

# A standardized framework for risk-based assessment of treatment effect heterogeneity in observational healthcare databases

Alexandros Rekkas, MSc<sup>1</sup>      David van Klaveren, PhD<sup>2,3</sup>,      Patrick B. Ryan, PhD<sup>4</sup>  
Ewout W. Steyerberg, PhD<sup>3,5</sup>      David M. Kent, PhD<sup>2</sup>      Peter R. Rijnbeek, PhD<sup>1</sup>

<sup>1</sup> Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands

<sup>2</sup> Predictive Analytics and Comparative Effectiveness (PACE) Center, Institute for Clinical Research and Health Policy Studies (ICRHPS), Tufts Medical Center, Boston, MA, USA

<sup>3</sup> Department of Public Health, Erasmus University Medical Center, Rotterdam, Netherlands

<sup>4</sup> Janssen Research and Development, 125 Trenton Harbourton Rd, Titusville, NJ 08560, USA

<sup>5</sup> Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands

## Corresponding author

Alexandros Rekkas, MSc  
Department of Medical Informatics  
Erasmus University Medical Center  
3000 CA Rotterdam, P.O. Box 2040  
Email: a.rekkas@erasmusmc.nl

## Funding

This work has been performed in the European Health Data and Evidence Network (EHDEN) project. This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 806968. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

## Abstract

One of the aims of the Observational Health Data Sciences and Informatics (OHDSI) initiative is population-level treatment effect estimation in large observational databases. Since treatment effects are well-known to vary across groups of patients with different baseline risk, we aimed to extend the OHDSI methods library with a framework for risk-based assessment of treatment effect heterogeneity. The proposed framework consists of five steps: 1) definition of the problem, i.e. the population, the treatment, the comparator and the outcome(s) of interest; 2) identification of relevant databases; 3) development of a prediction model for the outcome(s) of interest; 4) estimation of propensity scores within strata of predicted risk and estimation of relative and absolute treatment effect within strata of predicted risk; 5) evaluation and presentation of results. We demonstrate our framework by evaluating heterogeneity of the effect of angiotensin-converting enzyme (ACE) inhibitors versus beta blockers on a set of 9 outcomes of interest across three observational databases. With increasing risk of acute myocardial infarction we observed increasing absolute benefits, i.e. from -0.03% to 0.54% in the lowest to highest risk groups. Cough-related absolute harms decreased from 4.1% to 2.6%. The proposed framework may be useful for the evaluation of heterogeneity of treatment effect on observational data that are mapped to the OMOP Common Data Model. The proof of concept study demonstrates its feasibility in large observational data. Further insights may arise by application to safety and effectiveness questions across the global data network.

**Keywords:** observational data, heterogeneity of treatment effect, risk stratification, subgroup analysis

# 1 Introduction

Understanding how a treatment's effect varies across patients—a concept described as heterogeneity of treatment effects (HTE)—has been central to the agenda for both personalized (or precision) medicine and comparative effectiveness research. More formally, HTE has been defined as the non-random variability in the direction or magnitude of a treatment effect, in which the effect is measured using clinical outcomes [1]. Usually, analyses focus on the relative scale, where treatment effects are assessed one at a time in patient subgroups defined from single covariates, an approach that suffers from low power and multiplicity issues [2,3]. However, even with well-established constant relative effects, treatment benefit (or harm) may vary substantially on the absolute scale. More recently, “predictive” HTE analyses have been described (and contrasted with “one-variable-at-a-time” subgroup analysis) as approaches that provide predictions of potential outcomes in a particular patient with one intervention versus an alternative, taking into account multiple relevant patient characteristics [4]. One promising approach is “risk modeling”, in which treatment effects are estimated in strata of predicted risk [5,6]. Such a risk-based approach first stratifies patients according to baseline risk predictions, using either an existing or an internally developed risk prediction model [5]. Then, relative and absolute treatment effects are estimated within risk strata.

While these approaches have generally been recommended for application to clinical trials, observational databases are also an appealing substrate. Observational healthcare databases, such as administrative claims and electronic health records, are already highly available for the analysis of pharmacoepidemiologic research questions [7,8]. They are also often larger than many typical trials, providing excellent power for HTE analysis, and include heterogeneous populations. However, unlike trials, treatment effects are subject to confounding while the unique structure of different databases calls for database-specific analysis plans that are often not easily transportable.

The Observational Health Data Sciences and Informatics (OHDSI) collaborative has established an international network of data partners and researchers that aim to bring out the value of health data through large-scale analytics by mapping all available databases to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) [9,10]. The common data structure enables analyses at a very large scale. For example, in a recent study, a large set of first-line treatments for hypertension was compared with respect to 55 outcomes in a network of databases, including 4.9 million patients from around the world [11].

We aimed to develop a framework for risk-based assessment of treatment effect heterogeneity in high-dimensional observational data. We implemented the framework using existing OHDSI methods for use in the OMOP-CDM, including the patient-level prediction framework and the population-level effect estimation framework based on new-user cohort design [12,13]. As a proof-of-concept we analyzed heterogeneity of the effects of first-line

1 hypertension treatment: we compared the effect of angiotensin converting enzyme (ACE) inhibitors to beta blockers  
2 on 9 outcomes across three different US claims databases.

## 3 2 Materials and Methods

4 The proposed framework defines 5 distinct steps that enable a standardized approach for risk-based assessment of  
5 treatment effect heterogeneity for databases mapped to the OMOP-CDM. These are: 1) general definition of the  
6 research aim; 2) identification of the database within which the analyses will be performed; 3) a prediction step  
7 where internal or external prediction models are used to assign patient-level risk predictions; 4) an estimation step  
8 where absolute and relative treatment effects are estimated within risk strata; 5) presentation and evaluation of  
9 the results. A simple overview of the procedure can be seen in Figure 1.

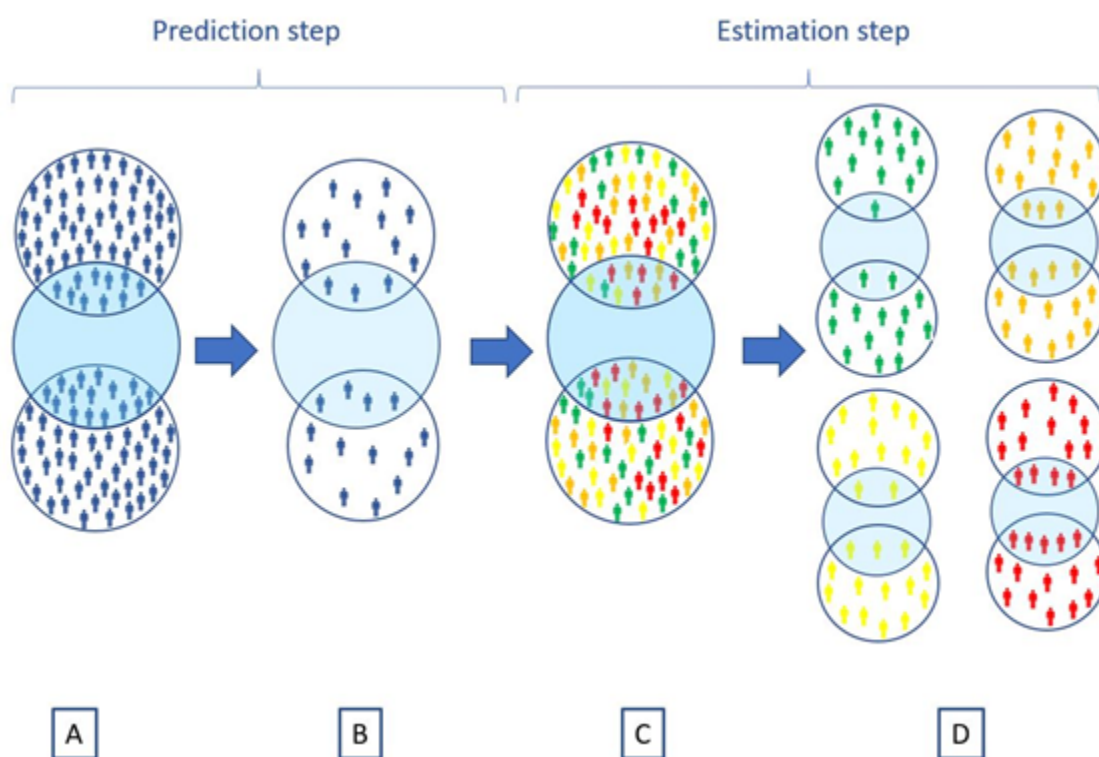


Figure 1: (A) Starting from a treatment (top), a comparator (bottom) and an outcome (middle) cohort we estimate the propensity scores on the entire target population. (B) We match patients on the propensity scores and estimate the prediction model. Since we match patients we develop the prediction model on smaller subset of the initial population and, therefore, the number of patients is smaller in B compared to A. (C) We apply the prediction model on the entire population (green: lower 25% of the risk distribution; yellow: patients with risk between 25% and 50% of the risk distribution; orange: patients with risk between 50% and 75% of the risk distribution; red: patients at risk higher than 75% of the risk distribution). (D) We separate in risk subgroups, here quarters. Within risk quarters propensity scores are estimated again and relative and absolute treatment effects are estimated.

## 2.1 Step 1: General definition of the problem

The typical research aim is: “to compare the effect of treatment  $T$  to a comparator treatment  $C$  in patients with disease  $D$  with respect to outcomes  $O_1, \dots, O_n$ ”. At least three cohorts are defined:

- A single treatment cohort ( $T$ ) which includes patients with disease  $D$  receiving the target treatment of interest. For example, a set of hypertension patients within a database that receive angiotensin-converting enzyme inhibitors, followed from the time of initiation until the time of censoring.
- A single comparator cohort ( $C$ ) which includes patients with disease  $D$  receiving the comparator (control) treatment. For example, a set of patients in a database that receive beta blockers, followed from the time of initiation until the time of censoring.
- One or more outcome cohorts ( $O_1, \dots, O_n$ ) that contain patients developing the outcomes of interest. For example, the set of patients in a database that have at least one occurrence of acute myocardial infarction in their record.

## 2.2 Step 2: Identification of the database

The aim of this step is the inclusion of databases that represent the patient population of interest. The inclusion of multiple databases potentially increases the generalizability of results. Furthermore, the cohorts should preferably have adequate sample size to ensure precise effect estimation, even within smaller risk strata.

## 2.3 Step 3: Prediction

We adopt the standardized framework for the generation of patient-level prediction models using observational data that ensures adherence to existing guidelines [14,15]. This prediction framework requires the definition of two essential cohorts: a target cohort and an outcome cohort.

To generate the target cohort we pool the already defined treatment cohort and comparator cohort. However, for risk-based analysis of treatment effects it is necessary to avoid differentially fitting the prediction model to patients across the treatment arms in order to avoid inducing spurious interactions [16,17]. To do this, we develop the patient-level prediction model in the propensity score-matched subset of the population (1:1), where treatment assignment is well-balanced. The propensity scores are based on LASSO logistic regression for modeling the association between treatment assignment and all available demographics, drug exposures, diagnoses, measurements and medical procedures. Finally, we need to define the time horizon within which we aim to make predictions and we also need to select the machine-learning algorithm we want to use to generate patient-level predictions. Currently, the available options are regularized logistic regression, random forest, gradient boosting machines,

1 decision tree, naive Bayes, K-nearest neighbors, neural network and deep learning (convolutional neural networks,  
2 recurrent neural network and deep nets).

## 3 **2.4 Step 4: Estimation**

4 We use the patient-level prediction model to divide the target population into a set of equally-sized risk strata,  
5 typically 4 risk quarters. Then, we estimate propensity scores within risk strata. These propensity scores are used  
6 when estimating treatment effects, either by matching of patients from different treatment cohorts, by stratification  
7 of patients into groups with similar propensity scores, or by weighing patients' contribution to the estimation  
8 process. Within risk strata we estimate treatment effect both on the relative and the absolute scale. It is important  
9 to evaluate treatment effects in both scales, as effect cannot remain constant on both the relative and the absolute  
10 scale at the same time, assuming a non-zero treatment effect. Any appropriate method for the evaluation of  
11 relative and absolute treatment effects can be considered, as long as the this is done consistently in all risk strata.

## 12 **2.5 Step 5: Result presentation and evaluation**

13 The number of patients and person years by treatment arm along with the number of outcomes should be reported.  
14 A performance overview of the derived prediction models, including discrimination and calibration both in the  
15 propensity score matched subset, the entire population and separately for treated and comparator patients should  
16 also be reported. This is quite relevant as the performance of the prediction models is directly related to our ability  
17 to single out patient subgroups where treatment may be highly beneficial or unsafe. Kent et al [18] demonstrated  
18 that the event rate and the discriminative ability of the prediction model can predict very well the distribution of  
19 predicted risk. Lower event rate and higher c-statistic (given good calibration) result in high risk heterogeneity,  
20 thus making estimated average treatment effects uninformative. In this case, risk stratified analysis of HTE can  
21 be more effective in singling out patient subgroups that stand to benefit (or be harmed) most by treatment in  
22 question.

23 In every risk stratum propensity score distributions by treatment group and covariate balance plots should be made  
24 available along with event rates, hazard ratios and absolute risk differences. Finally, the results should be generated  
25 with a standardized format to allow for combination of results from multiple data sources. This also enables the  
26 development of scalable demonstration tools such as R-shiny applications, interactive tables and figures.

## 3 Results

As a proof of concept, we focus on the comparison of angiotensin converting enzyme (ACE) inhibitors to beta blockers. ACE inhibitors are among the most common treatment classes for hypertension, with well-established effectiveness. Beta blockers, even though initially widely used for the treatment of hypertension, more recent trials and meta-analyses have cast doubt on their relative effectiveness [19]. As a result, newer US guidelines do not consider them for initial treatment for hypertension while in the EU guidelines combination with other antihypertensive treatments is recommended [20,21]. However, another meta-analysis suggested that the efficacy profile of beta blockers is similar to other major treatment classes in younger hypertensive patients and, thus, countries like Canada still include them as a first-line treatment candidate [22,23].

### 3.1 Step 1: General definition of the problem

We demonstrate the framework with the following research aim: “to compare the effect of ACE-inhibitors ( $T$ ) to the effect of beta blockers ( $C$ ) in patients with established hypertension ( $D$ ) with respect to 9 outcomes ( $O_1, \dots, O_9$ )”. The cohorts are:

- Treatment cohort: Patients receiving any drug within the ACE-inhibitor class with at least one year of follow-up before treatment initiation and a recorded hypertension diagnosis within that year.
- Comparator cohort: Patients receiving any drug within the beta blocker class with at least one year of follow-up before treatment initiation and a recorded hypertension diagnosis within that year.
- Outcome cohorts: We consider 3 main and 6 safety outcome cohorts. These are patients in the database with a diagnosis of: acute myocardial infarction (MI); hospitalization with heart failure; ischemic or hemorrhagic stroke (efficacy outcomes); hypokalemia; hyperkalemia; hypotension; angioedema; cough; abnormal weight gain (safety outcomes).

All cohort definitions can be found in the supplementary material.

### 3.2 Step 2: Identification of the databases

We used the following databases:

- IBM MarketScan Medicare Supplemental Beneficiaries (MDCR): Represents health services of retirees (aged 65 or older) in the United States with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service or capitated health plans. These data include adjudicated health insurance claims (e.g. inpatient, outpatient and outpatient pharmacy). Additionally, it captures laboratory tests for a subset of the covered lives.

- 1     ▪ IBM MarketScan Medicaid (MDCD): Adjudicated US health insurance claims for Medicaid enrollees from  
2         multiple states. It includes hospital discharge diagnoses, outpatient diagnoses and procedures and outpatient  
3         pharmacy claims as well as ethnicity and Medicare eligibility.
- 4     ▪ IBM MarketScan Commercial Claims and Encounters (CCAЕ): Data from individuals enrolled in US employer-  
5         sponsored insurance health plans. The data includes adjudicated health insurance claims (e.g. inpatient,  
6         outpatient, and outpatient pharmacy) as well as enrollment data from large employers and health plans who  
7         provide private healthcare coverage to employees, their spouses and dependents. Additionally, it captures  
8         laboratory tests for a subset of the covered lives.

### 9     **3.3 Step 3: Prediction**

10    To obtain a target cohort for developing patient-level predictions we first merged the ACE-inhibitors cohort with  
11    the beta blockers cohort. We then matched patients in the ACE-inhibitor cohort to patients in the beta blockers  
12    cohort on the propensity score. We focused on the efficacy outcomes (acute MI, hospitalization with heart failure  
13    and hemorrhagic or ischemic stroke) for risk stratification of the patient population. In each database, for each  
14    main outcome, we developed a different prediction model. We chose a time horizon of 2 years after inclusion into  
15    the target cohort. We developed the prediction models using LASSO logistic regression with 3-fold cross validation  
16    for hyper-parameter selection.

### 17    **3.4 Step 4: Estimation**

18    We used patient-level predictions to stratify the patient population into 4 risk quarters. We estimated relative  
19    and absolute treatment effects for all 9 outcomes of interest. In order to estimate risk quarter-specific treatment  
20    effects we first estimated propensity scores within risk quarters. We then used the propensity scores to stratify  
21    patients into 5 strata.

### 22    **3.5 Step 5: Result presentation and evaluation**

23    Here we present the results of the analysis in the CCAE database with stratification based on risk predictions  
24    of acute MI. Results of analyses in the other databases and with other risk stratifications are included in the  
25    supplementary material.

26    For each outcome and in each risk stratum there were adequate numbers of patients (Table 1). The discriminative  
27    ability of the prediction models was moderate in the matched development subset (c-index 0.76 for acute MI ; 0.79  
28    for hospitalization with heart failure; 0.74 for stroke; ), in the general population (c-index 0.74 for acute MI; 0.77  
29    for hospitalization with heart failure; 0.73 for stroke), in the treatment cohort (c-index for acute MI it was 0.71,



for hospitalization with heart failure was 0.76 and for stroke it was 0.72) and in the comparator cohort (c-index for acute MI it was 0.79 for hospitalization with heart failure was 0.79 and for stroke it was 0.75).

Table 1: Number of patients, person years and events within quarters of predicted risk for hospitalization with heart failure for the 3 main outcomes of the study (acute myocardial infarction, hospitalization with heart failure and ischemic or hemorrhagic stroke).

Outcome	Risk quarter	ACE inhibitors			Beta blockers		
		Persons	Person years	Events	Persons	Person years	Events
Acute myocardial infarction	1	161,099	276,171	203	133,977	220,633	135
	2	204,882	372,197	534	90,193	169,231	321
	3	214,413	393,583	117	80,662	150,035	535
	4	204,167	351,727	2,095	90,908	154,419	1,520
Heart failure (hosp)	1	146,259	249,809	228	126,387	206,706	378
	2	188,006	341,014	457	84,280	158,425	340
	3	218,052	399,394	826	83,421	155,222	570
	4	230,226	400,330	2,012	98,380	169,139	1,773
Stroke (ischemic or hemorrhagic)	1	146,069	294,484	299	126,264	206,453	320
	2	187,524	340,234	554	84,000	157,913	351
	3	217,070	397,830	947	83,038	154,587	521
	4	226,128	393,861	1,718	97,628	167,810	1,077

Relative treatment effects of ACE-inhibitors vs beta blockers increased (hazard ratios decreased) with increasing acute MI risk, resulting in more pronounced absolute risk differences (ARD) with increasing acute MI risk (Figure 2).

Patients in the low risk quarter did not receive absolute benefit (-0.03%) while absolute risk was 0.54% lower (95% confidence interval 0.36%—0.71%) for patients in the high-risk quarter. In contrast, the absolute and relative effects of ACE-inhibitors on safety outcomes (e.g. cough and angioedema) are approximately constant or even slightly decreasing with increasing acute MI risk (Figure 3 and 4). Similar results were observed in the other two databases (see supplementary material).

This example nicely illustrates heterogeneity of absolute treatment effects, i.e. differences in absolute benefits and harms of ACE-inhibitors vs beta blockers for patients with different baseline risk. The results suggest that

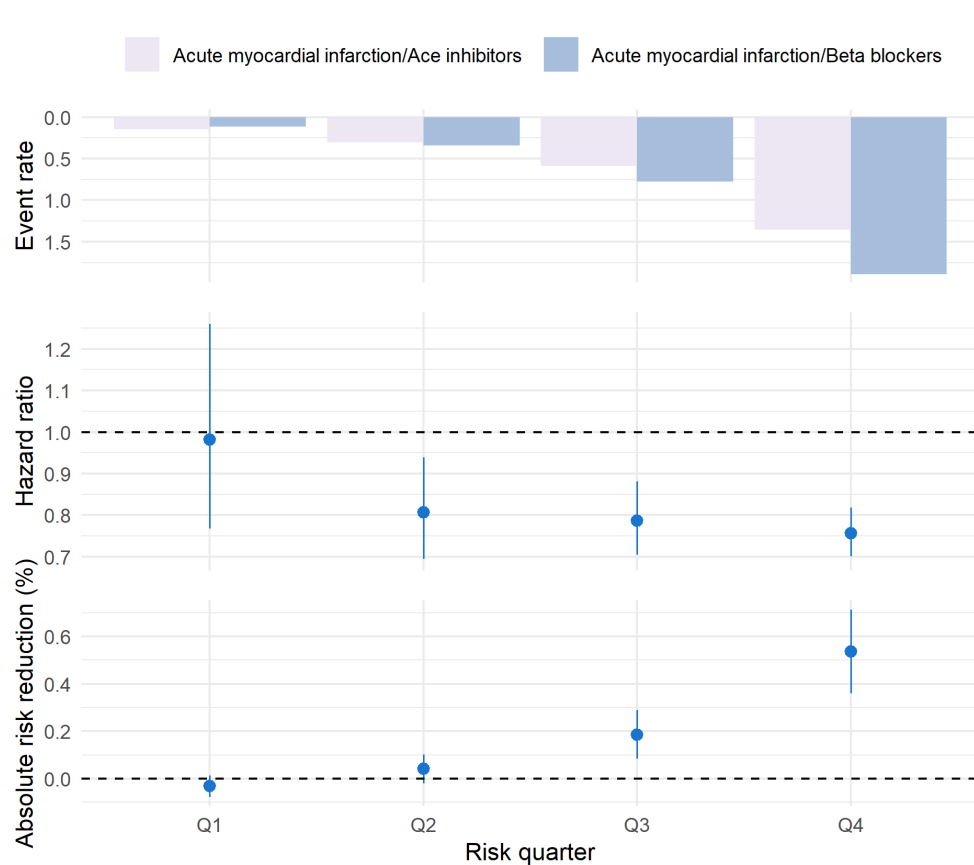


Figure 2: Overview of heterogeneity of ACE-inhibitors treatment within strata of predicted risk of acute MI. The top panel contains the observed acute rates of ACE-inhibitors and beta blockers within each quarter of predicted acute MI risk. These are derived using the KaplanMeier estimates at 730 days after inclusion. The middle panel, contains the hazard ratios of comparing ACE-inhibitors to beta blockers with regard to acute MI. These are estimated using Cox proportional hazards regression within quarters of predicted acute MI risk. The bottom panel contains absolute risk reduction for ACE-inhibitors compared to beta blockers. These are derived as the difference in Kaplan-Meier estimates at 730 after inclusion. Hazard ratios in the middle panel show a decreasing trend with increasing acute MI risk. Given the rather good discrimination of the prediction model ( $AUC=0.74$ ), this results in an increasing trend for absolute benefit in favor of ACE-inhibitors with increasing risk.

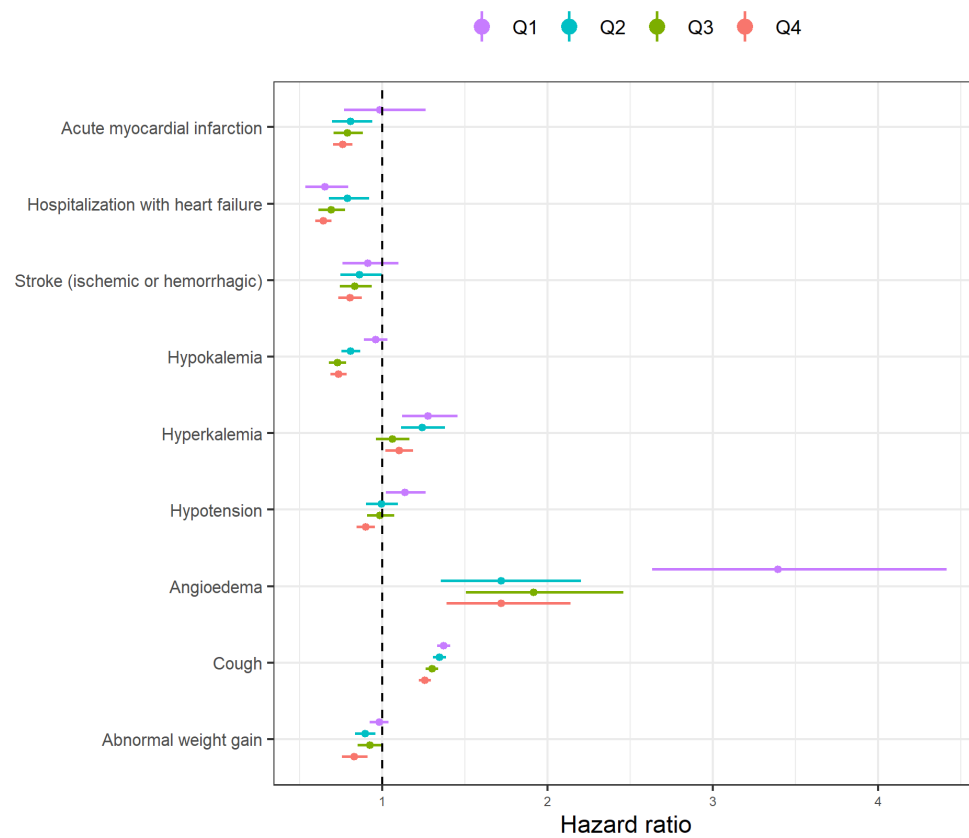


Figure 3: Hazard ratios (relative treatment effects) for the main and safety outcomes, estimated by fitting stratified Cox regression models within quarters of predicted risk of acute myocardial infarction (MI). The four risk quarters (Q1-Q4) are defined using the internally developed model for acute MI

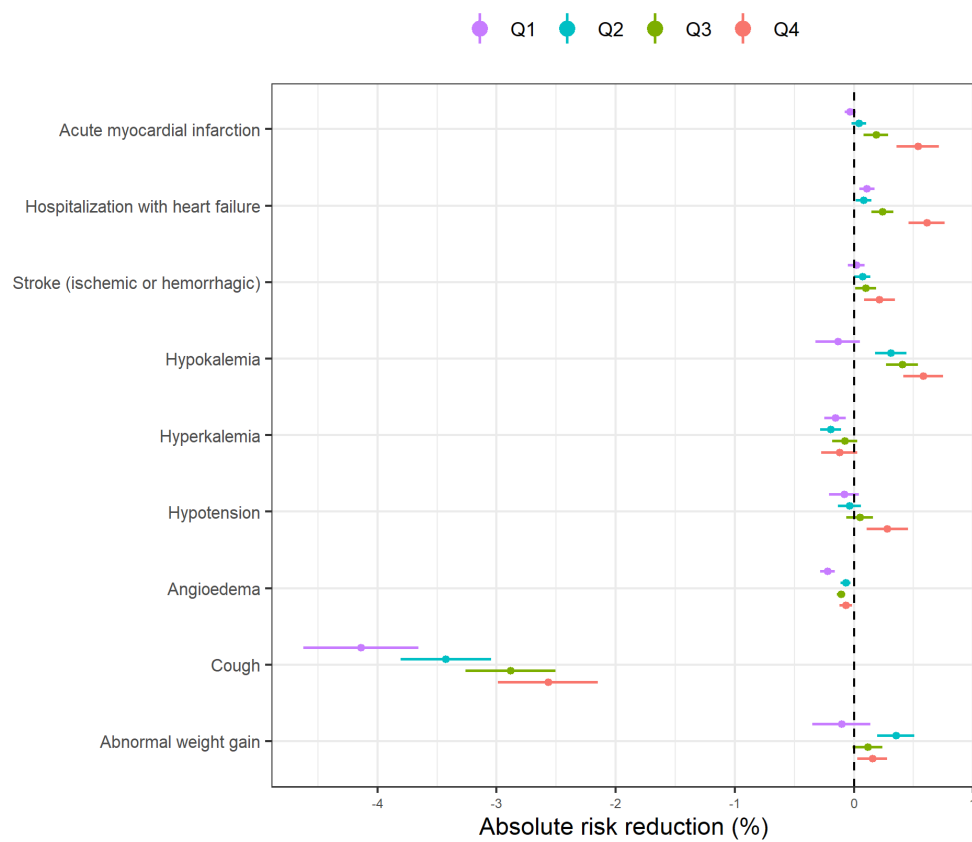


Figure 4: Absolute risk reduction for the main and safety outcomes, estimated by fitting stratified Cox regression models within quarters of predicted risk of acute myocardial infarction (MI). The four risk quarters (Q1-Q4) are defined using the internally developed model for acute MI

treatment with ACE-inhibitors, compared to treatment with beta blockers, may be focused on the higher risk patients, in whom the benefits outweigh the harms. However, treatment with beta blockers may be a viable option in lower risk patients, in whom the benefit-harm tradeoff is in favor of beta blockers. This is in accordance with earlier findings that beta blockers should also be considered as first-line treatment for younger hypertensive patients [22,24]. More thorough evaluation of these results is required in future research, however.

The results of the analyses performed can be accessed and assessed through a publicly available web application (<https://data.ohdsi.org/AceBeta9Outcomes>).

## 4 Discussion

We developed a framework for the assessment of heterogeneity of treatment effect in large observational databases using a risk modeling approach. The framework is implemented in an open source R-package in the OHDSI methods library (<https://github.com/OHDSI/RiskStratifiedEstimation>). As a proof-of-concept, we used our framework to evaluate heterogeneity of the effect of treatment with ACE-inhibitors compared to beta blockers on 3 efficacy and 6 safety outcomes.

In recent years several methods for the evaluation of treatment effect heterogeneity have been developed in the setting of RCTs [25]. However, low power and restricted prior knowledge on the mechanisms of variation in treatment effect are often inherent in RCTs, which are often adequately powered only for the analysis of the primary outcome. Observational databases contain a large amount of information on treatment assignment and outcomes of interest, while also capturing key patient characteristics. Our framework provides a standardized approach that can be used to leverage available information from these data sources, allowing for large-scale assessment of treatment effect heterogeneity. Multiple outcomes can be evaluated in patient subgroups of similar baseline outcome risk. Different outcome risk stratification schemes can also be considered. The standardized nature of the framework enables transportability to multiple databases, provided that they are mapped to the OMOP-CDM.

Recently, guidelines on the application of risk modeling approaches for the assessment of heterogeneity of treatment effect in RCT settings have been proposed [26,27]. Our framework aims to translate these guidelines to the observational setting while also providing a toolset for its implementation. Several considerations need to be made. First, estimates may be biased due to the observational nature of the data. We attempt to account for potential confounding by estimating propensity scores within strata of predicted risk. These scores are estimated using regularized logistic regression on a large set of pre-defined covariates. This specific approach gave accurate results in extensive simulation studies [28]. However, such approaches do not account for unobserved confounding [29]. Several sensitivity analyses have been proposed in the literature for measuring the robustness of results in the

1 presence of unobserved confounding. Another approach is to calibrate estimates and confidence intervals based on  
2 a large set of negative controls [30,31]. Negative controls are treatment-outcome pairs for which a null effect has  
3 been established. Estimating these effects within available data provides an approximation of the null distribution  
4 that can be used to empirically recalibrate effect estimates. Future work may extend our framework with this type  
5 of analyses.

6 Our method provides a risk-stratified assessment of treatment effect heterogeneity. However, even though  
7 stratification can provide a useful overview for clinical interpretation, it is not appropriate to guide clinical practice,  
8 where decisions need to be made at the individual level [26]. Presentation of treatment effects as a continuous  
9 function of risk would be more helpful, but is methodologically challenging. Future research is necessary for the  
10 development of methods for continuous risk-based assessment of HTE.

11 Externally derived and well transportable prediction models are preferred for analyzing treatment effect heterogeneity  
12 [5]. In the absence of such prediction models, simulations of RCTs have shown that internal models can be used to  
13 provide unbiased estimates of treatment effect across the spectrum of baseline risk [16]. However, in observational  
14 databases treatment arms may significantly differ in sample size. Because the prediction model will possibly better  
15 fit to the larger treatment arm, this may introduce spurious treatment-covariate interactions in the prediction  
16 model, leading to sub-optimal risk stratification. As a remedy, we first match the patients in the treatment and  
17 the comparator cohorts on the basis of propensity scores. Additionally, we propose to assess model performance in  
18 the separate treatment arms to evaluate its aptness for risk stratification.

19 Our contribution is a translation of the PATH statement principles to the OHDSI methods library [26,27]. Our  
20 method encourages open science as it requires clear definition of the research questions translated into clear and  
21 reproducible cohort definitions that can easily be shared among researchers. Our R-package provides a standardized  
22 stepwise procedure for the assessment of HTE. This enables source code to be easily shared and evaluated, allowing  
23 for reproducible research. Researchers with access to different databases mapped to OMOP-CDM can also very  
24 easily extend their overall analyses with risk-based assessment of treatment effect heterogeneity. This enables  
25 collaboration among multiple sites with access to different patient populations. We propose that the framework is  
26 implemented any time treatment effect estimation in high-dimensional observational data is undertaken.

27 Recently, disease risk scores have been explored as an alternative to propensity scores for balancing covariates  
28 [32,33]. In our method, the objective of risk stratification is not balancing, but assessing the variation of treatment  
29 effects on multiple outcomes across patients with different levels of baseline risk. Although using the same risk  
30 model for balancing and risk-based HTE analysis may sound attractive, we note that our method only uses one  
31 risk model for stratification and one propensity score model for balancing, while separate disease risk score models

1 would be required to analyze treatment effects for each of the multiple outcomes.

2 In conclusion, the proof-of-concept study demonstrates the feasibility of our framework for risk-based assessment  
3 of treatment effect heterogeneity in large observational data. The standardized framework is easily applicable  
4 and highly informative whenever treatment effect estimation in high-dimensional observational data is of interest.  
5 Our framework is a supplement to the population-level effect estimation framework developed within OHDSI and,  
6 in the presence of an adequately discriminating prediction model, can be used to make the overall results more  
7 actionable for medical decision making.

## 5 References

- 1 Kravitz RL, Duan N, Braslow J. Evidence-based medicine, heterogeneity of treatment effects, and the trouble with averages. *The Milbank Quarterly* 2004;**82**:661–87. doi:10.1111/j.0887-378x.2004.00327.x
- 2 Yusuf S. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA: The Journal of the American Medical Association* 1991;**266**:93. doi:10.1001/jama.1991.03470010097038
- 3 Garcia EF y, Nguyen H, Duan N *et al.* Assessing heterogeneity of treatment effects: Are authors misinterpreting their results? *Health Services Research* 2010;**45**:283–301. doi:10.1111/j.1475-6773.2009.01064.x
- 4 Varadhan R, Segal JB, Boyd CM *et al.* A framework for the analysis of heterogeneity of treatment effect in patient-centered outcomes research. *Journal of Clinical Epidemiology* 2013;**66**:818–25. doi:10.1016/j.jclinepi.2013.02.009
- 5 Kent DM, Rothwell PM, Ioannidis JP *et al.* Assessing and reporting heterogeneity in treatment effects in clinical trials: A proposal. *Trials* 2010;**11**. doi:10.1186/1745-6215-11-85
- 6 Kent DM, Steyerberg E, Klaveren D van. Personalized evidence based medicine: Predictive approaches to heterogeneous treatment effects. *BMJ* 2018;k4245. doi:10.1136/bmj.k4245
- 7 Adler-Milstein J, Holmgren AJ, Kralovec P *et al.* Electronic health record adoption in US hospitals: The emergence of a digital “advanced use” divide. *Journal of the American Medical Informatics Association* 2017;**24**:1142–8. doi:10.1093/jamia/ocx080
- 8 Dahabreh IJ, Kent DM. Can the learning health care system be educated with observational data? *JAMA* 2014;**312**:129. doi:10.1001/jama.2014.4364
- 9 Hripcsak G, Duke JD, Shah NH *et al.* Observational health data sciences and informatics (ohdsi): Opportunities for observational researchers. *Studies in health technology and informatics* 2015;**216**:574.
- 10 Overhage JM, Ryan PB, Reich CG *et al.* Validation of a common data model for active safety surveillance research. *Journal of the American Medical Informatics Association* 2012;**19**:54–60. doi:10.1136/amiajnl-2011-000376
- 11 Suchard MA, Schuemie MJ, Krumholz HM *et al.* Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: A systematic, multinational, large-scale analysis. *The Lancet* 2019;**394**:1816–26. doi:10.1016/s0140-6736(19)32317-7
- 12 Reips JM, Schuemie MJ, Suchard MA *et al.* Design and implementation of a standardized framework to generate and evaluate patient-level prediction models using observational healthcare data. *Journal of the American*



*Medical Informatics Association* 2018;**25**:969–75. doi:10.1093/jamia/ocy032

- 13 Ryan PB, Schuemie MJ, Gruber S *et al.* Empirical performance of a new user cohort method: Lessons for developing a risk identification and analysis system. *Drug Safety* 2013;**36**:59–72. doi:10.1007/s40264-013-0099-6
- 14 Collins GS, Reitsma JB, Altman DG *et al.* Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement. *BMC Medicine* 2015;**13**:1. doi:10.1186/s12916-014-0241-z
- 15 Moons KGM, Altman DG, Reitsma JB *et al.* Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): Explanation and elaboration. *Annals of Internal Medicine* 2015;**162**:W1. doi:10.7326/m14-0698
- 16 Burke JF, Hayward RA, Nelson JP *et al.* Using internally developed risk models to assess heterogeneity in treatment effects in clinical trials. *Circulation: Cardiovascular Quality and Outcomes* 2014;**7**:163–9. doi:10.1161/circoutcomes.113.000497
- 17 Klaveren D van, Balan TA, Steyerberg EW *et al.* Models with interactions overestimated heterogeneity of treatment effects and were prone to treatment mistargeting. *Journal of Clinical Epidemiology* 2019;**114**:72–83. doi:10.1016/j.jclinepi.2019.05.029
- 18 Kent DM, Nelson J, Dahabreh IJ *et al.* Risk and treatment effect heterogeneity: Re-analysis of individual participant data from 32 large clinical trials. *International Journal of Epidemiology* 2016;dyw118. doi:10.1093/ije/dyw118
- 19 Wiysonge CS, Bradley HA, Volmink J *et al.* Beta-blockers for hypertension. *Cochrane database of systematic reviews* 2017.
- 20 Whelton PK, Carey RM, Aronow WS *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the american college of cardiology/american heart association task force on clinical practice guidelines. *Hypertension* 2018;**71**. doi:10.1161/hyp.0000000000000065
- 21 Williams B, Mancia G, Spiering W *et al.* 2018 ESC/ESH guidelines for the management of arterial hypertension. *European Heart Journal* 2018;**39**:3021–104. doi:10.1093/eurheartj/ehy339
- 22 Khan N. Re-examining the efficacy of  $\beta$ -blockers for the treatment of hypertension: A meta-analysis. *Canadian Medical Association Journal* 2006;**174**:1737–42. doi:10.1503/cmaj.060110

- 23 Rabi DM, McBrien KA, Sapir-Pichhadze R *et al.* Hypertension canada's 2020 comprehensive guidelines for the prevention, diagnosis, risk assessment, and treatment of hypertension in adults and children. *Canadian Journal of Cardiology* 2020;**36**:596–624. doi:10.1016/j.cjca.2020.02.086
- 24 Cruickshank JM. Are we misunderstanding beta-blockers. *International Journal of Cardiology* 2007;**120**:10–27. doi:10.1016/j.ijcard.2007.01.069
- 25 Rekkas A, Paulus JK, Raman G *et al.* Predictive approaches to heterogeneous treatment effects: A scoping review. *BMC Medical Research Methodology* 2020;**20**. doi:10.1186/s12874-020-01145-1
- 26 Kent DM, Paulus JK, Klavaren D van *et al.* The predictive approaches to treatment effect heterogeneity (PATH) statement. *Annals of Internal Medicine* 2019;**172**:35. doi:10.7326/m18-3667
- 27 The predictive approaches to treatment effect heterogeneity (path) statement: Explanation and elaboration. *Annals of Internal Medicine* 2020;**172**:W1–W25. doi:10.7326/M18-3668
- 28 Tian Y, Schuemie MJ, Suchard MA. Evaluating large-scale propensity score performance through real-world and synthetic data experiments. *International Journal of Epidemiology* 2018;**47**:2005–14. doi:10.1093/ije/dyy120
- 29 Liu W, Kuramoto SJ, Stuart EA. An introduction to sensitivity analysis for unobserved confounding in nonexperimental prevention research. *Prevention Science* 2013;**14**:570–80. doi:10.1007/s11121-012-0339-5
- 30 Schuemie MJ, Ryan PB, DuMouchel W *et al.* Interpreting observational studies: Why empirical calibration is needed to correct p-values. *Statistics in Medicine* 2014;**33**:209–18. doi:https://doi.org/10.1002/sim.5925
- 31 Schuemie MJ, Hripcsak G, Ryan PB *et al.* Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data. *Proceedings of the National Academy of Sciences* 2018;**115**:2571–7. doi:10.1073/pnas.1708282114
- 32 Glynn RJ, Gagne JJ, Schneeweiss S. Role of disease risk scores in comparative effectiveness research with emerging therapies. *Pharmacoepidemiology and Drug Safety* 2012;**21**:138–47. doi:10.1002/pds.3231
- 33 Hansen BB. The prognostic analogue of the propensity score. *Biometrika* 2008;**95**:481–8. doi:10.1093/biomet/asn004