Study protocol: Adherence to the Major Classes of Antihypertensive Therapy

Background

High blood pressure is the risk factor attributable to the largest numbers of deaths in the world (1). Still only about 50% of patients with hypertension are adherent to prescribed therapy (2) and the World Health Organization (WHO) has concluded this to be the most important cause of uncontrolled hypertension (3). This is true even in high-income countries, where effective and cheap medicines are readably available (4). In current European hypertension guidelines, four classes of antihypertensive therapy are given equal footing as first-line monotherapy choices for uncomplicated hypertension, because they lower cardiovascular morbidity and mortality equally well (5).

Results from randomized clinical trial settings may differ from those observed in clinical practice (6), where the effectiveness in prevention against adverse outcomes may be more dependent on the drugs' effects on tolerability and adherence than any blood pressure-lowering effects. In fact, several observational studies indicate there are clinically significant differences in the degree of adherence between the recommended drug classes, (7-12) but results are conflicting.

Ideally, the important question of differences between drug classes in adherence and consequently on adverse outcomes should be answered using a pragmatic randomized trial, performed under real-life conditions and with a head-to-head design including all four drug classes. This study will likely never be performed. As a second choice therefore, an observational study design emulating that trial could be used (13). The optimal pragmatic randomized clinical trial is visualized and then used for designing the observational study (14). We will use this trial emulation method in conjunction with the hitherto largest sample of initiators of blood pressure-lowering drugs, in a setting of universal health care with minimal copayment and minimal loss to follow-up, by combining data from four Swedish national all-covering registers.

Aims

1. To explore patterns of adherence and persistence to blood pressure-lowering drugs and how these are associated with risk of adverse cardiovascular outcomes.
2. To determine if adherence and persistence differ between the major classes of blood pressure-lowering drugs.
3. To determine if the initial blood pressure-lowering drug class choice is associated with risk of a subsequent adverse cardiovascular outcome, and if so, if this is mediated by adherence and persistence.

Methods

Setting

We will conduct an observational cohort study by creating a database of four cross-referenced national Swedish registers: The National Prescription register (contains complete coverage of all retrieved prescribed drugs in Sweden since 2005), the National Patient Register (contains Information regarding all Swedish secondary and tertiary health-care since 1987), the National Cause of Death Register (contains registrations of cause of death as judged by a clinician or by autopsy for all deceased in Sweden) and the Longitudinal integrated database for health insurance and labour market studies (LISA) Register (contains demographic information about all the citizens of Sweden). The registers have previously been descripted in the following list of references, (15-18)

Study sample

Base cohort

A theoretical randomized target trial was constructed and used to create the template for the emulated trial based on observational data used in this study, as displayed in Table 1 and Table 2. We will include Swedish residents, who at index were 40 years or older and received blood pressure-lowering drugs for the first time between 1 of January 2011 and the 31 of December 2018 using one of the following blood pressure-lowering drug classes in a single pill: Angiotensin receptor blocker (ARB), Angiotensin converting enzyme inhibitor (ACEi), dihydropyridine calcium channel blocker (CCB), Thiazide/thiazide-like diuretic (TZD) or a single combination pill of ARB+TZD, ARB+CCB, ACEi+TZD or ACEi+CCB.

The retrieved prescription will be identified in the national prescription register using Anatomical Therapeutic Chemical (ATC) codes as defined by the WHO collaboration center for drug statistics methodology. To ensure participants were treatment-naïve and only started treatment using one pill, the prescription register will be searched for retrieved prescriptions of blood pressure-lowering drugs in the 5 years prior to and on the date of inclusion according to the following ATC groups: C09, C07, C08, C03 and C02. If prevalent (not including the index prescription), the participant will be excluded. Lastly participants are only allowed to be included once. This will be the base cohort (Table 1), which will be used to study general adherence and persistence patterns as described in Aim 1. The base cohort will then be further processed and participants with compelling indications or possible contraindications to a specific class of therapy according to the European hypertension guidelines (19) of 2013 will be censored. Lastly participants with health conditions believed to significantly affect adherence or where fluctuation of disease will affect side effects and/or blood pressure lowering effects significantly will be removed to minimize residual confounding (Table 2) generating the final cohort that will be used to answer Aims 2 and 3.

Table 1. Base cohort

Target trial	**Emulated trial**
Inclusion criteria	*Inclusion criteria modified for observational data*
1. Male or female aged ≥40 years	1. Male or female aged ≥40 years according to the Lisa register on the date of inclusion.

2. Planned treatment with one of the following blood pressure lowering drugs in a single pill: ARB ACEi CCB TZD/TZD like ACEi + TZD ACEi + CCB ARB + TZD ARB + CCB	2. A retrieved prescription of ARB, ACEi, CCA, TZD in monotherapy or a single combination pill containing ACEi + diCCA, ACEi+ TZD, ARB+ TZD or ARB + CCB between 1 of January 2011 and 31 of December 2018 in the national prescription register, *ATC:* *C09C (ARB)* *CO9A (ACEi)* *C08CA (CCB)* *C03AA (TZD), C03BA (thiazide-like/chlortalidone)* *C09BA (ACEi + TZD)* *C09BB (ACEi + CCB)* *C09DA (ARB + TZD))* *C09DB (ARB + CCB)*
3. No prior or current antihypertensive treatment	3. No current or prior antihypertensive treatment on the date of inclusion or in the prior 5 years in the National prescription register, ATC: C09 (RAS) C07 (BB) C08 (CCB) C03 (diuretics) C02 (Other blood pressure-lowering drugs)

Table 2. Final cohort

Target trial	**Emulated trial**
Exclusion criteria	*Exclusion criteria modified for observational data*

1.Previous or current health condition with compelling indication for specific class of antihypertensive*. Heart failure Diabetes Kidney disease Ischemic heart disease Atrial fibrillation Peripheral artery disease Asymptomatic atherosclerosis Aortic aneurysm Left ventricular hypertrophy (LVH)	1. As indicated by ICD code as a main- or bi-diagnosis in the National patient register: I11, I50 (heart failure) E10-14 (diabetes) N18.3-N18.5, N18.9, I12-13 (renal failure stage 3 to 5 or hemo-/peritoneal dialysis) *N10,11,12,14,15,16 (*tubulointerstitial nephritis) *I15.0-1* (renovascular hypertension) I20-25 (ischemic heart disease) I48 (atrial fibrillation or flutter) I70 (atherosclerosis) I71.1-9 (aortic aneurism) I51.7 (cardiomegaly (includes LVH) As indicated by retrieval of at least one prescription of the following medications during the 5 years prior to, or on the date of inclusion in the national prescription register using ATC code: A10 (antidiabetics) C01AA (digitalis) As indicated by a medical or surgical procedure, by KVÅ code in the national patient register DR012-13, DR023-24 (peritoneal dialysis) DR014-17, DR020, DR060-61 (Hemodialysis) DR018 (Hemoperfusion) DR055 (Citrate dialysis) DR056 (Heparin free dialysis)

2. Possible contraindications for specific therapies Gout Hyperkalemia Hypokalemia Angioneurotic oedema Current treatment with medication that interacts with one or more of the study medications.	2. As indicated by ICD code as a main- or bi-diagnosis in the National patient register: *M10 (gout)* *E87.5 (hyperkalemia)* *E87.6 (hypokalemia)* *E26 (hyperaldosteronism)* T783 (angioneurotic edema) As indicated by retrieval of at least two prescriptions of at least 110 tablets during the 5 years prior to or on the date of inclusion according to ATC: M04A (gout medication) As indicated by retrieved prescriptions of at least 110 tablets and two prescriptions in the year prior to, or ont the date of inclusion according to ATC: M01A (NSAID) A12BA (potassium supplements) C10AC01 (cholestyramine) C10AC02 (colestipol) N03A (anti-epileptics) J02AB (Imidazole derivates-antimycotic) J02AC (Triazole and tetrazole derivate - antimycotic) J05AE (Protease inhibitor-HIV drug) V03AX03 (cobicistat-HIV drug) L02BB (Antiandrogen) J04AB02 (Rifampicin)

3. A health condition that may significantly affect adherence, blood pressure-effects or side-effects Dementia A history of serious mental conditions Chronic hepatic disease Alcohol mediated hepatic disease Active Malignant neoplasm Active thyroiditis or thyrotoxicosis Acute or serious hepatic disease (not necessarily chronic) in the last year Active endocrine disease that effects blood pressure Active health condition that requires longer periods of system corticosteroids	3. As indicated by ICD code as a main- or bi-diagnosis in the National patient register: F00-03 (dementia) F20 -29 (Schizophrenia, schizotypal disorders and delusional disorder) F32.2-32.3 (major depressive episode) F33 (recurrent depression) F34 (chronical mood disorder) F60-61 (personality disorder) K72.1 (Chronic hepatic failure) K74.0, K74.2-6 (*Hepatic fibrosis or cirrhosis*) K76.1 chronic passive congestion of liver K73 (Chronical hepatitis not classified in an other location) K70 (hepatic disease because of alcohol) As indicated by a main diagnosis of ICD code in the national patient register in the 1 year before or on date for inclusion in study: C00-43 and C45-97 (malignant neoplasm) E05 (thyrotoxicosis), E06 (thyroiditis) K71 (toxic hepatic disease) K72.0 (acute and subacute hepatic failure) K72.9 (Hepatic failure unspecified) K75 (other inflammatory liver diseases) K76.2 (Central hemorrhagic necrosis of the liver) K76.3 (infarction of the liver) K76.4 (Peliosis hepatis) K76.5 (hepato veno occlusive disease) K76.6 (porta hypertension) K76.7 (hepatorenal syndrome) K77 (liver disorders in diseases classifeid elsewhere) E27 (Disorders of the adrenal gland, including Addison but not Cushing syndrome.) C74.1 (malignant neoplasm of adrenal gland) I15.2 (hypertension secondary to endocrine disorders) I15.8-9 (other secondary hypertension/secondary hypertension unspecified)

	a) As indicated by Retrieval of at least two prescriptions of at least 110 tablets during the 1 year prior to, or on the date of inclusion according to ATC: H02A (systemic corticosteroids)

Follow up will be determined by prospective searches in the above databases using ATC and ICD codes until the end of follow up, the 31 of December 2019, allowing between 1 to 9-years of follow-up time in each patient.

Exposures

Adherence and persistence in earlier studies

Before designing this study, a literature search was made to identify relevant previous studies with the primary aim of comparing adherence between the four classes of blood pressure-lowering drugs recommended in European guidelines(5). First a search string for pubmed.org (se Appendix 1) was constructed which generated 692 studies of possible interest. These were then manually reviewed and 19 observational studies (using register data) and one pragmatic RCT trial was identified that fulfilled the inclusion. Of the observational studies, 13 used the gap-method to determine persistence, which was often defined as the opposite to discontinuation. Typically, the gap-method was applied by calculating the number of days an iterated prescription was expected to last if the patient followed the prescription fully and then add a gap of 30 to 90 days (depending on the study) during which the patient did not collect a new prescription in order to be seen as a discontinuer. The majority of studies used an allowed gap of 60 days (7, 20-25)

Adherence was defined by retrieval of dosage information, the collected number of pills in each prescription and then calculating the number of days the patient should be covered. The number of days covered were then divided with the number of days in the corresponding treatment period, generating a medication possession ratio (MPR). A similar construct used in some studies was the proportion of days covered (PDC), which is calculated in the same way but with the exception that PDC can never be more than one. If a patient displayed an adherence of 80% or more (according to MPR or PDC) he or she was generally considered adherent. This is also at least partly in agreement with the degree of adherence considered adherent in several clinical trials (26).

Adherence and persistence definitions in the present study

The prescribed number of pills and dosage information of each iteration will be collected and the PDC will be calculated prospectively. If a new prescription is collected before the PDC is less then 1, the patient will be listed as perfectly adherent for as long as the prescriptions keeps being refilled in time. If, however no new prescription is retrieved before the PDC is less then 1 the patient will first enter a period of PDC 0.8<1, followed by a period of PDC 0.6<0.8 and lastly if still no new retrieved prescription a period of PDC <0.6 (Figure 2). Treatment periods with a PDC of ≥0.8 are considered adherent, and treatment periods of less than 0,6 are considered as not persistent. When or if a new prescription is retrieved the individual once again enter a treatment period of PDC = 1 (Figure 1). If an individual has a surplus of medication when the next prescription is retrieved this will be accumulated and used for subsequent calculations of PDC. Lastly if a patient is hospitalized, they will be assumed to receive their medication through the hospital while indwelling and these days will be added in the PDC calculations

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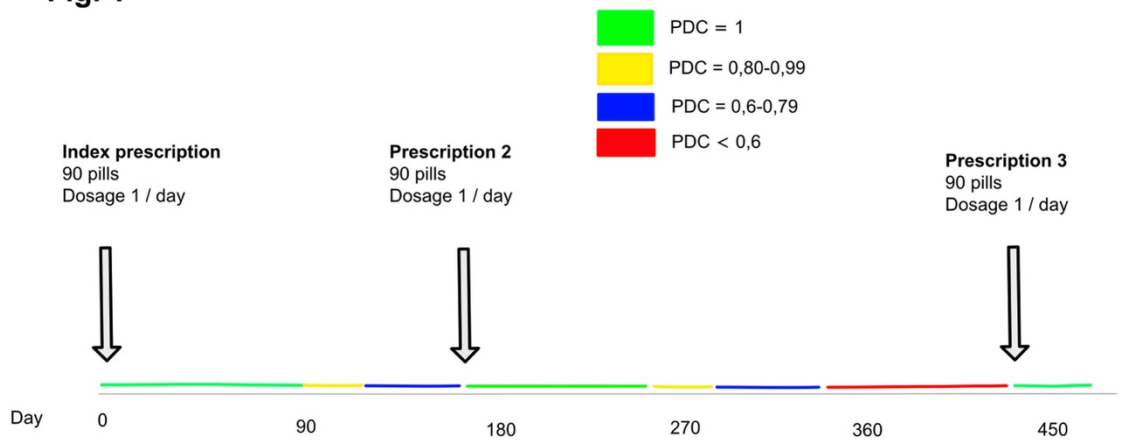
Fig. 1



Shows a fictional patient receiving consecutive prescriptions and how the periods in-between are classified in different degrees of adherence according to PDC.

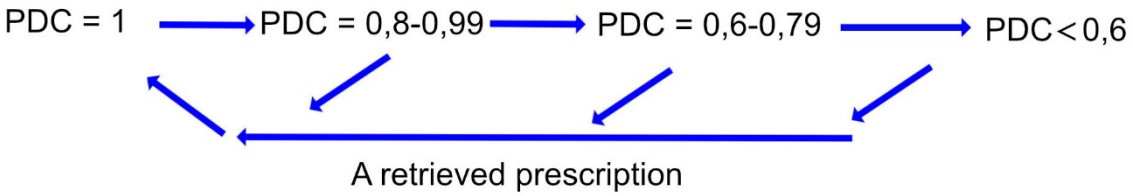
The reason PDC <0.6 was chosen as the lower limit of persistence is that iterations in Sweden are usually prescribed for a duration of 90 days. A PDC of 0.6 then corresponds to a 90 days long period of PDC = 1 + a gap of 60 days.

Outcomes

The multistate model

The PDC periods of every individual will be put into a temporal multistate-model where patients can move freely between PDC periods according to their latest prescription as described in Figure 2.

Fig. 2



Therapy adherence (Aim 1)

To explore the general patterns of adherence and persistence, analyses will be performed in both the base cohort and the final cohort to investigate the fraction of blood pressure-lowering drug initiators that continue treatment with any of the recommended blood pressure-lowering drug classes during the study period. Every individual will be followed longitudinally regarding prescriptions of blood pressure-lowering drugs, and PDC will be calculated as described above. If a blood pressure-lowering drug is added or switched, adherence will be calculated and reported for the blood pressure-lowering drug with the highest PDC, according to Figure 3. This will be accounted for in the multistate model but to make sure discontinuation is not caused by death this will be added as an absorbing state. In the final cohort, we will analyze if the first blood pressure-lowering drug choice is associated with subsequent adherence to any blood pressure-lowering drug class.

Fig. 3.

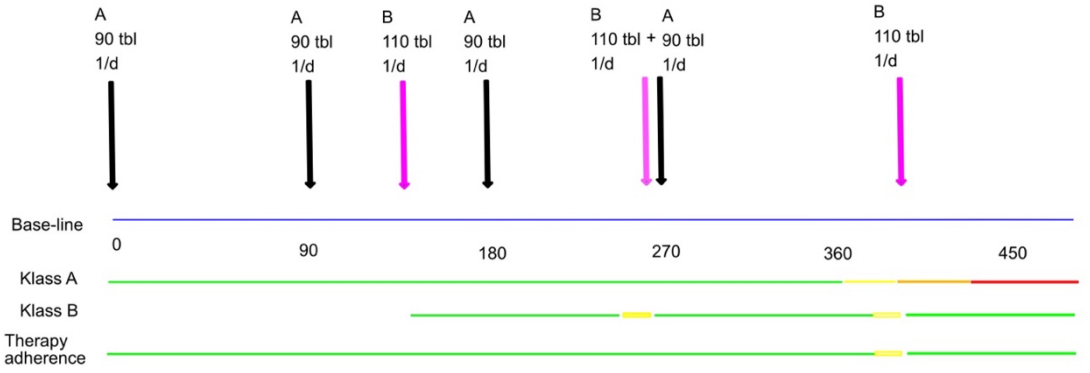


Fig 3. Visar förskrivningsmönster för medicin från klass A och B och hur dessa sedan tillsammans blir therapy adherence hos en person med indexpreparatet A

Class adherence (Aim 2)

To determine whether there is a difference in adherence and persistence between the included classes of blood pressure-lowering drugs, a longitudinal analysis will be done following only prescriptions of the first drug class retrieved. Participants are allowed to change drug within the class (example losartan for candesartan) but not between

different classes of blood pressure-lowering drugs. PDC periods will be calculated and analyzed using a multistate model, with death and first adverse cardiovascular event as absorbing states. If another class of blood pressure-lowering drug is added, calculations will still only consider the index drug class. The proportion of adherent and persistent individuals at 1, 2 and 5 years will be presented and comparisons between the classes using adjusted and crude data will be made). Secondary analyses will analyze the fraction of individuals switching to or adding another blood pressure-lowering drug class after 1, 2 and 5 years. Lastly analysis will be done to display if age or sex changes whitch blood-pressure lowering medication generates best adherence.

Adverse cardiovascular outcomes (Aim 3)

First adverse cardiovascular disease events will be determined on an intention to treat level using the national patient register and the national cause of death register prospectively from the index date and until the end of study; with individual follow-up ending at first cardiovascular event, death or emigration. The following diagnoses will be considered as cardiovascular events or cardiovascular death:

In the national patient register:

Hemorrhagic stroke I60, I61, I62
Ischemic stroke I63.0-5, I63.8-9
Acute stroke unspecified I64
TIA G45.0-3, G45.8-9
Myocardial infarction: I21
Heart failure: I50, I11.0, I13.0, I13.2, I42, I43, I25.5

In the national cause of death register:

I00-I99

Statistical analysis

The classes of antihypertensive medication will be compared using a Poisson regression model. While the Cox proportional hazards model is the standard model of choice with time to event outcomes, it allows only one timescale in the analysis. The cohort in this study is recruited over a number of years, individuals are of different ages at baseline and the time from the first prescription may be of interest. Poisson models allow for multiple timescales to enter the model simultaneously and the connection between the Cox model and Poisson regression using time-split data is well known. Poisson models also allow treatment-timescale interaction, also known as non-proportional hazards, to be studied using interaction terms.

Follow-up time within each individual will be split into intervals of 3 months in which the outcome rate is assumed to be constant. A change of state also splits follow-up time at the time of the event.

All timescales will be modeled using cubic splines with five knots placed at percentiles selected so that the number of outcomes is roughly the same between the knots

All models will include the following confounders at baseline: Sex, origin of birth, age, Socioeconomic index or income, year of initiation and obesity (see DAG before and after restriction, fig 1 and 2). Pregnancy is unfortunately unobserved since the database does not contain this information. Since only 5,5 % of mothers of Sweden are 40 years or older during pregnancy (2021 SCB) (27) this limitation is not expected to cause any major bias.

Origin of birth is divided in: born in Sweden, born outside Sweden but in the Nordic countries, born in Europe outside the Nordic countries, or born anywhere else. Socioeconomic index is a combination of education level, income and marital status. Obesity is gathered by ICD66

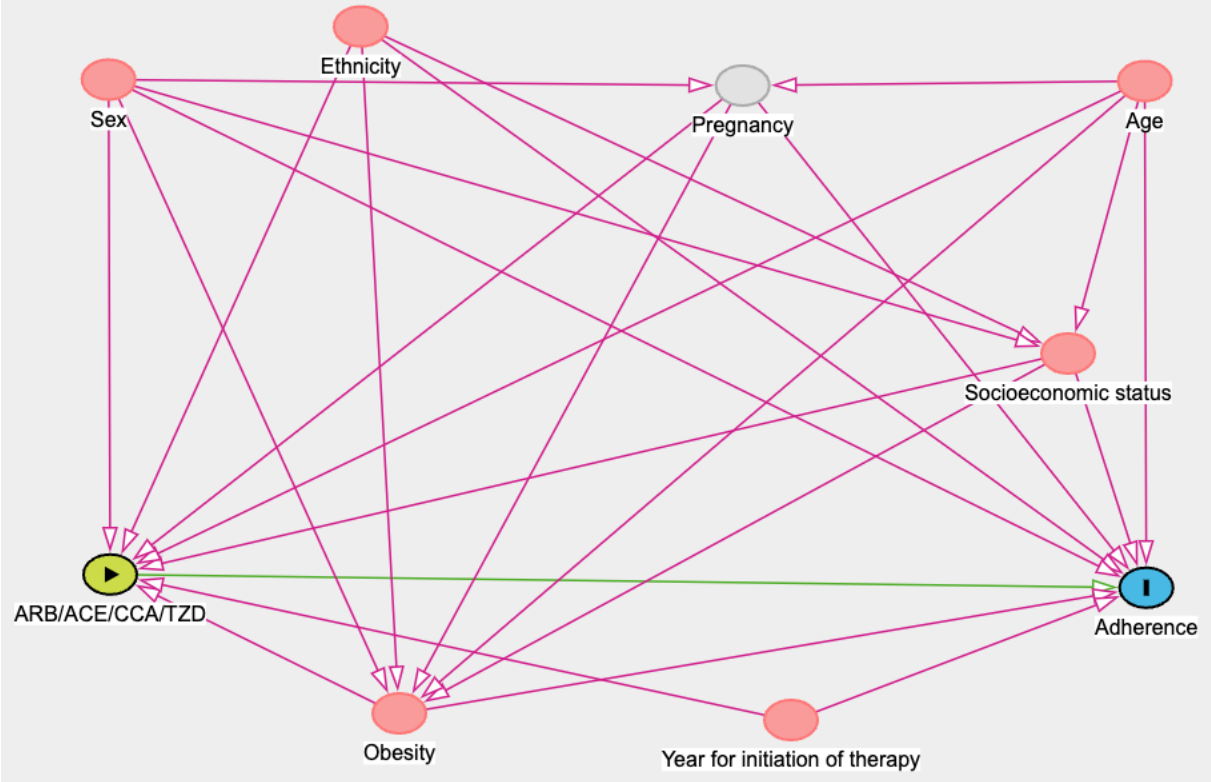


Fig. 4. DAG after restriction. Displays plausible confounders remaining after restriction/ in final cohort.

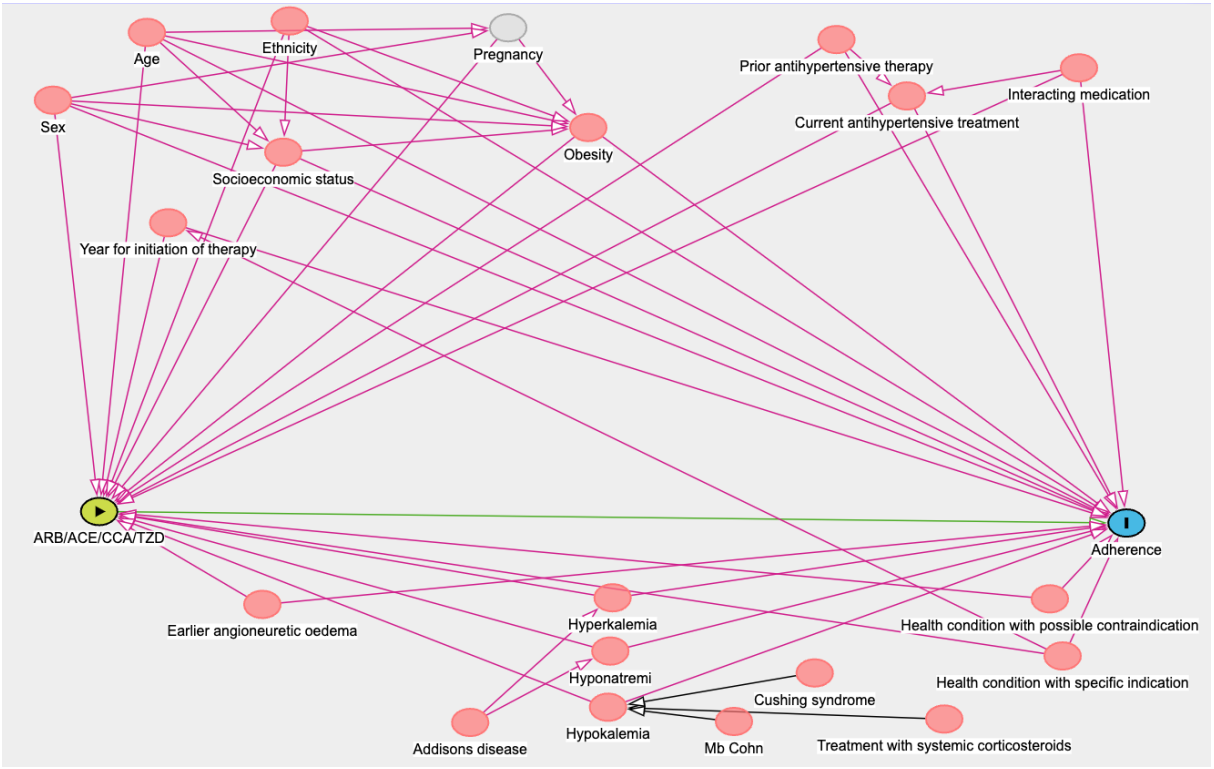


Fig 5. DAG before restriction. Displays plausible confounders before restriction/in base-cohort.

Significance of results

Therapy adherence

Studies indicate that adherence to blood pressure-lowering drugs is generally low and discontinuation often happens in the first year after initiation (2). This suggests a window of opportunity for doctors for active early follow-up. Earlier studies had limited possibility to capture actual medication taking behavior because of limitations in their model of measuring adherence. Our belief is that our dynamic multistate model, where a patient can become persistent again after a period of neglect, might describe actual medication behavior better. Hence, earlier studies may have exaggerated discontinuation rates because of an inability to capture "re-starters". If this so, our study could be of great benefit to better make prioritizations in further health-care-programs to manage hypertension.

Class adherence and cardiovascular outcomes

If one class of blood pressure-lowering drugs displays a significantly and clinically important difference in adherence compared to other classes, this suggest that the drug classes' equal footing in current hypertension guidelines may be invalid. Furthermore, if sex or age impact which class of blood pressure-lowering drugs that is best tolerated, this will provide evidence for clinicians to further tailor prescribed antihypertensive medication to their patients. If one blood pressure-lowering drug class is associated with both better adherence and fewer adverse cardiovascular outcomes, this would highlight drug adherence as an important treatment target in clinical practice, and would emphasize optimizing drug adherence as an important target for future research .

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