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The definition of treatment assignment in observational emulations of target trials – an empirical examination in the Swedish Primary Care Cardiovascular Database

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ABSTRACT

Background: In randomized trials, the intention-to-treat effect is the effect of assignment to treatment strategies. The concept of assignment may not be clearly defined when using observational data to emulate a target trial.
Aims: We aimed to assess the practical implications of using data on prescription versus dispensation as analogues of treatment assignment in observational analyses.
Methods: We used the primary care-derived Swedish Primary Care Cardiovascular Database of individuals with newly diagnosed hypertension between 2006 and 2014 and linked registers. We compared the effect of two antihypertensive drug classes on the five-year risk of cancer and ischemic heart disease. Treatment assignment was first mapped using prescription data, and then dispensation data. With unique confounding structures, we sequentially adjusted for different classes of risk factor due to uncertainty over the choice of relevant confounders for prescription vs. dispensation.
Results: 7770 individuals were eligible when assignment was defined using prescription compared with 5964 when defined using dispensation. For both cancer and ischemic heart disease outcomes, both higher and lower relative risks of the outcome were consistent with our data. Effect estimates did not vary with the choice of prescription or dispensation data as analogues of assignment, nor with sequential adjustment for class of risk factor.
Conclusion: The mapping of prescription or dispensation data to treatment assignment influences the size and characteristics of the study population and the structure of confounding. However, we found no clear numerical differences in effect estimates in this study. Further investigation is required in other settings.

Introduction

In randomized trials, the term "intention-to-treat effect" is the effect of assignment to the treatment strategies specified in the study protocol. Assignment to a treatment strategy occurs randomly after trial participants have confirmed their initial willingness to follow any strategy that they happen to be allocated to. Participants may be unaware ("blinded" design) or aware ("open label" design) of their assigned treatment strategy.

Using observational healthcare data to estimate the effects of medications can be viewed as attempting to emulate a target trial, a hypothetical randomized trial that would answer the causal question of

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interest [1]. This process has two steps: (i) specifying the protocol of the target trial, and (ii) emulating the target trial using the available observational data [2]. A goal of the analysis may then be to estimate the effect of assignment to the treatment strategies specified in the protocol. In the target trial, assignment is the set of experimental procedures by which individuals are allocated to a particular treatment strategy; in the observational emulation, assignment refers to the procedure used to classify individuals into the treatment strategies of interest. This raises the question of how to map the concept of treatment assignment to observational emulations. Two possible analogues of treatment assignment in observational emulations using healthcare data are i) the issuing of a *prescription* for a treatment by a clinician, and ii) the first *dispensation* of the treatment to the patient at the pharmacy.

Compared with dispensation, a prescription in routine clinical care may be viewed as a better mapping of assignment in an experimental setting [1]. However, while some databases only have data on treatment prescriptions (e.g., the UK's Clinical Practice Research Datalink), many others (such as health insurance and pharmacy claims databases, or databases derived from pharmacy records) only have data on treatment dispensations (e.g. registries on dispensed prescriptions in Sweden and Denmark [3–5]). In practice, investigators often choose between using prescription vs. dispensation based on the available data.

The choice of mapping of treatment assignment has implications not only for the interpretation of the observational effect estimates, but also for the ability to adjust for confounding because the prognostic factors that affect prescription may differ from those that affect dispensation. However, as far as we are aware, no empirical applications have explored the importance of using either prescription or dispensation to map treatment assignment in observational emulations.

Here, we describe a case study of the impact of using either prescription or dispensation to map treatment assignment when estimating the effect of antihypertensive drugs. Using observational data from the Swedish Primary Care Cardiovascular Database (SPCCD) [6], we consider two outcomes: (i) cancer and (ii) ischemic heart disease. While the differences in effectiveness between different classes of antihypertensives are expected to be negligible for both outcomes [7–10], the magnitude of confounding is expected to be greater for ischemic heart disease than for cancer because the choice between classes of antihypertensives may more strongly depend on factors that are prognostic of heart disease.

Methods

The target trial

The protocol of the target trial is outlined in Supplementary Table 1 and summarized below.

Individuals are eligible if they have a first diagnosis of hypertension (International Classification of Diseases code I10) within the last year, are 30 years or older, attended one of 48 primary healthcare centres in South-West Stockholm and Skaraborg, Sweden, between the 1st of July 2006 and the 31st of December 2014, had a prescription for an antihypertensive medication, and had no previous prescription of an antihypertensive medication, no diagnosis of cancer, and no contraindications (heart failure for certain calcium channel blockers) or other indications (secondary prevention for ischemic heart disease, or heart failure for agents that act on the renin-angiotensin system) for the study drugs in the previous year.

The two treatment strategies are initiation of 1) a single agent that acts on the renin-angiotensin system (angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)) and 2) a single agent calcium channel blocker. Doses and subsequent treatment changes are left to the physician's discretion. Eligible individuals in the target trial are randomly assigned to one of the treatment strategies, and they and their clinicians are aware of which strategy they have been assigned to.

The two outcomes of interest are an incident diagnosis of cancer and an incident diagnosis of ischemic heart disease. A near-null effect is expected for both outcomes [7,8]. Each eligible individual is followed from assignment until the outcome, migration out of Sweden, five years, or the end of the study period (31st of December 2016), whichever occurs first.

The causal contrast is the effect of assignment (intention-to-treat effect), defined as the total effect of treatment assignment on the outcome [11]. The intention-to-treat analysis estimates the 5-year outcome risk in each treatment group. Were the target trial conducted, these risks could be estimated via a nonparametric Kaplan-Meier estimator or a pooled logistic regression model for the weekly probability of the outcome with an indicator for assigned treatment group, a flexible time-varying intercept (e.g., cubic splines) and product terms between treatment group and the time variables. To address any imbalances in prognostic factors between the randomized groups or to improve efficiency, baseline variables could also be used in the analysis (e.g., entered as covariates in the logistic model, followed by standardization of the model estimates to the distribution of the baseline covariates). Nonparametric bootstrapping could be used to estimate percentile-based 95 % confidence intervals.

Observational emulation of the target trial

SPCCD is an observational database composed of over 75,000 individuals aged 30 years or older with a recorded diagnosis of hypertension (International Classification of Diseases code I10) across 48 participating primary healthcare centres in South-West Stockholm and Skaraborg, Sweden [6]. SPCCD contains electronic medical records from primary care, linked by a unique personal identifier to the National Prescribed Drug Register, the National Patient Register, the National Cause of Death Register, and the Longitudinal Integrated Database for Health Insurance and Labour Market Studies [4,12–14].

The National Prescribed Drug Register, which only contains information on filled prescriptions (from 1st of July 2005), was used to identify dispensation dates, whilst primary care records were used to identify prescription dates of medications. A small number of individuals may have received a prescription before their first hypertension diagnosis and dispensed their medication; these individuals would not be included in our study.

Comorbidities, creatinine (in plasma or serum) and office blood pressure were extracted from primary care records. The Sweden-wide National Patient Register, which records diagnoses from inpatient hospitalizations and specialist outpatient medical care, was additionally used to identify comorbidities. Cancer was defined as the first diagnosis of a malignant neoplasm recorded in the National Patient Register, and ischemic heart disease was defined using both the National Patient Register in addition to primary care records. For a small number of individuals who may have migrated within Sweden, information derived from primary care is missing.

Data on emigration, country of birth, education and income were extracted from the Longitudinal Integrated Database for Health Insurance and Labour Market Studies, and deaths from the National Cause of

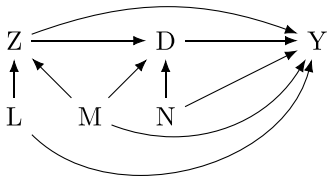
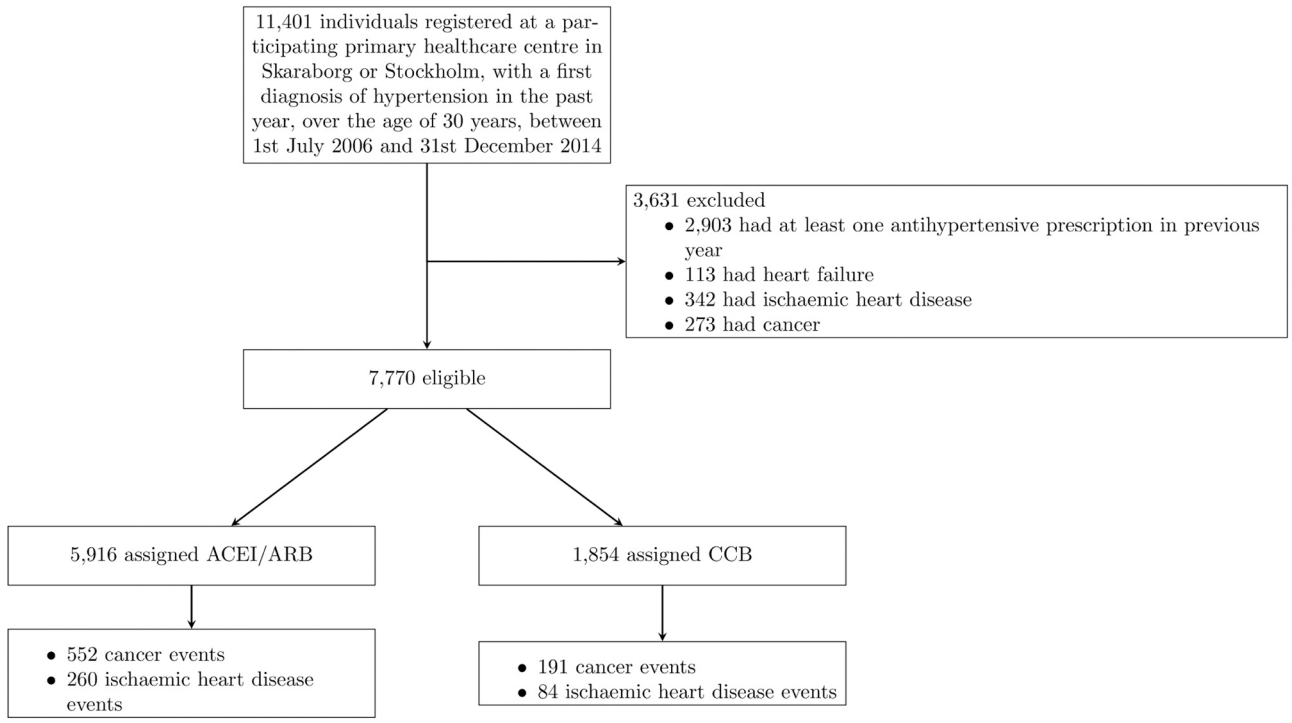
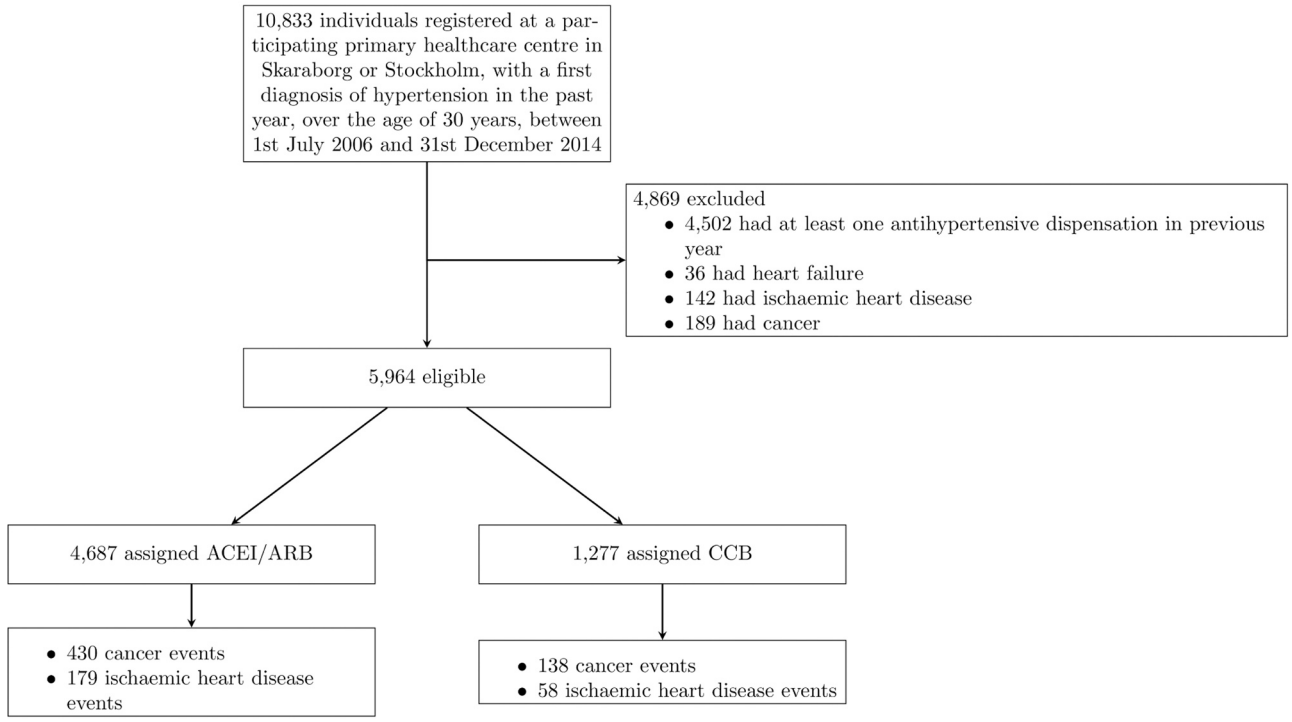


Fig. 1. Causal directed acyclic graph showing prescription (*Z*: 0 – ACE inhibitor or angiotensin receptor blocker prescription, 1 – calcium channel blocker prescription), dispensation (*A*: 0 – ACE inhibitor or angiotensin receptor blocker dispensation, 1 – calcium channel blocker dispensation, 2 – no dispensation) and cancer (*Y*: 0 – yes, 1 - no).



(a) Prescription as an analogue of assignment.



(b) Dispensation as an analogue of assignment.

Fig. 2. Flow chart for the selection of eligible individuals into an emulation of a target trial comparing angiotensin converting enzyme inhibitors/angiotensin receptor blockers to calcium channel blockers.

Table 1
Baseline characteristics using prescription as an analogue of assignment, Swedish Primary Care Cardiovascular Database 2006–2014.

	ACE inhibitor/ARB	CCB	SMD	Missing (%)
Number	5916	1854		
Age (years)	61.3 (11.7)	64.7 (12.6)	0.277	0
Female	2767 (46.8)	933 (50.3)	0.071	0
Country of birth			0.047	0
Sweden	5346 (90.4)	1653 (89.2)		
Other Nordic countries	247 (4.2)	81 (4.4)		
Europe excluding the Nordic countries	190 (3.2)	74 (4.0)		
Outside of Europe	132 (2.2)	46 (2.5)		
Educational level			0.098	1.7
Pre-secondary education less than 9 years	1278 (21.9)	460 (25.4)		
Pre-secondary education of 9 years (equivalent)	751 (12.9)	219 (12.1)		
Secondary education up to 2 years	2023 (34.7)	626 (34.6)		
Secondary education of 3 years	659 (11.3)	185 (10.2)		
Post-secondary education less than 3 years	525 (9.0)	155 (8.6)		
Post-secondary education 3 years or more	578 (9.9)	163 (9.0)		
Postgraduate education	12 (0.2)	1 (0.1)		
Yearly disposable income (multiple of 100 Swedish Kronor)*	1811.0 [1260.0, 2500.0]	1627.0 [1207.2, 2416.0]	0.02	0.6
Systolic BP (mmHg)	160.2 (19.4)	162.0 (21.9)	0.085	9.7
Diastolic BP (mmHg)	90.1 (12.1)	90.4 (13.6)	0.017	9.7
Estimated GFR (mL/min/1.73m^2)	88.8 (14.6)	85.4 (15.8)	0.228	22.7
Diabetes	992 (16.8)	159 (8.6)	0.248	0
Cerebrovascular disease	225 (3.8)	130 (7.0)	0.142	0
Atrial fibrillation and flutter	98 (1.7)	39 (2.1)	0.033	0
Chronic kidney disease	72 (1.2)	30 (1.6)	0.034	0
Aspirin	567 (9.6)	217 (11.7)	0.069	0
Antidiabetic medication	630 (10.6)	72 (3.9)	0.263	0
Lipid lowering medication	890 (15.0)	245 (13.2)	0.053	0
Number of classes of drugs previously prescribed			0.113	0
None	523 (8.8)	141 (7.6)		
1–3 drug classes	2119 (35.8)	606 (32.7)		
4–6 drug classes	1664 (28.1)	513 (27.7)		
7–10 drug classes	1049 (17.7)	380 (20.5)		
11 + drug classes	561 (9.5)	214 (11.5)		
Time from diagnosis to assignment (days)*	0.0 [0.0, 7.0]	0.0 [0.0, 13.0]	0.073	0

Number and percentage presented for categorical variables, and mean and standard deviation for continuous variables, unless otherwise indicated. * median and interquartile range. SMD – standardized mean difference, ARB – angiotensin receptor blocker

Death Register. For about 0.1 % of individuals with known year, but unknown month, of death, we assigned death to July 1st, or if month and year were known, but not date, to the 1st of the month. The covariates smoking status, body mass index and blood lipids could not be used due to a large proportion of missing data, whilst data on healthcare utilization was not available. Further detail, including International Classification of Disease codes, is available in Supplementary Tables 2 and 3.

We identified individuals in SPCCD who met the eligibility criteria, and then assigned them to the treatment strategy that was compatible with their prescription data at the time of eligibility. Assignment was assumed to be as if randomized conditional on baseline covariates (see below). We then followed eligible individuals in each group as described for the target trial above and estimated the observational analogue of effect of assignment (the intention-to-treat effect). The statistical analysis was the same as for the target trial with adjustment for baseline covariates.

We then emulated a second trial in which treatment prescription was replaced by treatment dispensation both to map treatment assignment and to define the eligibility criteria. As a result, the study population may change because individuals need to meet the eligibility criteria at the time of dispensation (rather than prescription) and, most importantly, because only individuals who receive an eligible dispensation are included in the analysis.

Choice of confounders

The validity of the observational effect estimates requires sufficient adjustment for confounders, i.e., prognostic factors that affect the prescription or dispensation of antihypertensive drugs.

Prescription is expected to depend on clinical guidelines, physician and patient's preferences, and access to treatment, that is, the clinical characteristics of the patients and features of the health system. On the other hand, as dispensation (conditional on prescription) often requires a visit to the pharmacy and an upfront payment, it may be the result of a complex underlying process that includes socioeconomic and demographic factors. If these factors are associated with either outcome, then they would be confounders too.

This situation is approximately represented by the simplified causal directed acyclic graph in Figure 1, where Z is an indicator for prescription (0: ACE inhibitor/ARB, 1: calcium channel blocker), D for dispensation (0: ACE inhibitor/ARB, 1: calcium channel blocker, or 2: an individual does not dispense their index medication), and Y for cancer by 5 years (0: no, 1: yes). Estimating the effect of $Z = 1$ vs $Z = 0$ generally requires adjusting for the common causes L and M, and estimating the effect of $D = 1$ vs $D = 0$ generally adjusting for the common causes L, M and N. Note that, when using prescription, the value of D may remain unknown and, when comparing $D = 1$ vs $D = 0$, non-dispensers ($D = 2$) are excluded from the analyses.

We classified the available risk factors (other than age and sex) into comorbidities (atrial fibrillation/flutter, cerebrovascular disease, chronic kidney disease and type 2 diabetes mellitus), medications (current use of lipid lowering drugs, aspirin, and antidiabetic drugs and number of classes of medicine previously treated with), clinical measurements (systolic blood pressure, diastolic blood pressure, estimated glomerular filtration rate), and socio-economic/demographic factors (individual disposable income, education, and country of birth). We used the same set of covariates for all analyses due to uncertainty over which variables were represented by L, M and N.

Statistical analysis

As described for the target trial, we fit separate pooled logistic

Table 2
Baseline characteristics using dispensation as an analogue of assignment, Swedish Primary Care Cardiovascular Database 2006–2014.

	ACE inhibitor/ARB	CCB	SMD	Missing (%)
Number	4687	1277		
Age (years)	60.8 (11.5)	63.8 (12.3)	0.257	0
Female	2193 (46.8)	627 (49.1)	0.046	0
Country of birth			0.046	0
Sweden	4245 (90.6)	1145 (89.7)		
Other Nordic countries	194 (4.1)	52 (4.1)		
Europe excluding the Nordic countries	151 (3.2)	46 (3.6)		
Outside of Europe	96 (2.0)	34 (2.7)		
Educational level			0.064	1.6
Pre-secondary education less than 9 years	970 (21.0)	284 (22.7)		
Pre-secondary education of 9 years (equivalent)	621 (13.4)	153 (12.2)		
Secondary education up to 2 years	1640 (35.5)	457 (36.6)		
Secondary education of 3 years	523 (11.3)	135 (10.8)		
Post-secondary education less than 3 years	409 (8.8)	100 (8.0)		
Post-secondary education 3 years or more	454 (9.8)	119 (9.5)		
Postgraduate education	5 (0.1)	1 (0.1)		
Yearly disposable income (multiple of 100 Swedish Kronor)*	1845.0 [1280.0, 2515.5]	1671.5 [1221.8, 2490.2]	0.004	0.4
Systolic BP (mmHg)	163.1 (17.9)	166.5 (20.4)	0.176	5.9
Diastolic BP (mmHg)	91.8 (11.5)	93.0 (12.8)	0.098	5.9
Estimated GFR (mL/min/1.73m^2)	89.5 (13.9)	86.1 (15.3)	0.233	17.6
Diabetes	724 (15.4)	88 (6.9)	0.274	0
Cerebrovascular disease	93 (2.0)	53 (4.2)	0.126	0
Atrial fibrillation and flutter	36 (0.8)	14 (1.1)	0.034	0
Chronic kidney disease	47 (1.0)	17 (1.3)	0.031	0
Aspirin	266 (5.7)	79 (6.2)	0.022	0
Diabetes medication	383 (8.2)	26 (2.0)	0.282	0
Lipid lowering medication	443 (9.5)	102 (8.0)	0.052	0
Number of classes of drugs previously dispensed			0.059	0
None	500 (10.7)	132 (10.3)		
1–3 drug classes	1847 (39.4)	488 (38.2)		
4–6 drug classes	1295 (27.6)	341 (26.7)		
7–10 drug classes	717 (15.3)	220 (17.2)		
11 + drug classes	328 (7.0)	96 (7.5)		
Time from diagnosis to assignment (days)*	0.0 [0.0, 8.5]	0.0 [0.0, 8.0]	0.075	0

Number and percentage presented for categorical variables, and mean and standard deviation for continuous variables, unless otherwise indicated. * median and interquartile range. SMD – standardized mean difference, ARB – angiotensin receptor blocker

models for the weekly probability of each outcome. The model included an indicator for assigned treatment group, cubic splines for week of follow-up (we used 3 knots), product terms between treatment group and the time variables, age, sex, and each class of baseline risk factors sequentially. Because the effect of antihypertensives on both outcomes is expected to be null, sizeable deviation of the effect estimates from the null would then illustrate the relative importance of different classes of confounders. Continuous variables were modelled with restricted cubic splines with 3 knots [15] or, if they had missing data, categorized to include a missing indicator. Categorical variables with missing data also included a missing indicator. We standardized the estimated probabilities to the distribution of the baseline covariates. For all analyses, we used nonparametric bootstrapping with 500 samples to compute percentile-based 95 % confidence intervals.

Sensitivity analyses

To explore the impact of the choice of adjustment method, we adjusted for baseline covariates using inverse probability weighting. To explore the impact of assumptions about missing data, we conducted separate analyses in which we excluded individuals with missing baseline covariate data and we imputed the median value for missing continuous variables.

Results

Baseline characteristics

When using prescription as assignment, 7770 individuals were eligible (Figure 2). Compared with those in the ACE inhibitor/ ARB group, individuals in the calcium channel blocker group were on average older, had a lower estimated glomerular filtration rate, lower prevalence of diabetes, and higher prevalence of cerebrovascular disease (Table 1). The groups did not differ in the time between diagnosis and treatment assignment.

When using dispensation as assignment, 5964 individuals were eligible (Figure 2). Differences between the ACE inhibitor/ ARB and calcium channel blocker groups were similar to those in Table 1, except that individuals in the calcium channel blocker group had higher blood pressure (Table 2).

Compared with individuals eligible for the trial with prescription as assignment, the subset eligible for the trial with dispensation as assignment had on average higher blood pressure, a lower prevalence of cerebrovascular disease, fewer previous classes of drugs previously treated with, and a lower prevalence of aspirin and lipid lowering drug use (Supplementary Table 4).

Cancer

With assignment as prescription, the estimated 5-year risk of cancer was 10.8 % (9.9 %, 11.7 %) for ACE Inhibitor/ARBs and 10.2 % (8.8 %, 11.8 %) for calcium channel blockers, corresponding to a risk difference of −0.6 % (-2.2 %, 1.2 %) and a risk ratio of 0.95 (0.80, 1.11) (Table 3). With assignment as dispensation, the estimated risks were 10.6 % (9.6 %, 11.6 %) under ACE inhibitors/ARBs and 10.7 % (9.0 %, 12.4 %) under calcium channel blockers, corresponding to a risk difference of 0.1 % (-1.9 %, 1.9 %) and a risk ratio of 1.01 (0.83, 1.19). For both prescription and dispensation, all estimates were highly compatible, regardless of how many variables were used for the adjustment.

Table 3
Estimated 5-year risk of cancer and ischemic heart disease with sequential adjustment for covariates, Swedish Primary Care Cardiovascular Database 2006–2014.

	Treatment assignment defined using prescription				Treatment assignment defined using dispensation			
Covariates adjusted for	ACE Inhibitor/ARB Risk (95%CI)	Calcium channel blocker Risk (95%CI)	Risk difference (95%CI)	Risk ratio (95%CI)	ACE Inhibitor/ARB Risk (95%CI)	Calcium channel blocker Risk (95%CI)	Risk difference (95%CI)	Risk ratio (95%CI)
Cancer:								
Age + sex	10.8 (9.9, 11.7)	10.2 (8.7, 11.6)	-0.6 (-2.2, 1.0)	0.94 (0.80, 1.10)	10.6 (9.6, 11.5)	10.8 (9.0, 12.4)	0.2 (-1.7, 2.1)	1.02 (0.84, 1.20)
+ Comorbidities	10.8 (9.9, 11.7)	10.2 (8.8, 11.7)	-0.6 (-2.3, 1.1)	0.94 (0.80, 1.11)	10.6 (9.6, 11.5)	10.8 (9.0, 12.5)	0.2 (-1.6, 2.1)	1.02 (0.85, 1.20)
+ Clinical measurements	10.8 (9.9, 11.6)	10.3 (8.9, 11.8)	-0.5 (-2.1, 1.2)	0.96 (0.81, 1.12)	10.6 (9.6, 11.5)	10.8 (9.0, 12.4)	0.1 (-1.8, 2.0)	1.01 (0.84, 1.20)
+ Medication	10.8 (9.9, 11.7)	10.2 (8.8, 11.7)	-0.6 (-2.3, 1.1)	0.94 (0.80, 1.11)	10.6 (9.6, 11.5)	10.7 (8.9, 12.3)	0.1 (-1.8, 1.9)	1.00 (0.83, 1.18)
+ SE/demographic	10.8 (9.9, 11.7)	10.2 (8.8, 11.8)	-0.6 (-2.2, 1.2)	0.95 (0.80, 1.11)	10.6 (9.6, 11.6)	10.7 (9.0, 12.4)	0.1 (-1.9, 1.9)	1.01 (0.83, 1.19)
Ischaemic heart disease:								
Age + sex	4.9 (4.3, 5.5)	4.4 (3.4, 5.3)	-0.5 (-1.6, 0.6)	0.89 (0.69, 1.13)	4.2 (3.6, 4.9)	4.4 (3.2, 5.7)	0.1 (-1.2, 1.6)	1.03 (0.75, 1.42)
+ Comorbidities	4.8 (4.3, 5.4)	4.5 (3.6, 5.5)	-0.3 (-1.4, 0.8)	0.93 (0.71, 1.17)	4.1 (3.6, 4.8)	4.6 (3.3, 6.0)	0.5 (-0.9, 2.0)	1.12 (0.80, 1.51)
+ Clinical measurements	4.8 (4.2, 5.4)	4.6 (3.6, 5.6)	-0.2 (-1.4, 1.0)	0.95 (0.73, 1.22)	4.1 (3.5, 4.8)	4.7 (3.4, 6.1)	0.5 (-0.8, 2.2)	1.13 (0.80, 1.57)
+ Medication	4.8 (4.2, 5.4)	4.5 (3.5, 5.5)	-0.3 (-1.4, 0.9)	0.93 (0.72, 1.19)	4.1 (3.5, 4.8)	4.5 (3.4, 6.0)	0.4 (-1.0, 2.0)	1.09 (0.78, 1.51)
+ SE/demographic	4.8 (4.2, 5.4)	4.4 (3.5, 5.5)	-0.4 (-1.5, 0.8)	0.92 (0.71, 1.18)	4.1 (3.5, 4.8)	4.5 (3.4, 5.9)	0.4 (-1.0, 2.0)	1.09 (0.78, 1.49)

ARB – angiotensin receptor blocker, ACE Inhibitor – angiotensin converting enzyme inhibitor, CI – confidence interval, SE – socio economic

Ischemic heart disease

With assignment as prescription, the 5-year risk was 4.8 % (4.2 %, 5.4 %) under ACE inhibitor/ARB and 4.4 % (3.5 %, 5.5 %) under calcium channel blockers, corresponding to a risk difference of −0.4 % (-1.5 %, 0.8 %) and a risk ratio of 0.92 (0.71, 1.18) (Table 3). With assignment as dispensation, the estimated risks were 4.1 % (3.5 %, 4.8 %) under ACE inhibitors/ARBs and 4.5 % (3.4 %, 5.9 %) under calcium channel blockers, corresponding to a risk difference of 0.4 % (-1.0 %, 2.0 %) and a risk ratio of 1.09 (0.78, 1.49). For both prescription and dispensation, all estimates were highly compatible, regardless of how many variables were used for the adjustment.

Results for the sensitivity analysis were similar to the main results (Supplementary Tables 5 through 7).

Discussion

We used both prescription and dispensation to map treatment assignment when estimating the observational analogue of the "intention-to-treat effect" of different classes of antihypertensive drugs on cancer and ischemic heart disease. Under conventional statistical criteria, both higher and lower risk of both outcomes for ACE Inhibitor/ARBs compared to calcium channel blockers were highly compatible with our data. This conclusion did not vary by choice of analogue of assignment and of risk factors for adjustment.

However, we found the use of either prescription or dispensation as analogue of assignment affects the time of start of follow-up (time zero) and may impact the characteristics and size of the study population when eligible individuals are required to have either a prescription or a dispensation. When using dispensation, individuals in our study had higher baseline blood pressure, a lower prevalence of cerebrovascular disease and less polypharmacy than when using prescription. Also, the population defined by assignment as dispensation was smaller because (i) some individuals did not dispense their prescription at a pharmacy (between 10 % and 17 % [16–19] in other countries and likely lower in Sweden [20]), (ii) some individuals met the eligibility criteria for the prescription cohort but not for the dispensation cohort (because, for example, the look back period of one year for a new diagnosis of hypertension starts from different dates in each cohort), and (iii) some individuals were excluded from the dispensation cohort because they had a dispensation in the previous year (which did not occur to the same extent in the prescription cohort because a single prescription is valid for several refills in a year).

Alternatively, we could have estimated (i) the effect of prescription and (ii) the effect of dispensation in a common population defined by prescription only, or defined by eligibility for the treatments and clinical indications for their use (regardless of prescription or dispensation). Such an approach could be viewed as analogous to estimating (i) the intention-to-treat effect and (ii) a per-protocol effect in a randomized trial, with prescription as the analogue of assigned treatment and dispensation as the analogue of received treatment. While that would be arguably the preferred approach, it requires data on both prescription and dispensation, but most available data sources have only one of these two pieces of information. Future research may investigate the implications of different definitions of treatment assignment on the per protocol effect (effect of full adherence to the treatment strategy) [21].

Our study had several strengths. The use of electronic health records data from primary care, with linkage to national registers allows access to both prescription and dispensation dates, ensures that all diagnoses and routine measurements are captured, and minimises loss to follow up. In addition, these data were linked to other population-based registries which provide data on socio-economic and demographic factors. Limitations include the lack of data on potentially important prognostic factors (such as previous healthcare usage, high/low density lipoprotein cholesterol levels, and smoking), which are not recorded or are recorded with a high proportion of missing data.

In summary, when emulating a target trial, investigators need to decide how to map treatment assignment to the observational data. The choice of mapping has implications for the size and characteristics of the population as well as for the confounding structure. Although we did not find clear numerical differences in any of our analyses, the implications of using prescription versus dispensation as assignment analogues need to be investigated in other settings. For example, in the treatment of diseases with acute onset or in countries with different healthcare systems, where adherence patterns may be different.

Ethical approval and data availability

The data are confidential. Researchers only had access to pseudonymized data for this register-based study, which was approved by the Regional Ethical Review Board in Gothenburg (569–08 and 577–17). To access the data, individuals need to fulfil legal requirements regarding personal sensitive data in accordance with Swedish laws and regulations.

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CRediT authorship contribution statement

Anita Berglund: Writing – review & editing, Methodology. **Anna B. C. Humphreys:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Björn Wettermark:** Writing – review & editing, Methodology, Data curation. **Bertil Lindahl:** Writing – review & editing, Methodology. **Miguel A. Hernán:** Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Thomas Kahan:** Writing – review & editing, Methodology, Data curation. **Anthony A. Matthews:** Writing – review & editing, Visualization, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Issa J. Dahabreh:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Jessica C. Young:** Writing – review & editing, Methodology.

Disclosures

Miguel Hernán is a consultant to ProPublica and Adigens Health, a company of which he owns equity, and a member of ADIALab's Advisory Board. His interests were declared, reviewed, and approved by Harvard University in accordance with its institutional compliance policies. Issa J. Dahabreh reports consulting fees from Elixir Medical.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Miguel A. Hernan reports a relationship with ProPublica that includes: consulting or advisory. Miguel A. Hernan reports a relationship with Adigens Health that includes: consulting or advisory and equity or stocks. Miguel A. Hernan reports a relationship with ADIALab that includes: board membership. Issa J. Dahabreh reports a relationship with Elixir Medical that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.annepidem.2025.06.003.

Data availability

The authors do not have permission to share data.

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