface

In Chapter 4, we found that CCBs and thiazide diuretics were two of the most commonly prescribed classes in primary care patients, prescribed for extended periods of time. These findings helped us understand the importance of investigating the long-term safety of these drug classes. In Chapter 5, we found that thiazide diuretics were not associated with an increased risk of colorectal cancer compared with dCCBs. While these findings provided some reassurance, additional research is needed to corroborate the elevated risks observed among patients with inflammatory bowel disease and a history of polyps. Thus, there remains important gaps in the long-term safety of thiazide diuretics and dCCBs, especially with respect to gastrointestinal cancers.

Two large meta-analyses of RCTs reported an increased risk of any cancer with the use of dCCBs.[30,31] However, none were designed to assess the long-term cancer safety of antihypertensive drugs. In observational studies, five of the six studies investigating the association between CCBs and cancer reported numerically elevated effect estimates for pancreatic cancer.[40-42,171,173] Importantly, most studies had potentially important methodological limitations or did not distinguish between dCCBs and non-dCCBs. Thus, there remains a need to generate stronger evidence of this potential association through methodologically rigorous studies using clinically relevant populations. The following chapter, Chapter 6, builds on the findings of Chapter 4 and, along with Chapter 5, provides much needed evidence on the gastrointestinal cancer safety of dCCBs. In Chapter 6, we investigated whether dCCBs were associated with an increased risk of pancreatic cancer compared with thiazide diuretics, an active comparator. Manuscript 3 has been submitted to *Circulation.*

Dihydropyridine calcium channel blockers and risk of pancreatic cancer: a population-based cohort study

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Keywords: antihypertensive drugs, dihydropyridine calcium channel blockers, calcium channel blockers, thiazide diuretics, pancreatic cancer, cancer, cohort study, propensity score

Non-standard abbreviations and acronyms: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; dCCBs, dihydropyridine calcium channel blockers; CPRD, Clinical Practice Research Datalink; CI, confidence interval; GOLD, Gp OnLine Data; HR, Hazard ratio; RCT, randomized controlled trial; sRAGE, soluble receptor for advanced glycation end products; UK, United Kingdom

ABSTRACT

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

Methods: We conducted a new user, active comparator, population-based cohort study using the United Kingdom Clinical Practice Research Datalink. We identified new users of dCCBs and new users of thiazide diuretics between 1990 and 2018, with follow-up until 2019. Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for pancreatic cancer, comparing dCCBs with thiazide diuretics. Models were weighted using standardized morbidity ratio weights based on calendar time-specific propensity scores. We also conducted secondary analyses by cumulative duration of use, time since initiation, individual molecules, and assessed for the presence of effect modification by age, sex, smoking status, body mass index, history of chronic pancreatitis, and diabetes.

Results: The cohort included 344,480 initiators of dCCBs and 357,968 initiators of thiazide diuretics, generating 3,360,745 person-years of follow-up. After a median follow-up of 4.5 years, the weighted incidence rate per 100,000 person-year was 37.2 (95% CI: 34.1-40.4) for dCCBs and 39.4 (95% CI: 36.1-42.9) for thiazide diuretics. Overall, dCCBs were not associated with an increased risk of pancreatic cancer (weighted HR: 0.93, 95% CI: 0.80-1.09). Similar results were observed in secondary analyses.

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

CLINICAL PERSPECTIVE

WHAT IS NEW?

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

WHAT ARE THE CLINICAL IMPLICATIONS?

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

INTRODUCTION

Dihydropyridine calcium channel blockers (dCCBs) are among the most commonly prescribed antihypertensive drugs in primary care practices.[1,2] This drug class is recommended as a first-line treatment for the management of hypertension, and has a favorable cardiovascular safety profile comparable to other antihypertensive drugs.[3-5] Recently, however, there have been concerns that dCCBs might be associated with an increased risk of pancreatic cancer.

To date, three large meta-analyses of RCTs investigated the safety of antihypertensive drugs with respect to cancer outcomes.[6-8] Of these, two reported an increased risk of any cancer with the use of dCCBs.[7,8] However, none of the RCTs included in these meta-analyses were designed to assess the long-term cancer safety of antihypertensive drugs. In observational studies, five of the six studies investigating the association between CCBs (i.e., dCCBs and non-dCCBs) and cancer reported numerically elevated effect estimates for pancreatic cancer, ranging between 1.10-2.07,[9-13] while one study reported an effect estimate below the null (0.85).[14] However, some studies had confidence intervals (CIs) that included the null value. Importantly, most studies investigating this association had potentially important methodological limitations, such as small sample sizes, prevalent user bias, and confounding by indication,[15] or did not distinguish between dCCBs and non-dCCBs. Finally, these inconclusive findings mirror the conflicting biological mechanisms associating dCCBs with cancer, with laboratory studies suggesting that dCCBs may inhibit apoptosis and promote tumor growth or, conversely, may have antitumor effects .[16-18]

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

pancreatic cancer compared with thiazide diuretics, another commonly prescribed antihypertensive drug class.

METHODS

Data Source

We conducted this study using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD) Gp OnLine Data (GOLD). The CPRD GOLD is an electronic primary care database containing the health records of over 20.7 million patients and has been shown to be representative of the UK general population in terms of age and sex.[19] A key strength of the CPRD is the inclusion of anthropometric data (e.g., body mass index) and lifestyle information (e.g., smoking status, alcohol use). It also includes medical diagnoses and procedures, recorded using Read codes, and prescriptions recorded using the British National Formulary dictionary.[19] Pancreatic cancer is well recorded in the CPRD, with a positive predictive value of 96% and sensitivity of 92% when compared with the UK National Cancer Data Repository.[20,21]

The study protocol was approved by the CPRD Research Data Governance (protocol number 22_001791) and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Study Population

We identified a new-user, active comparator cohort of primary care patients initiating either a dCCB or a thiazide diuretic between January 1, 1990 and March 31, 2018. The cohort consisted of all patients initiating a dCCB (amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, and nisoldipine, alone or with other antihypertensive drugs except thiazide diuretics), and compared with patients initiating a thiazide diuretic (hydrochlorothiazide, bendroflumethiazide, chlorothiazide, trichlormethiazide, methyclothiazide, polythiazide, quinethazone, hydroflumethiazide, benzthiazide, cyclopenthiazide, mefruside,

indapamide, chlorthalidone, clopamide, xipamide, and metolazone, alone or with other antihypertensive drugs except dCCBs; the British National Formulary codes are listed in **Supplementary Tables 1-2**). Cohort entry was defined as the date of the first prescription for either a dCCB or thiazide diuretic during the study period. We selected dCCBs rather than all CCBs as this subclass is usually preferred over non-dCCBs for the treatment of hypertension.[4,5,22] We also selected thiazide diuretics as the active comparator group as this drug class has not been previously associated with pancreatic cancer,[11] and to minimize confounding by indication as thiazide diuretics are recommended for the same indication and stage as dCCBs.[3-5]

To be included in the cohort, patients were required to be at least 40 years of age and have a minimum of one year of medical history in the CPRD before cohort entry; the latter served as a washout period necessary to identify new users. We excluded patients with concomitant prescriptions for both study drugs at cohort entry, as well as those previously diagnosed with rare genetic conditions or interventions that have been associated with an elevated incidence of pancreatic cancer at any time before cohort entry (Lynch syndrome, hereditary pancreatitis, Peutz-Jeghers syndrome, familial atypical multiple mole and melanoma syndrome, ataxia-telangiectasia, hereditary breast and ovarian cancer syndrome, multiple endocrine neoplasia type 1, von Hippel Lindau syndrome, neurofibromatosis type 1, cystic fibrosis, and solid organ transplant).[23-26] To identify incident events during follow-up, we excluded patients previously diagnosed with pancreatic cancer or those who underwent a total pancreatectomy at any time before cohort entry. Finally, patients were required to have at least one year of follow-up after cohort entry to allow for a minimum cancer latency period and minimize the detection of prevalent pancreatic cancer events. Thus, person-time at risk started one year after the cohort entry date.

Exposure Definition

Patients meeting the inclusion criteria were followed one year after cohort entry (i.e., the date of the new prescription for a dCCB or a thiazide diuretic) until the first of the following events: an incident diagnosis of pancreatic cancer identified using Read codes (**Supplementary Table 3**), one year after switching to one of the study drugs, death from any cause, end of registration with the general practice, or end of the study period (March 31, 2019). A figure depicting the exposure definition is available in the Supplement (**Supplementary Figure 1**).

Potential Confounders

All models were adjusted for the following variables measured at or before cohort entry: age (modeled flexibly as a continuous variable), sex, body mass index (most recent measurement at or before cohort entry), smoking status (most recent measurement at or before cohort entry), alcohol-related disorders, hypertension (captured as a recorded diagnosis or a minimum of three systolic or diastolic blood pressure measurement readings ≥140mmHg or ≥90mmHg, respectively, in the year prior cohort entry),[27] myocardial infarction, heart failure, stroke, atrial fibrillation, coronary artery disease, peripheral vascular disease, angina, chronic obstructive pulmonary disease, end-stage kidney disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease, other), cholecystectomy, previous cancer diagnoses other than non-melanoma skin cancer, chronic pancreatitis, cirrhosis of the liver, helicobacter pylori infection, and hepatitis B infection. We also included the following prescriptions drugs, all measured at any time before cohort entry: statins, aspirin and other non-steroidal anti-inflammatory drugs, antidiabetic drugs (including insulin, metformin, sulfonylureas, incretin-based drugs, sodium-glucose cotransporter-2 inhibitors, and other antidiabetic drugs), antihypertensive drugs (other than the study drugs which included

angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, non-dCCBs, diuretics other than thiazide diuretics, beta-blockers, and other antihypertensive drugs), proton pump inhibitors, vitamin D supplements, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors. Finally, we considered the following variables in the year before cohort entry as proxies for healthcare utilization and health-seeking behaviors: influenza vaccination and screening procedures, including fecal occult blood test or participation in the national bowel screening programme, mammography, and prostate-specific antigen testing.

Statistical Analyses

We used calendar time-specific propensity scores to account for secular trends in the prescribing of antihypertensive drugs, changes in pancreatic cancer incidence over time, and heterogeneity in the covariates during the study period.[28,29] We used a multivariable logistic regression model to estimate the predicted probability of receiving a dCCB versus a thiazide diuretic conditional on the covariates listed above. Propensity scores in the non-overlapping regions were trimmed. As the average treatment effect in the treated population was the target of inference, we used the propensity scores to generate standardized morbidity ratio weights. Patients initiating a dCCB were given a weight of 1 while patients initiating a thiazide diuretic were given a weight of the odds of treatment probability.[30,31] Extreme weights were truncated at 0.1 or 10. We evaluated covariate balance for each exposure group using absolute standardized differences, with pre-defined differences lower than 0.10 indicative of an achieved balance.[32] Finally, we calculated weighted incidence rates of pancreatic cancer with 95% CIs based on the Poisson distribution, and presented weighted cumulative incidence using the Kaplan-Meier curves. Weighted Cox proportional hazard models stratified on five-year calendar bands at cohort entry were fit to

estimate hazard ratios (HRs) and 95% CIs of pancreatic cancer associated with dCCBs using robust variance estimators.

Secondary and Sensitivity Analyses

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

We conducted three sensitivity analyses. First, we modified the length of the lag period to three years, five years, and 10 years to account for uncertainties related to the latency time window of pancreatic cancer. Second, analogous to an intention-to-treat analysis, we did not censor patients at the time of switch from a dCCB to a thiazide diuretic or from a thiazide diuretic to a dCCB. In this analysis, switching was ignored, and patients were followed until a pancreatic cancer event or censoring on death from any cause, de-registration from the general practice, or end of study

period. Third, we investigated the impact of potential informative censoring due to switching between the two study drugs and due to all-cause mortality as a competing event. For this analysis, we used stabilized inverse probability of censoring weighting (IPCW) where we estimated the probabilities of (1) remaining uncensored due to switching and (2) death for any cause, separately for dCCBs and thiazide diuretics. The product of the stabilized IPCW and the standardized morbidity ratio weights was used to re-weigh the cohort (**Supplementary Method 1**). All analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC) and R (version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

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

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

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

There was no duration-response relation in secondary analyses investigating cumulative duration of use (**Table 2**). After more than 10 years of cumulative duration of use, the weighted HR was 1.25 (95% CI: 0.68-2.31), which had a wide CI and was based on few events. Consistent with the weighted cumulative incidence curve, the time since initiation analysis showed a lower point estimate for dCCBs after more than 10 years since initiation (weighted HR 0.77, 95% CI: 0.47-1.26). However, CIs were wide and overlapping across the different time since initiation

categories. In the secondary analysis by individual dCCB agents, there was no evidence of an association with any of the individual agents and risk of pancreatic cancer, with weighted HRs ranging from 0.62 to 1.12 (**Supplementary Table 4**). Similarly, there was no evidence of an association in the analyses investigating potential effect modification by sex, age, smoking status, body mass index, history of chronic pancreatitis, and diabetes (**Supplementary Tables 5-10**).

Results from sensitivity analyses are presented in **Figure 2**. The sensitivity analyses using different lag periods (3 years, 5 years, 10 years) were consistent with the primary analysis, generating weighted hazard ratios ranging between 0.92-0.99 (**Supplementary Table 11**). The weighted HRs were also highly consistent in the intention-to-treat analysis (0.96, 95% CI: 0.85-1.09, **Supplementary Table 12**) and the inverse probability of censoring weighting (marginal HR 0.91, 95% CI: 0.78-1.06, **Supplementary Table 13**).

DISCUSSION

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

The biological mechanisms behind a possible association between dCCBs and pancreatic cancer are limited. It has been suggested that some antihypertensive drug classes, including dCCBs, might improve prognosis and survival in patients with pancreatic cancer.[38] It has been shown that high levels of soluble receptor for advanced glycation end products (sRAGE) might play a protective role in pancreatic cancer formation, and previous studies have shown that some dCCBs increase sRAGE concentrations, thus inhibiting the pro-inflammatory RAGE signalling pathway.[39,40] Contrastingly, sRAGE levels have been reported to be significantly lower in users of some dCCBs compared with users of other antihypertensive drugs and non-users.[10] Some studies have also suggested that dCCBs may inhibit apoptosis and promote tumor growth through the inhibition of DNA fragmentation.[17,18] Overall, our findings do not support an association between dCCBs and pancreatic cancer.

To date, six observational studies have investigated this possible association. Two earlier Danish studies reported standardized incidence rates of 1.20 (95% CI: 0.70-1.20) and 0.86 (95% CI: 0.57-1.25) for pancreatic cancer in users of any CCBs compared with the general population.[13,14] In a 1998 case-control study, the use of any CCBs was not associated with an overall increased risk of pancreatic cancer (relative risk 1.1, 95% CI: 0.70-1.80), although a higher point estimate was observed in patients who used these drugs for >5 years (relative risk 1.80, 95% CI: 0.80-4.00).[9] More recently, a 2018 Women's Health Initiative cohort study of 145,551 menopausal women reported that ever users of short-acting CCBs, such as the dCCB nifedipine, had a 66% increased risk of pancreatic cancer compared with ever users of other antihypertensive drugs (HR 1.66, 95% CI: 1.20-2.28), with a doubling of the risk associated with >3 years of use (HR 2.07, 95% CI: 1.42-3.02).[10] A 2019 cohort study of 8,311 patients with chronic pancreatitis found that users of any CCBs had a 56% increased risk of pancreatic cancer compared with non-users, although the CIs were wide and crossed the null value (HR 1.56, 95% CI: 0.76-3.22).[11] Finally, a 2021 cohort study of 70,549 patients reported a moderately elevated point estimate in users of any CCBs compared with non-users, but with the CI crossing the null value (HR 1.32, 95% CI: 0.79-2.20).[12]

Of these six studies, however, only two were specifically designed to investigate associations between any CCBs and pancreatic cancer,[10,11] with one of those studies restricted to patients with chronic pancreatitis.[11] Although chronic pancreatitis is an important risk factor for pancreatic cancer, it represents a specific and small subset of the patient population using antihypertensive drugs.[36] Importantly, neither of the two studies distinguished between dCCBs and non-dCCBs. This is important because the American College of Cardiology/American Heart Association, Hypertension Canada, and the International Society of Hypertension guidelines more

specifically recommend dCCBs over non-dCCBs as a first-line treatment for hypertension due to their more potent vasodilatory effects.[4,5,22] Additionally, some of these studies had potentially important, conclusion-altering biases, such as prevalent user bias, latency bias, recall bias, and confounding by indication by comparing CCB users with non-users or the general population.[15,41-43] In addition to these biases, only two studies assessed a potential association by duration of use, and none reported analyses by individual agents. Further, with the largest study only including 145,000 patients, none were adequately large to rule out clinically meaningful effects. This is especially important given that the incidence of pancreatic cancer ranges between 5.6-9.9 per 100,000 person-years in Europe, North America, Australia, and New Zealand, which represent the regions with the highest incidence rates.[44]

Finally, evidence from RCTs is limited. To date, three large meta-analyses of RCTs have investigated the safety of antihypertensive drugs with respect to cancer outcomes.[6-8] Of those, one meta-analysis reported an odds ratio of 1.06 (95% CI: 1.01-1.12) with dCCBs for any cancer,[7] and one meta-analysis reported a HR of 1.06 (95% CI: 1.01-1.11).[8] Both meta-analyses concluded that an excess risk for dCCBs could not be ruled out, and that the risk of cancer needed to be further investigated.[7,8] However, only one of the three meta-analyses investigated site-specific cancers, which included five cancer sites (colorectal, breast, lung, prostate, and skin) but not pancreatic cancer.[8] To date, no meta-analyses of RCTs have included pancreatic cancer. Further, these meta-analyses had important limitations in their assessment of cancer safety. First, none of the RCTs included in the three meta-analyses were designed to assess cancer safety outcomes.[6-8] Second, some site-specific cancers were represented by few RCTs, limiting the sample size available to detect these outcomes.[8] Third, the reported duration of follow-up was relatively short, where the majority of the RCTs included in the site-specific meta-analysis had less than five years of follow-

up.[8] Finally, generalizing these findings to the real-world patient population is difficult considering the strict selection of patients in RCTs.

Strengths and Limitations

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

The study has some limitations. First, prescriptions in the CPRD represent those issued by primary care physicians, and therefore no information is available on medications prescribed by specialists which can potentially lead to some misclassification of the exposure. In the UK, however, primary care physicians predominantly manage patients treated with antihypertensive

drugs.[52,53] Furthermore, the CPRD does not contain information on dispensation or adherence to treatment, possibly leading to additional exposure misclassification. However, our cumulative duration analysis, which captures repeated prescriptions and therefore some indication of treatment adherence, showed consistent findings. Second, misclassification of pancreatic cancer is possible although unlikely, as it has been shown to have a high positive predictive value and sensitivity compared with the National Cancer Data Repository.[20,21] Third, we were unable to stratify on grade and stage or distinguish between pancreatic ductal adenocarcinoma and other sub-types of pancreatic cancer, as these are not well recorded in the CPRD. However, pancreatic ductal adenocarcinoma represents the majority of pancreatic tumours.[54] Finally, although we were unable to capture potential risk factors for pancreatic cancer, such as diet and chemical and heavy metal exposure, these variables would be unlikely to be differentially distributed among patients prescribed dCCBs versus thiazide diuretics.

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

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JR received consulting fees for work unrelated to this project from Biogen. LA received consulting fees from Janssen and Pfizer for work unrelated to this paper. EGM, TS, and JMB have nothing to disclose.

Authorship and contributorship

Acquisition of study data (LA). Conception and planning of the study (JR, LA). Study design, interpretation of the data, critical revision of the manuscript for important intellectual content, and approval of the final version of the manuscript (JR, EGM, TS, JMB, LA). Data analysis and

manuscript draft (JR). Attestation that all authors meet authorship criteria and that no others meeting the criteria have been omitted (LA.). Accountable to all aspect of the work (JR, EGM, TS, JMB, LA).

Ethics approval

The study protocol was approved by the CPRD Research Data Governance (number 22_001791) and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Availability of data and materials

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

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FIGURE LEGENDS

Figure 1. Study flow diagram of patients initiating dihydropyridine calcium channel blockers and thiazide diuretics in the Clinical Practice Research Datalink between January 1, 1990 and March 31, 2018.

Figure 2. Forest plot presenting weighted hazard ratios and 95% confidence intervals for the primary and sensitivity analyses.

Table 1. Baseline characteristics of initiators of dihydropyridine calcium channel blockers and initiators of thiazide diuretics before and after weighting

	Before weighting			After weighting [a]		
Characteristics	**dCCB**	**Thiazide diuretic**	**ASD**	**dCCB**	**Thiazide diuretic**	**ASD**
Total	344,480	357,968		344,480	339,912	
Mean age, years (SD)	63.6 (11.5)	64.7 (12.1)	0.09	63.6 (11.5)	63.9 (11.3)	0.02
Male, n (%)	187,261 (54.3)	143,926 (40.2)	0.28	187,261 (54.3)	183,731 (54.0)	0.00
BMI, n (%)						
<25 kg/m^2	84,924 (24.6)	90,121 (25.1)	0.01	84,924 (24.6)	83,848 (24.6)	0.00
25-29.9 kg/m^2	122,243 (35.4)	119,961 (33.5)	0.03	122,243 (35.4)	120,056 (35.3)	0.00
≥30 kg/m^2	99,876 (28.9)	90,217 (25.2)	0.08	99,876 (28.9)	98,837 (29.0)	0.00
Unknown	37,437 (10.8)	57,669 (16.1)	0.15	37,437 (10.8)	37,169 (10.9)	0.00
Smoking status, n (%)						
Ever	166,363 (48.2)	157,524 (44.0)	0.08	166,363 (48.2)	164,129 (48.2)	0.00
Never	164,566 (47.7)	169,315 (47.3)	0.00	164,566 (47.7)	162,259 (47.7)	0.00
Unknown	13,551 (3.9)	31,129 (8.7)	0.19	13,551 (3.9)	13,524 (3.9)	0.00
Alcohol-related disorders, n (%) [b]	17,076 (4.9)	10,326 (2.8)	0.10	17,076 (4.9)	16,641 (4.9)	0.00
Medical history, n (%) [c]						
Hypertension	279,347 (81.0)	281,108 (78.5)	0.06	279,347 (81.0)	277,497 (81.6)	0.01
Myocardial infarction	17,782 (5.1)	10,306 (2.8)	0.11	17,782 (5.1)	19,166 (5.6)	0.02
Heart failure	7,430 (2.1)	7,498 (2.0)	0.00	7,430 (2.1)	8,576 (2.5)	0.02
Stroke	12,372 (3.5)	12,945 (3.6)	0.00	12,372 (3.5)	13,320 (3.9)	0.01
Atrial fibrillation	11,353 (3.3)	11,206 (3.1)	0.00	11,353 (3.3)	12,001 (3.5)	0.01
Coronary artery disease	74,438 (21.6)	58,008 (16.2)	0.13	74,438 (21.6)	76,489 (22.5)	0.02
PVD	14,544 (4.2)	9,920 (2.7)	0.07	14,544 (4.2)	15,710 (4.6)	0.01
Angina	33,214 (9.6)	18,918 (5.2)	0.16	33,214 (9.6)	34,793 (10.2)	0.01
COPD	31,707 (9.2)	35,850 (10.0)	0.02	31,707 (9.2)	31,791 (9.3)	0.00
End-stage kidney disease	1705 (0.4)	512 (0.1)	0.06	1705 (0.4)	1890 (0.5)	0.00
Ulcerative colitis	2,227 (0.6)	1,915 (0.5)	0.01	2,227 (0.6)	2,155 (0.6)	0.00
Crohn's disease	1,198 (0.3)	973 (0.2)	0.01	1,198 (0.3)	1,121 (0.3)	0.00
Other IBD	621 (0.1)	403 (0.1)	0.01	621 (0.1)	600 (0.1)	0.00
Cholecystectomy	13,820 (4.0)	14,418 (4.0)	0.00	13,820 (4.0)	13,681 (4.0)	0.00
Previous cancer	19,877 (5.7)	18,462 (5.1)	0.02	19,877 (5.7)	19,744 (5.8)	0.00
History of chronic pancreatitis	388 (0.1)	249 (0.1)	0.01	388 (0.1)	382 (0.1)	0.00
Cirrhosis of the liver	564 (0.1)	409 (0.1)	0.01	564 (0.1)	562 (0.1)	0.00
Helicobacter pylori infection	2,399 (0.7)	1,403 (0.3)	0.04	2,399 (0.7)	2,316 (0.6)	0.00
Hepatitis B	223 (0.1)	89 (0.0)	0.01	223 (0.1)	216 (0.1)	0.00
Medications, n (%)						
Statins	115,475 (33.5)	65,394 (18.2)	0.35	115,475 (33.5)	116,710 (34.3)	0.01
Aspirin	95,062 (27.6)	73,981 (20.6)	0.16	95,062 (27.6)	97,557 (28.7)	0.02
Other NSAIDs	218,574 (63.4)	220,083 (61.4)	0.09	218,574 (63.4)	215,130 (63.2)	0.00
Insulin	9,169 (2.6)	5,230 (1.4)	0.08	9,169 (2.6)	10,056 (2.9)	0.01
Metformin	27,285 (7.9)	14,117 (3.9)	0.16	27,285 (7.9)	28,434 (8.3)	0.01
Sulfonylureas	18,544 (5.3)	11,211 (3.1)	0.11	18,544 (5.3)	20,015 (5.8)	0.02
Incretin-based drugs	2,773 (0.8)	633 (0.1)	0.09	2,773 (0.8)	2,772 (0.8)	0.00
SGLT-2 inhibitors	309 (0.1)	60 (0.0)	0.03	309 (0.1)	309 (0.1)	0.00
Other antidiabetic drugs	6,437 (1.8)	3,538 (0.9)	0.07	6,437 (1.8)	6,727 (1.9)	0.00
ACE inhibitors	117,812 (34.2)	74,350 (20.7)	0.30	117,812 (34.2)	122,915 (36.1)	0.04
ARBs	26,181 (7.6)	18,233 (5.0)	0.10	26,181 (7.6)	22,761 (8.1)	0.02
Non-dihydropyridine CCBs	11,768 (3.4)	12,719 (3.5)	0.00	11,768 (3.4)	12,992 (3.4)	0.02
Other diuretics	35,916 (10.4)	34,684 (9.6)	0.02	35,916 (10.4)	38,346 (11.2)	0.02
Beta-blockers	105,267 (30.5)	94,064 (26.2)	0.09	105,267 (30.5)	106,954 (31.4)	0.01
Other antihypertensive drugs	8,950 (2.6)	9,258 (2.5)	0.00	8,950 (2.6)	9,054 (2.6)	0.00
Proton pump inhibitors	126,895 (36.8)	81,532 (22.7)	0.31	126,895 (36.8)	125,233 (36.8)	0.00

Vitamin D supplement	26,089 (7.5)	17,978 (5.0)	0.10	26,089 (7.5)	26,253 (7.7)	0.00
SSRIs and SNRIs	67,858 (19.7)	52,887 (14.7)	0.13	67,858 (19.7)	66,930 (19.6)	0.00
Screening and other health behaviors, n (%)						
Influenza vaccination	105,766 (30.7)	130,167 (36.3)	0.12	105,766 (30.7)	108,062 (31.7)	0.02
Fecal occult blood test [d]	11,746 (3.4)	3,566 (1.0)	0.16	11,746 (3.4)	11,073 (3.2)	0.00
Mammography	23,667 (6.8)	25,994 (7.2)	0.01	23,667 (6.8)	23,373 (6.8)	0.00
PSA test	20.688 (6.0)	11,425 (3.1)	0.13	20.688 (6.0)	20,044 (5.9)	0.00
Cohort entry year, n (%)						
1990-1993	8,517 (2.4)	16,995 (4.7)	0.12	8,517 (2.4)	8,831 (2.6)	0.01
1994-1998	20,310 (5.9)	42,930 (11.9)	0.21	20,310 (5.9)	20,695 (6.0)	0.00
1999-2003	41,410 (12.0)	129,262 (36.1)	0.58	41,410 (12.0)	42,088 (12.3)	0.01
2004-2008	99,613 (28.9)	117,570 (32.8)	0.08	99,613 (28.9)	99,929 (29.4)	0.01
2009-2013	108,788 (31.6)	41,776 (11.6)	0.50	108,788 (31.6)	108,737 (31.9)	0.00
2014-2018	65,788 (19.1)	9,435 (2.6)	0.55	65,788 (19.1)	59,631 (17.5)	0.04

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ASD, absolute standardized difference; BMI, body mass index; COPD, chronic obstructive pulmonary disease; dCCB, dihydropyridine calcium channel blocker; IBD, inflammatory bowel disease; NSAID, non-steroidal anti-inflammatory drugs; SGLT-2, sodium-glucose cotransporter-2; PVD, peripheral vascular disease; PSA, prostate-specific antigen; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors

[a] Characteristics weighted using standardized morbidity ratio weighting. [b] Includes alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and hepatic failure. [c] Not mutually exclusive. [d] Includes participation in the national bowel screening programme

Table 2. Crude and adjusted hazard ratios for pancreatic cancer comparing dihydropyridine calcium channel blockers with thiazide diuretics

Exposure	Events	Person years	Weighted incidence rate (95% CI) [a,b]	Crude hazard ratio	Weighted hazard ratio (95% CI) [b,c]
Primary analysis					
Thiazide diuretics	707	1,895,844	39.4 (36.1-42.9)	1.00 [Reference]	1.00 [Reference]
dCCBs	545	1,464,901	37.2 (34.1-40.4)	1.02	0.93 (0.80-1.09)
Cumulative duration < 5 years [d]					
Thiazide diuretics	534	1,506,828	38.2 (34.7-42.0)	1.00 [Reference]	1.00 [Reference]
dCCBs	441	1,197,058	36.8 (33.4-40.4)	1.06	0.96 (0.81-1.14)
Cumulative duration 5-10 years [d]					
Thiazide diuretics	141	317,570	47.0 (37.7-57.9)	1.00 [Reference]	1.00 [Reference]
dCCBs	85	226,444	37.5 (29.9-46.4)	0.85	0.80 (0.57-1.11)
Cumulative duration >10 years [d]					
Thiazide diuretics	32	71,026	37.1 (18.5-66.6)	1.00 [Reference]	1.00 [Reference]
dCCBs	19	40,867	46.4 (27.9-72.6)	1.04	1.25 (0.68-2.31)
Time since initiation < 5 years					
Thiazide diuretics	390	1,148,239	36.3 (32.5-40.3)	1.00 [Reference]	1.00 [Reference]
dCCBs	357	1,008,706	35.3 (31.8-39.2)	1.04	0.97 (0.79-1.18)
Time since initiation 5-10 years [e]					
Thiazide diuretics	211	528,658	44.5 (37.8-52.0)	1.00 [Reference]	1.00 [Reference]
dCCBs	136	348,898	38.9 (32.7-46.1)	0.97	0.87 (0.66-1.15)
Time since initiation >10 years [e]					
Thiazide diuretics	106	219,119	63.0 (48.6-80.3)	1.00 [Reference]	1.00 [Reference]
dCCBs	52	107,168	48.5 (36.2-63.6)	1.00	0.77 (0.47-1.26)

Abbreviations: dCCBs; dihydropyridine calcium channel blockers, CI; confidence interval.
[a] Per 100,000 person-years [b] Weighted using standardized morbidity ratio weights [c] Stratified by 5-year calendar bands. [d] Cumulative duration was modeled in a time-varying fashion. [e] Propensity score was re-estimated and weights were re-calculated for these categories.

Figure 1. Study flow diagram of patients initiating dihydropyridine calcium channel blockers and thiazide diuretics in the Clinical Practice Research Datalink between January 1, 1990 and March 31, 2018.

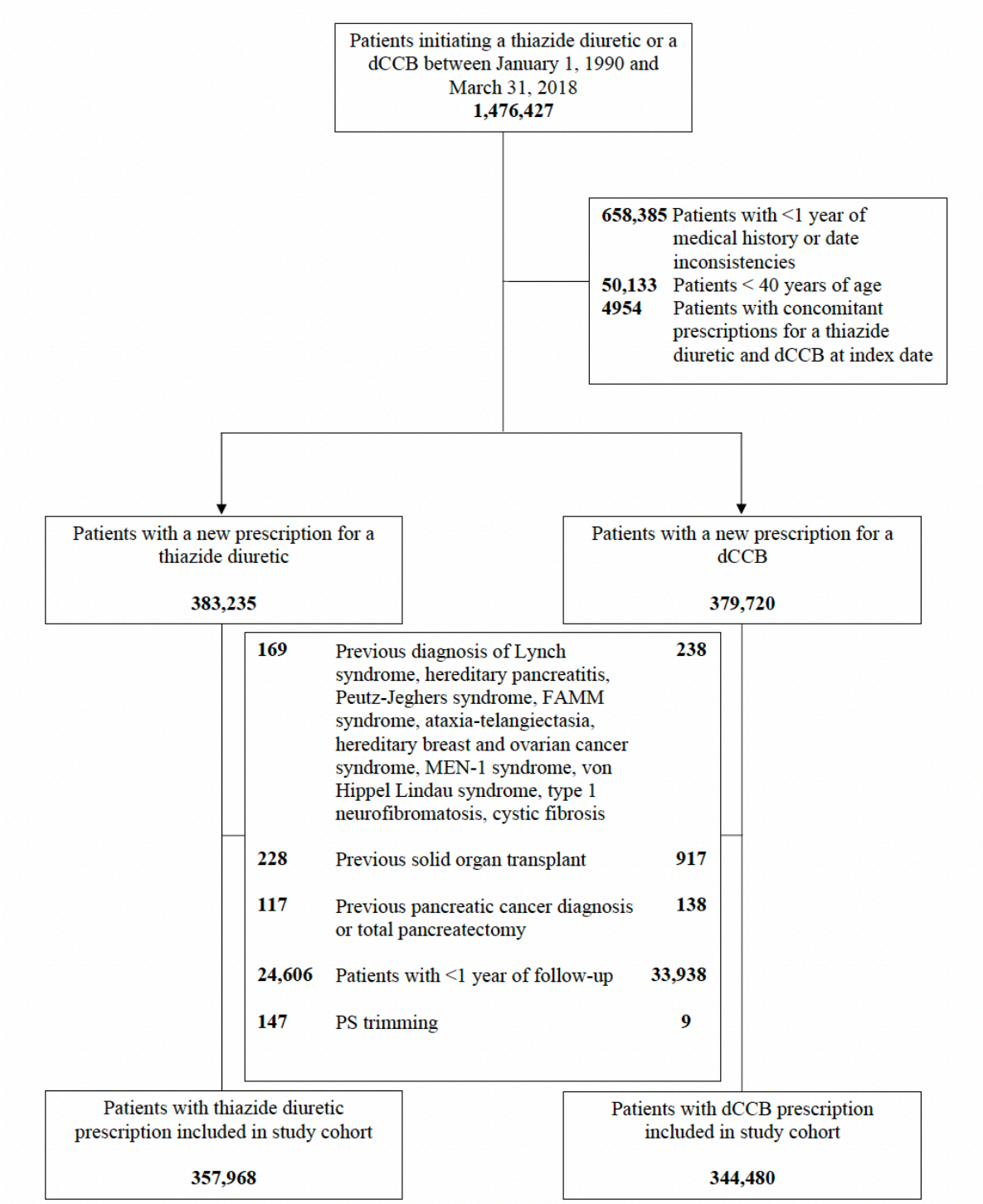
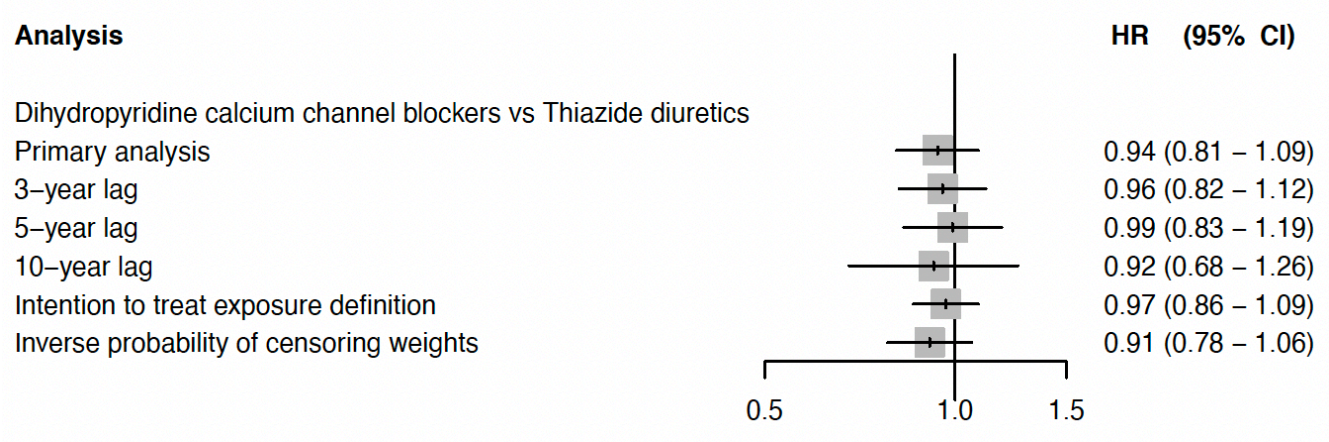


Figure 2. Forest plot presenting weighted hazard ratios and 95% confidence intervals for the primary and sensitivity analyses



SUPPLEMENTARY MATERIAL

Dihydropyridine calcium channel blockers and risk of pancreatic cancer: a population-based cohort study

Supplementary Table 1. British National Formulary (BNF) codes for dihydropyridine calcium channel blockers

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

Supplementary Table 2. British National Formulary (BNF) codes for thiazide diuretics

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

Supplementary Table 3. Read codes for pancreatic cancer

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

Supplementary Table 4. Crude and adjusted hazard ratios for the association between individual dihydropyridine calcium channel blocker agents and risk of pancreatic cancer

Exposure	Events	Person years	Weighted incidence rate (95% CI) [a,b]	Crude hazard ratio	Weighted hazard ratio (95% CI) [b,c]
Thiazide diuretics	707	1,895,844	39.4 (36.1-42.9)	1.00 [Reference]	1.00 [Reference]
Individual dCCB agent					
Amlodipine	346	973,458	35.5 (31.8-39.4)	0.98	0.89 (0.75-1.05)
Nifedipine	120	270,858	44.3 (36.7-52.9)	1.18	1.12 (0.91-1.39)
Felodipine	64	166,166	38.5 (29.6-49.1)	1.05	0.97 (0.74-1.28)
Lercanidipine	10	33,719	29.6 (14.2-54.5)	0.82	0.75 (0.70-1.42)
Other [d]	5	20,698	24.1 (7.8-56.3)	0.64	0.62 (0.25-1.49)

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

[a] Per 100,000 person-years. [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands.
[d] Other include nimodipine, nisoldipine, nicardipine, isradipine, lacidipine, combinations

Supplementary Table 5. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (effect modification by sex)

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

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

Supplementary Table 6. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (effect modification by age)

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

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

[a] Per 100,000 person-years. [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands

Supplementary Table 7. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (effect modification by smoking status) [a]

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

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

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

Supplementary Table 8. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (effect modification by body mass index) [a]

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

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

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

Supplementary Table 9. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (effect modification by history of chronic pancreatitis)

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

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

[a] Per 100,000 person-years. [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands

Supplementary Table 10. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (effect modification by history of diabetes)

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

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

[a] Per 100,000 person-years. [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands

Supplementary Table 11. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (different lag periods)

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

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

[a] Per 100,000 person-years [b] Weighted using standardized morbidity ratio weights [c] Stratified by 5-year calendar bands

Supplementary Table 12. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (intention-to-treat exposure definition)

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

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

[a] Per 100,000 person-years. [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands

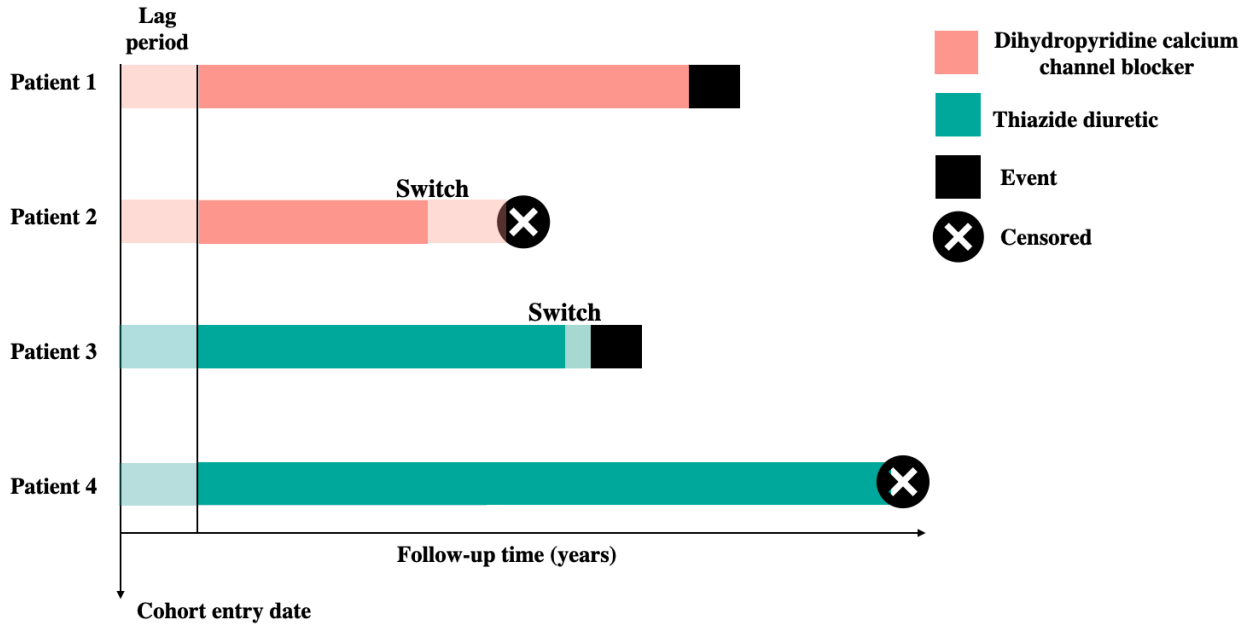
Supplementary Table 13. Crude and adjusted hazard ratios for the association between dihydropyridine calcium channel blockers and risk of pancreatic cancer (inverse probability of censoring weighting)

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

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

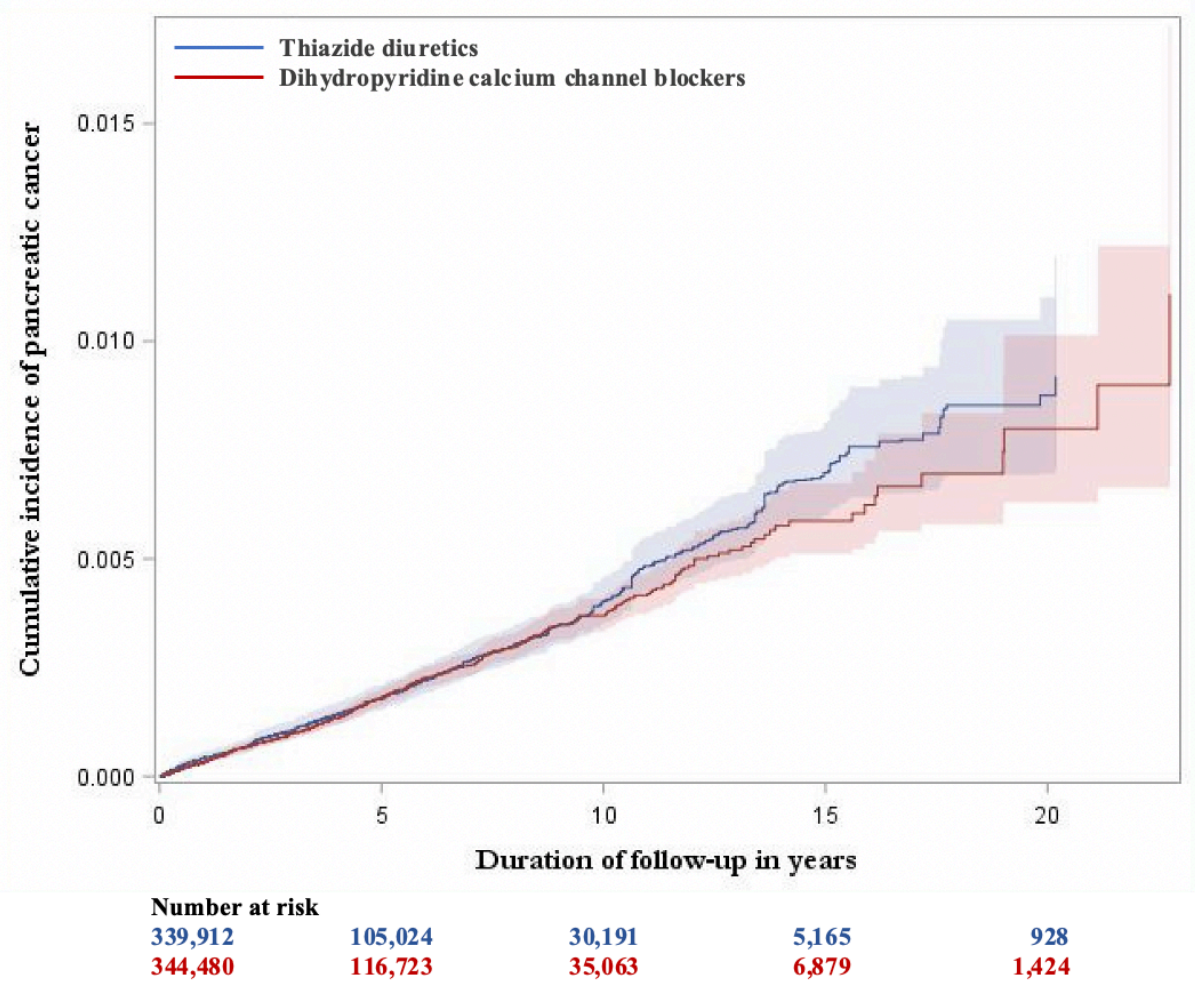
[a] Per 100,000 person-years. [b] Weighted using standardized morbidity ratio weights. [c] Stratified by 5-year calendar bands

Supplementary Figure 1. Exposure definition



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

Supplementary Figure 2. Weighted Kaplan-Meier curve for cumulative incidence of pancreatic cancer [a,b]



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

Supplementary Method 1. Inverse probability of censoring weighting

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

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

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

ratios and confidence intervals of pancreatic cancer associated with dCCBs using robust variance estimators.

CHAPTER 7. DISCUSSION

The overall purpose of this thesis was to address some of the knowledge gaps in the prescribing patterns of antihypertensive drugs and generate new evidence on the long-term gastrointestinal cancer safety of thiazide diuretics and dCCBs. First, I described the treatment and prescribing trends of antihypertensive drugs in primary care practices over time. This was followed by two large population-based cohort studies to investigate the association between thiazide diuretics and risk of colorectal cancer, when compared with dCCBs, and to evaluate the association between dCCBs and risk of pancreatic cancer, compared with thiazide diuretics.

7.1 Summary and interpretation of research findings

Manuscript 1, titled "*Treatment and prescribing trends of antihypertensive drugs in 2.7 million UK primary care patients over 31 years: a population-based cohort study*", described the treatment and prescribing trends of antihypertensive drugs in primary care practices over time. In this large population-based study, the prevalence of patients prescribed antihypertensive drugs increased during the study period but has remained relatively steady since 2006, with nearly one-quarter of primary care patients receiving antihypertensive drugs by the end of the study period. ACE inhibitors and CCBs were the most prevalent classes. We also highlighted an age and sex difference in beta-blockers prescriptions; beta-blockers were the first-ever drug class for more than one-third of patients and were predominantly prescribed in the youngest patients, primarily females, and without hypertension or other cardiovascular indications. For the treatment trends in patients with hypertension, we found that most patients initiated guideline-recommended first-line agents, with thiazide diuretics and beta-blockers representing the most common first-line drugs before 2007 and ACE inhibitors and CCBs after 2007. Fewer females initiated recommended first-

line agents, and one-fifth of patients were prescribed three or more antihypertensive drug class after failure on first-line monotherapy, with some patients being prescribed up to seven classes. These findings show that some patient subgroups may be less likely to receive first-line agents while others are more likely to be overprescribed antihypertensive drugs, potentially leading to less effective treatment and higher risk of adverse effects.

Manuscript 2, titled "*Thiazide diuretics and risk of colorectal cancer: a population-based cohort study*", aimed to evaluate the association between thiazide diuretics and risk of colorectal cancer compared with dCCBs. In this population-based, new-user, active comparator cohort study of 742,084 primary care patients, the use of thiazide diuretics was not associated with an increased risk of colorectal cancer when compared with dCCBs. There was no evidence of an association by cumulative duration of use, including in patients with over ten years of thiazide diuretic use, and no individual thiazide diuretic molecules were found to be associated with colorectal cancer. We conducted several sensitivity analyses by using different lag periods, intention-to-treat exposure definition, and inverse probability of censoring weights, with results consistent with the primary analysis. However, we found an increased risk of colorectal cancer among thiazide diuretic initiators with inflammatory bowel disease and a history of polyps.

Manuscript 3, titled "*Dihydropyridine calcium channel blockers and risk of pancreatic cancer: a population-based cohort study*", aimed to assess the association between dCCBs and the risk of pancreatic cancer compared with thiazide diuretics. The findings from this large, new-user, active comparator, population-based cohort study of 702,448 patients indicated that dCCBs were not associated with an increased risk of pancreatic cancer when compared with thiazide diuretics. In secondary analyses, there was no evidence of an association with long-term use of dCCBs, and no individual dCCB agents were found to be associated with pancreatic cancer. These findings

remained consistent in other secondary analyses, including time since initiation and effect modification, and in sensitivity analyses, including the use of different lag periods, intention-to-treat exposure definition, and inverse probability of censoring weights.

7.2 Strengths and limitations

This thesis contains important strengths. First, the execution of the three objectives filled important research gaps in the understanding of treatment and prescribing trends of antihypertensive drugs over time, and generated new knowledge on the long-term cancer safety of thiazide diuretics and dCCBs while addressing limitations of previous studies. In Manuscript 2 and Manuscript 3, the identification of new users minimized left truncation and allowed us to properly assess the cancer risk with cumulative duration and time since initiation. Additionally, the use of an active comparator minimized confounding by indication while offering a comparator drug that can be equally prescribed to patients according to current and past hypertension management guidelines.[48-53,203] These design choices, together with defining the initiation of treatment as the start of person-time at risk, eliminated immortal time bias which can be an important and potentially conclusion-altering bias.[159,204] Second, the use of the CPRD allowed for the inclusion of more than 2.7 million patients in Manuscript 1, representing the largest and most comprehensive study to date on the prescribing trends of antihypertensive drugs, which also included prescribing trends by drug class, sex, age group, and comorbidities. The extended follow-up of patients in the CPRD allowed for the investigation of prescribing trends over a 31-year study period, providing the longest follow-up to date to capture major changes in UK treatment guidelines over time and a detailed picture of the treatment lines used in the management of patients with hypertension. Further, we were able to follow some patients for extended periods of

time in Manuscripts 2 and 3, with a maximum follow-up of nearly 28 years in our studies. Additionally, using the CPRD allowed for the adjustment of potentially important confounders and risk factors for colorectal and pancreatic cancer, such as smoking status, BMI, and alcohol use, has been shown to be representative of the UK population, and undergoes regular data quality checks to ensure its validity.[181]

This thesis also contains limitations. First, the CPRD contains only prescriptions issued by general practitioners rather than specialists, potentially introducing some exposure misclassification. However, in the UK, it is well documented that most patients treated with antihypertensive drugs are managed by general practitioners, thus minimizing the impact of this misclassification.[205,206] The CPRD also captures prescriptions rather than dispensing information, and therefore it is possible that some patients may not fill a prescription or adhere to the prescription. However, Manuscript 1 focused on prescriptions rather than use of antihypertensive drugs, and analyses investigating repeated prescriptions, as in the cumulative duration analyses in Manuscript 2 and Manuscript 3, are likely indicative of some treatment adherence. Second, for the treatment trajectory cohort, the analysis was limited to patients with a recorded diagnosis of hypertension through a robust algorithm. However, it is possible that some patients were not captured by this definition, leading to an underestimation of the number of patients included in the cohort. However, there is no evidence suggesting that these patients would differ by type of antihypertensive drug class. Third, for Manuscript 2, it was not possible to stratify colorectal cancer cases by cancer stage or site, as these details are not available in the CPRD. However, we conducted a secondary analysis stratifying by type (colon, rectal), which provided findings consistent with our primary analysis. For Manuscript 3, we were unable to stratify on cancer grade and stage or distinguish between pancreatic ductal adenocarcinoma and other sub-types of

pancreatic cancer. However, pancreatic ductal adenocarcinoma represents the majority of pancreatic tumours.[207] Finally, residual confounding is possible, as the CPRD does not contain information on some risk factors for colorectal and pancreatic cancer such as diet, physical activity, and chemical and heavy metal exposure. However, our choice of an active comparator design and inclusion of health-related behaviour variables aimed at reducing the potential impact of unmeasured confounding.

7.3 Implications of findings

This thesis provided important advancements in the understanding of the long-term prescribing practices through an updated and comprehensive evaluation of the treatment and prescription patterns of antihypertensive drugs. Although previous studies examined trends in antihypertensive drug prescriptions, it was often conducted within a short time period, with a focus on a specific class, or presented as a group of medications overall. Given the long-standing prescribing history of antihypertensive drugs, and the several hypertension management guidelines published over time, this thesis aimed to fill an important gap in the prescription pattern landscape and present a comprehensive yet detailed picture of antihypertensive drug prescribing practices from the inception of hypertension management guidelines to today. Through its findings, this thesis can help better inform both clinical practice and pharmacoepidemiologic research.

First, it confirms that hypertension management guidelines are closely reflected, for the most part, in primary care prescribing practices. Its findings that 22% of patients were prescribed antihypertensive drugs in 2018, compared to only 8% in 1988, also helps appreciate the increase in primary care physicians' workload over time around the disease management of a substantial proportion of their patients. This thesis also helps understand the potential medication burden in

some patient subgroups and the importance of carefully re-evaluating this burden. It highlighted that 20% of patients were prescribed three or more antihypertensive drug classes, with some patients concomitantly receiving up to seven classes, omitting the capture other possible medications that patients might be prescribed. A long-term, multifaceted approach that would address this increased management workload, and patient medication burden, while focusing on primary and secondary disease prevention would be needed. In the clinical community, there has been a growing emphasis on deprescribing, notably in Canada through the Choosing Wisely Canada campaign.[208-210] Deprescribing is defined as the supervised adjustment of medications that may no longer be of benefit or needed, so that the benefits of medications outweigh the medication burden or harms.[209,211] Deprescribing is thus increasingly important in the current polypharmacy landscape, as the inappropriate over-prescription of medication have been shown to lead to higher risk of adverse events.[212]

Second, this thesis helps inform the study design of drug safety and effectiveness studies. Understanding the prevalence and time period of availability of each class over time helps in the selection of the most appropriate exposure and comparison group that best answer a specific study question, particularly for comparative effectiveness and safety studies. In Manuscript 1, the analyses on the time from initial treatment to a switch or add-on of other antihypertensive drug classes help understand the length of time patients are on treatment and the switching patterns in the real world of clinical practice. This provides valuable information to pharmacoepidemiologists to help define the exposure definition.

Through Manuscript 2 and Manuscript 3, this thesis provides important evidence to the body of research on the long-term cancer safety of thiazide diuretics and dCCBs. Although these classes have been prescribed for several decades, opportunities to address long-term safety

concerns are more contemporary. Indeed, we have recently gained the computational capabilities to analyze large datasets, the maturity of research services such as the CPRD to grow into large population-based databases, and the structural infrastructure to study rare outcomes such as cancer. Although RCTs have attempted to provide answers to the cancer safety of medications, these RCTs often have relatively shorter follow-up than population-based studies, a fundamental aspect in the study of cancer outcomes.[195] For example, a large 2021 meta-analysis of RCTs examining antihypertensive drugs and risk of cancer, which specifically only included RCTs with "long-term" follow-up, only had an upper interquartile range of five years of follow-up, while this thesis provided an upper interquartile range of nearly ten years of follow-up and a maximum follow-up of 28 years. This thesis further provided specific evidence of the comparative long-term safety of thiazide diuretics and dCCBs through the use of a clinically relevant comparator and a specifically designed cohort study to address these cancer safety questions. Overall, it provided much needed reassurance to physicians and patients regarding the long-term gastrointestinal safety of thiazide diuretics with respect to colorectal cancer and of dCCBs regarding pancreatic cancer. More well-conducted, population-based studies that address a specific cancer safety question are fundamental however in generating a stronger assurance of the long-term safety of medications with respect to cancer.[195]

7.4 Future directions

This thesis helped filled important knowledge gaps in the prescribing patterns of antihypertensive drugs and the comparative gastrointestinal cancer safety of thiazide diuretics and dCCBs, two commonly prescribed drugs. Much remains to be investigated however. In Manuscript 1, we reported that 17% of patients with hypertension were not prescribed recommended first-line

drugs, which suggest that some patient subgroups may be less likely to receive first-line agents. Future research should investigate whether this may lead to suboptimal cardiovascular outcomes. This is especially relevant because hypertension management guidelines are often based on evidence from older RCTs and with comparisons between specific antihypertensive agents rather than classes.[118] For example, the recommendations forming the basis of the 2017 American College of Cardiology/American Heart Association hypertension management guidelines were predominantly based on RCTs conducted more than 20 years ago.[118] Therefore, there remains a need for more evidence on the comparative effectiveness of different antihypertensive agents and classes. Further, studies should investigate which specific treatment trajectory optimizes cardiovascular outcomes in patients with hypertension.

We also found that fewer females initiated recommended first-line agents. This sex difference may perhaps be explained by dissimilar presentations of cardiovascular symptoms,[213] which may in turn be reflected in the clinical decisions leading to prescribing practices. Nonetheless, further research should focus on better understanding these sex differences in prescribing practices and whether these differences impact cardiovascular outcomes. We also showed an age and sex difference in propranolol prescriptions, a beta-blocker, which was predominantly prescribed in the youngest patients, primarily females, and without hypertension or other cardiovascular indications. A recent study found a 2.5-fold increase in the prevalence of propranolol prescriptions for anxiety in UK primary care practices between 2003 and 2018, with a higher incidence for female patients and patients aged <45 years old.[214] Although propranolol is licensed for use in anxiety symptoms management,[215] there is currently limited evidence of its long-term effectiveness and safety[216,217] and no specific recommendations exist regarding its use in anxiety.[218] Further, the UK Healthcare Safety Investigation Branch recently informed of a

potential risk of propranolol toxicity in overdose, reporting a 33% increase in deaths potentially associated with propranolol overdose between 2012 and 2017.[218] We also found a sharp increase in patients aged 80 and over with beta-blockers prescriptions, representing the largest age group with prescriptions for this class. Beta-blockers, and specifically non-cardioselective beta-blockers such as propranolol, have been associated with an increased risk of fall in the elderly.[219] Together, these findings warrant further investigation to understand the benefits and safety of beta-blockers, especially propranolol.

In Manuscript 2, we found that the effect of thiazide diuretics on colorectal cancer varied by strata of previous history of inflammatory bowel disease, and perhaps history of polyps. While these conditions are known risk factors for colorectal cancer,[135,136] additional research will be needed to corroborate these findings and determine whether patients with these conditions represent susceptible individuals.

In Manuscript 2 and Manuscript 3, we investigated the risk of colorectal cancer and pancreatic cancer in thiazide diuretics and dCCBs, respectively. However, much remain to be investigated in the field of cancer safety. Several observational studies have reported that thiazide diuretics may be associated with a doubling of the risk of renal cell carcinoma, although the majority of those studies were conducted between 1966 and 1998.[220,221] More recent studies found an elevated risk, although with wide CIs crossing the null value, or mixed results depending on renal cell carcinoma type (clear renal cell vs papillary).[222,223] These studies, however, had potentially important limitations, such as confounding by indication, immortal time bias, and time window bias, or included both prevalent and new users.[43,158,159,224] Renal cell carcinoma is one of the most aggressive urological cancers, with an increasing incidence worldwide and is highest in North America (11.7 per 100,000 population).[225] The biological mechanism for this association is

plausible, as thiazide diuretics are diuretics that act directly in the nephron, the functional unit of the kidney that contains the glomerulus and the renal tubule (see **Section 2.2.1 Thiazide diuretics**).[59,60]

Meta-analyses of RCTs investigating cancer risk in antihypertensive drugs reported no overall increased risk of any cancer for ARBs, ACE inhibitors, thiazide diuretics, and beta-blockers.[29-31] However, as discussed in **Section 2.4.3 Long-term cancer safety of antihypertensive drugs**, these meta-analyses contain important limitations for the assessment of long-term cancer safety. Further, as discussed in Section **2.6.2. Dihydropyridine calcium channel blockers and risk of pancreatic cancer**, using a composite cancer outcome of any cancer in these meta-analyses can be problematic and would masks any true association. Several large population-based studies recently reported associations between antihypertensive drugs and cancer risk not previously detected by meta-analyses of RCTs. For example, four large population-based studies reported an elevated risk of skin cancer in users of hydrochlorothiazide, a thiazide diuretic prescribed for more than sixty years, with a stronger association after more than five years of use.[226-229] Other observational studies reported an increased risk of lung cancer in ACE inhibitors users.[230,231] These potential associations were not reported in a large meta-analysis of RCTs, even among those capturing site-specific cancers including lung and skin cancers.[31] Therefore, large population-based are uniquely positioned to address the limitations encountered in many RCTs. Additional population-based studies specifically designed to investigate cancer associations should thus be conducted to both complement the evidence provided by RCTs as well as provide specific evidence on the safety of antihypertensive drugs for outcomes such as cancer.

Finally, it has been demonstrated that well-designed, population-based studies using an active comparator enhance the validity of non-randomized real-world evidence studies against

RCTs.[232,233] These population-based studies should be undertaken as a complement to RCTs or in situations where evidence from RCTs is not available or cannot be practically generated.[195] In cancer pharmacoepidemiology, assessing the comparative safety of medications through large, population-based studies using an active comparator group offer a substantial advantage in terms of duration of follow-up and cohort size. Given that the prescription prevalence and drug expenditure on antihypertensive drugs and other medications is increasing,[234-236] there is a growing need for large population-based studies assessing the long-term comparative cancer safety of medications.

7.5 Conclusions

This thesis advances the field of pharmacoepidemiologic research in three important ways. First, it includes the most comprehensive study to date on the treatment and prescription patterns of antihypertensive drugs, described over a 31-year period. We found that nearly one-quarter of primary care patients were prescribed antihypertensive drugs by the end of the study period, with half of those concomitantly receiving two or more classes, and that most patients with hypertension initiated a thiazide diuretic or beta-blocker before 2007 and an ACE inhibitor or CCB after 2007. It also brought important contributions to the comparative cancer safety research landscape, particularly with respect to colorectal and pancreatic cancer. We reported that thiazide diuretics were not associated with an increased risk of colorectal cancer when compared with dCCBs. We also reported that dCCBs were not associated with an increased risk of pancreatic cancer compared with thiazide diuretics. Together, the evidence generated through this thesis helps inform clinical practice and future comparative effectiveness and safety studies while providing specific

reassurance to physicians and patients regarding the long-term gastrointestinal safety of thiazide diuretics and dCCBs with respect to colorectal and pancreatic cancer.

CHAPTER 8. REFERENCES

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CHAPTER 9. APPENDIX

9.1 Ethics approval certificates

Manuscript 1: Treatment and prescribing trends of antihypertensive drugs in 2.7 million UK primary care patients over 31 years: a population-based cohort study

The study protocol was approved by the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink (protocol number 19_153A) and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Manuscript 2: Thiazide diuretics and risk of colorectal cancer: a population-based cohort study

The study protocol was approved by the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink (protocol number 19_121A) and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Manuscript 3: Dihydropyridine calcium channel blockers and risk of pancreatic cancer: a population-based cohort study

The study protocol was approved by the Clinical Practice Research Datalink Research Data Governance (protocol number 22_001791) and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.