Undiagnosed Alzheimer's Pathology in Cardiovascular Patients and its Implications for Prevention: BROADWAY Trial Dissected

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BACKGROUND

- Despite frequent monitoring, patients aged 50 to 70 with atherosclerotic cardiovascular disease (ASCVD) are rarely screened for cognitive health[1,2]
- Dysregulation of lipid metabolism plays a central role in both ASCVD and Alzheimer's disease (AD)[3]
  - Carriers of the apolipoprotein E4 (*APOE4*) allele exhibit a dysregulated lipid profile which increases the risk of both cardiovascular disease and AD[3]
- Emerging evidence suggests that patients with ASCVD may carry undiagnosed AD pathology[1,2]
  - Recent reports indicate that over half of community-dwelling cardiovascular patients without cognitive impairment diagnoses have elevated plasma levels (>0.42 pg/mL) of tau phosphorylated at threonine 217 (p-tau217), more than double the prevalence observed in age-matched general populations[2,4]
- In these vascular cohorts, elevated p-tau217 correlates with cognitive impairment: nearly one-third meet criteria for mild cognitive impairment (MCI) on formal testing yet remain undiagnosed[2]

OBJECTIVE

To evaluate baseline plasma p-tau217 levels in a large multinational ASCVD cohort

METHODS

- BROADWAY (NCT05142722) was a phase 3, randomized, double-blind, placebo-controlled trial evaluating the effect of obicetrapib 10 mg as an adjunct to maximally tolerated lipid-lowering therapy (LLT) over 1 year
- A prespecified substudy within the BROADWAY trial measured plasma AD biomarkers and included participants with known apolipoprotein (*APOE)* status, baseline p-tau217 above the lower limit of quantification, and available end-of-study p-tau217
  - Of the 2530 randomized BROADWAY participants, 1535 met the inclusion criteria, including 367 *APOE4* carriers (*APOE3*/*E4* or *APOE4*/*E4*)
- The baseline p-tau217 and *APOE* status were analyzed
  - Plasma p-tau217 was measured using the ALZpath SIMOA assay
  - Elevated p-tau217 was defined using established thresholds: >0.42 pg/mL (preclinical AD pathology) and **>0.62 pg/mL** (established AD pathology)

RESULTS AND DISCUSSION

- Demographic and baseline characteristics for the analysis population are shown in **Table 1 and Figure 1**
  - The median age was 67 years, 67% of participants were male, and 84.5% were Caucasian
- Nearly half (45.9%, n=730) of BROADWAY participants exceeded the 0.42 pg/mL p-tau217 threshold despite receiving regular cardiovascular care and having no neurological evaluation (**Figure 2**)
  - E4/E4 homozygotes showed 73.3% prevalence of elevated p-tau217 vs 42.3% in E3/E3 individuals
  - Among those with the highest p-tau217 levels (>0.62 pg/mL), *APOE4* carriers were disproportionately represented: one-third (33.6%) carried at least one E4 allele compared to 18% of those below the 0.42 pg/mL threshold (**Figure 3**)
- Recent reports demonstrate that elevated p-tau217 accurately predicts cognitive impairment in cardiovascular patients (area under the curve [AUC] 0.78 to 0.94).[2] The high prevalence of elevated p-tau217 observed in this ASCVD cohort suggests a substantial burden of underlying AD-related pathology; however, cognitive assessments were not evaluated in BROADWAY

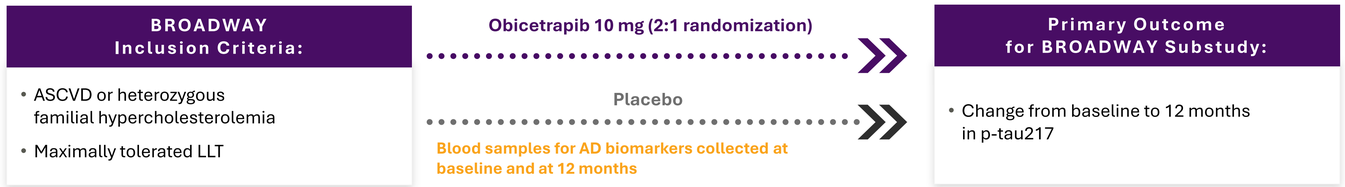


Figure 1. Baseline AD Biomarkers

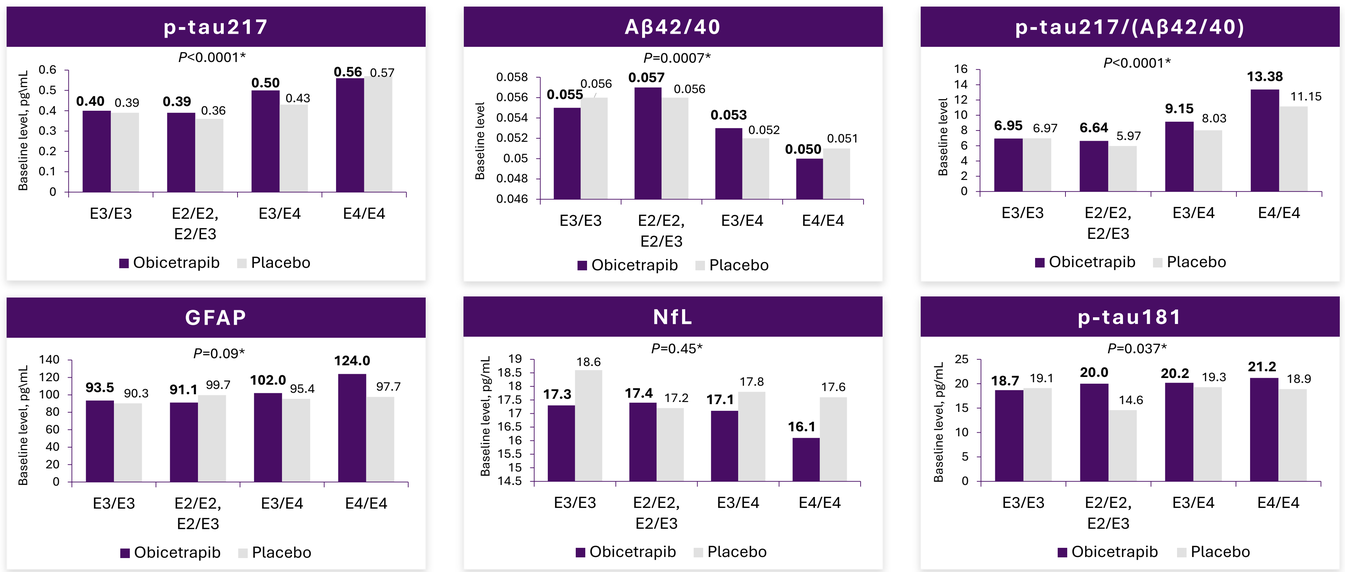


Table 1. Demographics and Baseline Characteristics

Baseline Demographics	
Study Population, N	1535
Age, y	67
Female sex, n (%)	506 (33.0)
Race, n (%)	
White	1297 (84.5)
Asian	133 (8.7)
Black	86 (5.6)
Other	19 (1.2)
Medical History, n (%)	
Diabetes	580 (37.8)
Hypertension	1301 (84.8)
ASCVD	1337 (87.1)

Figure 2. Baseline p-tau217 by *APOE* Status†

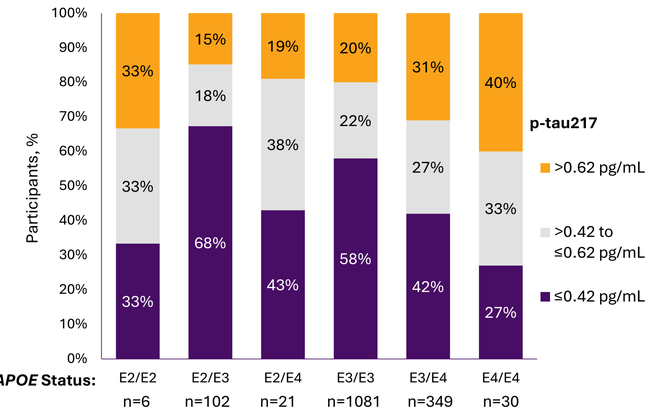
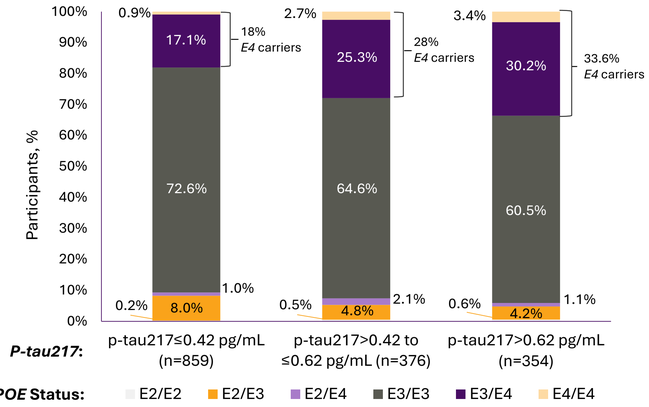


Figure 3. *APOE* Status by Baseline p-tau217†



*P values for comparisons between *APOE* status (pooled across treatment groups) by Kruskal-Wallis or chi-square tests.
†Values may not add up to 100% due to rounding.
Aβ, amyloid beta; GFAP, glial fibrillary acidic protein; NFL, neurofilament light; p-tau181, tau phosphorylated at threonine 181.

CONCLUSIONS

- Approximately half of ASCVD patients (ages 50 to 70 years) under regular medical care have plasma p-tau217 levels indicative of preclinical AD pathology, with a significant proportion likely meeting criteria for undiagnosed MCI
  - This represents a critical gap between cardiovascular and dementia care
- The disproportionate enrichment of *APOE4* carriers among those with highest biomarker elevations suggests shared lipid-mediated pathophysiology amenable to intervention
- These findings support incorporating AD biomarker screening into cardiovascular practice and identify ASCVD cohorts as high-yield populations for AD prevention trials targeting upstream lipid dysregulation

AFFILIATIONS AND DISCLOSURES

John JP Kastelein, Andrew Hsieh, Marc Ditmarsch, Adam Johnson, Nancy Ortiz, Douglas L Wicks, Danielle Curcio, Douglas Kling, and Michael H Davidson are employees of NewAmsterdam Pharma and hold stocks or options. Philip Scheltens is a full-time employee of EQT LifeSciences, emeritus prof at Amsterdam University Medical Center, and consultant to New Amsterdam Pharma. Michael Szarek reports receiving salary support from CPC, a nonprofit academic research organization affiliated with the University of Colorado. Dr. Szarek also reports serving as a consultant or research support (or both) from Amarin, Lexicon, NewAmsterdam Pharma, Novartis, Regeneron, Sanofi, Silence, and Tourmaline. Everard Vijverberg received consultancy fees (paid to the university) for New Amsterdam Pharma, Treeway, ReMynd, Vivoryon, Biogen,Vigil Neuroscience, ImmunoBrain Checkpoint, Muna Therapeutics, Esai,Eli Lilly, CogRX, Therini, UCB and Roche. Within his university affiliation he is PI of studies of DIAN, AC immune, Alnylam, CogRX therapeutics, New Amsterdam Pharma, Janssen, UCB, Roche, Vivoryon, ImmunoBrain, GSK, MSD, Biogen, Alector, Eli Lilly, AriBio Fuij FilmToyama, GemVax. Co-founder van het CANDIDATE Center AmsterdamUMC. Scientific projects with the Dutch Soccer Association (KNVB).

REFERENCES

1. van Nieuwkerk AC et al. *Stroke*. 2023;54(8):2181-2191. **2.** French SR et al. *Alzheimers Dement*. 2025;21(8):e70565. **3.** Davidson MH et al. *J Prev Alzheimers Dis*. 2026;13(1):100394. **4.** Mielke MM et al. *Nat Med*. 2022;28(7):1398-1405. **5.** Davidson MH et al. *Am J Prev Cardiol*. 2026;26:101442. **6.** Davidson MH et al. *J Prev Alzheimers Dis*. 2026;13(suppl 1):100394.