Randomized, controlled trial of a vascular therapy for early Alzheimer's disease

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cerezen™

Causes of Alzheimer's Disease (AD)

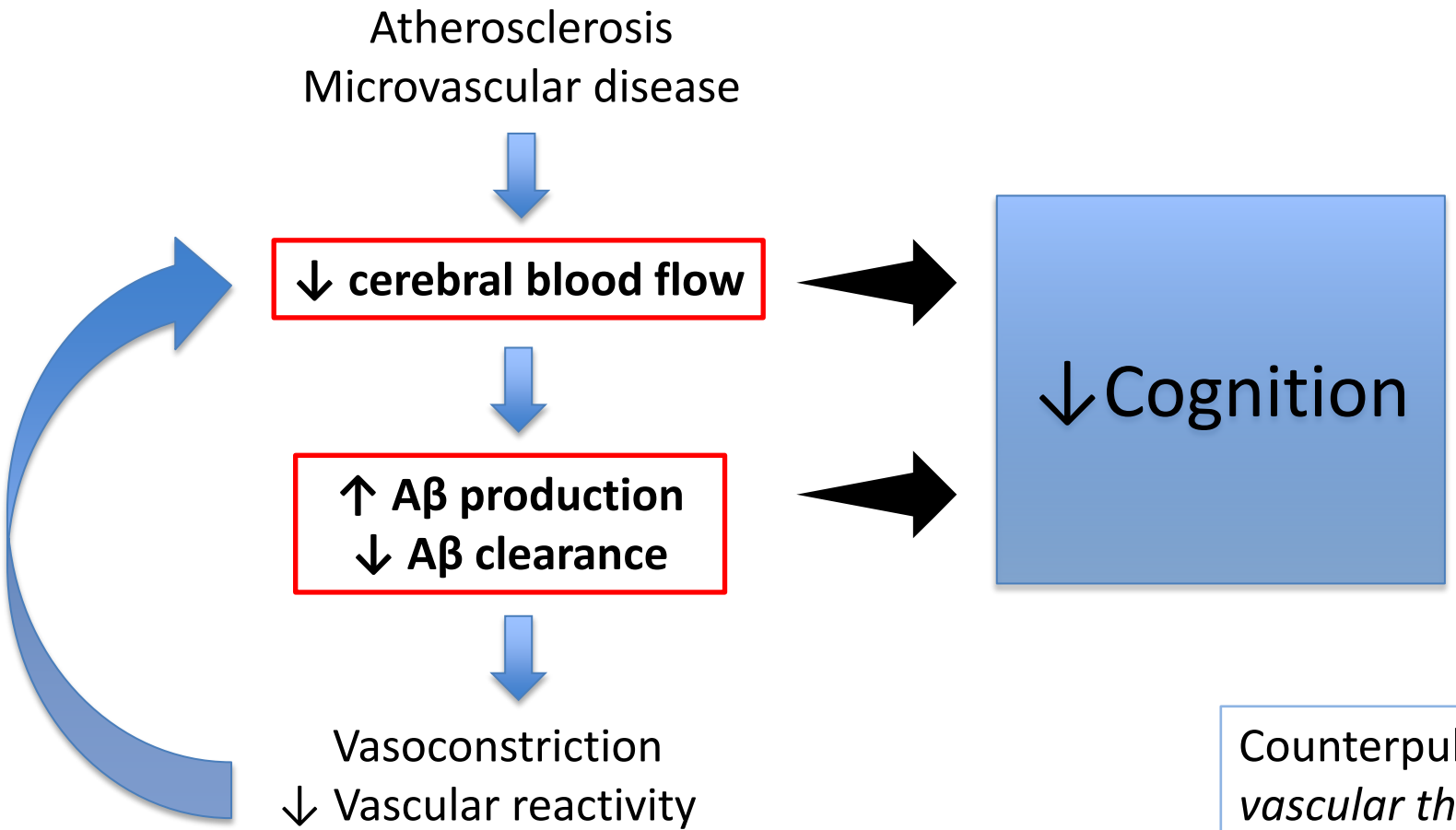
Amyloid hypothesis

- Aβ plaques and tau neurofibrillary tangles are the pathologic definition of AD.
- Plaques and tangles lead to a cascade of functional and anatomic abnormalities.
- Although Aβ plaques are characteristic of AD
    - Many individuals with amyloid build-up never develop dementia.
    - Clearing Aβ plaques slows but does not halt or reverse progression.

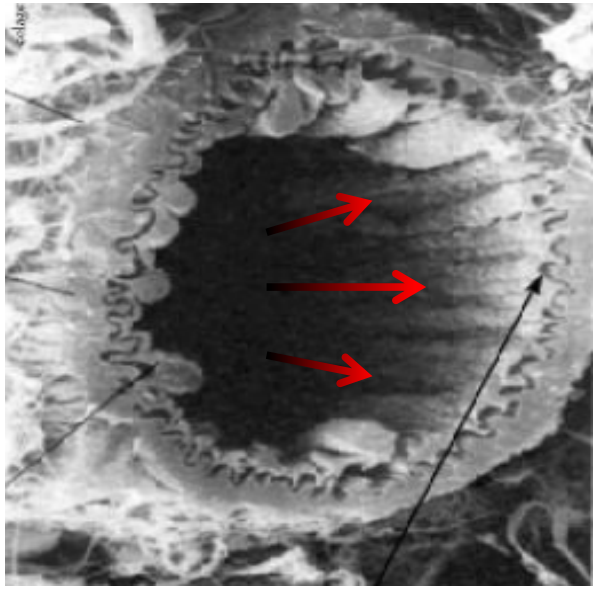
Vascular hypothesis

- >80% of AD patients have buildup of cholesterol plaque in brain arteries (atherosclerotic cerebrovascular disease).
- Up to 90% of AD patients have Aβ accumulations in arteries of the brain (CAA).
- All Alzheimer's patients:
    - Reduced brain blood flow (years before Aβ buildup)
    - Small-vessel disease

The Two-Hit Hypothesis



Counterpulsation is a *direct vascular therapy* for early AD.



Adapted from Alberts et al. 1995

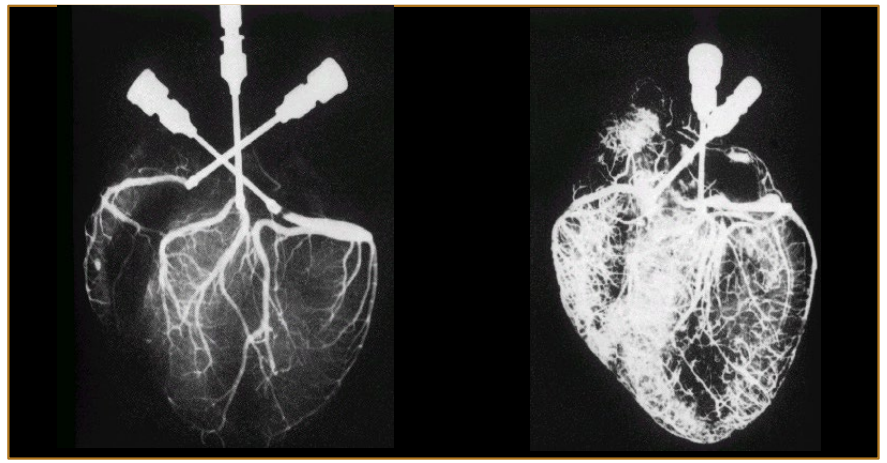
Rapid back & forth movement of blood

- Tugs on arterial lining (mechanoreceptors)
- Triggers a cascade of changes like those seen with intense exercise.

Counterpulsation is a powerful vascular therapy

Changes similar to those of intense exercise:

- ↑ Increased Nitric Oxide production
- ↓ Vascular inflammation
- ↑ Arterial flexibility (compliance)
- ↑ Vascular reactivity
- ↑ Vascular Collateralization



No counterpulsation Counterpulsation

Canine Heart

Jacobey et al. AJC 11(2):218

Randomized, Controlled Trial NCP-5-1001

190 patients

- Mild Cognitive Impairment due to Alzheimer's Disease (n=137)
- Mild Alzheimer's Disease (n=53)
- 70% of patients referred to the study met criteria for inclusion

True placebo not possible, so subjects were randomized to either:

- Low-pressure Treatment (25-50 mmHg) a.k.a. "**Sham**"
- Full-pressure Treatment (150-300 mmHg, based on patient comfort) a.k.a. **Cerezen**

Treatment:

- 1-hour treatments
- 3-5x weekly for 35 treatments then 2x per week out to 6 months.
- After 6 months (24 weeks), no further treatments.

Randomized, Controlled Trial NCP-5-1001

Evaluations:

- 6, 12, 18 weeks, 6 and 9 months, and 1 year

Outcomes:

- ADAS-cog 14 – Alzheimer's Disease Assessment Scale
- VADAS-cog – Vascular Dementia Assessment Scale

} Memory, reasoning, cognition

- ADCS-ADL – Activities of Daily Living ← Independent functioning
- ADCS-CGIC – Clinician's Global Assessment of Change
- MMSE – Mini-mental Status Exam
- Trail Making Test B

Randomized, Controlled Trial run across 10 sites - 2018 through 2021

University of Kansas Medical Center	Kansas City
Irvine Clinical Research	Irvine, CA
iResearch Savannah	Savannah, GA
Neuro-Behavioral Clinical Research, Inc.	Canton, OH
Northwest Clinical Research Center	Bellevue, WA
Cardiovascular Advantages LLC	Baton Rouge, LA
Xenoscience	Phoenix, AZ
Miami Dade Medical Research Institute	Miami, FL
iResearch Atlanta, LLC	Decatur, GA
Charter Research	Lady Lake, FL

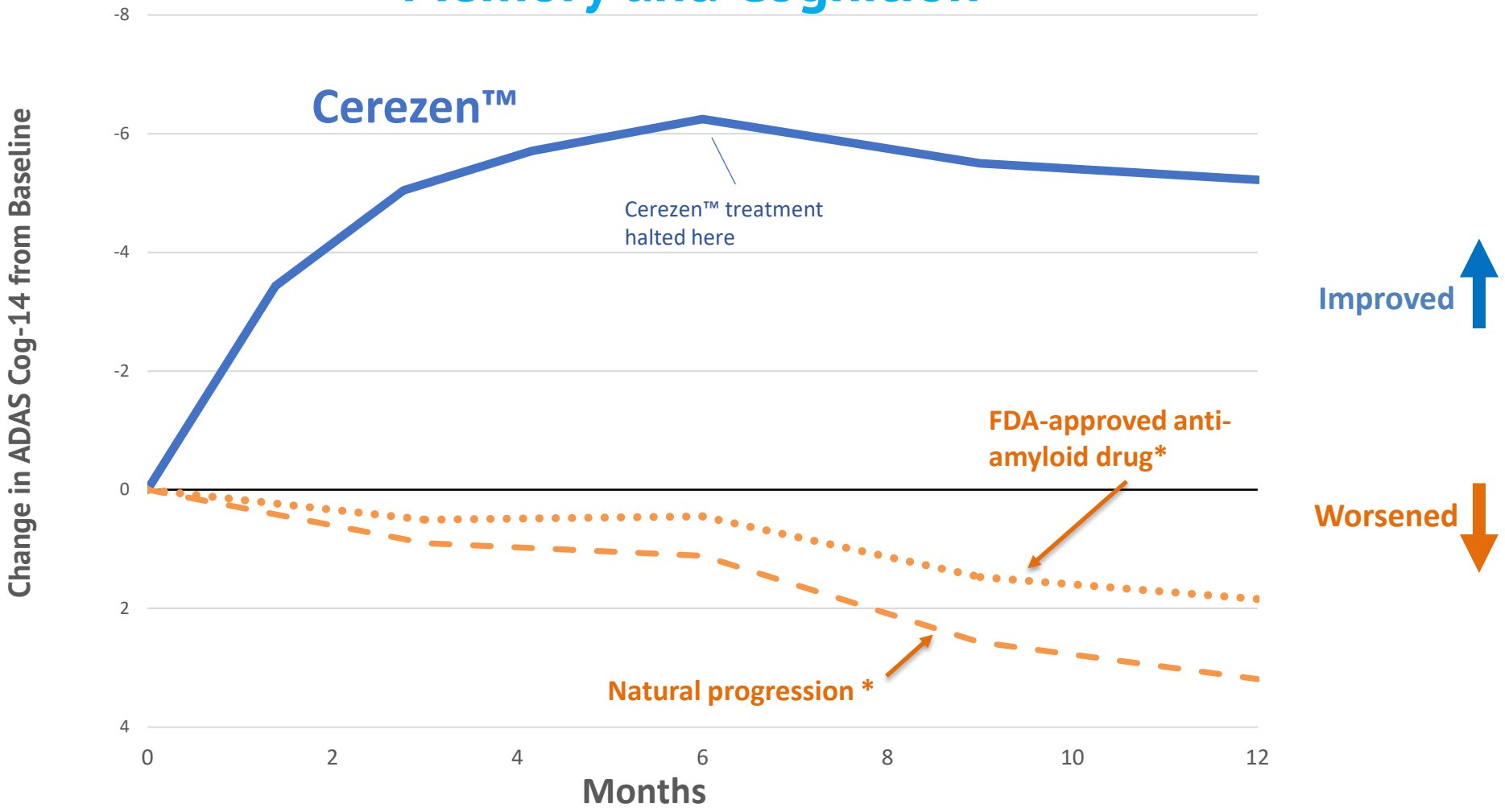
Among most diverse demographics of any AD therapy trial to date

- 14% African American
- 19% Hispanic
- 4% Asian
- 61% Women

(Note U.S. population: 51% women, 12 % African American, 18.7% Hispanic)

Results met ALL primary endpoints and most secondary endpoints

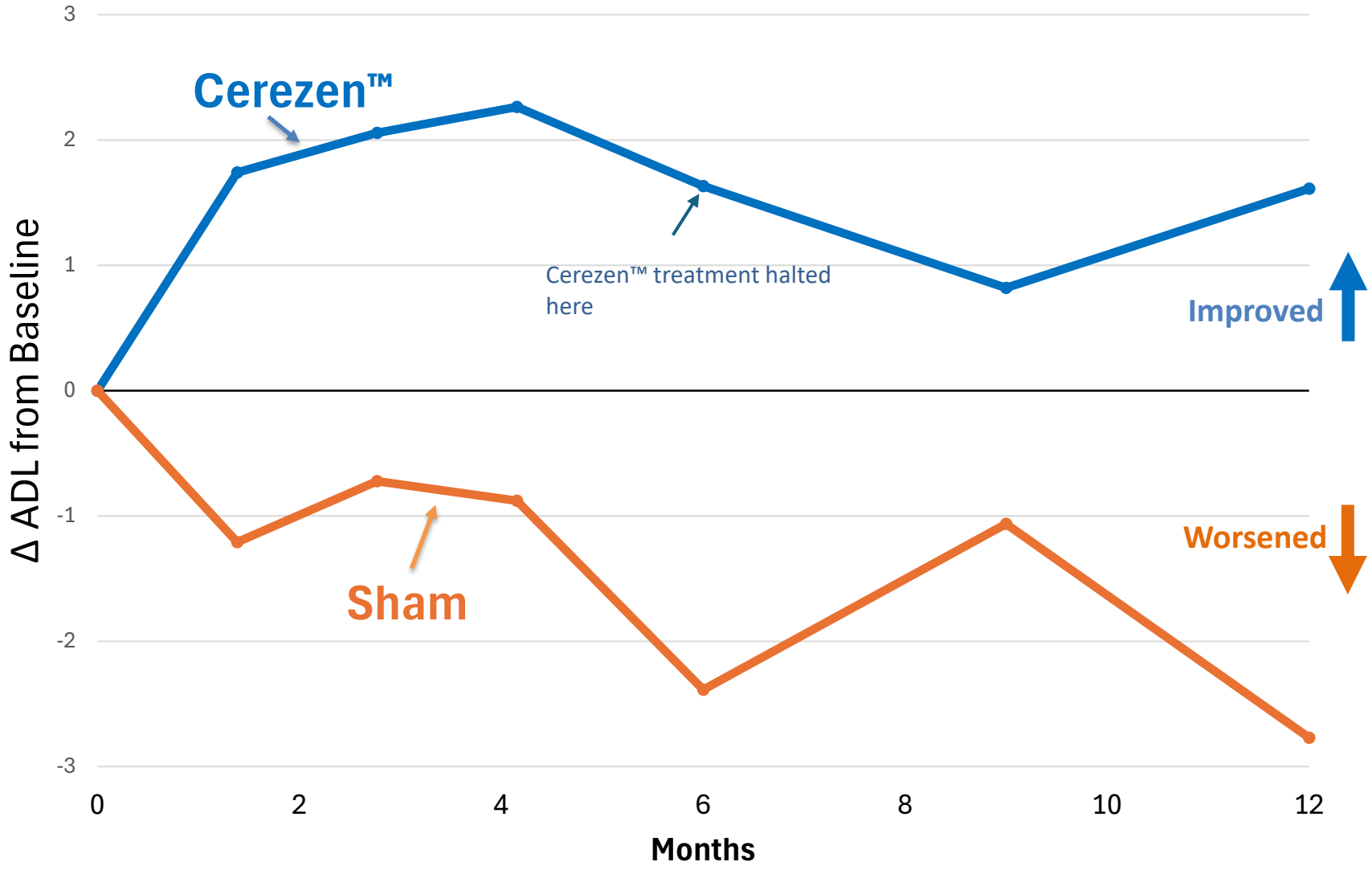
Memory and Cognition



* Adapted from New England Journal of Medicine. 2023;388(1):9-21.

Moriarty PM, et al: Arteriosclerosis, Thrombosis, and Vascular Biology. 2022;42(Suppl_1):A483-A483

Functional Independence (ADL)



Moriarty PM, et al: Arteriosclerosis, Thrombosis, and Vascular Biology. 2022;42(Suppl_1):A483-A483

Cerezen™ treatment had particularly beneficial effects† on those patients (39/190) who had co-existing type II diabetes.

Alzheimer's pathology related to that of diabetes:

- ↓ Vascular insulin receptors *
- ↓ Vasoreactivity to local need *
- ↓ Arteriolar / capillary density *
- ↑ Vascular inflammation *

* Factors known to benefit systemically from counterpulsation

†Moriarty PM, et al: Neurology. 2022;98 (18_supplement):3139

Adverse events

- No serious device-related adverse events were seen.
- 16.3% of patients had skin chaffing or bruising, none of which required discontinuation of treatment.
  - Generally eliminated with cuff or clothing adjustments.

Study conclusions

- Cerezen™ treatment was well-tolerated with no serious adverse events.
- The majority of patients *improved* over their own baseline.
- At one year, most patients were still improved in *both* cognition and independent function.
- Cerezen™ is an effective and low-risk treatment for early Alzheimer's disease

Cerezen™ is certified under the EU MDR

Indication

Cerezen™ is indicated for the treatment of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease.

Intended Use

Cerezen™ is intended for use as a component in the overall management of symptoms of cognitive and/or functional impairment experienced by patients with mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease. It is intended for use under the oversight of a healthcare professional.

Intended Patient Population

Cerezen™ is intended for use in adults suffering from mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease.

Cerezen is CE-marked in the European Union. It is not cleared by the U.S. Food and Drug Administration and is not available for sale in the United States.