OHDSI Comparison of combination treatment in hypertension

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# List of abbreviations

RCT Randomized Clinical Trial

RAAS Renin-Angiotensin-Aldosterone System

DM Diabetes Mellitus

CKD Chronic Kidney Disease

MACCE Major Advance CardioCerebral Event

DCSI Diabetes Complications Severity Index

MedDRA Medical Dictionary for Regulatory Activities

OHDSI Observational Health Data Sciences and Informatics

OMOP Observational Medical Outcomes Partnership

PRR Proportional Reporting Ratio

PS Propensity Scores

NHIS-NSC National Health Insurance Service-National Sample Cohort

# Abstract

High blood pressure is the leading global burden of death and disability. Recently, growing evidence has supported the effectiveness of initiation of dual anti-hypertensive drug. However, the real-world evidence regarding to the optimal regimen of combination is still lacking. The goal of this protocols is conducting comparative effectiveness research to establish evidences for optimal anti-hypertensive combination strategy among patients without cardiovascular outcome from various databases across world.

# Rationale and Background

High blood pressure is the leading global burden of death and disability1. Extensive evidences support the beneficial effects in tight control of blood pressure. Since monotherapy is often insufficient or slow to reach blood pressure target quickly2, combination therapy is recommended as the first-line treatment for selected patients with hypertension by the recent guideline to reduce cardiovascular risk3. Retrospective observational studies and meta-analysis have suggested that initial combination hypertensive treatment confers decreased risk for cardiovascular events than monotherapy4–7. Only a few randomized clinical trials, however, have directly compared the effects of different regimens of combination8–11. In addition to limited number of evidences from head-to-head comparison, baseline high risk for cardiovascular outcome and previous history of anti-hypertensive medication of participants also make the findings from RCTs difficult to apply to clinical practice. To the best of our knowledge, real-world comparative effectiveness research comparing the various regimens of combination treatment in patients with essential hypertension has not been conducted until now.

# Research Questions and Objectives

## Research Questions

Growing evidence has supported the benefit of initial combination treatment for hypertension. It is well known that dual RAAS blocker-based combination is harmful. Only a few randomized clinical trials have directly compared the effects of different regimens of combination. The results from these RCTs are not only conflicting with each other, they did not adopt new-user setting.

We have scientific questions about the benefits and harms of each combination therapy for hypertension in a new user setting.

## Objectives

The goal of this protocols is conducting comparative effectiveness research to establish evidences for optimal anti-hypertensive combination strategies among patients without cardiovascular outcome from various databases across world.

# Research methods

## Study Design

### Overview

This study will be a retrospective, observational, new-user cohort study.

The treatment and comparator cohort will be patients initiating dual antihypertensive medications because of hypertension. Direct head-to-head comparison will be conducted for the major advance cardiocerebral events. Adjustment for baseline confounders will be done by propensity model.

### Study population

Inclusion criteria

* Adults who initiated two anti-hypertensive drugs within 30 days
* Exposure to dual hypertensive medication more than 180 consecutive days
* At least 181 days of pre-observation period before initiating the drugs

Exclusion criteria

* Any diagnosis for ischemic heart disease, heart failure, stroke before or within 180 days after drug initiation
* Death within 180 days after drug initiation
* Use other anti-hypertensive drugs except the two before or within 180 days after drug initiation

Subgroups

* Patients with diabetes mellitus (DM)
* Patients without DM
* Patients with chronic kidney disease (CKD)
* Patient without CKD
* Patients over 55
* Patients under 55

### Additional analysis details

The propensity model will be fitted using a regularized logistic regression with a LaPlace prior. The regularization hyperparameter will be selected by optimizing the likelihood in a 10-fold cross-validation.

Variable-ratio propensity score matching will be performed using greedy matching12. A caliper of 0.25 times the standard deviation of the propensity score distribution will be used.

The outcome model will be fitted using a regularized conditional Cox regression with a LaPlace prior. The regularization hyperparameter will be selected be selected by optimizing the likelihood in a 10-fold cross-validation. No regularization will be applied to the coefficient corresponding to the treatment variable (i.e. those representing the hazard ratio of interest).

### Analysis variations

The following variations of the analysis will be performed:

Primary analysis:

* Using a PS model to match treated and comparator. The outcome model will be condition on the matched sets, and will include all covariates.

## Variables

### Exposures

#### Hypertensive medication

Hypertensive medication is classified into four classes:

RAAS blocker (ACEi / ARB) as **A**, beta-blocker as **B**, calcium channel blocker as **C**, thiazide-diuretics as **D**.

Index rule defining the index date:

* First exposure to any two drugs containing the RxNorm ingredient of hypertensive medication more than 180 days (drug\_era table)

Inclusion rules based on the index date:

* At least 180 days of observation time prior to and after the index date
* Diagnosed as hypertension within 365 days before or 30days the index day
* No exposure to other classes of anti-hypertensive drug except the specific two classes.
* No previous ischemic heart disease, heart failure, stroke or death
* Without early outcome of ischemic heart disease, heart failure, stroke or death within 180 days after the index date

### Outcomes

#### Primary outcome: composite endpoint of major adverse cardio/cerebral events (MACCE)

Primary outcome includes the four major adverse cardio/cerebral events:

Myocardial infarction, heart failure, stroke and all-cause death

These four MACCEs are defined below.

#### Secondary outcome: Myocardial Infarction

Index rule defining the index date:

* Occurrence of a myocardial infarction code as a diagnosis in an inpatient or emergency room setting

Inclusion rules based on the index date:

* At least 180 days of observation time prior to and after the index date
* Have prior diagnosis of hypertension

#### Secondary outcome: Heart Failure

Index rule defining the index date:

* Occurrence of a heart failure code as a diagnosis in an inpatient or emergency room setting

Inclusion rules based on the index date:

* At least 180 days of observation time prior to and after the index date
* Have prior diagnosis of hypertension

#### Secondary outcome: Stroke

Index rule defining the index date:

* Occurrence of a heart failure code as a diagnosis in an inpatient or emergency room setting

Inclusion rules based on the index date:

* At least 180 days of observation time prior to and after the index date
* Have prior diagnosis of hypertension

#### Secondary outcome: All-cause mortality

Index rule defining the index date:

* Any Death

Inclusion rules based on the index date:

* Have prior diagnosis of hypertension

#### Secondary outcome: New-onset diabetes mellitus, type II

Index rule defining the index date:

* Occurrence of a diabetes code as a diagnosis
* Starting anti-diabetic medication

Inclusion rules based on the index date:

* At least 180 days of observation time prior to and after the index date
* Have prior diagnosis of hypertension

#### Secondary outcome: New-onset chronic kidney disease

Index rule defining the index date:

* Occurrence of a chronic kidney disease code as a diagnosis

Inclusion rules based on the index date:

* At least 180 days of observation time prior to and after the index date
* Have prior diagnosis of hypertension

### Potential confounders

The following will be included as potential covariates: (note: most covariates are assessed on or in the 365 days prior to index date)

* Demographics (age in 5-year increments, gender, race, ethnicity, year of index date, month of index date)
* Condition occurrence (one or more variables per diagnose code)
* Condition era (one or more variables per diagnose code)
* Condition group (one or more variables per MedDRA group or SNOMED groups)
* Drug exposure (one or more variables per drug code)
* Drug era (one or more variables per RxNorm ingredient)
* Drug group (one or more variables per ATC group)
* Procedure occurrence (one or more variables per procedure code)
* Observations (one or more variables per observation concept ID)
* Measurements (one or more variables per measurement concept ID, including variables for within / above / below normal range)
* Risk scores (including Charleston, DCSI, CHADS2, CHADS2VASc

For the full details see the OHDSI CohortMethod package (<https://github.com/OHDSI/CohortMethod>).

Variables with less than 100 non-zero values are discarded. All covariates were used in both the propensity model and the outcome model.

### Negative and positive controls

We believe that negative controls as well as positive controls are necessary for confidentiality of study design and statistical method. We are looking for appropriate negative and positive controls now.

### Other variables

None

## Data Sources

The analyses will be performed across a network of observational healthcare databases. All databases have been transformed into the OMOP Common Data Model, version 4 or OMOP Common Data Model, version 5. The complete specification for OMOP Common Data Model, version 4 is available at: <http://omop.org/cdm>. The complete specification for OMOP Common Data Model, version 5 is available at: <https://github.com/OHDSI/CommonDataModel>. The following databases will be included in this analysis:

* National Health Insurance Service-National Sample Cohort (NHIS-NSC)

National Health Insurance Service-National Sample Cohort (NHIS-NSC)

NHIS has an administrative health claims database for virtually whole population in Korea. The NHIS established the NHIS-NSC, which was population based cohort to provide representative, useful health insurance and health examination data to public health researchers and policy makers in 2015. About one million subjects, 2% of the Korean whole population, were selected by stratified random sampling from 2002 Korean health insurance database. Longitudinal health records in these population were collected for 11 years from 2002 to 2013. To preserve total number of subjects in the cohort, a representative sample of newborn was added annually as expired or emigrated subjects were excluded.  
The NHIS-NSC database can be assessed on the website [http://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do]*.*

Source codes used in CCAE include: conditions- KCD (KCD-10); drugs: EDI; procedures: EDI; lab: EDI.

## Sample Size and Study Power

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## Quality control

We will evaluate the confidentiality of this study by using positive and negative controls.

## Strengths and Limitations of the Research Methods

Strength

* CohortMethod will match PS on large number of baseline potential confounders
* Through this study, we will able to investigate differences in the response of hypertension medication under diverse geographical, ethnic and medical systems.
* Use of negative and positive control outcomes allow for evaluating the study design as a whole in terms of residual bias.

Limitations

* Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured or misspecified confounders.
* Misclassification of the outcome is expected as a result of diagnostic or codding errors.

# Protection of Human Subjects

The study is using only de-identified data. Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians.

# Plans for Disseminating and Communicating Study Results

The study results will be posted on the OHDSI website after completion of the study. At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal.

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