

## Background

- Overall treatment effect estimates derived from the LEGEND-Hypertension study may not apply similarly to all individual patients
- As conventional subgroup analyses fail to capture the multivariate nature of heterogeneity of treatment effect (HTE), we opt for a risk modeling approach
- Outcome risk is a summary score that determines treatment effect—unlike individual variables that may or may not modify treatment effect
- We have developed a standardized easily scalable framework that enables risk-based assessment of HTE within the OHDSI paradigm
- Our work builds upon existing tools in the OHDSI Methods Library and previous work carried out during the LEGEND-Hypertension study

## Methods

### Databases

- IBM MarketScan® Medicare Supplemental Database (MDCR)
- IBM MarketScan® Commercial Database (CCAE)

### Cohorts

Cohort definitions of the LEGEND-Hypertension study were used for both treatments and outcomes. We focus on the comparison of new users of ACE inhibitors to 4 other major classes of antihypertensive treatments:

- Angiotensin receptor blockers (ARB)
- Beta blockers
- Calcium channel blockers (CCB)
- Diuretics

We evaluated treatments regarding 55 outcome cohorts, including both main hypertension outcomes and safety outcomes.

### Framework

The framework consists of six distinct steps:

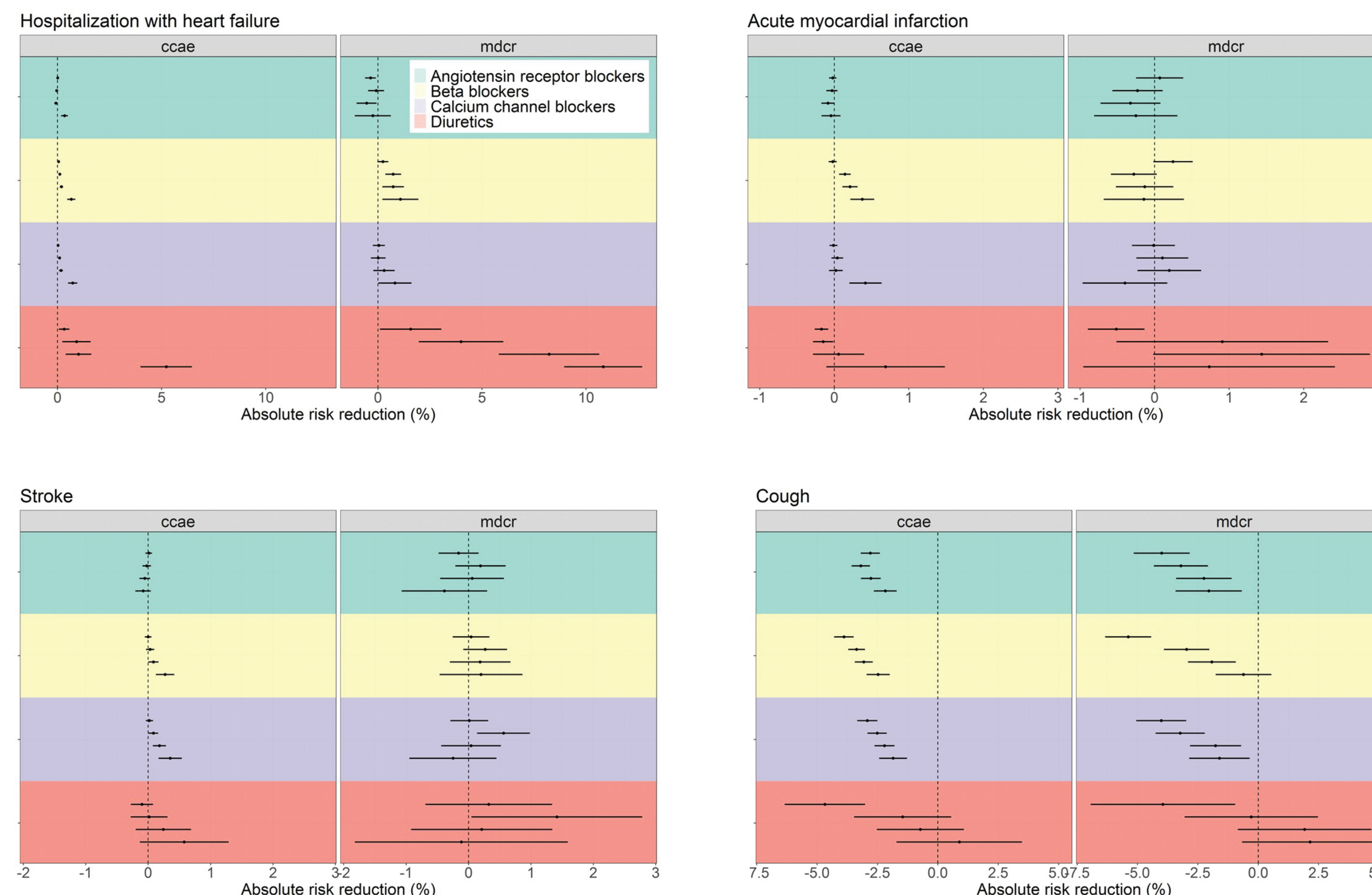
- Definition of the problem, i.e. the population the treatment, the comparator and the outcome(s)
- Selection of the databases and the patient population
- Development of prediction models for the outcome(s) of interest
- Estimation of propensity scores within strata of predicted risk
- Estimation of relative and absolute treatment effects within strata of predicted risk
- Evaluation and presentation of the results

We have implemented the suggested framework in a publicly available R-package (<https://github.com/OHDSI/RiskStratifiedEstimation>).

## Results

**Table:** Treatment cohort sizes in which our framework was applied

Treatment	MDCR	CCAE
ACE inhibitors	102,840	883,610
ARBs	32,275	274,368
Beta blockers	74,056	449,396
CCBs	50,088	311,032



**Figure:** Absolute risk reduction of treatment with ACE inhibitors compared to treatment with the other 4 treatment classes. The comparisons were made in strata of predicted risk for hospitalization with heart failure. Positive values favor ACE inhibitors.

When comparing ACE inhibitors to calcium channel blockers LEGEND-Hypertension study found a calibrated hazard ratio of 0.85 (95% CI = [0.72, 1.03]) in CCAE database. However, the absolute benefit is concentrated in the highest risk group (top left graph), while the rest of the population receives no absolute benefit. This trend, can be seen in MDCR as well. Similar, conclusions can be drawn in the case of beta blockers (top left, top right and bottom left graphs). ACE inhibitors may be unattractive for patients at lower risk of hospitalization with heart failure, because cough risk substantially increases with ACE inhibitors (bottom right graph). At the same time, heart failure rates are similar for both beta blockers and calcium channel blockers compared to ACE inhibitors.

A subset of our analyses can be explored by following the QR code.



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## Conclusions

Our framework for risk-based assessment of HTE is highly scalable and can be used to generate large amounts of evidence in a standardized and timely manner.

We aim to expand our analyses in both the direction of treatments compared, and databases considered, thus generating a vast amount of evidence that can better inform medical decision-making in hypertension.

**Limitations:** (1) Our method does not provide individualized estimates of treatment benefit, as we are still relying on subgroups; (2) Residual confounding is not evaluated within risk subgroups.