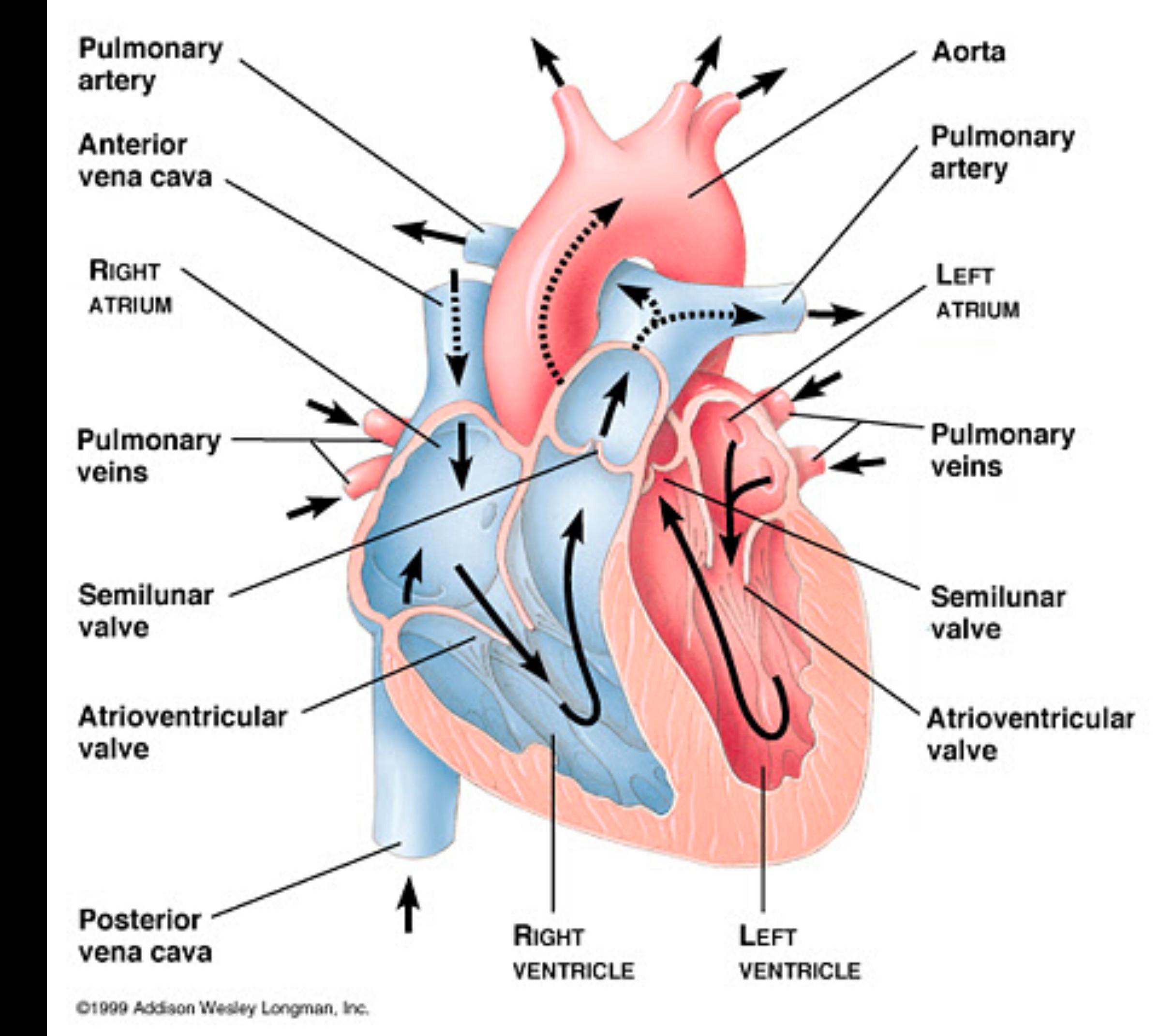


# **Beta blocker use and outcomes among Medicare beneficiaries with heart failure with reduced ejection fraction**

**Matthew Shane Loop, PhD FAHA**

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# What is heart failure?



# Why should we care about heart failure?

- Heart failure has a high mortality rate and hospitalization rate.
- The prevalence of heart failure has increased. The prevalence of HF in adults at least 20 years of age increased from 5.7 million Americans in 2009 - 2012 to 6.2 million in 2013 - 2016 — an increase of 9%.
- From 1998 - 2008, the nationwide 1-year mortality among Medicare beneficiaries was 30%.

Virani SS, Alonso A, Benjamin EJ, Bittencourt MS. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. Circulation. 2020. Available: <https://www.ahajournals.org/doi/abs/10.1161/CIR.0000000000000757>; Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013;6: 606–619. Chen J, Normand S-LT, Wang Y, Krumholz HM. ; National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998-2008. JAMA. 2011;306: 1669–1678.

# Beta blockers improve outcomes

- Beta blockers allow the heart to relax and facilitate cardiac remodeling
- Three beta blockers have been shown to decrease mortality and hospitalization
  - Carvedilol (COPERNICUS trial)
  - Bisoprolol (CIBIS-II trial)
  - Sustained-release metoprolol succinate (MERIT-HF trial)

# Pharmacotherapy is difficult

- Beta blockers don't make you feel very good
- Patients tend to have other comorbidities for which they are taking medication
- Some of these comorbidities are contraindications, such as symptomatic COPD



Photo by Zoë Gayah Jonker

**“A beta blocker is recommended for patients with stable HFrEF to reduce the risk of hospitalization and death. [Class IA]”**

**- 2021 guidelines of European Society of Cardiology**

McDonagh TA, Metra M, Adamo M. ... Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart .... Eur Heart J. 2021. Available: <https://academic.oup.com/eurheartj/article-abstract/42/36/3599/6358045>

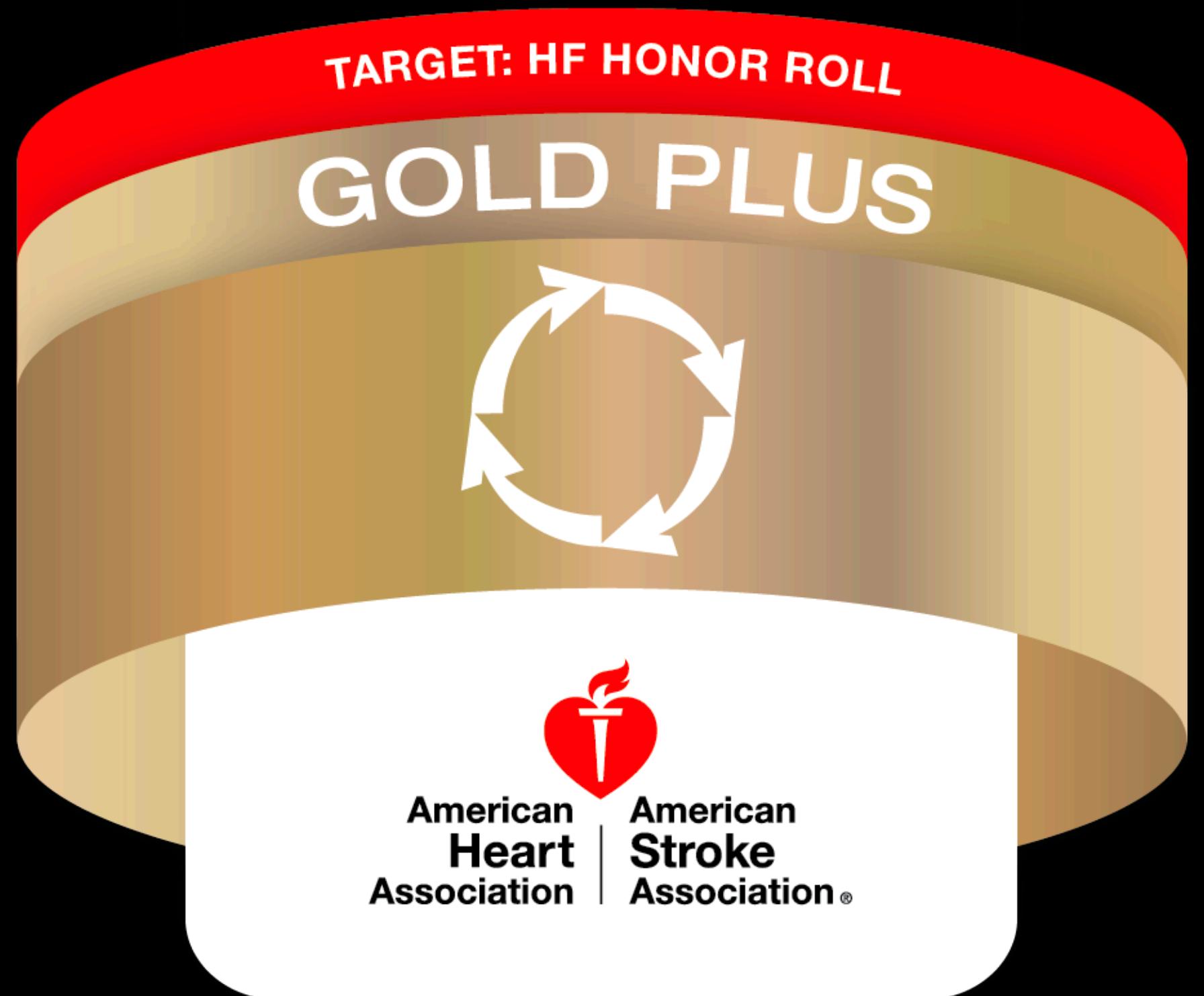
# 2018

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### HEART FAILURE



# OPTIMIZE-HF

- Enrolled 48,000 patients across 259 US hospitals
- 73% of all patients were discharged with a prescription for a beta blocker
- However, ...

**Dosing of Beta-Blocker Therapy Before, During, and After Hospitalization for Heart Failure (from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure)**

Gregg C. Fonarow, MD<sup>a,\*</sup>, William T. Abraham, MD<sup>b</sup>, Nancy M. Albert, PhD, RN<sup>c</sup>, Wendy Gattis Stough, PharmD<sup>e,f</sup>, Mihai Gheorghiade, MD<sup>g</sup>, Barry H. Greenberg, MD<sup>h</sup>, Christopher M. O'Connor, MD<sup>i</sup>, Jie Lena Sun, MS<sup>j</sup>, Clyde W. Yancy, MD<sup>k</sup>, and James B. Young, MD<sup>d</sup>, on behalf of the OPTIMIZE-HF Investigators and Coordinators

A nighttime photograph of Duke University Hospital. The building features a modern design with a curved, illuminated entrance canopy. Large, illuminated letters spelling "DUKE UNIVERSITY" are mounted on the side of the building. A tall, rectangular tower with many windows is visible in the background. The sky is a deep purple.

DUKE UNIVERSITY



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RCTs and registries often focus on certain populations.

Are discharge prescriptions the same  
as prescription fills?

What if we're wrong about how  
things are going for typical patients?



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# Two questions for today

1. How often do Medicare beneficiaries with HFrEF fill prescriptions for beta blockers? How often does the dose of the fill change?
2. Does filling a prescription for a beta blocker have similar associations with lower mortality and hospital readmissions as seen in the clinical trials?

# Target population

- Medicare beneficiaries from 2007 - 2013
  - Only ~25% of Medicare beneficiaries would have met inclusion / exclusion criteria for beta blocker trials
- Discharged with a *primary* discharge diagnosis that indicated “systolic HF”
  - Used first admission in this time period as index admission. It almost always was not the first admission for these participants.
- Excluded some observations typical for Medicare analyses (see handout)
- For first question for today, included those discharged to a skilled nursing facility

How often do Medicare beneficiaries with HFrEF fill prescriptions for beta blockers? How often does the dose of the fill change?

# Methods

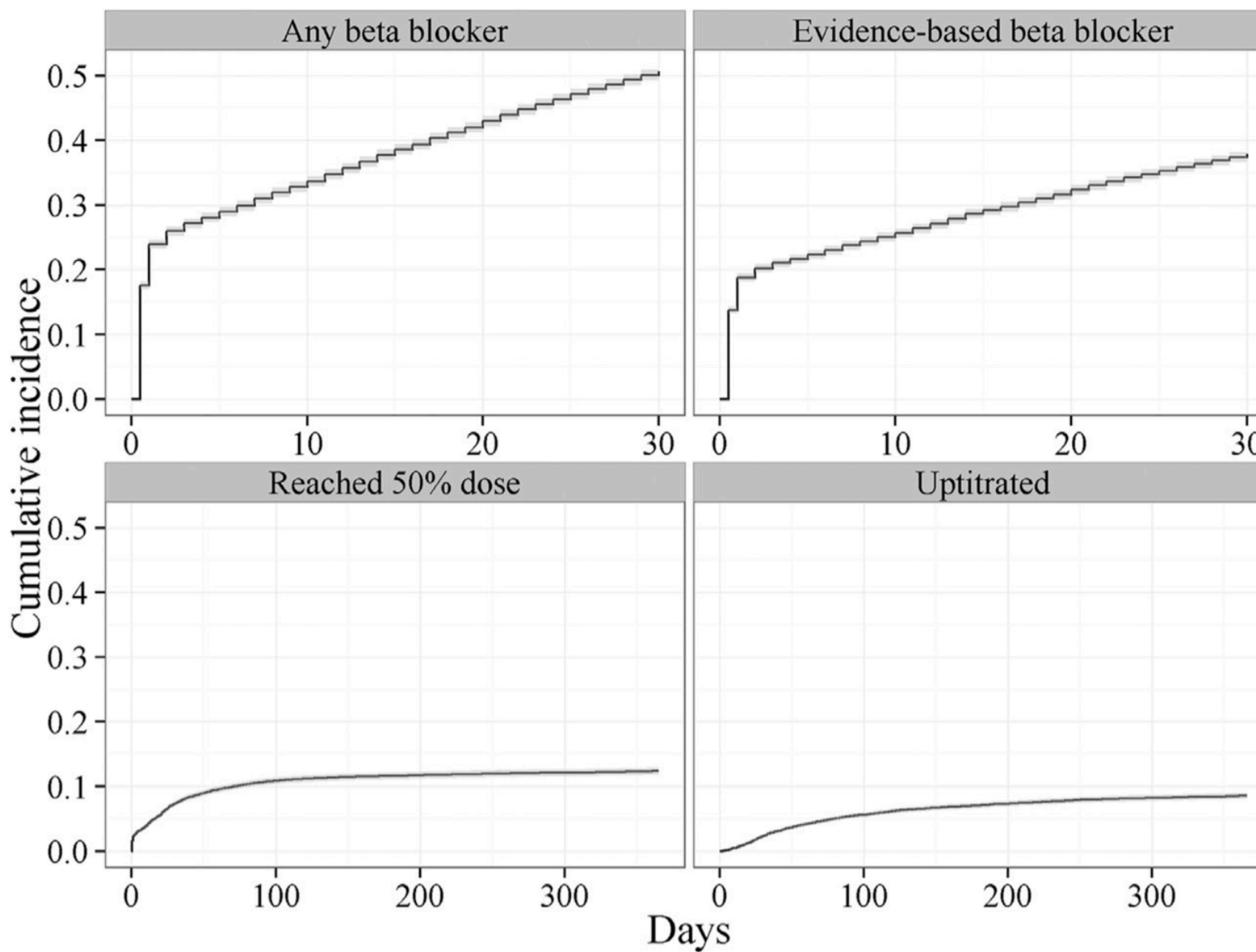
- Outcomes
  - 30-day follow up for fills of any beta blocker, as well as carvedilol, bisoprolol, or sustained-release metoprolol succinate
  - 365-day follow up for fills for an uptitrated dose
  - 365-day follow up for fills for a dose at least 50% of guideline-recommended dose
- Exposures
  - Potential contraindications: hypotension, COPD, syncope, and asthma
  - Potential confounders: see handout

# Methods

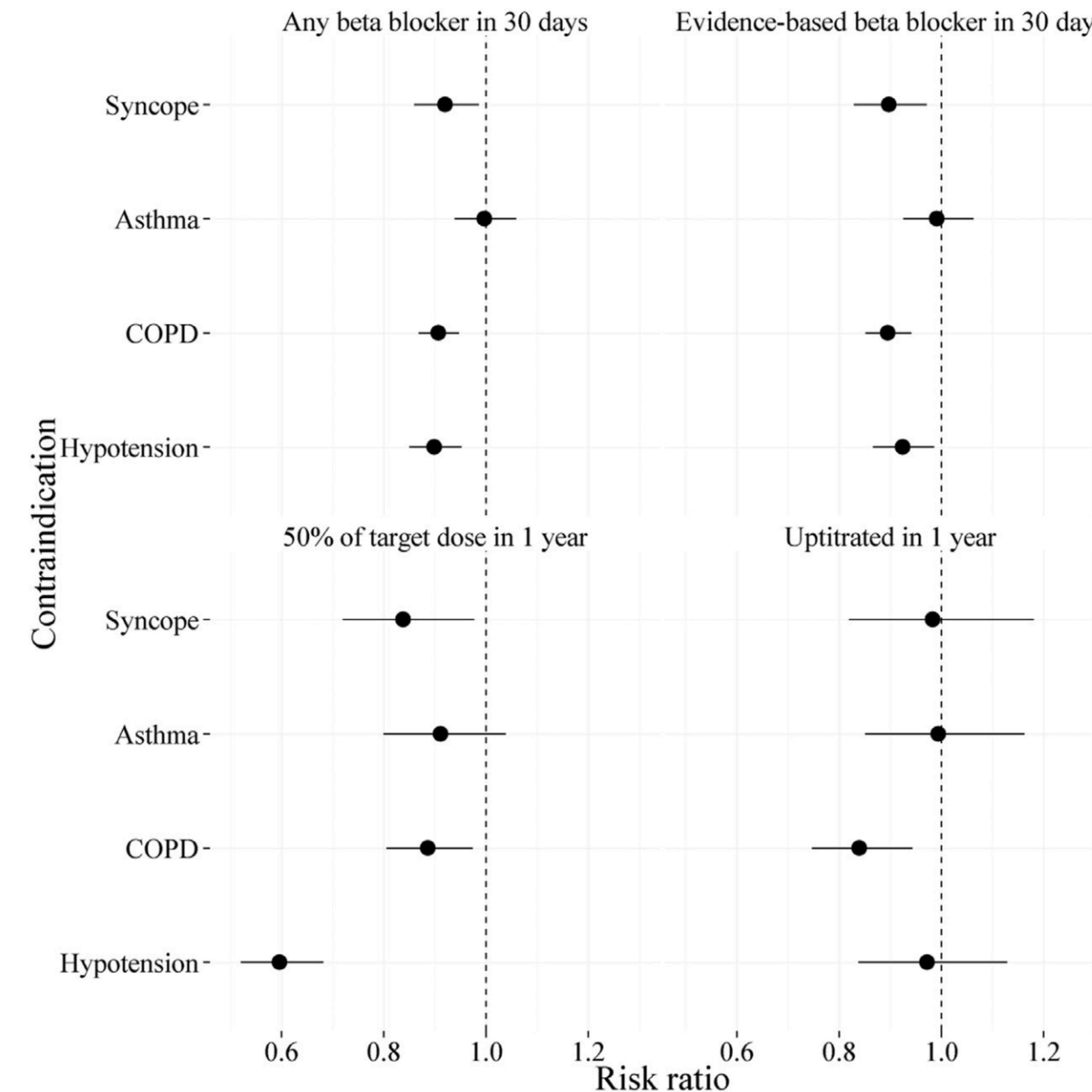
- Estimated cumulative incidence curves for fill outcomes
  - Accounted for competing risks of death and readmission using Fine and Gray method
  - Estimated hazard ratios for each of the 4 contraindications, in their own Cox models
    - Also used Fine and Gray adjustment to account for competing risks
  - Conducted sensitivity analyses that: (1) excluded those discharged to a SNF; (2) excluded those with days of a BB available at baseline; and (3) excluded participants with bradycardia or atrioventricular block
  - Also performed a sensitivity analysis that stratified by beta blocker use during the year prior to admission

# Results

- Of the 60,640 beneficiaries identified with heart failure as the primary discharge diagnosis, 15,205 beneficiaries included for analysis
  - The vast majority of these exclusions were because there was no mention of type of heart failure, or it was isolated diastolic heart failure
  - Hypotension: 21%
  - COPD: 48%
  - Asthma: 15%
  - Syncope: 12%



**Fig. 1.** Cumulative incidence functions for outcomes. Outcomes are receiving any beta-blocker within 30 days, receiving an evidence-based beta-blocker within 30 days, reaching at least 50% of the target dose of an evidence-based beta-blocker, and being up-titrated on an evidence-based beta-blocker within 1 year, given that the beneficiary has not died or been readmitted before the end of the follow-up period. Denominator for each panel is total cohort.



**Fig. 2.** Hazard/risk ratios (HR/RRs) for each contraindication for each outcome. Each competing risk model was adjusted for age, race, sex, region of residence, beta-blocker use during baseline, cardiac device, Medicaid eligibility on hospital admission, cost-sharing group, nursing home residence, coronary heart disease, stroke, hypertension, hyperlipidemia, diabetes, valvular or rheumatic heart disease, atrial fibrillation, other arrhythmia or conductive disorder, inflammatory or autoimmune disease, cancer, malnutrition, liver disease, anemia, depression, hospitalization, skilled nursing facility, and length of hospital stay during heart failure hospitalization. An HR/RR of 1 indicated no significant association. COPD, chronic obstructive pulmonary disease.

# Take aways from first question

- Medicare beneficiaries are filling prescriptions at lower rates than we thought based upon registries of prescriptions.
- Beneficiaries don't get treated anywhere close to the guideline-recommended doses used in the RCTs.
- Potential contraindications do not seem to explain the magnitude of difference in prescription rates/fill rates between Medicare and the OPTIMIZE-HF registry.
  - Contraindications did have more of an impact in beneficiaries who did not have any fills before the index hospitalization

Does filling a prescription for a beta blocker have similar associations with lower mortality and hospital readmissions as seen in the clinical trials?

# Methods

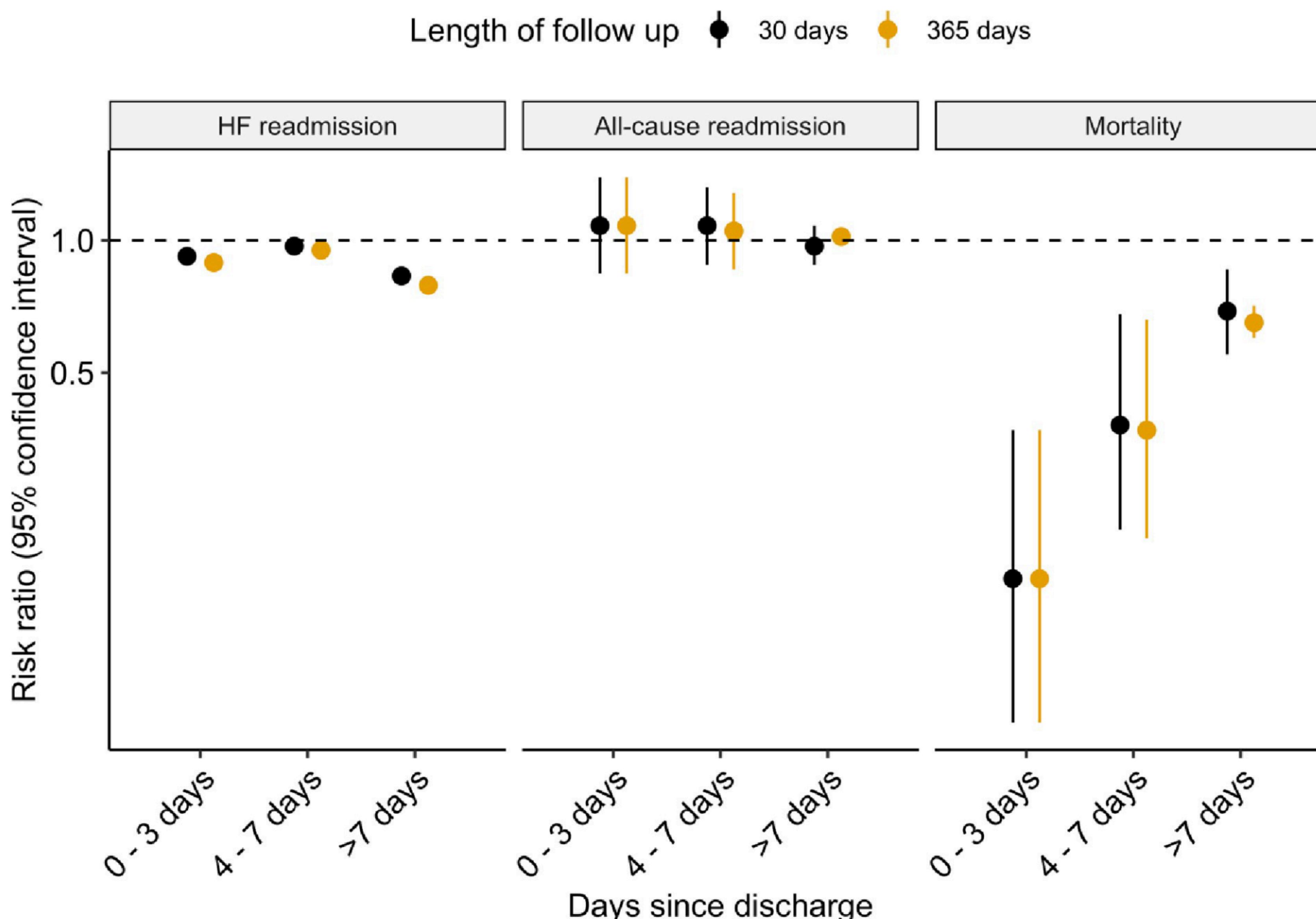
- Outcomes
  - 30-day and 365-day mortality, all-cause readmission, and HF readmission
- Exposure
  - Fill for an evidence-based beta blocker (time-varying; helps with immortal person-time bias)
    - Once a person filled a prescription for a beta blocker, their exposure status did not change
  - Hazard ratio was time-varying (0-3 days, 4-7 days, and >7 days)

# Methods

- Cox regression using the Fine and Gray method to account for competing risks
  - Analyses of HF readmission treated any non-HF readmission or death as a competing risk
  - Analyses of all-cause readmission used death as the competing risk
- Time-varying hazard ratios were used to account for non-proportional hazards concerning the beta blocker fill variable

# Results

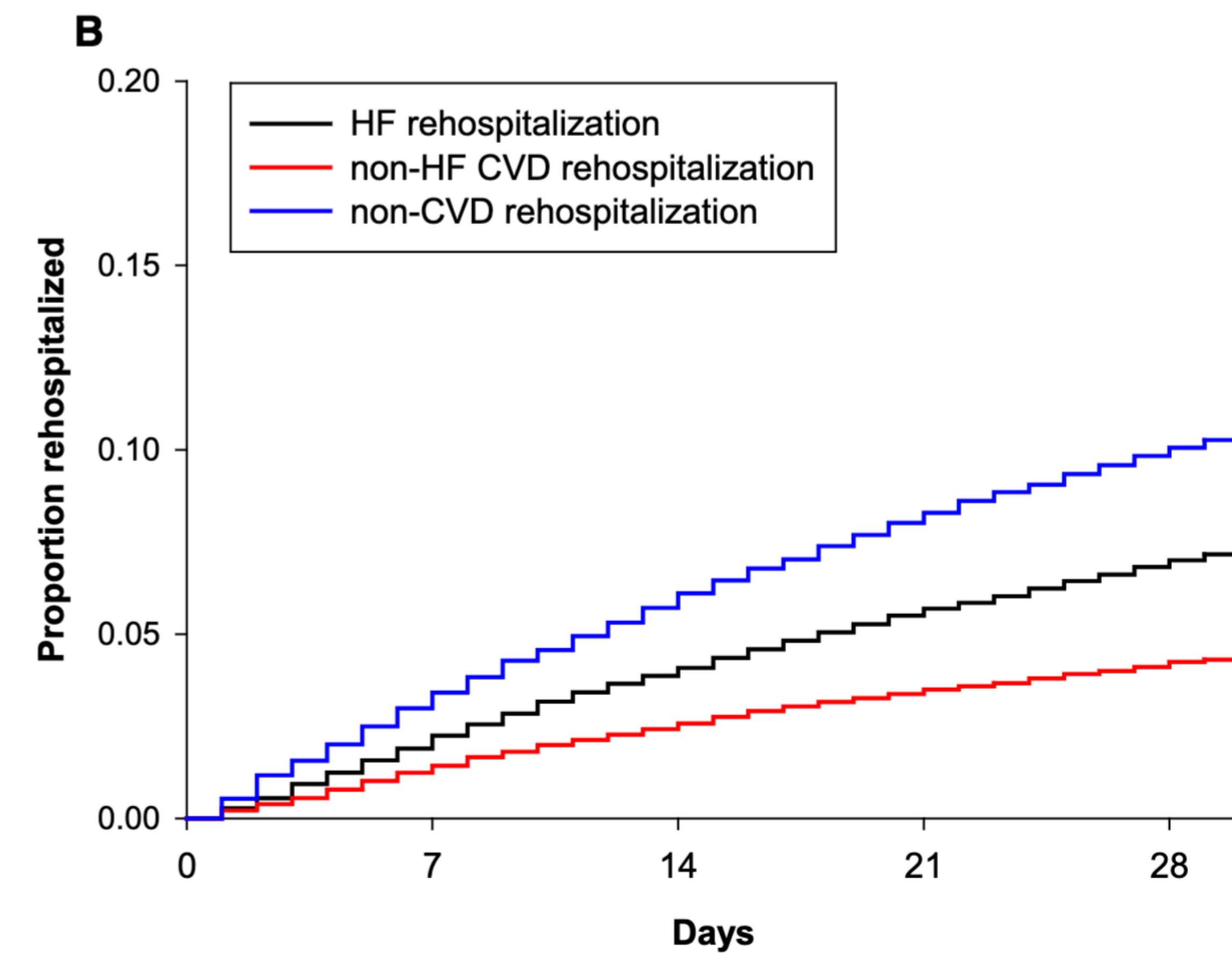
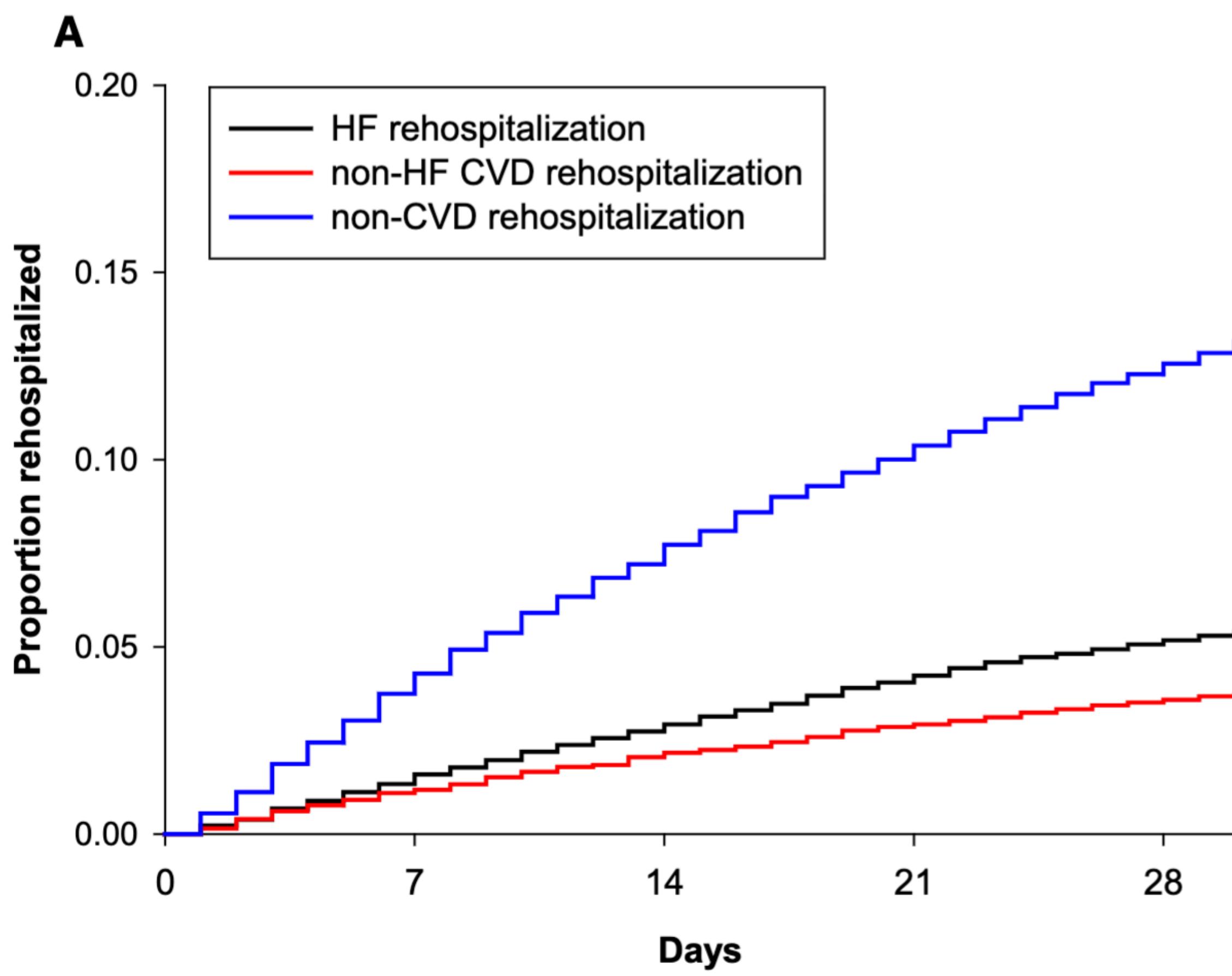
- 12,127 beneficiaries for analysis (of the original 60,640 with any type of HF)
- By 365 days of follow up, 62% of beneficiaries had been readmitted to the hospital and 27% had died.
- Median(IQR) time to filling a prescription for an evidence-based beta blocker was 5(24) days.



**Fig 1. Risk ratios (RRs) and 95% confidence intervals for filling a prescription for carvedilol, bisoprolol, or sustained-release metoprolol succinate after discharge from a hospitalization for heart failure with reduced ejection fraction (HFrEF).** Models were adjusted for age at admission, sex, race, US census region, year of HFrEF hospitalization, as well as several variables assessed during the year prior to hospitalization: type of beta blocker use (evidence-based beta blocker for HFrEF, any other beta blocker, or none), ACEI/ARB use, diuretic use, dual-eligibility, Medicare Part D subsidy, nursing home residence, atrial fibrillation, malnutrition, liver disease, anemia, depression, COPD, Charlson comorbidity index, hospitalization, and a skilled nursing facility (SNF) stay. An RR of 1 indicated no significant association. Although confidence intervals are plotted, the intervals are so narrow that some are hard to see.

# Take aways from second question

- The associations between filling a prescription for a beta blocker and all-cause readmission and mortality (in the >7 day period) resemble the RCT results.
- Almost equal hazards for HF-readmission in those who filled versus didn't fill was unexpected.
- The hazards may have been similar because the proportion of beneficiaries who were kept out of the hospital because of the remodeling effect of the beta blocker was small.



**Figure.** Temporal patterns for causes of readmission among Medicare beneficiaries with HFpEF versus HFrEF. A, Medicare beneficiaries hospitalized for HFpEF. B, Medicare beneficiaries hospitalized for HFrEF. CVD indicates cardiovascular-related; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

# Limitations

- We focused only on beta blockers, not ACE inhibitors, etc.
- We don't know the factors associated with receiving a prescription and not filling it.
- We didn't have access to quantitative measurements about beneficiary health such as ejection fraction.
- Confounding by indication is always a difficult problem.

# Conclusions

- Increasing beta blocker use in Medicare beneficiaries who are currently not filling prescriptions for them may not cause a big reduction in readmissions.
  - The effect of the treatment on the untreated is usually smaller than the effect of the treatment on the treated.
  - Then again, if beneficiaries' doses were increased more aggressively towards the guideline-recommended levels, perhaps those who filled a prescription would be readmitted to the hospital less often.
  - Reducing hospitalizations caused by non-CVD and non-HF causes may have a larger effect on readmissions.

# Acknowledgements

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