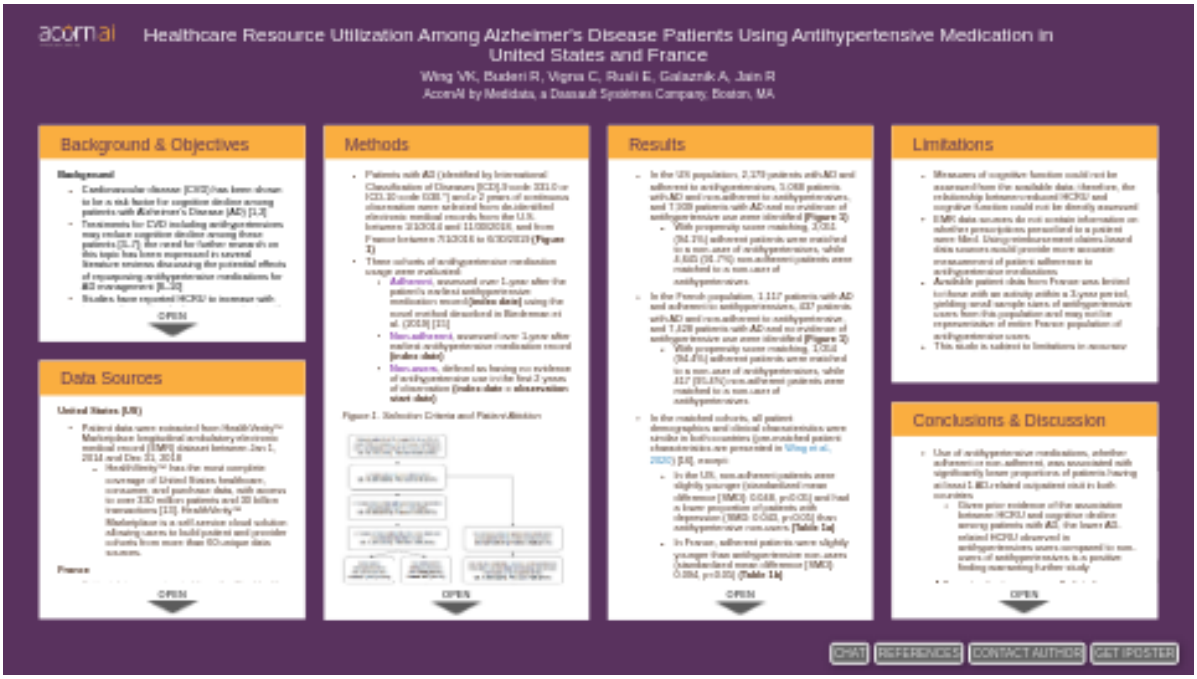
# Healthcare Resource Utilization Among Alzheimer's Disease Patients Using Antihypertensive Medication in United States and France

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**PRESENTED AT:**

# BACKGROUND & OBJECTIVES

**Background**

- Cardiovascular disease (CVD) has been shown to be a risk factor for cognitive decline among patients with Alzheimer's Disease (AD) [1,2]
- Treatments for CVD including antihypertensives may reduce cognitive decline among these patients [3–7]; the need for further research on this topic has been expressed in several literature reviews discussing the potential effects of repurposing antihypertensive medications for AD management [8–10]
- Studies have reported HCRU to increase with increased cognitive decline among patients with AD, and to be lower among patients treated with medications for AD compared to untreated patients with AD [11,12]
- Healthcare resource utilization (HCRU) may be lower among antihypertensives users in patients with AD due to its potential effects on cognitive function as described in prior literature

**Objectives**

- The objectives of this study were to describe and compare HCRU among patients with AD with and without antihypertensive medication use

# DATA SOURCES

**United States (US)**

- Patient data were extracted from HealthVerity™ Marketplace longitudinal ambulatory electronic medical record (EMR) dataset between Jan 1, 2014 and Dec 31, 2018
  - HealthVerity™ has the most complete coverage of United States healthcare, consumer, and purchase data, with access to over 330 million patients and 30 billion transactions [13]. HealthVerity™ Marketplace is a self-service cloud solution allowing users to build patient and provider cohorts from more than 60 unique data sources.

**France**

- Patient data was extracted from the The Health Improvement Network® (THIN®) France database between July 1, 2016 and June 30, 2019
  - THIN® is an anonymized EMR powered by Cegedim Health Data®–division. THIN® is a large European database, collecting data at the physicians' level.

All data were converted to the Observational Medical Outcomes Partnership (OMOP) Common Data Model, version 5 [14].

Analyses were conducted in Aginity Workbench for Redshift v4.9.3.2873 and R v1.1.456.

# METHODS

- Patients with AD (identified by International Classification of Diseases [ICD]-9 code 331.0 or ICD-10 code G30.*) and ≥ 2 years of continuous observation were selected from de-identified electronic medical records from the U.S. between 1/1/2014 and 11/30/2018, and from France between 7/1/2016 to 6/30/2019 **(Figure 1)**
- Three cohorts of antihypertensive medication usage were evaluated:
  - **Adherent**, assessed over 1-year after the patient's earliest antihypertensive medication record **(index date)** using the novel method described in Biederman et al. (2019) [15]
  - **Non-adherent**, assessed over 1-year after earliest antihypertensive medication record **(index date)**
  - **Non-users**, defined as having no evidence of antihypertensive use in the first 2 years of observation **(index date = observation start date)**

*Figure 1. Selection Criteria and Patient Attrition*

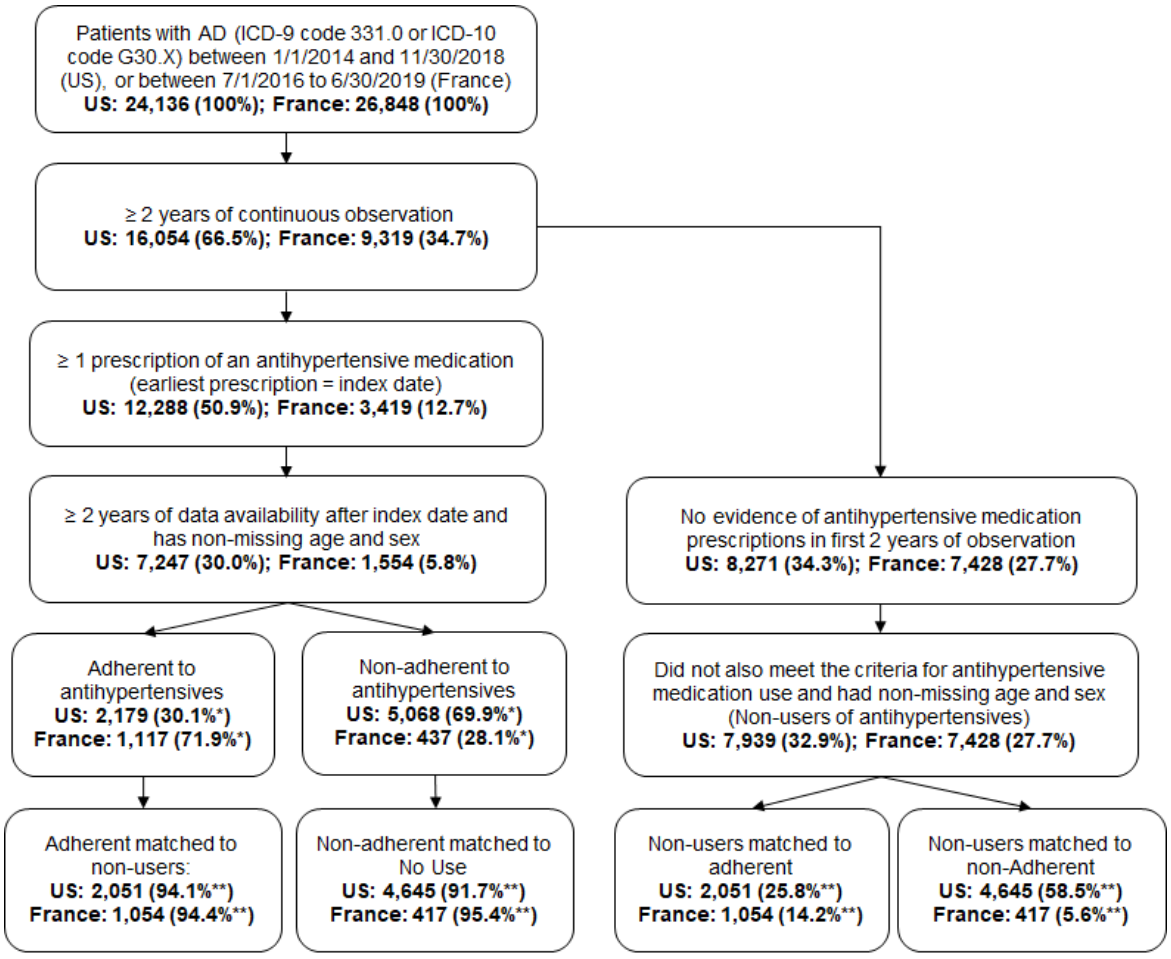



*Figure 2a. Study Timeline for Antihypertensive Use Cohorts*

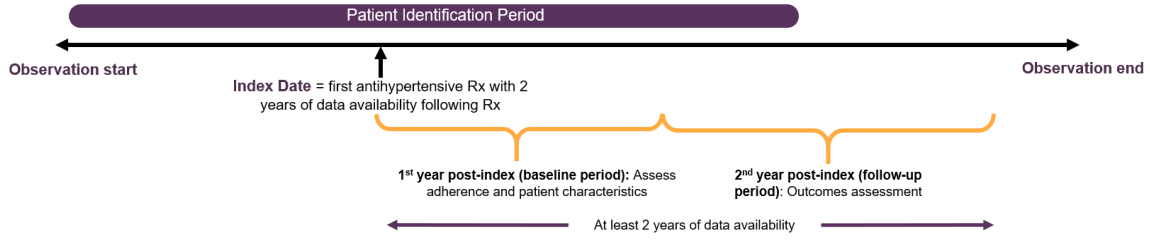
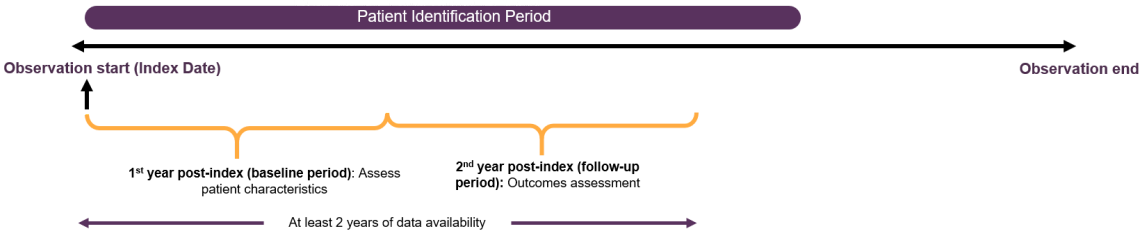



*Figure 2b. Study Timeline for Antihypertensive Non-Users Cohort*




- Greedy 1:1 matching on propensity score with a caliper of 0.01 was applied between the adherent and non-users cohort, and between the non-adherent and non-users cohort
  - Baseline demographic and clinical characteristics (measured during the first year post-index date and identified using ICD-9-CM, ICD-10-CM, Anatomical Therapeutic Chemical (ATC), and RxNorm codes) included in the propensity score model are listed in **Tables 1a and 1b**
- All-cause outpatient (AD) visits, AD-related OP visits (defined as encounters with a diagnosis code for AD), and laboratory test visits of the matched cohorts were assessed in the second year post-index period and compared using chi-squared (for categorical variables) and Student's t tests (for continuous variables) **(Figures 2 and 3)**

# RESULTS

- In the US population, 2,179 patients with AD and adherent to antihypertensives, 5,068 patients with AD and non-adherent to antihypertensives, and 7,939 patients with AD and no evidence of antihypertensive use were identified **(Figure 1)**
  - With propensity score matching, 2,051 (94.1%) adherent patients were matched to a non-user of antihypertensives, while 4,645 (91.7%) non-adherent patients were matched to a non-user of antihypertensives
- In the French population, 1,117 patients with AD and adherent to antihypertensives, 437 patients with AD and non-adherent to antihypertensive, and 7,428 patients with AD and no evidence of antihypertensive use were identified **(Figure 1)**
  - With propensity score matching, 1,054 (94.4%) adherent patients were matched to a non-user of antihypertensives, while 417 (95.4%) non-adherent patients were matched to a non-user of antihypertensives
- In the matched cohorts, all patient demographics and clinical characteristics were similar in both countries (pre-matched patient characteristics are presented in Wing et al., 2020 (/default.aspx?s=34-15-DC-54-8A-34-C1-99-79-DB-8E-B5-B9-2B-6D-07&guestview=true)) [16], except:
  - In the US, non-adherent patients were slightly younger (standardized mean difference [SMD]: 0.048, p<0.05) and had a lower proportion of patients with depression (SMD: 0.043, p<0.05) than antihypertensive non-users **(Table 1a)**
  - In France, adherent patients were slightly younger than antihypertensive non-users (standardized mean difference [SMD]: 0.094, p<0.05) **(Table 1b)**

*Table 1a. Matched Demographic and Clinical Characteristics in the US*

| | Adherent (Matched with Non-Users) | | Non-Users (Matched with Adherent) | | | Non-Adherent (Matched with Non-Users) | | Non-Users (Matched with Non-Adherent) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N= | 2,051 | N= | 2,051 | | N= | 4,645 | N= | 4,645 | |
| **Patient Characteristic** | **N/Mean** | **%/SD** | **N/Mean** | **%/SD** | **SMD** | **N/Mean** | **%/SD** | **N/Mean** | **%/SD** | **SMD** |
| Age (mean, SD) | 76.35 | 7.98 | 76.5 | 9.2 | 0.017 | 76.95 | 8.08 | 77.35 | 8.63 | 0.048* |
| Male (n, %) | 714 | 34.80% | 705 | 34.40% | 0.009 | 1,667 | 35.90% | 1,738 | 37.40% | 0.032 |
| Quan's Charlson Comorbidity Index score** (mean, SD) | 1.65 | 1.72 | 1.63 | 2 | 0.007 | 1.38 | 1.66 | 1.38 | 1.79 | <0.001 |
| Number of distinct concomitant medications*** (mean, SD) | 2.2 | 1.56 | 2.22 | 1.78 | 0.008 | 1.86 | 1.48 | 1.9 | 1.63 | 0.028 |
| Atrial fibrillation (n, %) | 298 | 14.50% | 292 | 14.20% | 0.008 | 469 | 10.10% | 451 | 9.70% | 0.013 |
| Bipolar disorder (n, %) | 19 | 0.90% | 26 | 1.30% | 0.033 | 38 | 0.80% | 45 | 1.00% | 0.016 |
| Coronary artery disease (n, %) | 339 | 16.50% | 326 | 15.90% | 0.017 | 578 | 12.40% | 612 | 13.20% | 0.022 |
| Depression (n, %) | 477 | 23.30% | 459 | 22.40% | 0.021 | 864 | 18.60% | 943 | 20.30% | 0.043* |
| Epilepsy (n, %) | 102 | 5.00% | 102 | 5.00% | <0.001 | 158 | 3.40% | 181 | 3.90% | 0.026 |
| Glaucoma (n, %) | 39 | 1.90% | 38 | 1.90% | 0.004 | 68 | 1.50% | 70 | 1.50% | 0.004 |
| Hearing loss (n, %) | 94 | 4.60% | 105 | 5.10% | 0.025 | 221 | 4.80% | 226 | 4.90% | 0.005 |
| Hyperthyroidism (n, %) | 15 | 0.70% | 18 | 0.90% | 0.016 | 22 | 0.50% | 27 | 0.60% | 0.015 |
| Hypothyroidism (n, %) | 339 | 16.50% | 345 | 16.80% | 0.008 | 655 | 14.10% | 666 | 14.30% | 0.007 |
| Mild cognitive impairment (n, %) | 93 | 4.50% | 103 | 5.00% | 0.023 | 200 | 4.30% | 199 | 4.30% | 0.001 |
| Osteoporosis (n, %) | 150 | 7.30% | 140 | 6.80% | 0.019 | 303 | 6.50% | 311 | 6.70% | 0.007 |
| Parkinson's disease (n, %) | 39 | 1.90% | 38 | 1.90% | 0.004 | 91 | 2.00% | 94 | 2.00% | 0.005 |
| Pneumonia (n, %) | 53 | 2.60% | 48 | 2.30% | 0.016 | 77 | 1.70% | 77 | 1.70% | <0.001 |
| Schizophrenia (n, %) | 8 | 0.40% | 3 | 0.10% | 0.047 | 20 | 0.40% | 21 | 0.50% | 0.003 |
| Stroke/Transient ischemic attack (n, %) | 127 | 6.20% | 115 | 5.60% | 0.025 | 253 | 5.40% | 228 | 4.90% | 0.024 |

*p<0.05

**Quan H, Sundararajan V, Halfon P, et al. Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative Data: Medical Care. 2005;43(11):1130-1139. doi:10.1097/01.mlr.0000182534.19832.83

***Included treatment agents from the following medication classes: Alzheimer's medications, antiplatelets, statins, antipsychotics, anxiolytics, and antidepressants

*Table 1b. Matched Demographic and Clinical Characteristics in France*

| | Adherent (Matched with Non-Users) | | Non-Users (Matched with Adherent) | | | Non-Adherent (Matched with Non-Users) | | Non-Users (Matched with Non-Adherent) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N= | 1,054 | N= | 1,054 | | N= | 417 | N= | 417 | |
| **Patient Characteristic** | **N/Mean** | **%** | **N/Mean** | **%** | **SMD** | **N/Mean** | **%** | **N/Mean** | **%** | **SMD** |
| Age (mean, SD) | 75.7 | 10.73 | 76.75 | 11.66 | 0.094* | 75.48 | 11.36 | 76.52 | 12.11 | 0.088 |
| Male (n, %) | 435 | 41.30% | 457 | 43.40% | 0.042 | 179 | 42.90% | 174 | 41.70% | 0.024 |
| Quan's Charlson Comorbidity Index score** (mean, SD) | 1.04 | 1.01 | 1.04 | 0.89 | 0.005 | 0.98 | 0.96 | 0.95 | 0.89 | 0.031 |
| Number of distinct concomitant medications*** (mean, SD) | 1.72 | 1.27 | 1.65 | 1.35 | 0.056 | 1.5 | 1.33 | 1.45 | 1.41 | 0.04 |
| Atrial fibrillation (n, %) | 2 | 0.20% | 2 | 0.20% | <0.001 | 0 | 0.00% | 0 | 0.00% | <0.001 |
| Bipolar disorder (n, %) | 1 | 0.10% | 0 | 0.00% | 0.044 | 1 | 0.20% | 1 | 0.20% | <0.001 |
| Coronary artery disease (n, %) | 56 | 5.30% | 51 | 4.80% | 0.022 | 18 | 4.30% | 15 | 3.60% | 0.037 |
| Depression (n, %) | 198 | 18.80% | 190 | 18.00% | 0.02 | 51 | 12.20% | 60 | 14.40% | 0.064 |
| Epilepsy (n, %) | 10 | 0.90% | 18 | 1.70% | 0.066 | 5 | 1.20% | 3 | 0.70% | 0.049 |
| Glaucoma (n, %) | 6 | 0.60% | 6 | 0.60% | <0.001 | 1 | 0.20% | 2 | 0.50% | 0.04 |
| Hearing loss (n, %) | 13 | 1.20% | 12 | 1.10% | 0.009 | 2 | 0.50% | 2 | 0.50% | <0.001 |
| Hyperthyroidism (n, %) | 6 | 0.60% | 8 | 0.80% | 0.023 | 3 | 0.70% | 2 | 0.50% | 0.031 |
| Hypothyroidism (n, %) | 99 | 9.40% | 100 | 9.50% | 0.003 | 35 | 8.40% | 43 | 10.30% | 0.066 |
| Mild cognitive impairment (n, %) | 1054 | 100.00% | 1054 | 100.00% | <0.001 | 417 | 100.00% | 417 | 100.00% | <0.001 |
| Osteoporosis (n, %) | 18 | 1.70% | 18 | 1.70% | <0.001 | 5 | 1.20% | 4 | 1.00% | 0.023 |
| Parkinson's disease (n, %) | 16 | 1.50% | 21 | 2.00% | 0.036 | 8 | 1.90% | 7 | 1.70% | 0.018 |
| Pneumonia (n, %) | 15 | 1.40% | 10 | 0.90% | 0.044 | 4 | 1.00% | 4 | 1.00% | <0.001 |
| Schizophrenia (n, %) | 0 | 0.00% | 0 | 0.00% | <0.001 | 0 | 0.00% | 0 | 0.00% | <0.001 |
| Stroke/Transient ischemic attack (n, %) | 45 | 4.30% | 47 | 4.50% | 0.009 | 17 | 4.10% | 12 | 2.90% | 0.065 |

*p<0.05

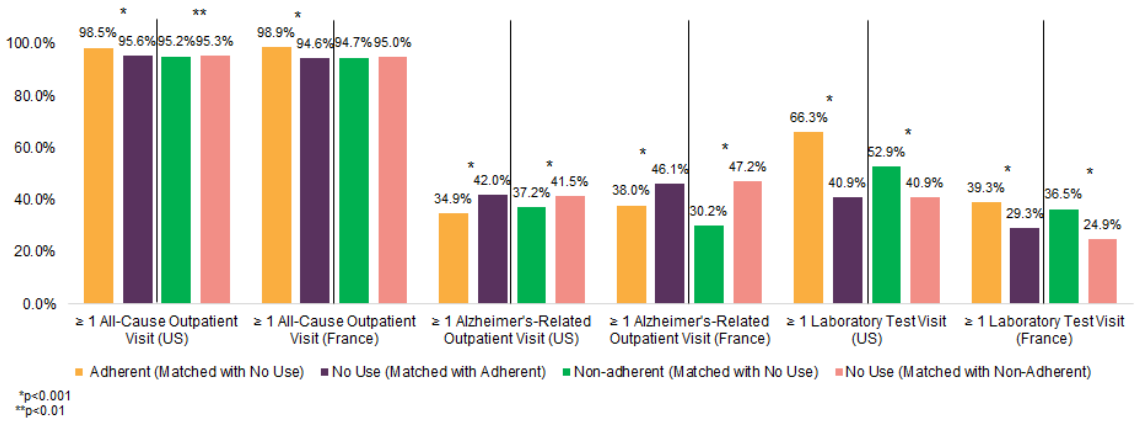
**Quan H, Sundararajan V, Halfon P, et al. Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative Data: Medical Care. 2005;43(11):1130-1139. doi:10.1097/01.mlr.0000182534.19832.83

***Included treatment agents from the following medication classes: Alzheimer's medications, antiplatelets, statins, antipsychotics, anxiolytics, and antidepressants

**Proportion of Patients with Healthcare Visits**

- In the US, compared to non-users of antihypertensives **(Figure 3)**:
  - Adherent patients had a higher proportion of patients with ≥ 1 all-cause outpatient visit, while non-adherent patients had a lower proportion (p<0.001 and p<0.01, respectively)
  - Adherent and non-adherent patients had a lower proportion of patients with ≥ 1 Alzheimer's-related outpatient visit (p<0.001)
  - Adherent and non-adherent patients had a higher proportion of patients with ≥ 1 laboratory test visit (p<0.001)
- In France, similar differences to the US were observed, except the proportion of non-adherent patients with ≥ 1 all-cause outpatient visit did not statistically differ from antihypertensive non-users

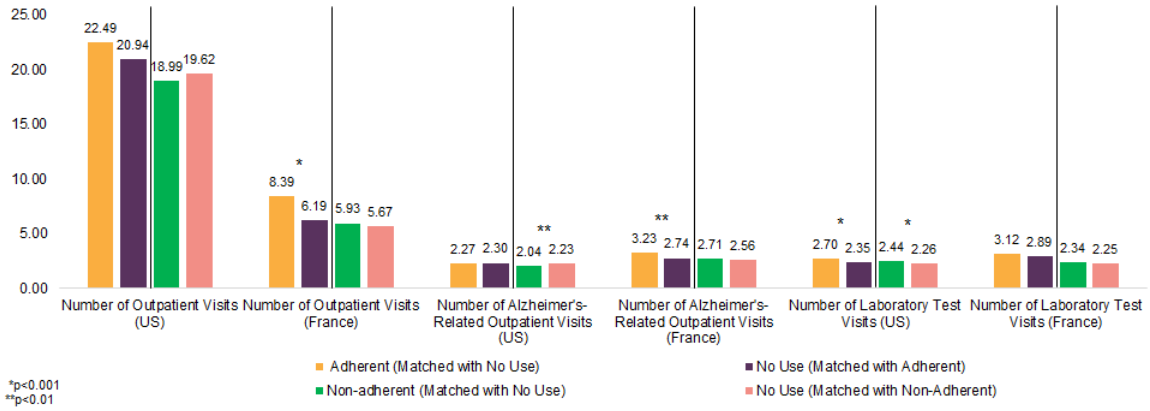
*Figure 3. Proportion of Patients with Healthcare Visits, by Country*




**Healthcare Visits Among Patients with At Least 1 Visit**

- In the US, compared to non-users of antihypertensives **(Figure 4)**:
  - Non-adherent patients had a lower number of Alzheimer's-related outpatient visits (p<0.01)
  - Adherent and non-adherent patients had a higher number of laboratory test visits (p<0.001)
- In France, compared to non-users:
  - Adherent patients had a higher number of all-cause outpatient visits and Alzheimer's-related outpatient visits (p<0.001 and p<0.01, respectively)

*Figure 4. Number of Healthcare Visits, Among Patients with ≥ 1 Visit, by Country*



# LIMITATIONS

- Measures of cognitive function could not be assessed from the available data; therefore, the relationship between reduced HCRU and cognitive function could not be directly assessed
- EMR data sources do not contain information on whether prescriptions prescribed to a patient were filled. Using reimbursement claims-based data sources would provide more accurate measurement of patient adherence to antihypertensive medications
- Available patient data from France was limited to those with an activity within a 3-year period, yielding small sample sizes of antihypertensive users from this population and may not be representative of entire France population of antihypertensive users
- This study is subject to limitations in accuracy and consistency of medical coding as is common for studies using EMR

# CONCLUSIONS & DISCUSSION

- Use of antihypertensive medications, whether adherent or non-adherent, was associated with significantly lower proportions of patients having at least 1 AD-related outpatient visit in both countries
  - Given prior evidence of the association between HCRU and cognitive decline among patients with AD, the lower AD-related HCRU observed in antihypertensives users compared to non-users of antihypertensives is a positive finding warranting further study
- Adherent patients were more likely to have an all-cause outpatient visit, potentially driven by activity to re-prescribe or monitor antihypertensive medication use
- Adherent and non-adherent patients were more likely to have a laboratory test visit, suggesting patients using antihypertensives may be more regularly interacting with the healthcare system than non-users of antihypertensives
- In France, the mean number of all-cause and Alzheimer's-related outpatient visits among patients with at least 1 visit were higher in adherent patients compared to non-users, indicating these patients are interacting with the healthcare system more often (consistent with the observed frequency of antihypertensive medication prescribing). These interactions may also be opportunities for concurrent AD care
- Future analyses can be conducted evaluating differences in utilization of inpatient visits and neurologist office visits to further investigate the impact of antihypertensive medication use on HCRU among patients with AD
- Incorporation of cognitive tests, such as the Mini-Mental State Examination (MMSE) could further allow exploration of HCRU associations with cognitive decline among antihypertensive users in patients with AD

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