Data Analysis for Drug Repurposing for Effective Alzheimer's Medicines – Propranolol/Carvedilol vs Atenolol/Bisoprolol/Sotalol

NCT05794997

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1. Comparison Details

a. Intended aim(s)
To evaluate the comparative risk of dementia onset between patients treated with Propranolol or Carvedilol versus Atenolol, Bisoprolol, Sotalol for hypertension.

b. Primary endpoint
Incident dementia (i.e., Alzheimer's disease, vascular dementia, senile, presenile, or unspecified dementia, or dementia in other diseases classified elsewhere).

2. Person responsible for implementation of replication in Aetion

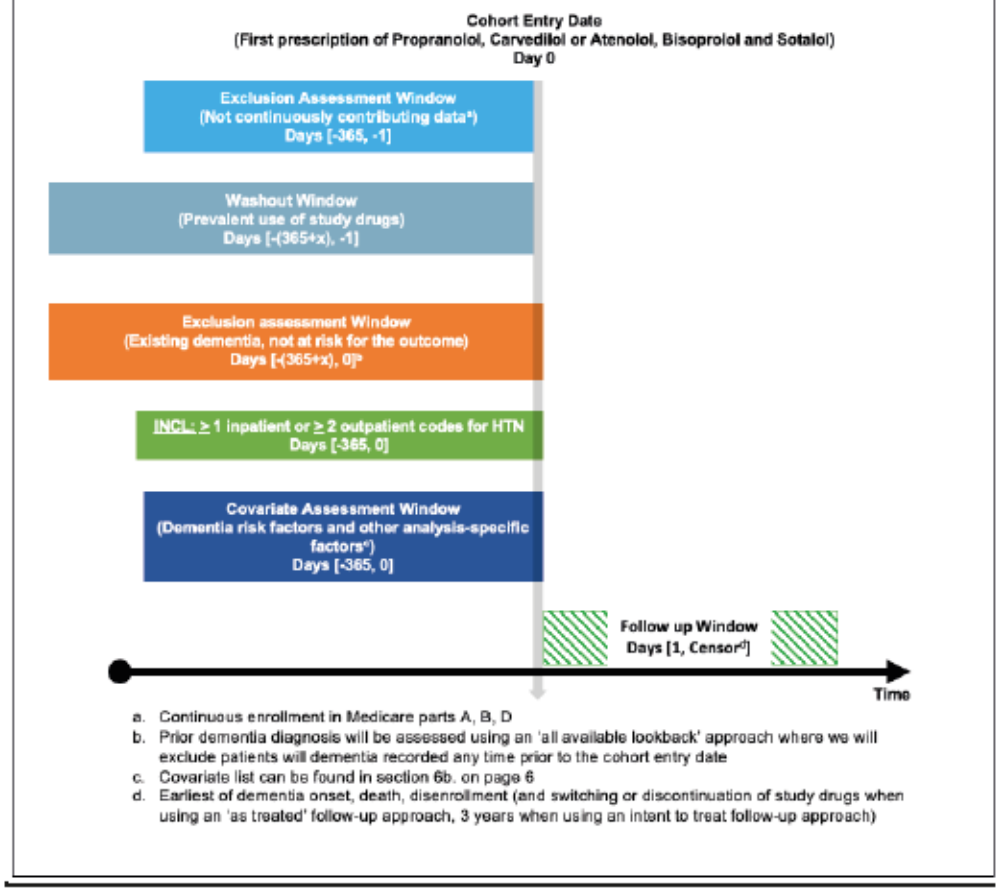
Mufaddal Mahesri

3. Data Source(s)

Medicare, 2008-2019

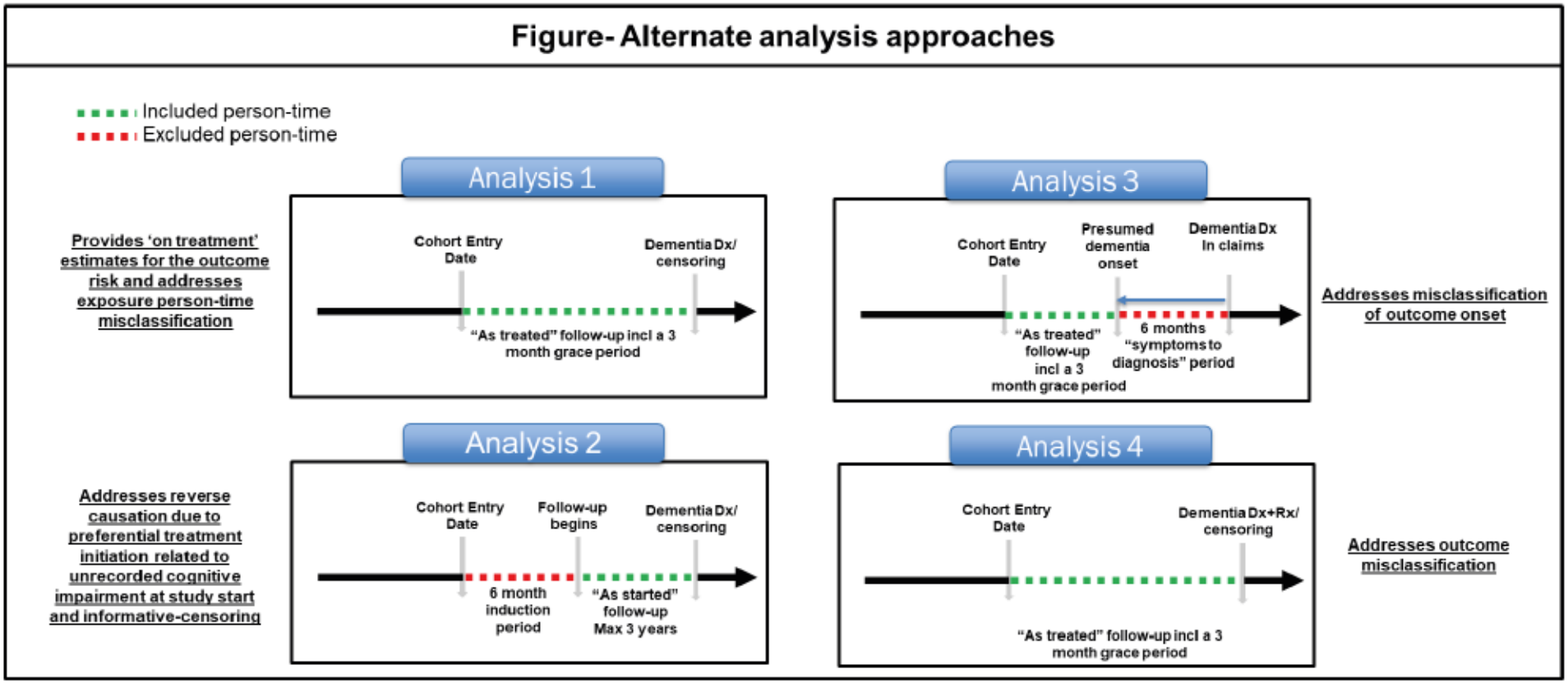
4. Study Design Diagrams

Figure – Basic study design



a. Continuous enrollment in Medicare parts A, B, D
b. Prior dementia diagnosis will be assessed using an 'all available lookback' approach where we will exclude patients will dementia recorded any time prior to the cohort entry date
c. Covariate list can be found in section 6b. on page 6
d. Earliest of dementia onset, death, disenrollment (and switching or discontinuation of study drugs when using an 'as treated' follow-up approach, 3 years when using an intent to treat follow-up approach)

Figure- Alternate analysis approaches



5. Cohort Identification

a. Cohort Summary

This study will employ a new user, active comparator, observational cohort study design comparing Propranolol or Carvedilol to hydrochlorothiazide. The patients will be required to have continuous enrollment during the baseline period of 365 days before initiation of Propranolol or Carvedilol or Atenolol, Bisoprolol or Sotalol (index date). Follow-up for the outcome (dementia) differs between analyses. Follow-up begins the day after drug initiation (analysis 1, 3, 4); 180 days after drug initiation (analysis 2).

b. Key details regarding cohort creation

Index date:

- Day of initiation of new Propranolol or Carvedilol or Atenolol, Bisoprolol or Sotalol use

Inclusion criteria for analyses 1, 3, 4:

- Aged ≥ 65 years on the index date
- 365 days enrollment in Medicare Parts A, B, and D with no HMO coverage
- No use of Propranolol, Carvedilol, Atenolol, Bisoprolol, Sotalol any time prior to index date (all available lookback approach with a minimum of 365 days)
- No use of Propranolol, Carvedilol and Atenolol, Bisoprolol, Sotalol concomitantly on index date
- No diagnosis of dementia any time prior to and including index date
- At least 1 inpatient claim or 2 outpatient claims with hypertension diagnosis recorded in 365 days prior to index date

Inclusion criteria for analysis 2:

- Aged ≥ 65 years on the index date
- 365 days enrollment in Medicare Parts A, B, and D with no HMO coverage
- No use of Propranolol, Carvedilol, Atenolol, Bisoprolol, Sotalol any time prior to index date (all available lookback approach with a minimum of 365 days)
- No use of Propranolol, Carvedilol and Atenolol, Bisoprolol, Sotalol concomitantly on index date
- No diagnosis of dementia any time prior to and including index date
- At least 1 inpatient claim or 2 outpatient claims with hypertension diagnosis recorded in 365 days prior to index

date

- 180-day continuous use of Propranolol or Carvedilol or Atenolol, Bisoprolol, Sotalol starting on the index date

c. Flowchart of the study cohort assembly

	Less Excluded Patients	Remaining Patients
All patients		27,099,355
Did not meet cohort entry criteria	-20,951,408	6,147,947
Excluded due to insufficient enrollment	-2,442,601	3,705,346
Excluded due to prior use of referent	-1,096,162	2,609,184
Excluded due to prior use of exposure	-1,644,383	964,801
Excluded because patient qualified in >1 exposure category	-88	964,713
Excluded based on Dementia Exclusion	-55,850	908,863
Excluded based on Nursing home admission	-46,478	862,385
Excluded based on Propranolol/Carvedilol OR Atenolol / Bisoprolol / Sotalol Copy	-27,923	834,462
Excluded based on Propranolol / Carvedilol AND Atenolol / Bisoprolol / Sotalol concomitantly on index date Copy	0	834,462
Excluded based on Hypertension: 1 inpatient or 2 outpatient claims within 365 days	-15,211	819,251
Excluded based on Age < 65 years	-1,914	817,337
Final cohort		817,337

6. Variables

a. Exposure-related variables:

Study drug:
The study exposure of interest is initiation of Propranolol or Carvedilol

Comparator:
Initiation of Atenolol, Bisoprolol or Sotalol

b. Covariates:

Demographics	
Age	Region
Gender	Calendar year of index date
Race	Low income subsidy

Dementia risk factors	
Diabetes	Anxiety
Obesity	Bipolar disorder
Coronary artery disease	Schizophrenia
Depression	

Markers for healthy behavior, frailty, healthcare use	
Smoking	Number of hospitalizations
Mammography	Number of physician office visits
Colonoscopy	Number of serum creatinine tests ordered
Fecal occult blood test	Composite frailty score
Influenza vaccination	Number of C-reactive protein tests ordered
Pneumococcal vaccination	Osteoporosis
Herpes zoster vaccination	Fractures

Bone mineral density test	Falls
Number of distinct generic agents	Use of supplemental oxygen
Number of emergency room visits	Combined comorbidity score
Number of outpatient visits	Number of Cardiologist visits

Comedication use	
Lithium	Nitrates
Anti-epileptic mood stabilizers	Lipid lowering drugs
Anti-epileptics (other than mood stabilizers)	Non-insulin diabetes medications
Atypical antipsychotics	Insulin
Benzodiazepines	Antidepressants
Serotonin-norepinephrine reuptake Inhibitors	Typical antipsychotics
Selective serotonin reuptake inhibitors	Anticoagulants
Tricyclic antidepressants (TCAs)	Antiplatelet agents

Comorbid conditions	
Atrial fibrillation	Chronic liver disease
Coronary artery disease	Asthma
Heart failure	Ischemic heart disease
Stroke or transient ischemic attack	Chronic obstructive pulmonary disease
Peripheral vascular disease	Malignancy
Hyperlipidemia	Drug or alcohol abuse or dependence
Renal dysfunction	Venous thromboembolism

ICD-9, ICD-10, HCPCS, and NDC codes used to define the covariates listed above are available in Appendix A.

c. Outcome variables and study follow-up:

- **Primary outcome**: incident dementia, i.e., Alzheimer's disease, vascular dementia, senile, presenile, or unspecified dementia, or dementia in other diseases classified elsewhere. Outcome will be defined by 1 inpatient claim or 2 outpatient claims in analysis 1, 2, 3. In analysis 4, the outcome will be defined by 1 inpatient or 1 outpatient claims and 1 prescription claim for a symptomatic treatment [donepezil, galantamine, rivastigmine, and memantine] within 6 months of each other with outcome date assigned to second event in the sequence.

- Secondary outcomes: Individual component:
  Alzheimer's disease

Condition	ICD-9 and ICD-10 codes
Alzheimer's disease	331.0*, F00*, G30*
Vascular dementia	290.4*, F01*
Senile, presenile, or unspecified dementia	290.0*, 290.1*. 290.3*, 797*, F03*
Dementia in other diseases classified elsewhere	331.1*, 331.2*, 331.7*, 294.1*, F02*

For analysis 1,3, and 4 the follow-up will start the day after initiation of Propranolol or Carvedilol and Atenolol, Bisoprolol or Sotalol and will continue until the earliest date of the following events:

- The first occurrence of the outcome of interest
- The date of end of continuous registration in the database,
- End of the study period,
- Measured death event occurs,
- The date of drug discontinuation, defined as the date of the last continuous treatment episode of the index drug (Propranolol or Carvedilol and hydrochlorothiazide) plus a defined grace period (i.e., 90 days after the end of the last prescription's days' supply in main analyses).

For analysis 2, the follow-up will start 180 days after initiation of Propranolol or Carvedilol and Atenolol, Bisoprolol or Sotalol and will continue until the earliest date of the following events:

- The first occurrence of the outcome of interest, unless otherwise specified for selected outcomes,
- The date of end of continuous registration in the database,
- End of the study period,
- Measured death event occurs,
- Maximum allowed follow-up time (1095 days) reached

7. Propensity score analysis

We will use a propensity-score (PS)[1]-based approach to account for measured confounding in this study. The PS will be calculated as the predicted probability of initiating the exposure of interest (i.e., the repurposing candidate) versus the reference drug conditional on baseline covariates using multivariable logistic regression constructed separately in each data source. On average, patients with similar PSs have similar distribution of potential confounders used to estimate the PS. Therefore, analyses conditioned on the PS provide effect estimates that are free from measured confounding. For all our analyses, initiators of each exposure of interest will be matched with initiators of the reference exposure based on their PS within each data source.[2] Pair matching will be conducted using a nearest-neighbor algorithm, which seeks to minimize the distance between propensity scores in each pair of treated and reference patients,[3] and a caliper of 0.025 on the natural scale of the PS will be used to ensure similarity between the matched patients.[4]

We report multiple diagnostics for PS analysis in this protocol. First, the PS distributional overlap is provided between two groups before and after matching to ensure comparability of these groups.[5] Next, balance in each individual covariate between two treatment groups is reported using standardized differences.[6]

8. Table for covariate balance

	Crude			PS-Matched		
Variable	Propranolol and Carvedilol (N = 583,870)	Atenolol, Bisoprolol, Sotalol (N = 233,467)	St. Diff	Propranolol and Carvedilol (N = 222,015)	Atenolol, Bisoprolol, Sotalol (N = 222,015)	St. Diff
Demographics						
Age, mean (SD)	75.02 (7.00)	74.75 (6.77)	0.04	74.77 (6.82)	74.75 (6.78)	0.00
Gender, n (%)						
Male	281,232 (48.2%)	97,628 (41.8%)	0.13	93,749 (42.2%)	94,142 (42.4%)	0.00
Female	302,638 (51.8%)	135,839 (58.2%)	-0.13	128,266 (57.8%)	127,873 (57.6%)	0.00
Race, n (%)						
White	451,438 (77.3%)	186,360 (79.8%)	-0.06	177,198 (79.8%)	176,941 (79.7%)	0.00
Black	79,181 (13.6%)	23,050 (9.9%)	0.12	22,448 (10.1%)	22,557 (10.2%)	0.00
Hispanic	18,869 (3.2%)	7,616 (3.3%)	-0.01	7,289 (3.3%)	7,209 (3.2%)	0.01
Asian	16,471 (2.8%)	8,738 (3.7%)	-0.05	7,954 (3.6%)	8,042 (3.6%)	0.00
North American Native	3,845 (0.7%)	1,494 (0.6%)	0.01	1,347 (0.6%)	1,426 (0.6%)	0.00
Other	10,192 (1.7%)	4,575 (2.0%)	-0.02	4,242 (1.9%)	4,273 (1.9%)	0.00
Unknown	3,874 (0.7%)	1,634 (0.7%)	0.00	1,537 (0.7%)	1,567 (0.7%)	0.00
Region, n (%)						
Northeast; n (%)	79,800 (13.7%)	41,038 (17.6%)	-0.11	37,554 (16.9%)	37,805 (17.0%)	0.00
South; n (%)	275,558 (47.2%)	102,251 (43.8%)	0.07	99,500 (44.8%)	98,821 (44.5%)	0.01
Midwest; n (%)	127,682 (21.9%)	49,611 (21.2%)	0.02	47,379 (21.3%)	47,515 (21.4%)	0.00
West; n (%)	99,172 (17.0%)	39,516 (16.9%)	0.00	37,582 (16.9%)	37,874 (17.1%)	-0.01
Other; n (%)	1,658 (0.3%)	1,051 (0.5%)	-0.03			
Calendar year of index date, n (%)						
2008	41,242 (7.1%)	22,822 (9.8%)	-0.10	21,021 (9.5%)	20,784 (9.4%)	0.00

2009	41,633 (7.1%)	23,317 (10.0%)	-0.10	21,612 (9.7%)	21,325 (9.6%)	0.00
2010	33,970 (5.8%)	14,179 (6.1%)	-0.01	13,633 (6.1%)	13,538 (6.1%)	0.00
2011	31,276 (5.4%)	12,573 (5.4%)	0.00	12,160 (5.5%)	12,081 (5.4%)	0.00
2012	29,262 (5.0%)	11,653 (5.0%)	0.00	11,275 (5.1%)	11,283 (5.1%)	0.00
2013	79,415 (13.6%)	36,290 (15.5%)	-0.05	34,117 (15.4%)	34,212 (15.4%)	0.00
2014	77,490 (13.3%)	32,016 (13.7%)	-0.01	30,163 (13.6%)	30,408 (13.7%)	0.00
2015	71,638 (12.3%)	27,434 (11.8%)	0.02	26,098 (11.8%)	26,324 (11.9%)	0.00
2016	48,353 (8.3%)	15,916 (6.8%)	0.06	15,423 (6.9%)	15,491 (7.0%)	0.00
2017	42,820 (7.3%)	12,385 (5.3%)	0.08	12,062 (5.4%)	12,146 (5.5%)	0.00
2018	44,058 (7.5%)	12,714 (5.4%)	0.09	12,447 (5.6%)	12,493 (5.6%)	0.00
2019	42,713 (7.3%)	12,168 (5.2%)	0.09	12,004 (5.4%)	11,930 (5.4%)	0.00
Low income subsidy, n (%)	163,393 (28.0%)	60,269 (25.8%)	0.05	58,330 (26.3%)	58,026 (26.1%)	0.00
Dementia risk factors, n (%)						
Anxiety	88,780 (15.2%)	33,787 (14.5%)	0.02	32,757 (14.8%)	32,295 (14.5%)	0.01
Bipolar disorder	6,969 (1.2%)	2,315 (1.0%)	0.02	2,299 (1.0%)	2,263 (1.0%)	0.00
Coronary artery disease	333,862 (57.2%)	99,371 (42.6%)	0.30	96,483 (43.5%)	96,613 (43.5%)	0.00
Depression	93,473 (16.0%)	33,665 (14.4%)	0.04	32,918 (14.8%)	32,329 (14.6%)	0.01
Diabetes, n (%)	451,149 (77.3%)	176,186 (75.5%)		168,274 (75.8%)	168,200 (75.8%)	0.00
Obesity	148,289 (25.4%)	50,211 (21.5%)	0.09	48,216 (21.7%)	48,375 (21.8%)	0.00
Schizophrenia	3,054 (0.5%)	1,101 (0.5%)	0.00	1,045 (0.5%)	1,064 (0.5%)	0.00
Markers for healthy behavior, frailty, healthcare use						
Bone mineral density test, n (%)	247 (0.0%)	135 (0.1%)	-0.04	141 (0.1%)	123 (0.1%)	0.00
Colonoscopy, n (%)	64,492 (11.0%)	26,148 (11.2%)	-0.01	24,751 (11.1%)	24,752 (11.1%)	0.00
Fecal occult blood test, n (%)	43,860 (7.5%)	19,665 (8.4%)	-0.03	18,342 (8.3%)	18,285 (8.2%)	0.00
Influenza vaccination, n (%)	355,785 (60.9%)	143,137 (61.3%)	-0.01	136,240 (61.4%)	136,167 (61.3%)	0.00

Mammography, n (%)	87,549 (15.0%)	43,295 (18.5%)	-0.09	40,715 (18.3%)	40,590 (18.3%)	0.00
Pneumococcal vaccination, n (%)	169,570 (29.0%)	55,949 (24.0%)	0.11	54,070 (24.4%)	54,269 (24.4%)	0.00
Smoking, n (%)	177,079 (30.3%)	54,670 (23.4%)	0.16	52,411 (23.6%)	52,816 (23.8%)	0.00
Number of C-reactive protein tests ordered, mean (SD)	0.21 (0.81)	0.21 (0.81)	0.00	0.21 (0.86)	0.21 (0.80)	0.00
Number of emergency room visits, mean (SD)	1.87 (3.20)	1.50 (2.71)	0.12	1.51 (3.04)	1.51 (2.69)	0.00
Number of distinct prescriptions, mean (SD)	14.66 (6.45)	13.23 (6.36)	0.22	13.44 (6.02)	13.34 (6.39)	0.02
Number of hospitalizations, mean (SD)	0.90 (1.23)	0.61 (1.02)	0.26	0.61 (1.00)	0.62 (1.03)	-0.01
Number of outpatient visits, mean (SD)	14.81 (17.01)	15.01 (18.07)	-0.01	15.04 (19.64)	14.87 (17.37)	0.01
Number of physician office visits, mean (SD)	5.43 (10.24)	5.76 (11.48)	-0.03	5.77 (12.39)	5.68 (10.95)	0.01
Number of Cardiologist visits, mean(SD)	4.28 (5.14)	3.70 (5.00)	0.11	3.66 (4.93)	3.67 (4.98)	0.00
Number of serum creatinine tests ordered, mean (SD)	4.37 (3.94)	3.85 (3.32)	0.14	3.90 (3.48)	3.88 (3.34)	0.01
Composite frailty score, mean (SD)	0.22 (0.06)	0.20 (0.06)	0.33	0.20 (0.06)	0.20 (0.06)	0.00
Falls, n (%)	29,969 (5.1%)	10,173 (4.4%)	0.03	9,818 (4.4%)	9,782 (4.4%)	0.00
Fractures, n (%)	41,635 (7.1%)	15,605 (6.7%)	0.02	14,813 (6.7%)	14,855 (6.7%)	0.00
Osteoporosis, n (%)	63,351 (10.9%)	28,996 (12.4%)	-0.05	27,367 (12.3%)	27,019 (12.2%)	0.00
Use of supplemental oxygen, n (%)	21,888 (3.7%)	5,840 (2.5%)	0.07	5,735 (2.6%)	5,696 (2.6%)	0.00
Combined comorbidity score, mean (SD)	5.66 (3.07)	4.41 (2.76)	0.43	4.48 (2.71)	4.47 (2.79)	0.00
Comedication use, n (%)						

Antidepressants	155,811 (26.7%)	57,867 (24.8%)	0.04	56,683 (25.5%)	55,691 (25.1%)	0.01
Insulin	136,095 (23.3%)	36,934 (15.8%)	0.19	36,455 (16.4%)	36,240 (16.3%)	0.00
Lipid lowering drugs	443,656 (76.0%)	163,735 (70.1%)	0.13	157,484 (70.9%)	157,194 (70.8%)	0.00
Nitrates	128,629 (22.0%)	33,284 (14.3%)	0.20	32,638 (14.7%)	32,626 (14.7%)	0.00
Non-insulin diabetes medications	310,939 (53.3%)	122,525 (52.5%)	0.02	117,674 (53.0%)	117,427 (52.9%)	0.00
Anticoagulants	107,632 (18.4%)	55,118 (23.6%)	-0.13	49,968 (22.5%)	49,752 (22.4%)	0.00
Anti-epileptic mood stabilizers	8,005 (1.4%)	2,725 (1.2%)	0.02	2,764 (1.2%)	2,658 (1.2%)	0.00
Antiplatelet agents	146,057 (25.0%)	38,480 (16.5%)	0.21	37,748 (17.0%)	37,750 (17.0%)	0.00
Atypical antipsychotics	11,643 (2.0%)	4,105 (1.8%)	0.01	4,059 (1.8%)	3,978 (1.8%)	0.00
Benzodiazepines	74,533 (12.8%)	28,965 (12.4%)	0.01	28,241 (12.7%)	27,664 (12.5%)	0.01
Lithium	797 (0.1%)	237 (0.1%)	0.00	228 (0.1%)	233 (0.1%)	0.00
Anti-epileptics (other than mood stabilizers)	108,520 (18.6%)	35,720 (15.3%)	0.09	35,144 (15.8%)	34,621 (15.6%)	0.01
Serotonin-norepinephrine reuptake inhibitors	29,400 (5.0%)	10,743 (4.6%)	0.02	10,731 (4.8%)	10,428 (4.7%)	0.00
Selective serotonin reuptake inhibitors	93,719 (16.1%)	34,751 (14.9%)	0.03	33,965 (15.3%)	33,404 (15.0%)	0.01
Tricyclic antidepressants (TCAs)	25,906 (4.4%)	10,286 (4.4%)	0.00	10,022 (4.5%)	9,858 (4.4%)	0.00
Typical antipsychotics	2,396 (0.4%)	942 (0.4%)	0.00	924 (0.4%)	905 (0.4%)	0.00
Comorbid conditions, n (%)						
Atrial fibrillation	153,296 (26.3%)	79,342 (34.0%)	-0.17	71,905 (32.4%)	71,714 (32.3%)	0.00
Asthma	104,291 (17.9%)	35,409 (15.2%)	0.07	34,135 (15.4%)	33,885 (15.3%)	0.00
Chronic obstructive pulmonary disease	175,599 (30.1%)	58,758 (25.2%)	0.11	56,819 (25.6%)	56,347 (25.4%)	0.00
Chronic liver disease	52,786 (9.0%)	17,419 (7.5%)	0.05	16,869 (7.6%)	16,796 (7.6%)	0.00

Drug or alcohol abuse or dependence	77,453 (13.3%)	23,239 (10.0%)	0.10	22,489 (10.1%)	22,579 (10.2%)	0.00
Heart failure	279,855 (47.9%)	60,940 (26.1%)	0.46	60,752 (27.4%)	60,584 (27.3%)	0.00
Hyperlipidemia	510,009 (87.3%)	201,744 (86.4%)	0.03	192,105 (86.5%)	191,970 (86.5%)	0.00
Ischemic heart disease	348,401 (59.7%)	107,358 (46.0%)	0.28	104,109 (46.9%)	104,139 (46.9%)	0.00
Malignancy	156,428 (26.8%)	62,247 (26.7%)	0.00	59,313 (26.7%)	58,882 (26.5%)	0.00
Peripheral vascular disease	129,600 (22.2%)	40,710 (17.4%)	0.12	39,670 (17.9%)	39,327 (17.7%)	0.01
Renal dysfunction	236,212 (40.5%)	56,863 (24.4%)	0.35	56,068 (25.3%)	56,128 (25.3%)	0.00
Stroke or transient ischemic attack	68,173 (11.7%)	23,278 (10.0%)	0.05	22,586 (10.2%)	22,216 (10.0%)	0.01
Venous thromboembolism	37,549 (6.4%)	11,617 (5.0%)	0.06	11,391 (5.1%)	11,122 (5.0%)	0.00

9. Statistical analysis plans

Incidence rates for the outcome will be estimated for the treatment and reference groups before and after PS matching. The competing risk of death could be of concern for the current set of analyses if mortality is frequent among patients included in the cohort and if differences in the risk of mortality between treatment and reference groups are substantial. In the PS-matched sample, we will use cause-specific hazard models[7] to provide hazard ratios averaged over the entire follow-up period as well as interval specific hazard ratios (1, 2, and 3 years) for the association between the treatment of interest and risk of ADRD after considering all-cause mortality as a competing event. Pre-specified subgroup analyses will be conducted based on age, sex, and baseline cardiovascular disease. In addition to the Medicare dataset, we will pursue a similar analysis within Clinical Practice Research Datalink (CPRD), a UK population health dataset, to validate our results.

10. References

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