

Tau PET-based Stratification For Anti-amyloid Drug Eligibility Using A Commercially Available Tau-PET Quantification Software

Rachid Fahmi, Bruce Spottiswoode
Siemens Medical Solutions USA, Inc., Molecular Imaging, Knoxville, TN, USA

SIEMENS
Healthineers

Background

Flortaucipir-PET (FTP-PET) quantitation was used as a stratification tool in phases 2 & 3 trials of the anti-amyloid drug, donanemab [1]. SUVR-based ranges of low, medium and high tau burden (Fig. 1) were determined using an investigational non-clinically approved tau- PET quantification software (SW1) [2].

Aim: to develop a surrogate tau PET quantitative measure consistent with donanemab trials' stratification using the clinically approved tau quantification software, *syngo.MI Neurology (SW2)* (Siemens Healthineers, Knoxville, TN, USA).

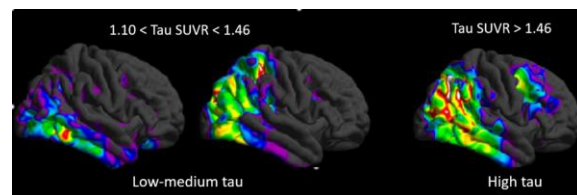


Figure 1: Low-medium and high tau populations determined using tau PET SUVR (adapted from a Eli Lilly symposium @ AAIC'2023).

Methods

- Baseline FTP-PET datasets (N=188) from a clinically heterogeneous cohort of an observational study (A05E, NCT02016560) were included in this analysis (Table 1).
- SW1 SUVRs were calculated using a voxel-weighted neocortical-target region (MUBADA) or an early-tau (eTau) region with reference to a cerebellar-crus ($SW1SUVR_{CC}$) or to a subject-specific white-matter (WM) ($SW1SUVR_{PERSI}$) [3].

Table 1. Demographics and clinical summary

	YC (N=15)	eCU (N=48)	MCI (N=85)	AD (N=85)
Age	28.3 (4.2)	67.8 (9.9)	70.4 (9.6)	75.5 (8.4)
Sex (M/F)	9/6	24/24	44/41	18/23
Visual A+ (%)	0	10.4	48.2	65*
Visual T+ (%)	0	4.1	34.1	51.2

YC: Young controls; eCU: elderly Cognitively Unimpaired; MCI: mild cognitively impaired.
AD: Alzheimer's disease; A+: amyloid positive; T+: tau positive.

Methods (Cont.)

- SW2 SUVRs were calculated as volume-weighted ratios using various individual and composite Braak regions, as well as a meta-temporal (MTR) and an eTau region with-reference-to either an inferior-cerebellar-gray region ($SW2SUVR_{inf_Crb}$) or to an atlas-based WM region ($SW2SUVR_{WM}$).
- Relationships between the two sets of SUVRs were examined using regression analyses.
- ROC analysis with Youden's index was used to compare SUVR-based classification performances by the two methods using the FDA-approved FTP-PET visual read as ground-truth.

Results

- Due to potential partial-volume effects, Braak 1-2 was excluded from SW2 analysis.
- $SW1SUVR_{CC}$ (corresponding to MUBADA and to eTau) showed significant linear and positive associations with $SW2SUVR_{inf_Crb}$ values: mean $R^2=0.9$ [0.858, 0.926], $p<0.001$ (Figs. 2-1 & 2-2).
- Strongest & weakest correlations were:
 - $SW1SUVR_{CC}$ (MUBADA) vs. $SW2SUVR_{inf_Crb}$ (MTR) and
 - $SW1SUVR_{CC}$ (MUBADA) vs. $SW2SUVR_{inf_Crb}$ (Braak5-6).
- Correlation improvements when $SW1SUVR_{PERSI}$ was compared to $SW2SUVR_{WM}$ vs. when compared to $SW2SUVR_{inf_Crb}$ values: mean $R^2=0.80$ [0.765, 0.823] vs. $R^2=0.75$ [0.729, 0.807] (Fig. 3).

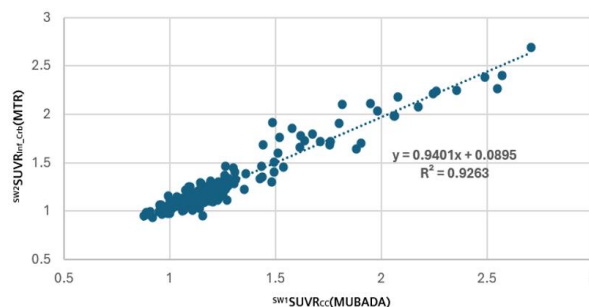


Figure 2.1: Regression plot showing strong association between $SW1SUVR_{CC}$ (MUBADA) and $SW2SUVR_{inf_Crb}$ (MTR).

Results (Cont.)

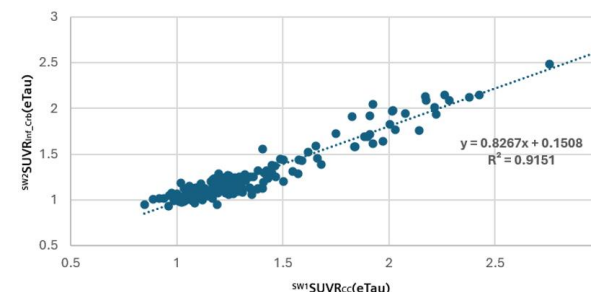
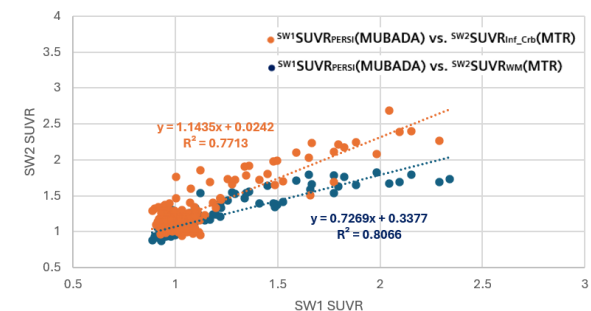
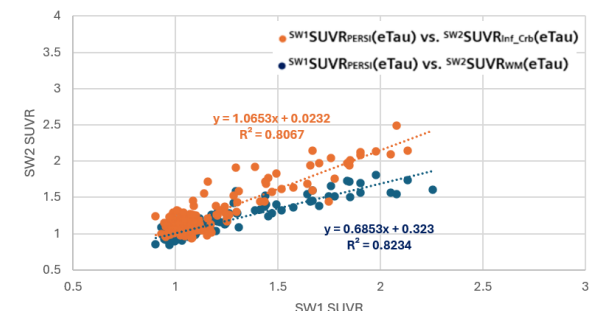


Figure 2.2: Regression plot showing strong association between $SW1SUVR_{CC}$ (eTau) vs. $SW2SUVR_{inf_Crb}$ (eTau).



Figures 3: Regression plots showing slight correlation improvements when SW1 PERSI SUVRs are compared to SW2 WM vs. when compared to SW2 SUVRs calculated with inferior cerebellum.

Results (Cont.)

- $SW1SUVR_{PERSI}$ (MUBADA) and $SW2SUVR_{inf_Crb}$ (MTR) led to comparable SUVR-based classifications with cutoff (Accuracy): 1.06 (89.0%) and 1.29 (91.3%), respectively (Fig. 4).

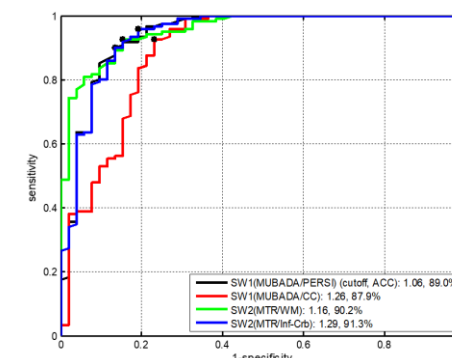


Figure 4: ROC analysis using different SUVR values calculated with both solutions using FTP-PET visual read as ground truth.

Conclusions

- $SW2SUVR$ values showed close associations and similar classification performance compared to $SW1SUVR$ s.
- SW2 could be used as a surrogate for tau-PET-based stratification similar to that adopted in donanemab trials.
- Next step is to process the trials' PET data to establish stratification ranges with SW2.

References

- [1] JR Sims et al. Donanemab in Early Symptomatic AD: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023.
- [2] M. Devous et al., "Test-Retest Reproducibility for the Tau PET Imaging Agent Flortaucipir F18". JNM 2018.
- [3] S. Southehal et al., "Flortaucipir Quantitation Using Parametric Estimation of Reference Signal Intensity". JNM 2018.

Disclosures

The authors are full-time employees of Siemens Medical Solutions USA, Inc.