

# Comparative Effectiveness and Safety of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) in Older Adults with Type 2 Diabetes

**First published:** 04/01/2022

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Study

Finalised

## Administrative details

### EU PAS number

EUPAS44899

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### Study ID

44900

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### DARWIN EU® study

No

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### Study countries

 United States

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### Study description

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are widely used blood pressure lowering drugs which work by inhibiting the renin-angiotensin system. There are several head-to-head trials assessing the relative effectiveness of these two drug classes. However, the available evidence is limited by small sample size and real-world evidence is conflicting. Therefore, it is necessary to perform a high-quality real-world study to assess the comparative effectiveness of ACEIs to ARBs. More than one-third of the adults with diabetes are currently aged 65 years or older and both ACEIs and ARBs are recommended as first line therapy in type 2 diabetes with hypertension. Thus, to reduce bias and achieve better baseline comparability in real-world study, we propose to assess the comparative effectiveness of ACEIs to ARBs in older adults with type 2 diabetes. We aim to 1) estimate absolute and relative rate and risk of in cardiovascular outcomes and all-cause mortality in Medicare beneficiaries with type 2 diabetes (T2D) initiating ACEIs or ARBs. 2) identify subgroups of Medicare beneficiaries with T2D that are more likely to benefit from ACEI's or ARBs to prevent cardiovascular outcomes and all-cause mortality using machine learning-based heterogeneous treatment effect analysis. We will conduct active-comparator, new-user cohort using a 20% random sample of Medicare data including patients with  $\geq 1$  prescription dispensing claim for ACEI or ARB between January 01, 2007, and December 30, 2019. We will assess the following outcome: (i) hospitalization of Heart failure (HHF) (ii) composite endpoint of inpatient myocardial infarction (MI), inpatient stroke or all-cause mortality (Major Cardiovascular Events, MACE outcome) (iii) the composite of MACE plus HHF. (iv) All-cause mortality. (v) end stage renal disease and dialysis.

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## **Study status**

Finalised

## **Research institutions and networks**

# Institutions

## University of North Carolina at Chapel Hill

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Institution

## Contact details

### Study institution contact

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Study contact

[sturmer@unc.edu](mailto:sturmer@unc.edu)

### Primary lead investigator

Til Stürmer

Primary lead investigator

## Study timelines

### Date when funding contract was signed

Planned: 01/08/2017

Actual: 01/08/2017

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### Study start date

Planned: 29/12/2021

Actual: 29/12/2021

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### **Date of final study report**

Planned: 29/12/2021

Actual: 29/12/2021

## Sources of funding

- Other

## More details on funding

National Institute on Aging at NIH

## Study protocol

[ACEI v ARB\\_RWE protocol\\_30DEC2021.pdf](#) (594.66 KB)

## Regulatory

### **Was the study required by a regulatory body?**

No

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### **Is the study required by a Risk Management Plan (RMP)?**

Not applicable

## Methodological aspects

### Study type

### Study type list

**Study topic:**

Disease /health condition  
Human medicinal product

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**Study type:**

Non-interventional study

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**Scope of the study:**

Drug utilisation  
Effectiveness study (incl. comparative)  
Safety study (incl. comparative)

**Data collection methods:**

Secondary use of data

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**Main study objective:**

1. To estimate absolute and relative rate and risk of in cardiovascular outcomes and all-cause mortality in Medicare beneficiaries with type 2 diabetes (T2D) initiating ACEIs or ARBs. 2. To identify subgroups of Medicare beneficiaries with T2D that are more likely to benefit from ACEI's or ARBs to prevent cardiovascular outcomes and all-cause mortality using machine learning-based analysis.

## Study Design

**Non-interventional study design**

Cohort  
Other

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**Non-interventional study design, other**

Active-comparator, new-user (ACNU) design

## Study drug and medical condition

### **Anatomical Therapeutic Chemical (ATC) code**

(C09AA) ACE inhibitors, plain

ACE inhibitors, plain

(C09CA) Angiotensin II receptor blockers (ARBs), plain

Angiotensin II receptor blockers (ARBs), plain

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### **Medical condition to be studied**

Type 2 diabetes mellitus

## Population studied

### **Short description of the study population**

1. Medicare FFS enrollees  $\geq 65$  years of age with T2D having continuous coverage in fee-for-service Medicare plans A (inpatient services), B (physician and outpatient services) and D (prescription drugs)
2. The base population for the analysis will consist of all beneficiaries with  $\geq 1$  prescription dispensing claim for ACEI or ARB between January 01, 2007, and December 30, 2019.

We will exclude the following patients:

- 1) To ensure new use of either ACEIs or ARBs, we will exclude all individuals who do not have at least 12 months of continuous enrollment (inpatient, outpatient, and prescription coverage) in the appropriate insurance database prior to the first prescription dispensing claim (12-month baseline period), during which no use of any of the study drug classes compared is detected.
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## **Age groups**

- Adults (65 to < 75 years)
  - Adults (75 to < 85 years)
  - Adults (85 years and over)
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## **Special population of interest**

Hepatic impaired

Immunocompromised

Other

Renal impaired

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## **Special population of interest, other**

Type 2 diabetes mellitus patients

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## **Estimated number of subjects**

100000

# Study design details

## **Outcomes**

The primary outcomes are (i) Hospitalization of Heart failure (HHF) (ii) composite endpoint of inpatient myocardial infarction (MI), inpatient stroke or all-cause mortality (Major Cardiovascular Events, MACE outcome) (iii) the composite of MACE plus HHF. (iv) All-cause mortality (v) end stage renal disease or dialysis, Secondary outcomes include individual components of the MACE outcome (non-fatal MI, stroke, and HHF), and MACE plus invasive cardiac procedures (stents, revascularization, bypass surgery).

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## **Data analysis plan**

We will estimate 2-year risks of outcomes of interest, risk differences (RD) and ratios (RR) for ACEIs vs. ARBs after weighting by IPTW and IPCW. Confidence intervals will be derived from 2.5th and 97.5th percentiles of estimates from 500 bootstrap resamples of the study population (random resampling with replacement). When estimating risks of cardiovascular outcomes in older Medicare patients, censoring those who died prior to having the outcome of interest, as commonly done in survival analyses, could bias the risks. To avoid this, we will use Aalen Johansen (AJ) estimators to estimate risks.

## Data management

### ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

## Data sources

### **Data source(s), other**

Medicare Fee-for-Service (FFS) Database

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### **Data sources (types)**

[Administrative healthcare records \(e.g., claims\)](#)

## Use of a Common Data Model (CDM)

## **CDM mapping**

No

## Data quality specifications

### **Check conformance**

Unknown

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### **Check completeness**

Unknown

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### **Check stability**

Unknown

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### **Check logical consistency**

Unknown

## Data characterisation

### **Data characterisation conducted**

No