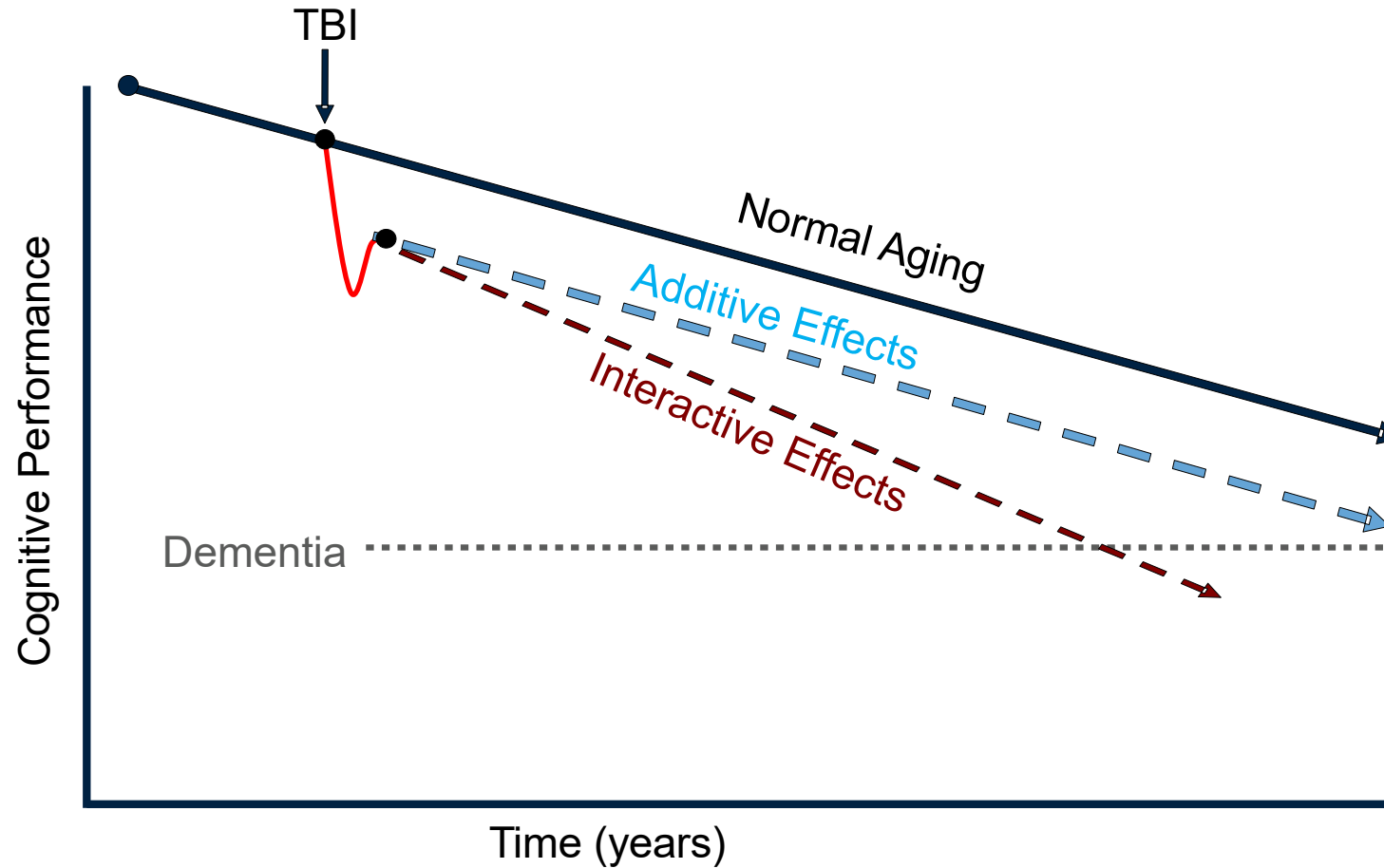


Session IV: Needs and Opportunities for Therapeutic Development

Ramon Diaz-Arrastia, MD, PhD
Professor, Department of Neurology
University of Pennsylvania School of Medicine



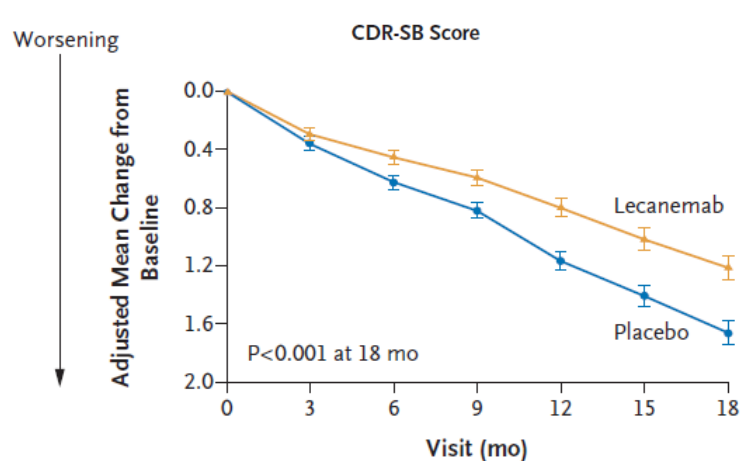
Hypothetical Models of Cognitive Decline after TBI



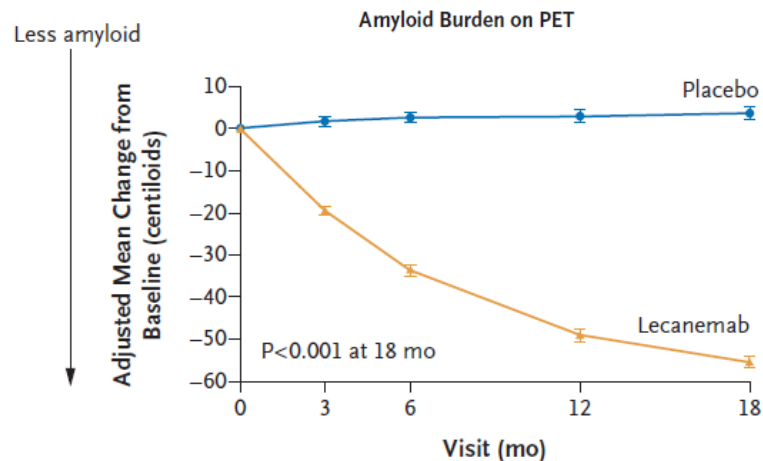
What are the pathologies contributing to long-term trauma-related neurodegeneration?

- Age-related pathologies (even if not accelerated by TBI)
 - Amyloid aggregation
 - Tau hyperphosphorylation
 - Microvasculopathy
 - Synucleinopathy
- Pathologies accelerated by TBI (also age-related)
 - Axonal degeneration
 - Microvasculopathy
 - Neuroinflammation

Era of anti-amyloid therapy is upon us

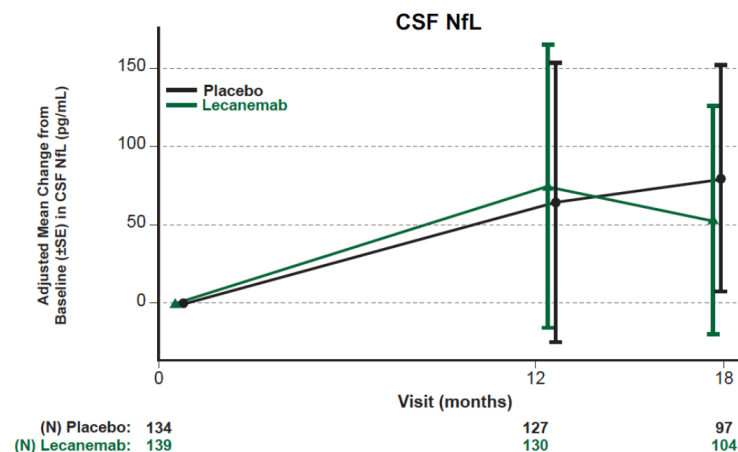
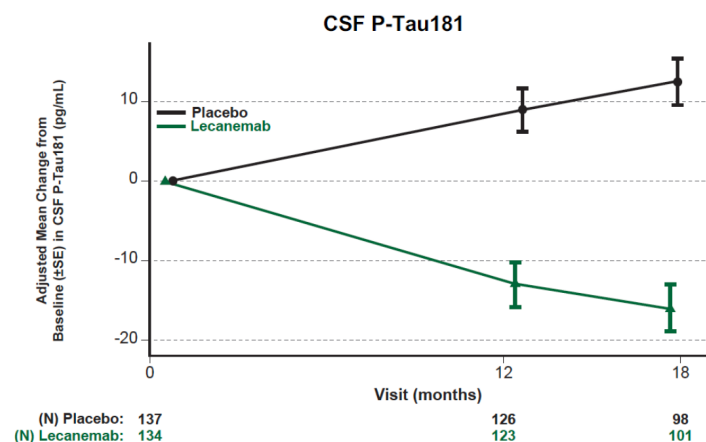


No. of Participants							
Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757



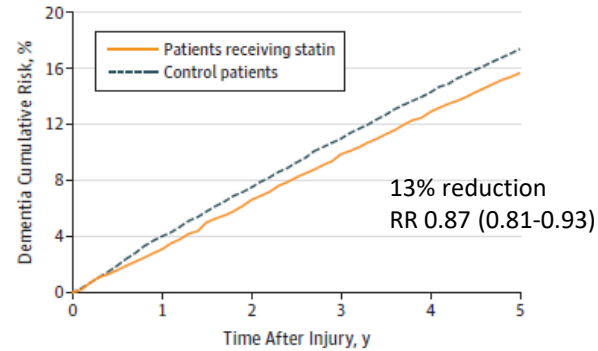
No. of Participants							
Lecanemab	354	296	275		276		210
Placebo	344	303	286		259		205

- Anti-amyloid Mabs very effective at removing Ab aggregates from brain
- Modestly effective in slowing cognitive decline
- Moderate effect on pTau 181, Tau
- No effect on NfL
- Should we consider anti-amyloid therapy in older individuals after TBI
 - More research warranted



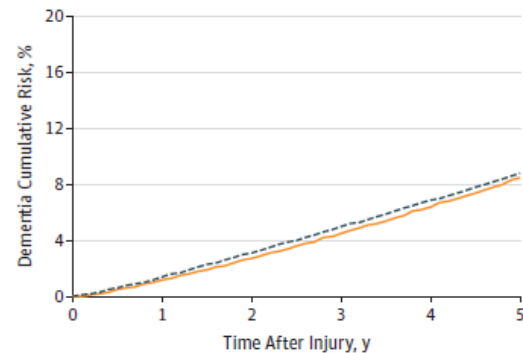
What to do about microvasculopathy after TBI?—Statins

A Patients with concussion



No. of patients						
Patients receiving statin	7058	6585	6130	5476	4528	3654
Control patients	21757	19822	18151	16312	14081	12186

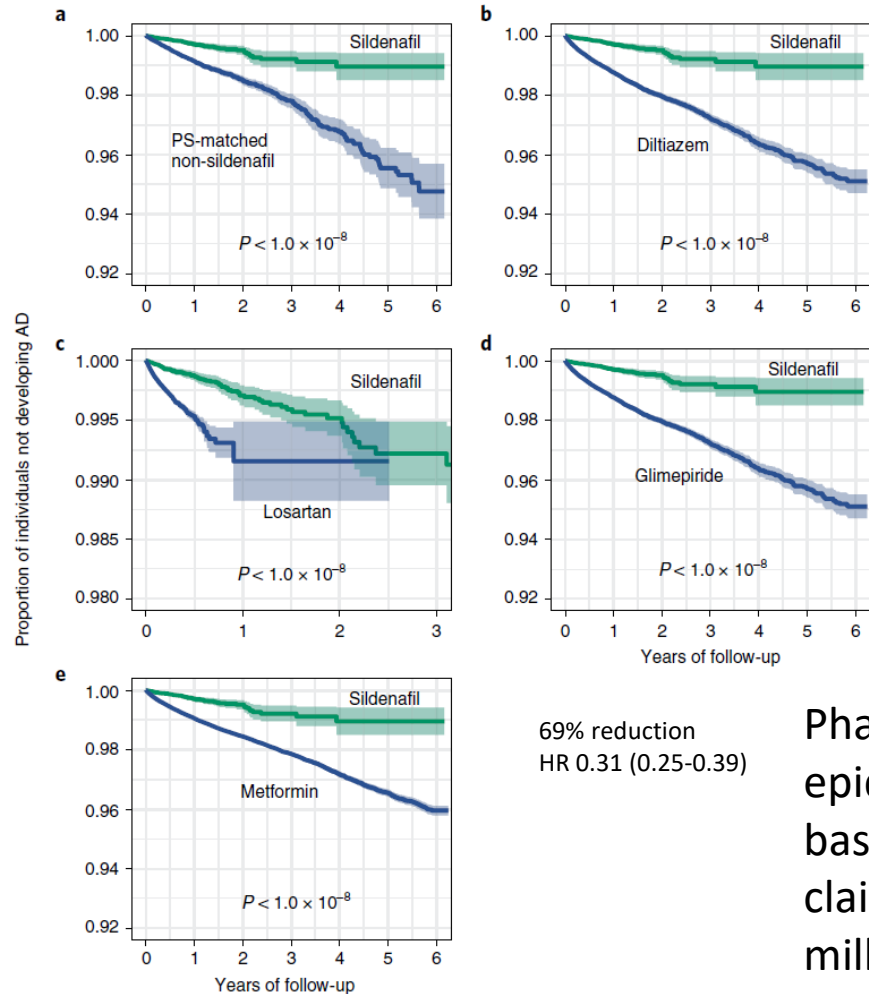
B Patients with ankle sprain



No. of patients						
Patients receiving statin	77898	75178	72072	67302	57812	49246
Control patients	229992	220347	210002	197448	178298	160707

- Pharmacoepidemiologic study of 28,815 Ontario residents >66 years old diagnosed with concussion over 10-yr period
 - Median age 76 years; 61.3% female
 - 7058 (24.5%) received a statin
 - 4727 (16%) diagnosed with dementia over mean 3.9 years follow-up
- Current recommendations for statin use based on history of vascular event, composite cardiovascular risk, and family history
 - Should TBI history be included?
 - More research is needed

What to do about microvasculopathy after TBI?—PDE-5 inhibitors

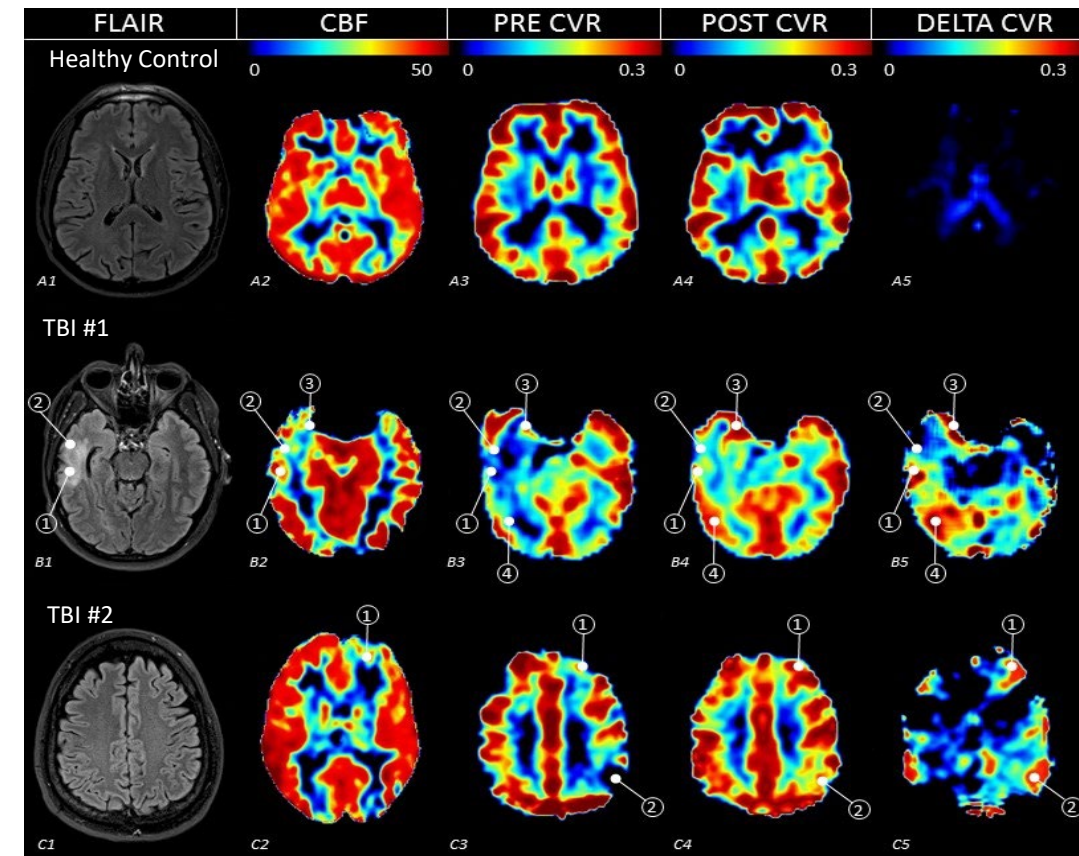


69% reduction
HR 0.31 (0.25-0.39)

Pharmaco-epidemiologic study based on insurance claim data from 7.23 million individuals at risk for AD

Fand et al *Nature Aging* 2021

Sildenafil potentiates cerebrovascular reactivity in the chronic stage after TBI



Kenney et al *Ann Clin Trans Neuro* 2018

Other therapies ready for clinical studies in elderly people after TBI

- GLP-1 antagonists
- PDE-5 inhibitors
- Anti-inflammatory agents
 - COX inhibitors (non-specific inhibitors and COX-2 specific inhibitors)
 - TNF- α inhibitors (etanercept, infliximab)
- Novel chemical entities
 - List is long
 - Anti-Tau immunotherapies
 - Anti-synuclein immunotherapies