

Implementing biomarker frameworks of Alzheimer's and vascular disease trials to reduce cognitive decline in type 2 diabetes

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Methodological Issue Being Addressed Type 2 Diabetes Mellitus (T2DM) is a known risk factor for cognitive decline, including Alzheimer's disease (AD) and vascular dementia. Existing trials often lack an integrated approach to AD-specific and cerebrovascular pathology, limiting their ability to stratify patients at risk, to assess outcome measures, and to infer treatment effects.

Introduction The present study integrates prevalent biomarker guidelines under the FDA's Biomarkers EndpointS and other Tools (BEST) resource, including the biological criteria for AD: the "ATNIVS" framework (amyloid, tau, neurodegeneration, inflammation, vascular, synaptic) and Standards for Reporting Vascular Changes on Neuroimaging-2 (STRIVE-2). We aim to address the complex interplay between commingling pathologies driving cognitive impairment in T2DM, to better target trials to susceptible individuals, and to predict and measure treatment effects with greater precision and accuracy.

Methods Our outcome of interest to investigate cognitive decline in T2DM will be the National Institute of Neurological Disorders and Stroke and Canadian Stroke Network (NINDS-CSN) neuropsychological battery, a reliable and valid assessment of cognitive function in patients with T2DM. The ATNIVS and STRIVE-2 criteria will inform selection of biomarkers, and the FDA-BEST framework will inform study design of observational and intervention trials in patients with T2DM. The ATNIVS framework categorizes biomarkers into six components: amyloid (A), tau (T), cortical atrophy (N), inflammation (I), and vascular features (V), and synaptic integrity via alpha-synuclein (S). Vascular features (V) will be expanded upon according to STRIVE-2 criteria, which provides criteria for classifying vascular features on neuroimaging such as white matter hyperintensities (WMH), lacunes, micro- and macro-bleeds, and perivascular spaces, as they are relevant to vascular contributions to cognitive impairment. Contexts of use of these specific biomarkers will be established under the FDA-BEST framework. Specifically, diagnostic capacity will evaluate the contribution of each biomarker to cognition cross-sectionally. Prognostic capacity will focus on baseline predictors of cognitive decline, and monitoring will include repeated biomarker assessments to track cognitive decline and pharmacological intervention effects. Effects will be evaluated under guideline-recommended statistical frameworks, including the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines for diagnostic markers, Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) for prognostic markers, and generalized estimating equations for monitoring.

Results This ATNIVS-STRIVE2 framework offers a thorough, multi-dimensional assessment of

common commingling causes of cognitive impairment in T2DM, with the goal of improving risk identification, tracking progression, and assessing the impact of interventions using surrogate biomarkers. However, while comprehensive, this approach is resource-intensive, requiring imaging, assays, and complex statistical modeling.

Conclusion This multi-framework design addresses the complexity of factors affecting cognitive decline in T2DM. By integrating both AD-specific and cerebrovascular biomarkers and applying the principles of the FDA-BEST framework, this comprehensive approach has the potential to transform the clinical landscape for T2DM patients. It will improve the precision of patient stratification, enable more accurate tracking of disease progression, and better assess therapeutic efficacy. These outcomes will enhance clinical trials and ultimately lead to improved patient outcomes, offering the possibility of personalized interventions to mitigate the effects of cognitive decline in T2DM.

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Keywords

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Guidelines I have read and understand the Poster Guidelines

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