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 overall-mortality. Adjustment for baseline confounders will be done by propensity model.

### Study population

Pre-defined drug period of primary analysis: 180 days

Pre-defined window period of primary analysis: 180 days

Inclusion criteria

* Adults who initiated two anti-hypertensive drugs within 30 days
* Exposure to dual hypertensive medication more than the drug period
* At least 365 days of pre-observation period before initiating the drugs

Exclusion criteria

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

Sensitivity analysis

-For sensitivity analysis, we conducted three more additional analyses with various drug periods and window periods (other conditions are identical).

If one drug combination is better than the other, we can assure by this sensitivity analysis whether the benefit of drug increases along the increase of drug period

* Drug period : 30 days, Window Period : 30 days
* Drug Period : 365 days, Window Period : 365 days
* Drug Period : 730 days, Window Period : 730 days

Subgroups

* Male patients with the drug and the window period of 180 days
* Female patients with the drug and the window period of 180 days
* Patients aged 60 or more with the drug and the window period of 180 days
* Patients under 60 with the drug and the window period of 180 days

### 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**.

### Outcomes

#### Primary outcome: All-cause mortality

Primary outcome is defined as any-death

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

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

Occurrence of myocardial infarction, heart failure, stroke (in-patient or emergency room setting), or all-cause mortality

#### Secondary outcome: Cardiovascular mortality

Secondary outcome includes mortality due to cardiovascular diseases

#### 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

#### 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:

#### 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:

### 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)
* 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 controls

We believe that negative controls are necessary for confidentiality of study design and statistical method. We used negative controls below:

|  |  |
| --- | --- |
| concept\_id | concept\_name |
| 381581 | Chalazion |
| 373478 | Presbyopia |
| 375552 | Pterygium |
| 376415 | Hypermetropia |
| 80809 | Rheumatoid arthritis |
| 133141 | Tinea pedis |
| 434872 | Infection by Trichomonas |
| 140480 | Impetigo |
| 140641 | Verruca vulgaris |
| 4329707 | Strabismus |
| 4280726 | Seasonal allergic rhinitis |
| 4288544 | Inguinal hernia |
| 4224118 | Bladder dysfunction |
| 194997 | Prostatitis |
| 195862 | Urethritis |
| 192367 | Dysplasia of cervix |
| 437409 | Intracranial injury |
| 4271016 | Disorder of skin of trunk |
| 198075 | Condyloma acuminatum |
| 199067 | Female pelvic inflammatory disease |
| 200169 | Pruritus ani |
| 4004352 | Irritant contact dermatitis |
| 29735 | Candidiasis of mouth |
| 74396 | Temporomandibular joint disorder |
| 74855 | Genital herpes simplex |
| 434272 | Varicella |
| 378424 | Astigmatism |
| 380038 | Viral conjunctivitis |
| 380731 | Otitis externa |
| 4267582 | Infestation by Sarcoptes |
| 4153877 | Post-traumatic wound infection |
| 134870 | Pityriasis versicolor |
| 135473 | Dermatophytosis |
| 137053 | Seborrheic dermatitis |
| 138102 | Benign neoplasm of skin |
| 139099 | Ingrowing nail |
| 4253054 | Fibrosis of the skin |
| 75344 | Intervertebral disc disorder |
| 4142905 | Fracture of rib |

### 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 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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