Data Analysis for Drug Repurposing for Effective Alzheimer's Medicines – Pentoxifylline vs Cilostazol

NCT05635370

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1. Comparison Details

a. Intended aim(s)

To evaluate the comparative risk of dementia onset between patients treated with Pentoxifylline versus cilostazol for peripheral artery disease (PAD).

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

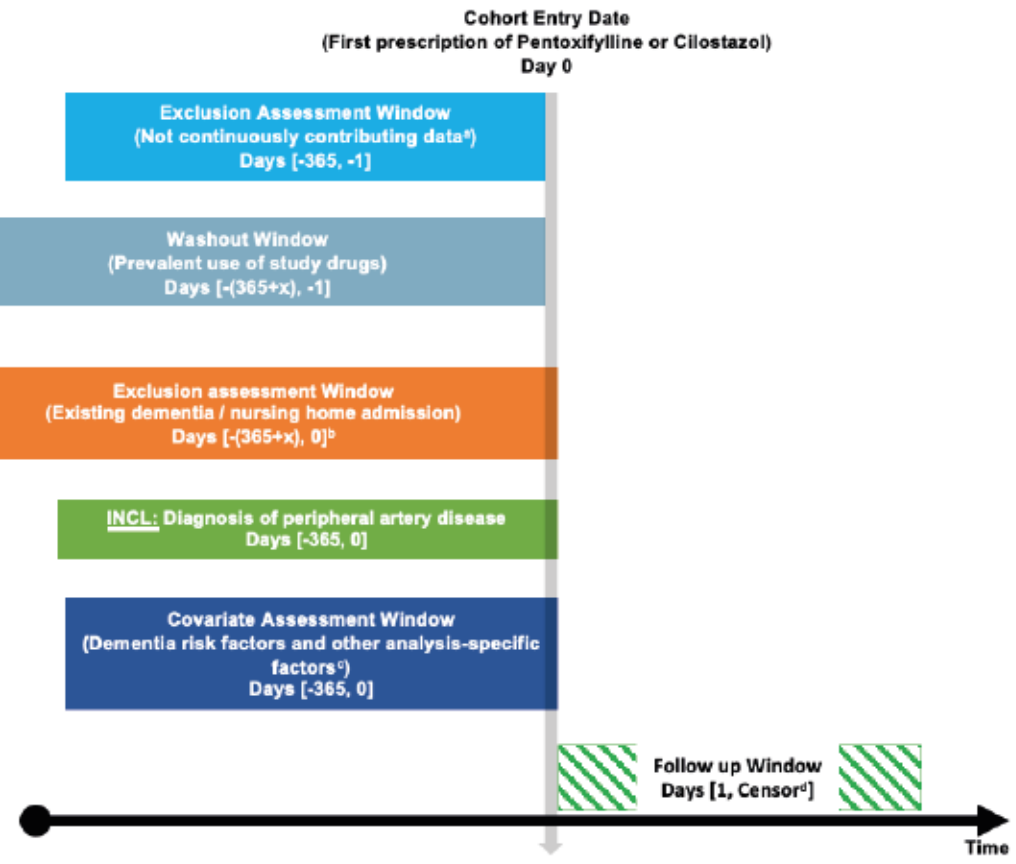
Seanna Vine

3. Data Source(s)

Medicare, 2008-2018

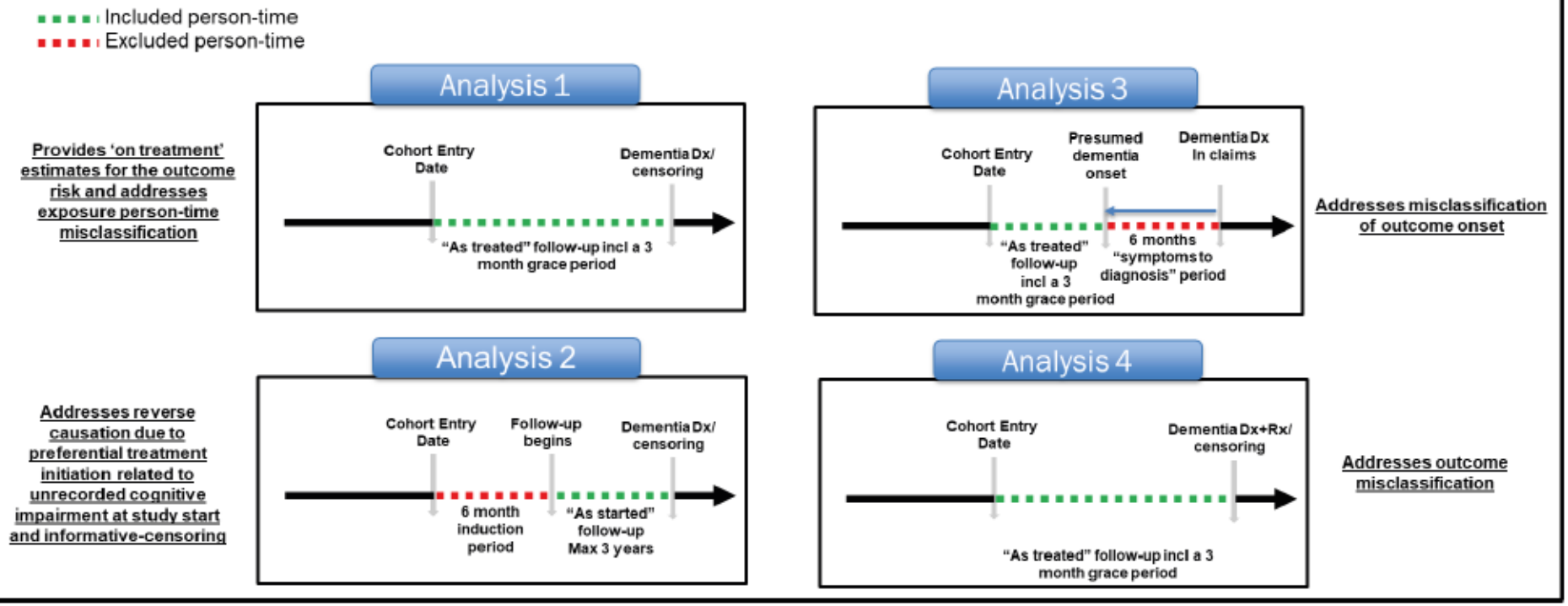
4. Study Design Diagrams

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 Pentoxifylline versus Cilostazol. The patients will be required to have continuous enrollment during the baseline period of 365 days before initiation of study drugs (cohort entry/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 Pentoxifylline versus Cilostazol 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 prior to index date
- No use of Pentoxifylline versus Cilostazol, any time prior to index date (all available lookback approach with a minimum of 365 days)
- No diagnosis of dementia any time prior to and including index date
- No history of nursing home admission recorded in any time prior to and including index date
- At least two claims with peripheral artery disease diagnosis recorded in 365 days prior to index date (ICD-9 or ICD-10 codes)[1]

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 prior to index date
- No use of Pentoxifylline versus Cilostazol, any time prior to index date (all available lookback approach with a minimum of 365 days)
- No diagnosis of dementia any time prior to and including index date
- No history of nursing home admission recorded in any time prior to and including index date
- At least two claims with peripheral artery disease diagnosis recorded in 365 days prior to index date (ICD-9 or ICD-10 codes)[1]

- 180-day continuous use of Pentoxifylline versus Cilostazol starting on the index date

c. Flowchart of the study cohort assembly

	Less Excluded Patients	Remaining Patients
All patients		23,466,175
Did not meet cohort entry criteria	-23,393,311	72,864
Excluded due to insufficient enrollment	-45,683	27,181
Excluded based on Dementia Exclusion	-6,100	21,081
Excluded based on Nursing Home Admission	-4,080	17,001
Excluded based on Peripheral artery disease Diagnosis	-4,524	12,477
Excluded anyone aged <65 at index	-2,079	10,398
Patients in Pentoxifylline group		1,701
Patients in Cilostazol group		8,697
Final cohort		10,398

6. Variables

a. Exposure-related variables:

Study drug:
The study exposure of interest is initiation of Pentoxifylline

Comparator:
Cilostazol

b. Covariates:

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

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

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	

Comedication use	
Lithium	Diuretics
Anti-epileptic mood stabilizers	Nitrates
Anti-epileptics (other than mood stabilizers)	Lipid lowering drugs

Atypical antipsychotics	Non-insulin diabetes medications
Benzodiazepines	Insulin
Serotonin-norepinephrine reuptake Inhibitors	Antidepressants
Selective serotonin reuptake inhibitors	Angiotensin II receptor blockers (ARBs)
Tricyclic antidepressants (TCAs)	Angiotensin converting enzyme inhibitors (ACEi)
Typical antipsychotics	Calcium channel blockers
Anticoagulants	Beta blockers
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
Rheumatoid Arthritis	Hypertension

Other PAD treatments and PAD severity indicators	
Critical limb ischemia	Number of cardiologist visits
Thrombolytic therapy (streptokinase, urokinase, alteplase, tissue plasminogen activator (tPA), pro-urokinase, reteplase, tenecteplase and Staphylokinase)	Number of hospitalizations with PAD

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 Pentoxifylline and Cilostazol 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 (Pentoxifylline and Cilostazol) 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 Pentoxifylline and Cilostazol 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)[2]-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.[3] 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,[4] and a caliper of 0.025 on the natural scale of the PS will be used to ensure similarity between the matched patients.[5]

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.[6] Next, balance in each individual covariate between two treatment groups is reported using standardized differences.[7]

8. Table for covariate balance

	Crude			PS-Matched		
Variable	**Pentoxifylline (N = 1,701)**	**Cilostazol (N = 8,697)**	**St. Diff**	**Pentoxifylline (N = 1,687)**	**Cilostazol (N = 1,687)**	**St. Diff**
Demographics						
Age, mean (SD)	76.2 (7.3)	75.3 (6.9)	0.13	76.2 (7.2)	76.3 (7.2)	-0.01
Gender, n (%)						
Male	828 (48.7)	4733 (54.4)	-0.12	822 (48.7)	827 (49)	-0.01
Female	873 (51.3)	3964 (45.6)	0.12	865 (51.3)	860 (51)	0.01
Race, n (%)						
White	1386 (81.5)	7096 (81.6)	0.00	1377 (81.6)	1347 (79.8)	0.05
Black	156 (9.2)	935 (10.8)	-0.05	156 (9.2)	176 (10.4)	-0.04
Hispanic	70 (4.1)	237 (2.7)	0.08	67 (4)	65 (3.9)	0.01
Other	89 (5.2)	429 (4.9)	0.01	87 (5.2)	99 (5.9)	-0.03
Region, n (%)						
Northeast; n (%)	274 (16.1)	1697 (19.5)	-0.09	272 (16.1)	288 (17.1)	-0.03
South; n (%)	795 (46.7)	3749 (43.1)	0.07	788 (46.7)	779 (46.2)	0.01
Midwest; n (%)	354 (20.8)	2069 (23.8)	-0.07	353 (20.9)	337 (20)	0.02
West; n (%)	273 (16)	1171 (13.5)	0.07	269 (15.9)	279 (16.5)	-0.02
Other; n (%)	5 (0.3)	11 (0.1)	0.04	5 (0.3)	4 (0.2)	0.01
Calendar year of index date, n (%)						
2014	444 (26.1)	2016 (23.2)	0.07	436 (25.8)	435 (25.8)	0.00
2015	338 (19.9)	1908 (21.9)	-0.05	336 (19.9)	310 (18.4)	0.04
2016	335 (19.7)	1713 (19.7)	0.00	335 (19.9)	349 (20.7)	-0.02
2017	303 (17.8)	1606 (18.5)	-0.02	300 (17.8)	296 (17.5)	0.01

2018	281 (16.5)	1454 (16.7)	-0.01	280 (16.6)	297 (17.6)	-0.03
Low income subsidy, n (%)	464 (27.3)	2035 (23.4)	0.09	459 (27.2)	492 (29.2)	-0.04
Dementia risk factors, n (%)						
Anxiety	247 (14.5)	1090 (12.5)	0.06	245 (14.5)	236 (14)	0.02
Bipolar disorder	15 (0.9)	67 (0.8)	0.01	15 (0.9)	13 (0.8)	0.01
Coronary artery disease	800 (47)	4789 (55.1)	-0.16	792 (46.9)	790 (46.8)	0.00
Depression	240 (14.1)	1027 (11.8)	0.07	236 (14)	226 (13.4)	0.02
Diabetes	826 (48.6)	4211 (48.4)	0.00	819 (48.5)	852 (50.5)	-0.04
Hypertension	1512 (88.9)	8055 (92.6)	-0.13	1500 (88.9)	1502 (89)	0.00
Obesity	325 (19.1)	1373 (15.8)	0.09	321 (19)	308 (18.3)	0.02
Schizophrenia	2 (0.1)	8 (0.1)	0.01			0.00
Markers for healthy behavior, frailty, healthcare use						
Bone mineral density test, n (%)	141 (8.3)	725 (8.3)	0.00	139 (8.2)	130 (7.7)	0.02
Colonoscopy, n (%)	143 (8.4)	861 (9.9)	-0.05	141 (8.4)	148 (8.8)	-0.02
Fecal occult blood test, n (%)	132 (7.8)	696 (8)	-0.01	131 (7.8)	131 (7.8)	0.00
Influenza vaccination, n (%)	1035 (60.8)	5419 (62.3)	-0.03	1026 (60.8)	978 (58)	0.06
Mammography, n (%)	281 (16.5)	1455 (16.7)	-0.01	279 (16.5)	283 (16.8)	-0.01
Pneumococcal vaccination, n (%)	652 (38.3)	3612 (41.5)	-0.07	649 (38.5)	621 (36.8)	0.03
Smoking, n (%)	599 (35.2)	3881 (44.6)	-0.19	595 (35.3)	580 (34.4)	0.02
Number of C-reactive protein tests ordered, mean (SD)	0.3 (1.2)	0.2 (0.7)	0.13	0.3 (0.9)	0.3 (1)	-0.02
Number of emergency room visits, mean (SD)	0.8 (1.4)	0.7 (1.3)	0.08	0.7 (1.4)	0.7 (1.4)	0.00
Number of distinct prescriptions, mean (SD)	13.9 (6.7)	12.4 (5.9)	0.23	13.7 (6.6)	13.8 (6.7)	0.00

Number of hospitalizations, mean (SD)	0.3 (0.7)	0.2 (0.6)	0.09	0.3 (0.7)	0.3 (0.6)	0.01
Number of outpatient visits, mean (SD)	15 (10.6)	13.1 (8.6)	0.20	14.8 (10.1)	14.9 (10)	-0.01
Number of serum creatinine tests ordered, mean (SD)	1.6 (2.7)	1.5 (2.3)	0.01	1.6 (2.7)	1.5 (2.2)	0.02
Composite frailty score, mean (SD)	0.2 (0.1)	0.2 (0.1)	0.21	0.2 (0.1)	0.2 (0.1)	0.02
Falls, n (%)	107 (6.3)	472 (5.4)	0.04	107 (6.3)	108 (6.4)	0.00
Fractures, n (%)	141 (8.3)	591 (6.8)	0.06	139 (8.2)	138 (8.2)	0.00
Osteoporosis, n (%)	247 (14.5)	1051 (12.1)	0.07	242 (14.3)	239 (14.2)	0.01
Use of supplemental oxygen, n (%)	26 (1.5)	150 (1.7)	-0.02	26 (1.5)	23 (1.4)	0.02
Combined comorbidity score, mean (SD)	3.4 (2.8)	2.9 (2.4)	0.18	3.3 (2.7)	3.4 (2.6)	-0.02
Comedication use, n (%)						
Angiotensin converting enzyme inhibitors (ACEi)	646 (38)	3657 (42)	-0.08	643 (38.1)	641 (38)	0.00
Angiotensin II receptor blockers (ARBs)	488 (28.7)	2519 (29)	-0.01	485 (28.7)	482 (28.6)	0.00
Antidepressants	435 (25.6)	2046 (23.5)	0.05	430 (25.5)	416 (24.7)	0.02
Beta blockers	894 (52.6)	4801 (55.2)	-0.05	887 (52.6)	884 (52.4)	0.00
Calcium channel blockers	593 (34.9)	3243 (37.3)	-0.05	588 (34.9)	590 (35)	0.00
DMARD	86 (5.1)	212 (2.4)	0.14	80 (4.7)	81 (4.8)	0.00
Diuretics	930 (54.7)	4251 (48.9)	0.12	918 (54.4)	925 (54.8)	-0.01
Insulin	228 (13.4)	1176 (13.5)	0.00	224 (13.3)	216 (12.8)	0.01
Lipid lowering drugs	1169 (68.7)	6557 (75.4)	-0.15	1161 (68.8)	1151 (68.2)	0.01
Nitrates	239 (14.1)	1355 (15.6)	-0.04	233 (13.8)	225 (13.3)	0.01

Non-insulin diabetes medications	477 (28)	2493 (28.7)	-0.01	473 (28)	481 (28.5)	-0.01
Anticoagulants	218 (12.8)	814 (9.4)	0.11	212 (12.6)	190 (11.3)	0.04
Anti-epileptic mood stabilizers	20 (1.2)	94 (1.1)	0.01	20 (1.2)	17 (1)	0.02
Antiplatelet agents	411 (24.2)	8697 (100)	-2.51			0.00
Atypical antipsychotics	25 (1.5)	102 (1.2)	0.03	25 (1.5)	22 (1.3)	0.02
Benzodiazepines	352 (20.7)	1416 (16.3)	0.11	347 (20.6)	331 (19.6)	0.02
Lithium	2 (0.1)	14 (0.2)	-0.01			0.00
Anti-epileptics (other than mood stabilizers)	459 (27)	2073 (23.8)	0.07	455 (27)	457 (27.1)	0.00
Serotonin-norepinephrine reuptake inhibitors	83 (4.9)	361 (4.2)	0.04	82 (4.9)	75 (4.4)	0.02
Selective serotonin reuptake inhibitors	222 (13.1)	1141 (13.1)	0.00	221 (13.1)	221 (13.1)	0.00
Tricyclic antidepressants (TCAs)	77 (4.5)	320 (3.7)	0.04	75 (4.4)	63 (3.7)	0.04
Typical antipsychotics	8 (0.5)	20 (0.2)	0.04	8 (0.5)	10 (0.6)	-0.02
Other PAD treatments and PAD severity indicators , n (%)						
Critical limb ischemia	394 (23.2)	1058 (12.2)	0.29	381 (22.6)	380 (22.5)	0.00
Thrombolytic therapy	10 (0.6)	26 (0.3)	0.04	9 (0.5)	6 (0.4)	0.03
Number of cardiologist visits, mean (SD)	3.5 (5.9)	4 (5.2)	-0.08	3.5 (5.9)	3.5 (4.9)	-0.01
Number of hospitalizations with PAD, mean (SD)	0 (0.1)	0 (0.2)	-0.04	0 (0.1)	0 (0.1)	0.01
Comorbid conditions, n (%)						
Atrial fibrillation	296 (17.4)	1195 (13.7)	0.10	290 (17.2)	296 (17.5)	-0.01

Chronic obstructive pulmonary disease	557 (32.7)	2821 (32.4)	0.01	550 (32.6)	556 (33)	-0.01
Chronic liver disease	91 (5.3)	591 (6.8)	-0.06	89 (5.3)	89 (5.3)	0.00
Drug or alcohol abuse or dependence	282 (16.6)	2134 (24.5)	-0.20	281 (16.7)	284 (16.8)	-0.01
Heart failure	336 (19.8)	1320 (15.2)	0.12	329 (19.5)	335 (19.9)	-0.01
Hyperlipidemia	1309 (77)	7176 (82.5)	-0.14	1300 (77.1)	1303 (77.2)	0.00
Ischemic heart disease	792 (46.6)	4714 (54.2)	-0.15	784 (46.5)	783 (46.4)	0.00
Malignancy	508 (29.9)	2426 (27.9)	0.04	502 (29.8)	517 (30.6)	-0.02
Peripheral vascular disease	1646 (96.8)	8451 (97.2)	-0.02	1634 (96.9)	1635 (96.9)	0.00
Rheumatoid Arthritis	112 (6.6)	348 (4)	0.12	108 (6.4)	100 (5.9)	0.02
Renal dysfunction	478 (28.1)	2178 (25)	0.07	471 (27.9)	478 (28.3)	-0.01
Stroke or transient ischemic attack	241 (14.2)	1170 (13.5)	0.02	236 (14)	242 (14.3)	-0.01
Venous thromboembolism	132 (7.8)	410 (4.7)	0.13	128 (7.6)	125 (7.4)	0.01

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[8] 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.

10. References

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