Study protocol: Adherence to the Major Classes of Antihypertensive Therapy

Introduction

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 a large 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 determine if the choice of first antihypertensive drug class or single pill combination, when initiating treatment for primary hypertension, determines later persistence to treatment.

Methods

Study 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).

Eligibility criteria

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 for the treatment of hypertension: 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 prescriptions 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 not be included. Additionally, participants are only allowed to be included once in the study.

The cohort will then be further processed with exclusion criteria (table 2) and participants with a compelling indication or possible contraindication for a specific class of therapy according to the contemporary European hypertension guidelines (19) of 2013 will be excluded (exclusion criteria 1-2). Further participants with a health condition 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. Lastly patient initiating treatment with pre dispensed packages will be excluded.

Table 1. Inclusion criteria at baseline

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 on the date of inclusion.

2. Planned treatment with one of the following blood pressure lowering drugs for hypertension in a single pill: ARB ACEi CCB TZD/TZD like ACEi + TZD ACEi + CCB ARB + TZD ARB + CCB	2. a. 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), C03BA04, C03BA11 (thiazide-like/chlortalidone + Indapamide)* *C09BA (ACEi + TZD)* *C09BB (ACEi + CCB)* *C09DA (ARB + TZD)* *C09DB (ARB + CCB)* *b. Dosage-information of index prescription stating treatment for hypertension.* *c. Prescription information not stating PRN/as needed*
3. Treatment naïve.	3. No prior retrieved prescription in the 5 years prior to inclusion of the following ATC in the national prescription register: C09 (RAS) C07 (BB) C08 (CCB) C03 (diuretics) C02 (Other blood pressure-lowering drugs)
4. No concurrent treatment of any other blood-pressure lowering drug.	4. More than one pill of antihypertensive retrieved at the date of inclusion using the following ATC: C09 (RAS) C07 (BB) C08 (CCB) C03 (diuretics) C02 (Other blood pressure-lowering drugs)

5. No prior inclusion in current study	5. No prior inclusion in current study

Table 2. Exclusion criteria at baseline

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 Stroke* Ischemic heart disease Atrial fibrillation Diabetes mellitus Hypertensive kidney disease/kidney failure Peripheral artery disease Asymptomatic atherosclerosis Aortic aneurysm Left ventricular hypertrophy (LVH) Peripheral oedema*	1. a. As indicated by ICD code as a main- or bi-diagnosis in the National patient register at the date of inclusion or earlier: I11.0, I13.0, 13.2, I50 (heart failure) I60-64, I66-67, I69, G45 (stroke and TIA) I20-25 (ischemic heart disease) I48 (atrial fibrillation or flutter) E10-14 (diabetes) N18.3-N18.5, N18.9, I12-13 (renal failure stage 3 to 5 + other) I13.1 (Hypertensive heart and renal disease with renal failure) I15.0-1 (renovascular hypertension) I73.9 (peripheral artery disease) I74 (arterial embolism and thrombosis I70 (atherosclerosis) I71.1-9 (aortic aneurism) I51.7 (cardiomegaly (includes LVH) I42.0 (dilated cardiomyopathy) I42.6 Alcoholic cardiomyopathy) b. 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) c. As indicated by a medical or surgical procedure, by KVÅ code in the national patient register at the date of inclusion or earlier: DR012-13, DR023-24 (peritoneal dialysis) DR014-17, DR020, DR060-61 (Hemodialysis) DR018 (Hemoperfusion) DR055 (Citrate dialysis) DR056 (Heparin free dialysis) d. Dosage information of the index prescription indicating the reason for the prescription was heart failure e. Dosage information of the index prescription indicating the reason for the prescription was peripheral oedema.

2. Possible contraindications for specific therapies Gout Hyperkalemia Hypokalemia Hyponatremia* Angioneurotic oedema Current treatment with medication that interacts with one or more of the study medications*.	2. a. As indicated by ICD code as a main- or bi-diagnosis in the National patient register at the date of inclusion or earlier: M10 (gout) E26 (hyperaldosteronism*)* T783 (angioneurotic edema) b. As indicated by ICD code as a main diagnosis or contributing diagnosis in the national patient register during the 1 year prior to, and on, the date of inclusion: E87.5 (hyperkalemia) E87.6 (hypokalemia*)* E871B (hyponatremia) c. As indicated by retrieval of at least two prescriptions during the 5 years prior to, and on, the date of inclusion according to ATC: M04A (gout medication) d. As indicated by retrieval of at least two prescriptions, during the 1 year prior to, and on, the date of inclusion according to ATC: A12BA (potassium supplements) C10AC01 (cholestyramine) C10AC02 (colestipol) N03A (anti-epileptics) J02AB (Imidazole derivates-antimycotic for systemic use) J02AC (Triazole and tetrazole derivate - antimycotic for systemic use) J05AE03 (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 Possible secondary hypertension not excluded earlier.	3. a. As indicated by ICD code as a main- or bi-diagnosis in the National patient register at the date of inclusion or earlier. F00-03 (dementia) F20 -29 (Schizophrenia, schizotypal disorders and delusional disorder) F60-61 (personality disorder) K74 (Hepatic fibrosis, sclerosis or cirrhosis) K73 (Chronical hepatitis not classified in another location) K70 (hepatic disease because of alcohol) b. As indicated by a main diagnosis of ICD code in the national patient register in the 1 year before, and on, the date for inclusion in study: C00-43 and C45-97 (malignant neoplasm) E05 (thyrotoxicosis), E06 (thyroiditis) K71 (toxic hepatic disease) K72 (acute and chronic hepatic failure) K75 (other inflammatory liver diseases) K76 (other liver disease) K77 (liver disorders in diseases classified elsewhere) E27 (Disorders of the adrenal gland, including Addison but not Cushing syndrome.) I15.2 (hypertension secondary to endocrine disorders) I15.8-9 (other secondary hypertension/secondary hypertension unspecified) I77.3 (Arterial fibromuscular dysplasia)

4. Medication received through pre-dispensed drug packages/APO-dos	4. The first index prescription is retrieved i pre-dosage packages

*Exclusion criteria not in contemporary ESC guide-lines, but are assessed logical or are current in other contemporary Swedish guide-lines.

Interventions/comparisons

ARB (*C09C)*
ACEi (CO9A)
CCB (C08CA)
TZD (C03AA). (C03BA04), (C03BA11)
SPC (C09BA), (C09BB), (C09DA), (C09DB)

Outcomes

Information regarding all iterations of the subjected drugs, including number of pills and dosage information, will be collected for all participants on an individual level. The number of pills in each iteration will be divided with the corresponding dosage information providing the number of days covered. A calculation will then be done to determine for how long the iteration would last if the individual were using the medication for 80% of the treatment days i.e., a proportion of days covered (PDC) of ≥ 0.8.

During the time the individual has iterations with a corresponding PDC of ≥ 0.8 she will be seen as persistent. *Example, if a patient retrieves a typical iteration of 100 pills, she will be deemed persistent until (100/0.8 =) 125 days later. On the opposite if no new prescription is collected before PDC is < 0.8 the patient is considered as being off*.

If a new prescription is retrieved before PDC is below 1, the surplus will be added to the next prescription under the following conditions: the total surplus is not allowed to surpass 30 daily doses and can at a maximum be 1 year old. If a patient is indwelling at the hospital, she is expected to receive treatment directly from the ward and these days are retracted from the PDC calculation.

A patient persistent to the index drug is seen as class persistent and a patient persistent to any class of antihypertensive is seen as therapy persistent. If a patient

switch to another antihypertensive of the same class or adds another class of antihypertensive she is still considered class persistent for as long as she keeps taking the index class.

Both class and therapy persistence will be handled in two different models. The first model, called Continuous Persistence is similar to the earlier used gap-methods (7-9, 11) and only regards the first persistence period and disregards the individual after she has entered the first off period. The second model, called Multiple Persistence, instead, allows for multiple persistence periods and looks at the proportion of individuals persistent at a certain time-period. Examples of the different definitions can be seen in figure 1.

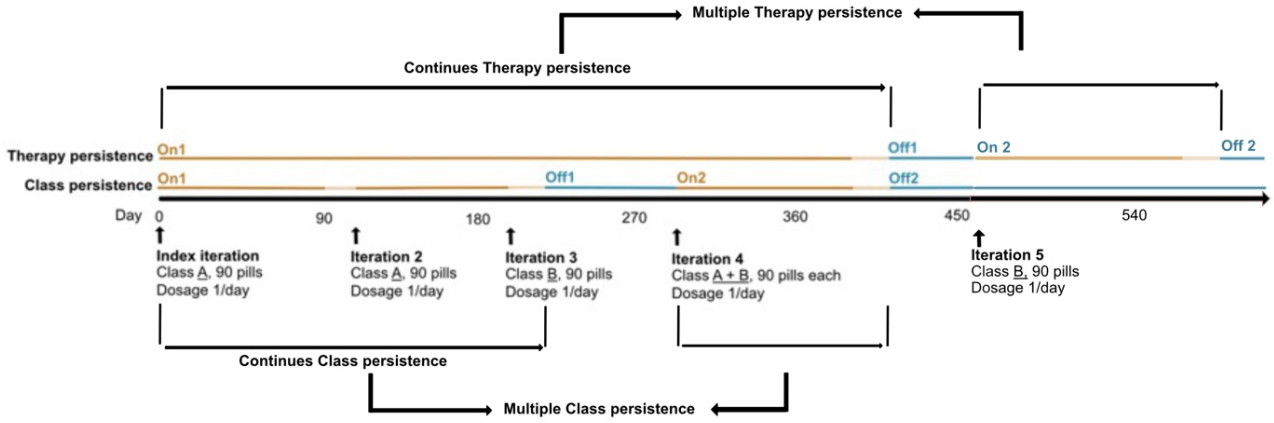


Figure 1

Participant time-line

Patient starting treatment between 31 dec 2011 and 31 dec 2018 are included. Follow up time is until 31 Dec 2019.

Statistical analysis

The demographic data will be presented as means with +/- standard deviations if normal distributed and if not as medians with Interquartile range. Outcomes will be presented as proportions with 95% confidence intervals. When appropriate also exact numbers will be given. Patients will be censored from further analysis if, and when the following occurs: death, emigration from Sweden, and at the end of follow-up.
For the main analysis the cohort will be divided into five stratas: one for each class in monotherapy, and one aggregated for all the individuals starting treatment with a single combination pill. The stratas will be analyzed in a multi-state framework with transient states = 80% adherence to drug class, and absorbing states = death or cardiovascular event. The following diagnosis and ICD codes will be considered a cardiovascular event: heart failure (I50, I11.0, I13), ischemic heart disease (I20-25), Stroke (I60, I61, I62, I64, I63.0-I63.5, I63.8-I63.9, G45.0-3, G45.8-9) and renal failure stage 4 (N18.4-5).

Adjustments will be made using a Poisson regression model on time-split data with the following confounders: age, sex, obesity, birth country, socioeconomic status (represented by income and marital status) and the year for initiation of therapy. 95% confidence intervals will be obtained by bootstrapping.

Conditional interaction analysis will be performed to determine the effect of sex and age and other cofactors. If significant interaction is seen we will try to translate this into clinically meaningful conditions, example woman 50-60 years.

A sensitivity analysis will be performed comparing the classes when a cardiovascular event is not considered an absorbing state.

Figure 2. DAG after exclusion criteria

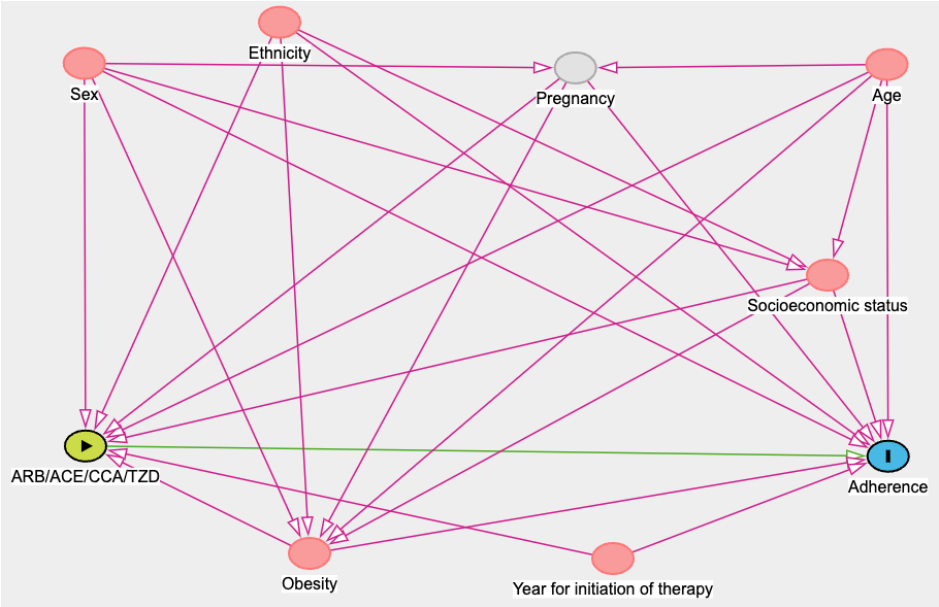
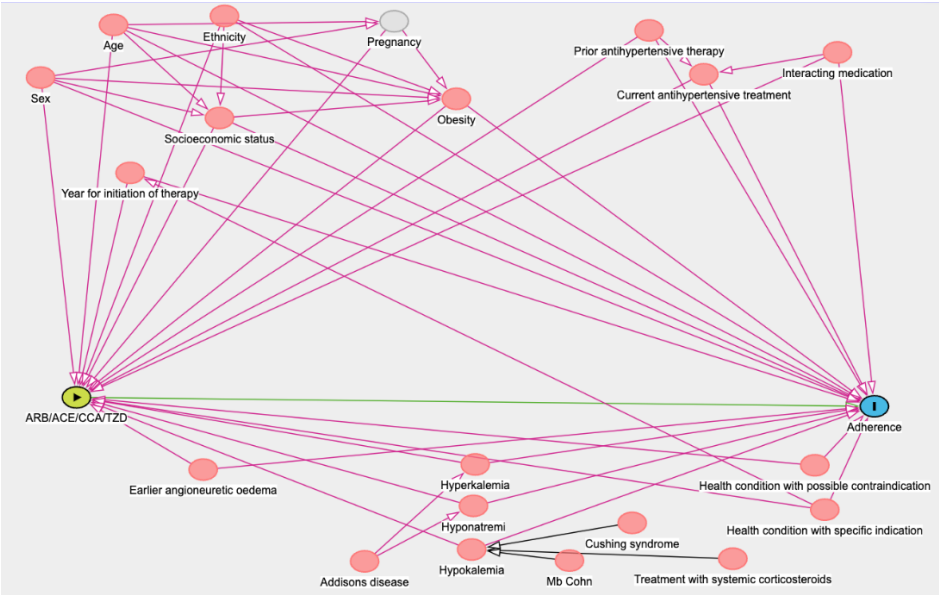


Figure 3. DAG before exclusion criteria



Significance of results

Multiple persistence

Studies indicate adherence and persistence 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 persistence. 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 so, our study could be of great benefit when making prioritizations in further health-care-programs to manage hypertension.

Class persistence

If one class of blood pressure-lowering drug displays a significantly and clinically important difference in persistence compared to other classes, this suggest that the drug classes' equal footing in current hypertension guidelines when given in monotherapy 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.

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