



Componente vascular en la enfermedad de Alzheimer

4 de julio de 2022

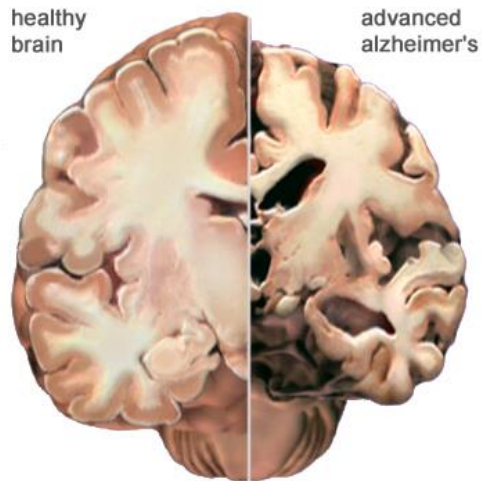
IV Reunión Anual del Área de Enfermedades Renales, Metabólicas y Cardiovasculares del IIS-FJD

Marta Cortés Canteli, PhD
Investigadora Miguel Servet II

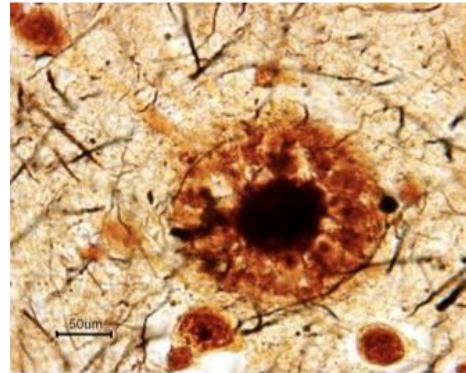


Alzheimer's disease

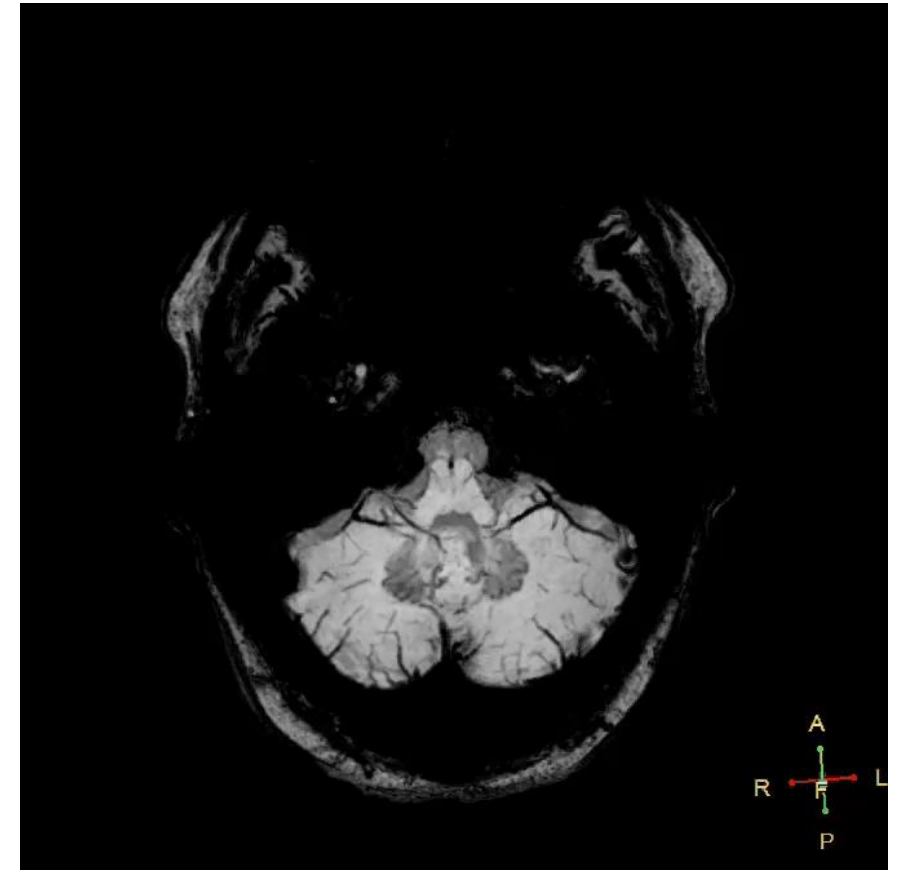
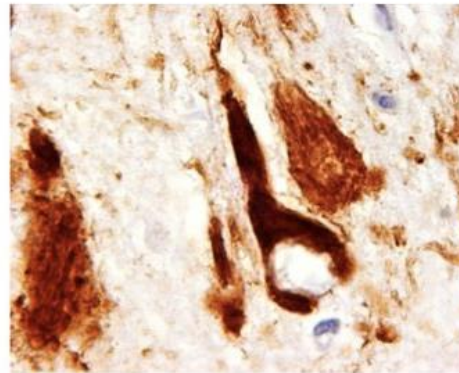
- ✓ Complex and multifactorial neurodegenerative disease.
- ✓ 35 million people affected (100 by 2050).
- ✓ Main pathological hallmarks: amyloid plaques & tau tangles.
- ✓ Treatment: Only symptomatic agents.
- ✓ Pharmacological & non-pharmacological approaches under development.



Plaques



Neurofibrillary Tangles



Dr. Alois Alzheimer

Auguste D. autopsy (1st patient with AD)

During the morning exitus letalis; cause of death: septicaemia due to decubitus; anatomical diagnosis: moderate hydrocephalus (external internal); cerebral atrophy; arteriosclerosis of the small cerebral blood vessels; ? ; pneumonia of both inferior lobes; nephritis.

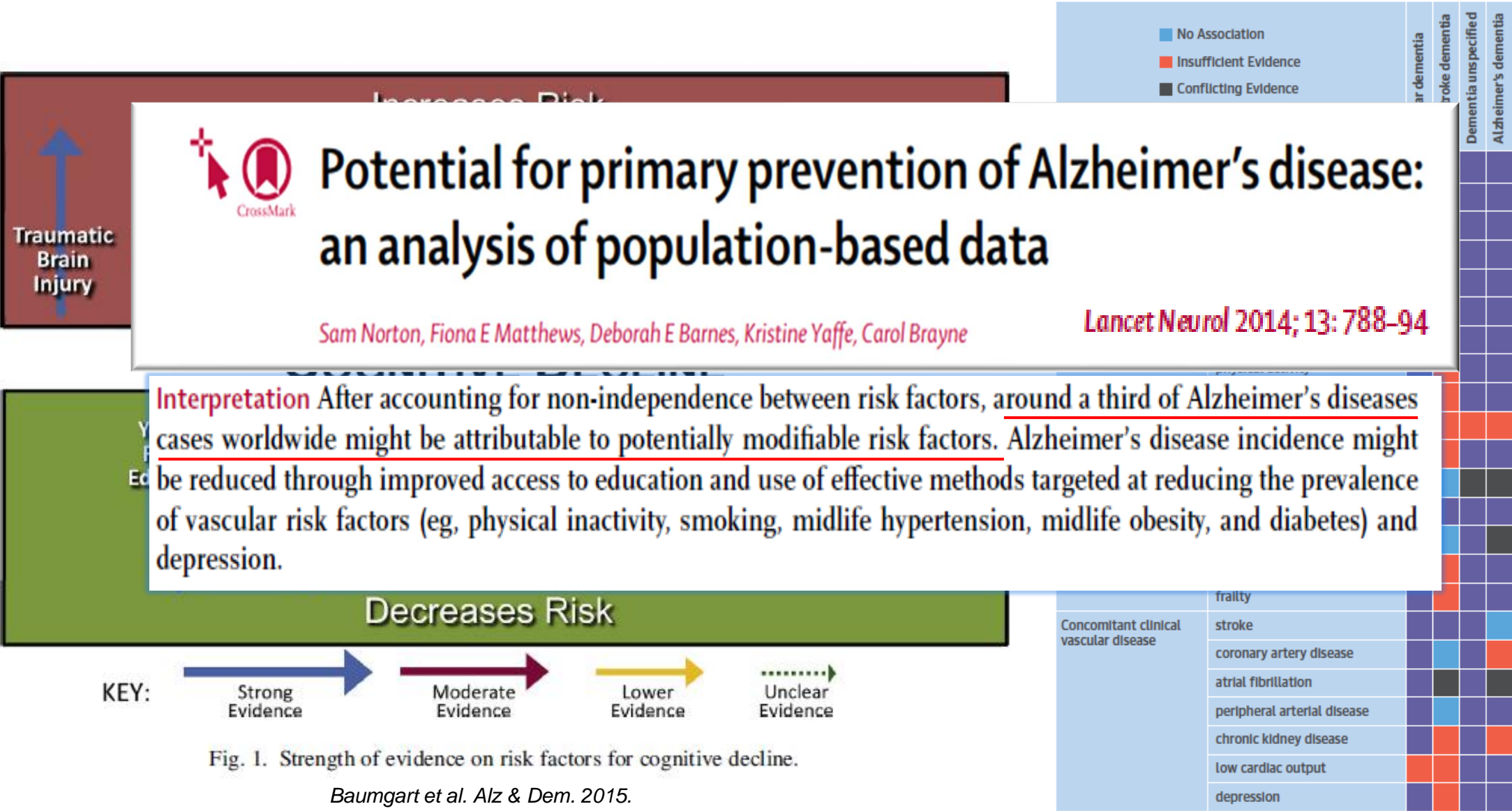
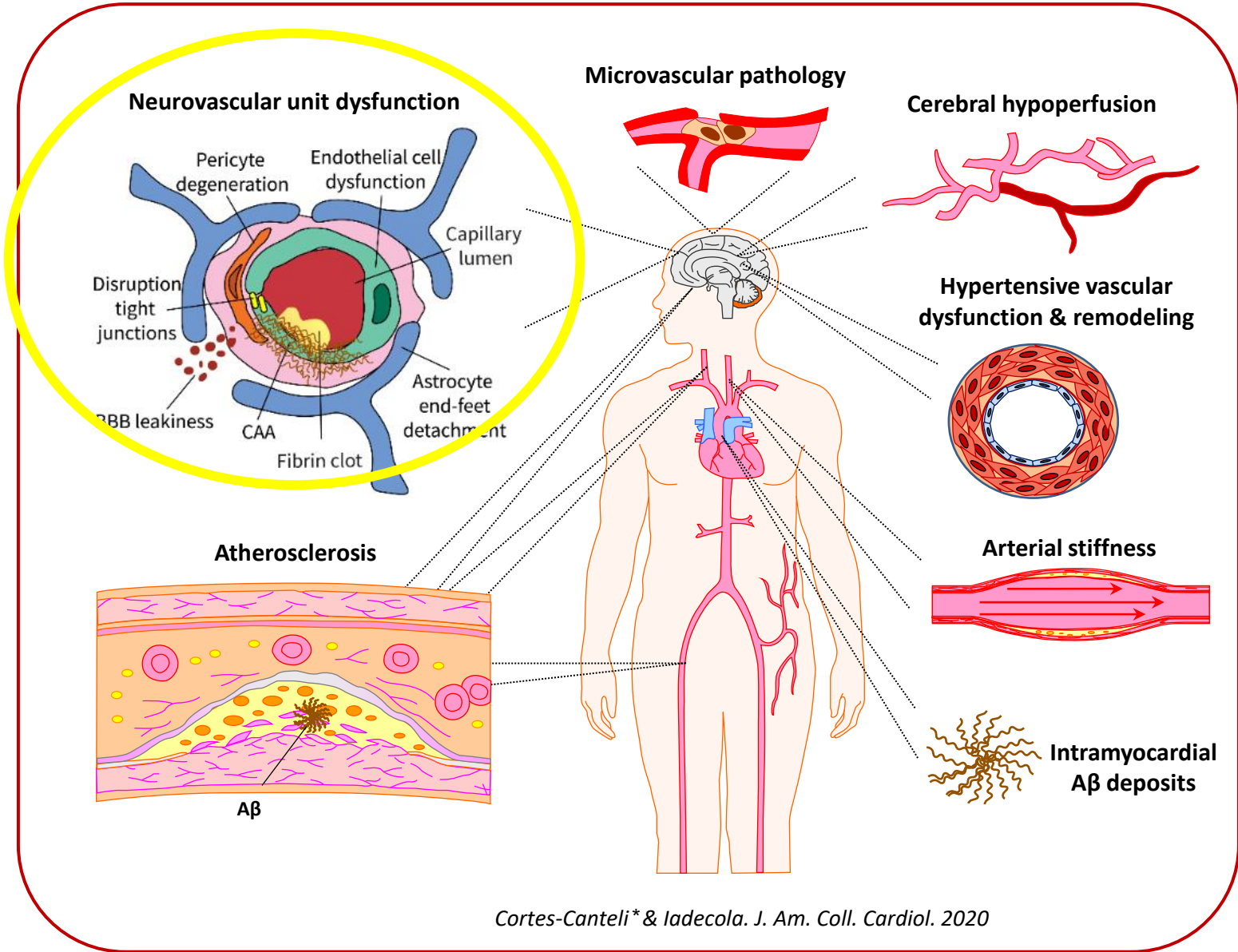
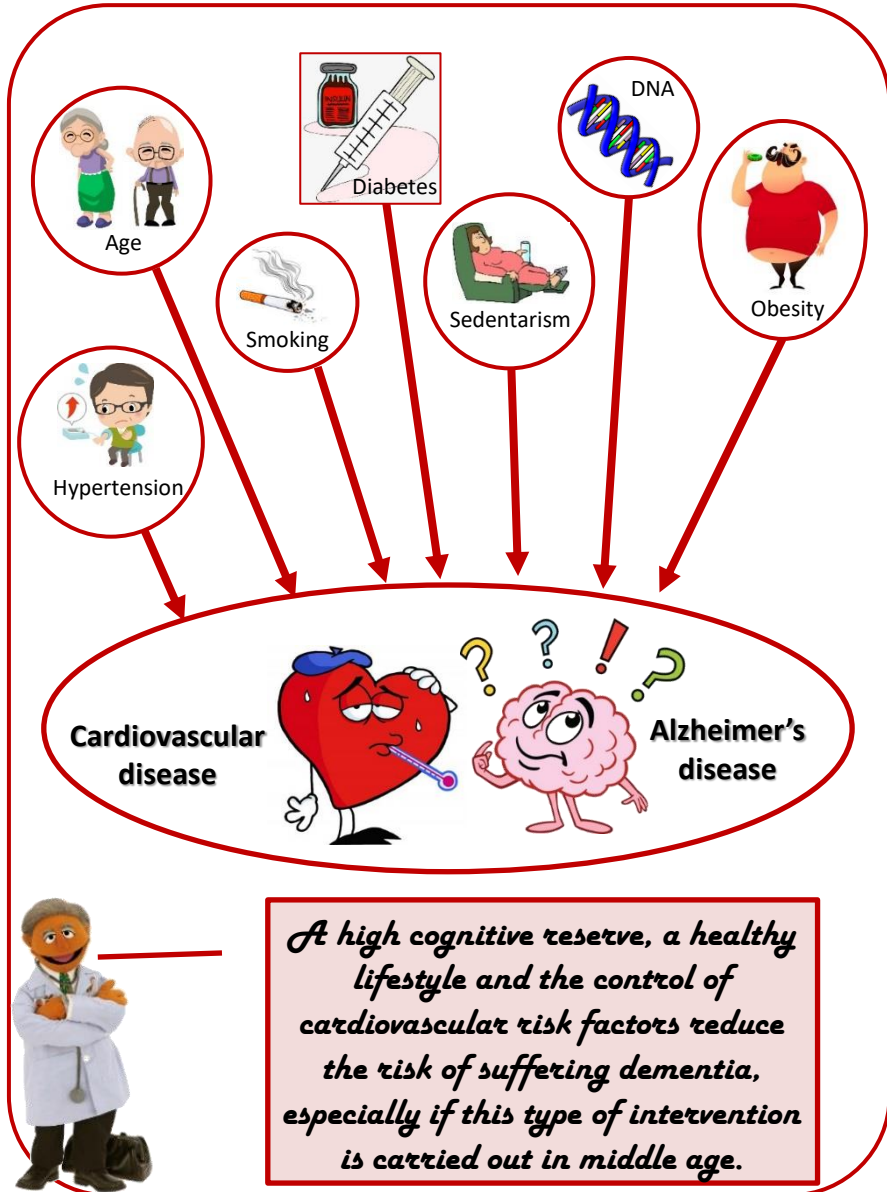




Fig. 1. Strength of evidence on risk factors for cognitive decline.

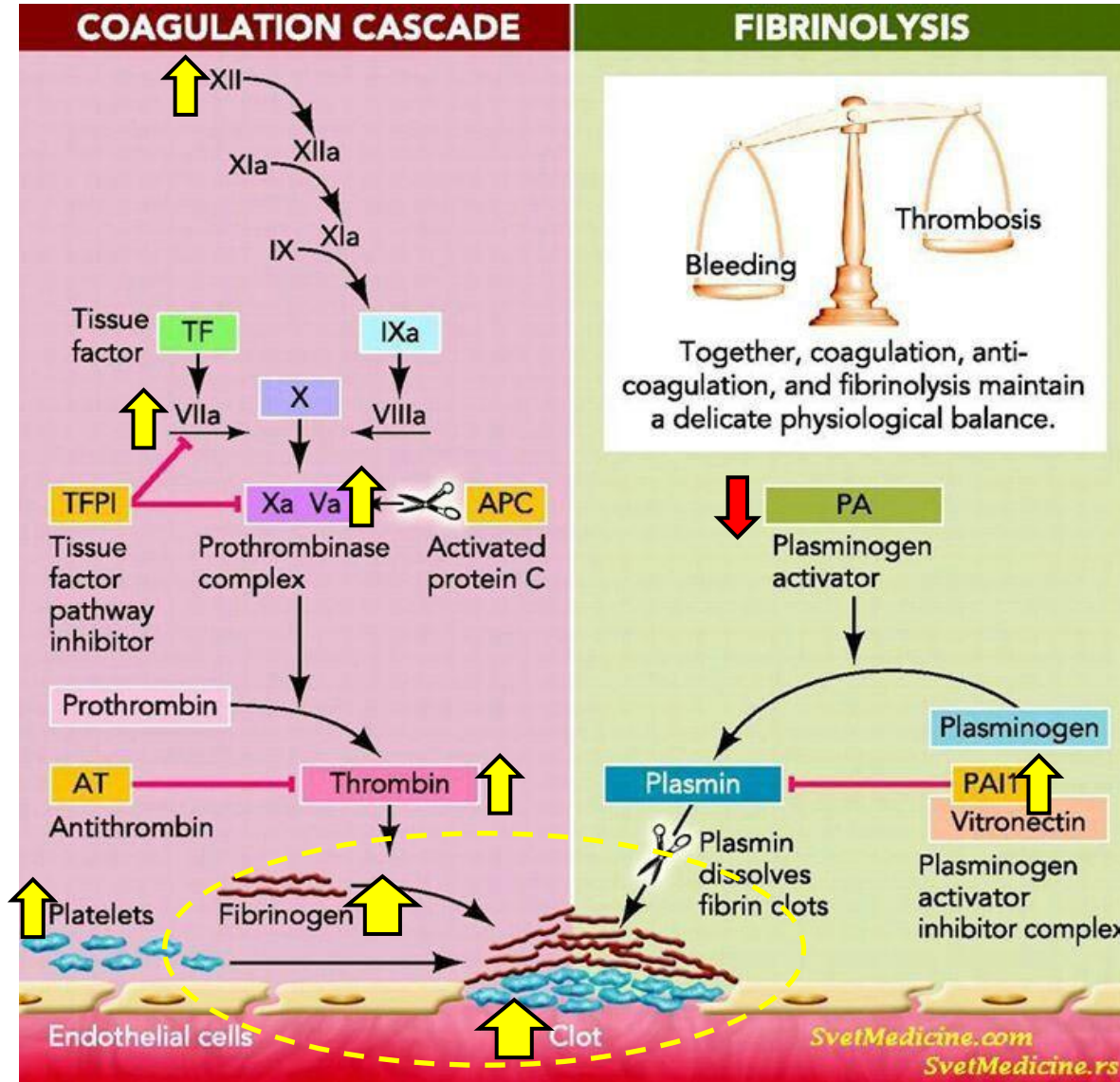
Baumgart et al. *Alz & Dem.* 2015.

The Heart-Brain Axis in Alzheimer's Disease



Pro-coagulant state in Alzheimer's disease

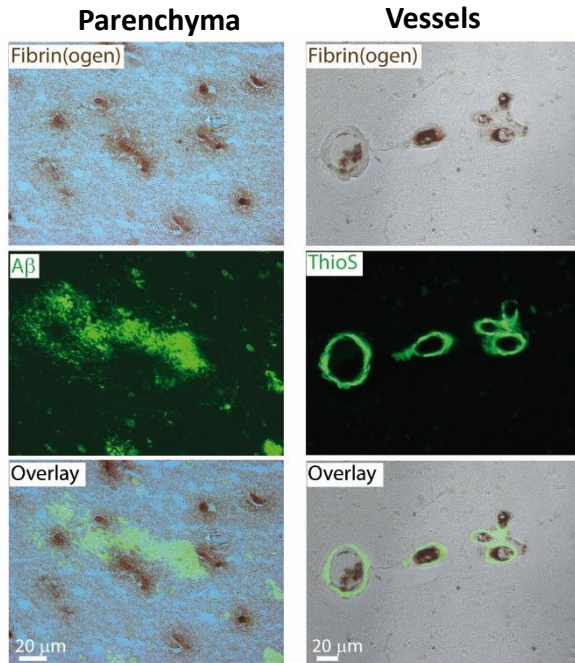
 Induced in AD
 Inhibited in AD



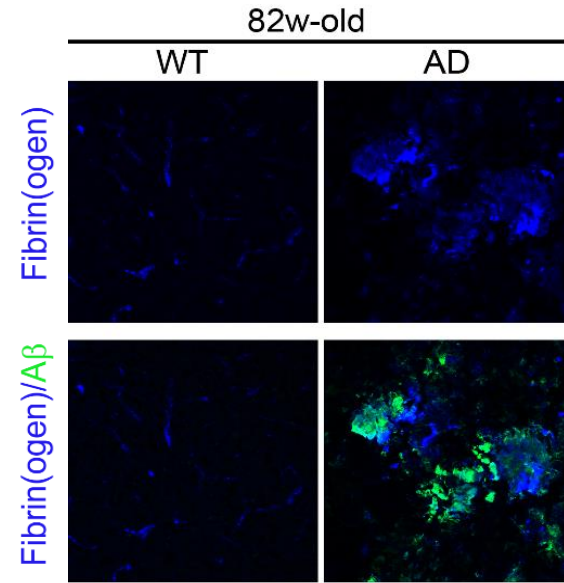
Fibrin(ogen) accumulation in AD?

Pro-coagulant state in Alzheimer's disease

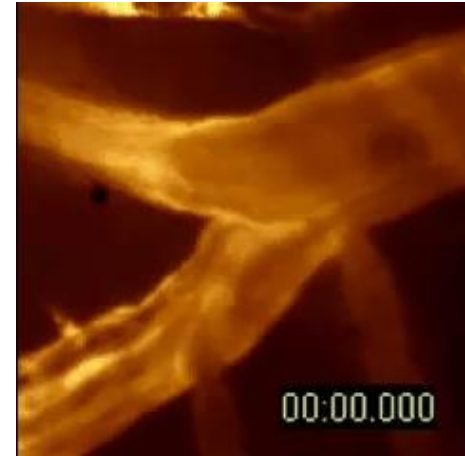
Human AD Brain



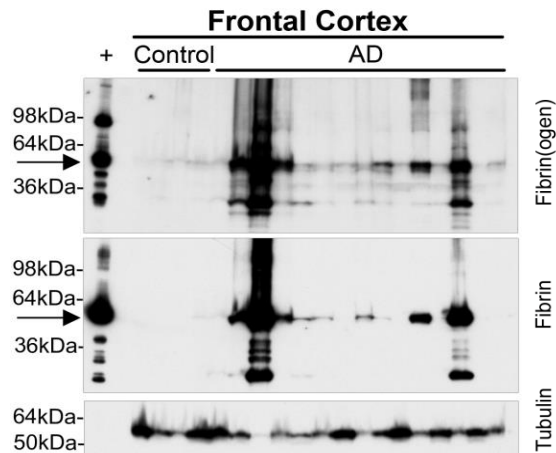
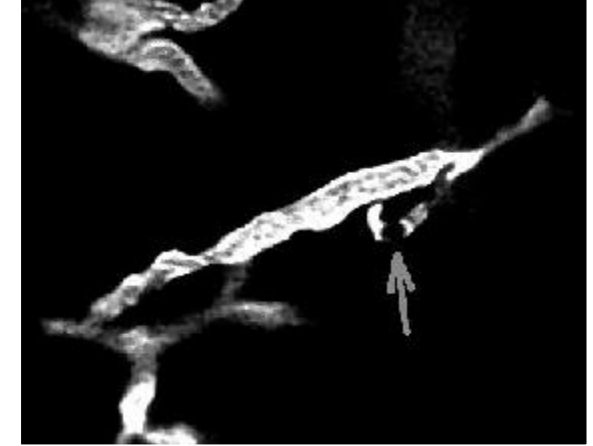
Mouse AD Brain



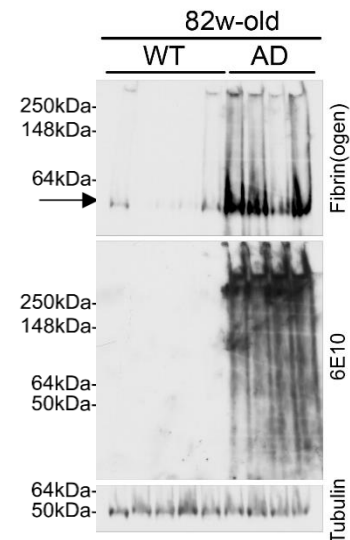
Thrombosis & Fibrinolysis in AD mice



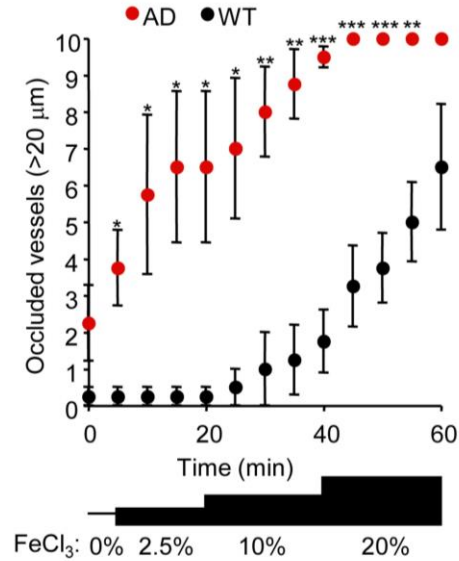
Increased Stalled Brain Capillaries in AD mice



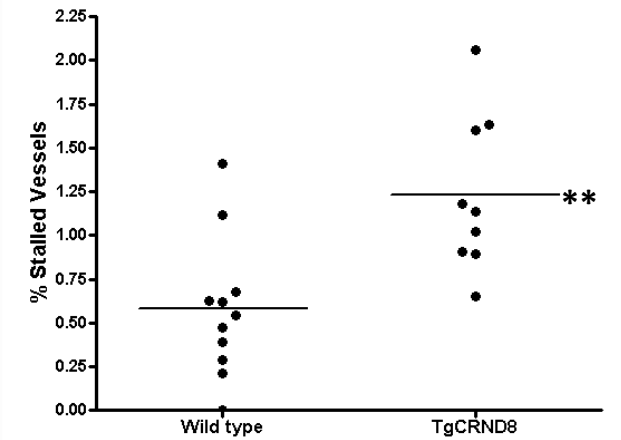
Cortes-Canteli et al. *J. Alz. Dis.* (2012)



Cortes-Canteli et al. *Neurobiol. Aging* (2015)




Cortes-Canteli, Paul et al *Neuron* (2010)



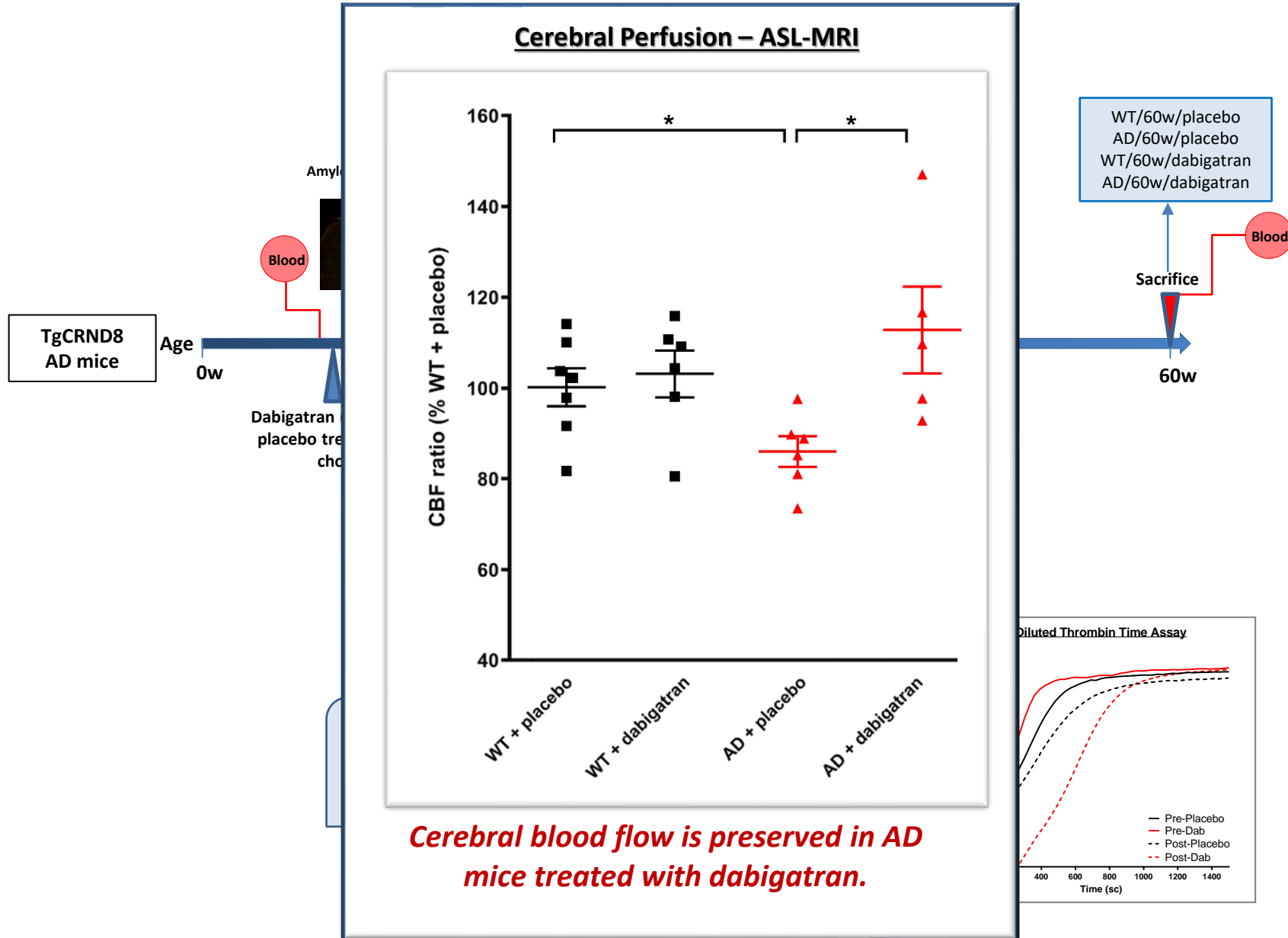
Cruz Hernandez; Bracko; Kersbergen; Muse; Haft-Javaherian; Berg; Park; Vinarcsik; Ivasyk; Kang; Cortes-Canteli, et al. *Nat. Neuroscience.* (2019)

Pro-coagulant state in AD



Would a therapeutic approach aimed at normalizing the thrombosis in AD be beneficial?

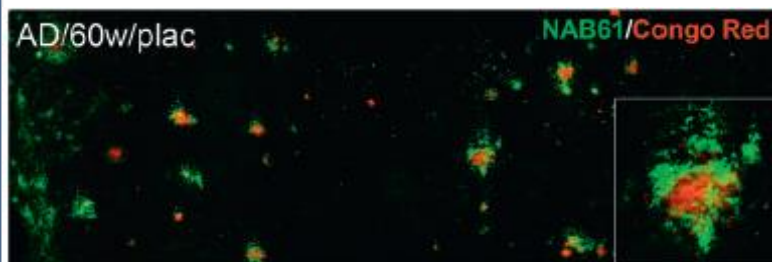
Dabigatran delays Alzheimer's disease pathogenesis



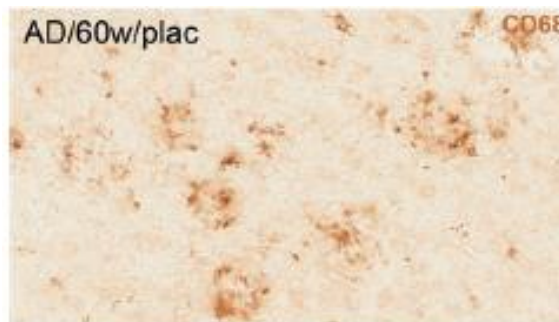
Dabigatran delays Alzheimer's disease pathogenesis

Brain Histology

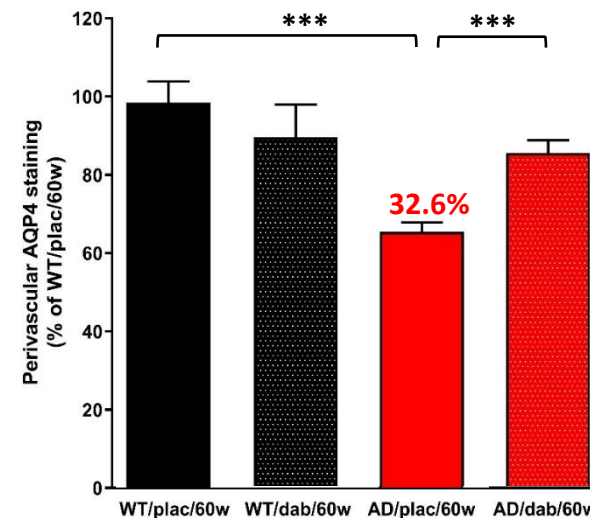
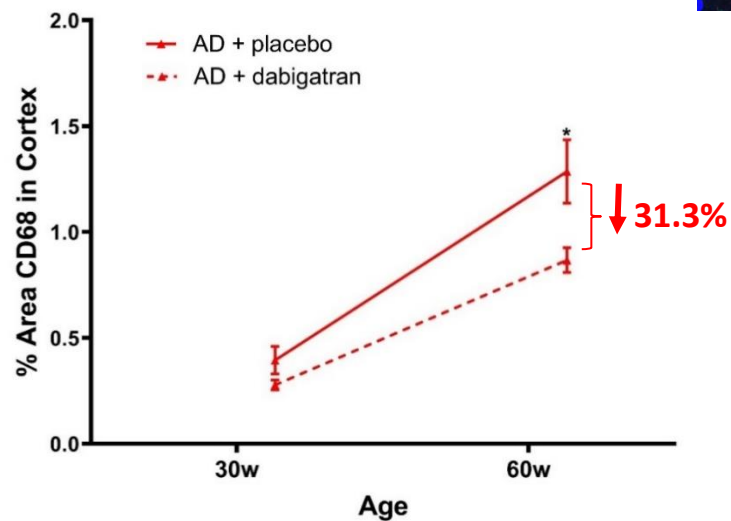
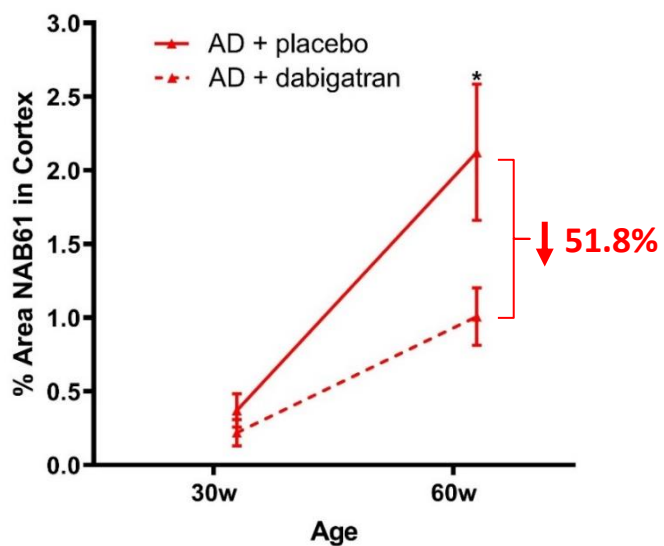
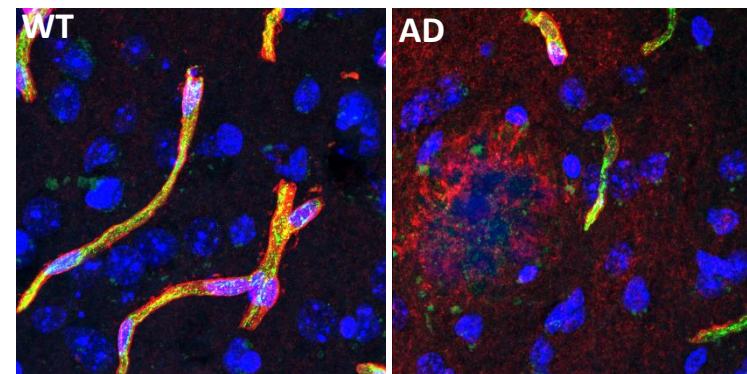
β – amyloid oligomers (Nab61)



Phagocytic microglia (CD68)



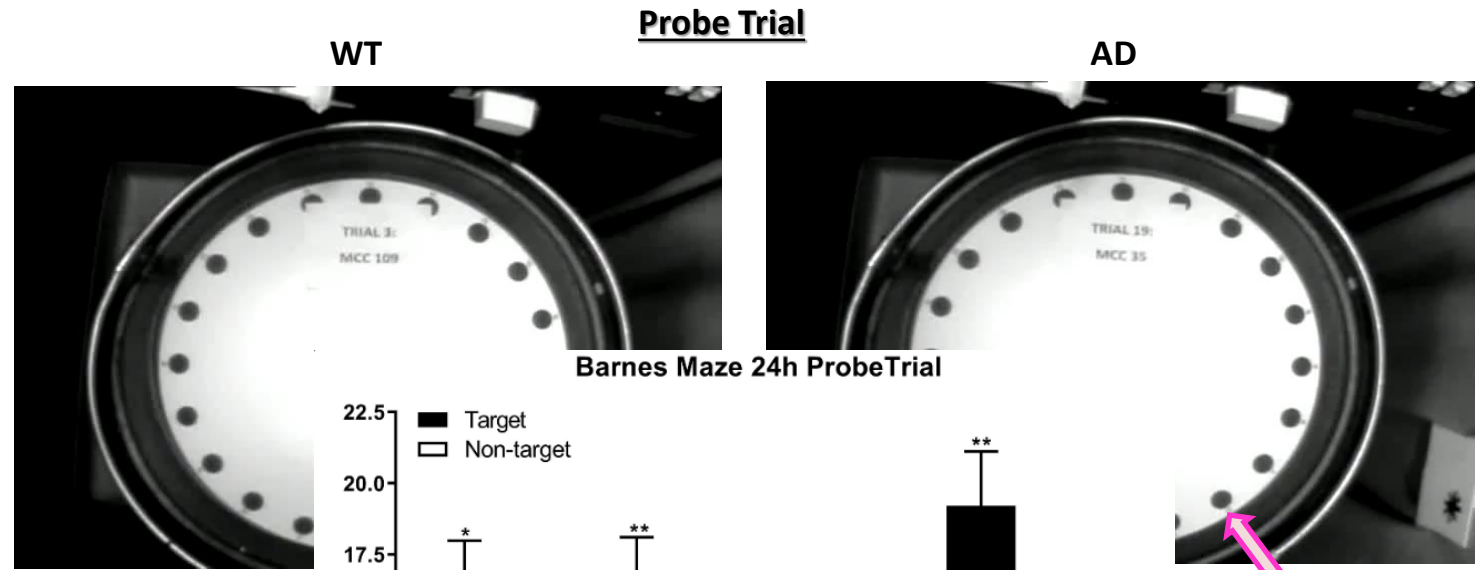
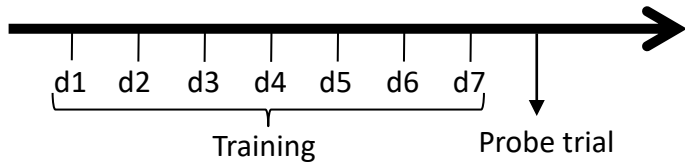
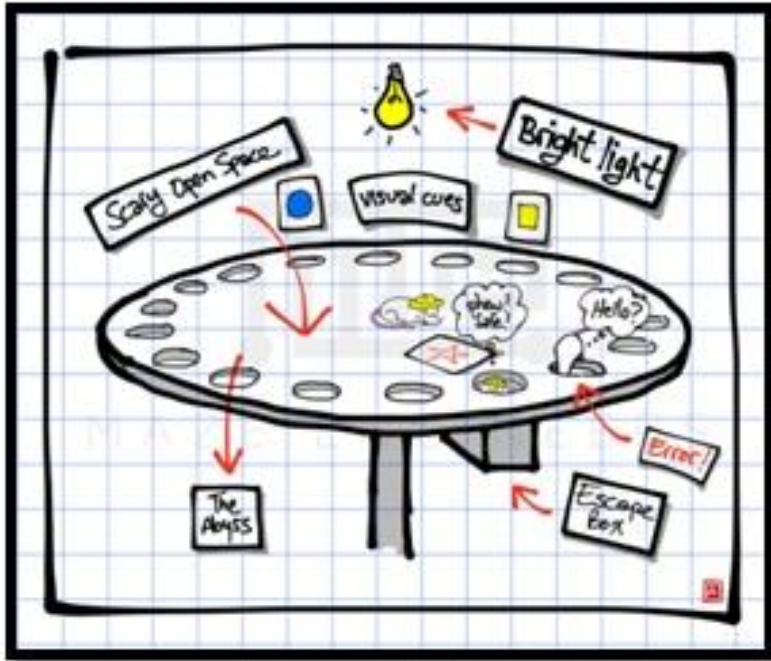
BBB- Astrocytic endfeet (AQP4)



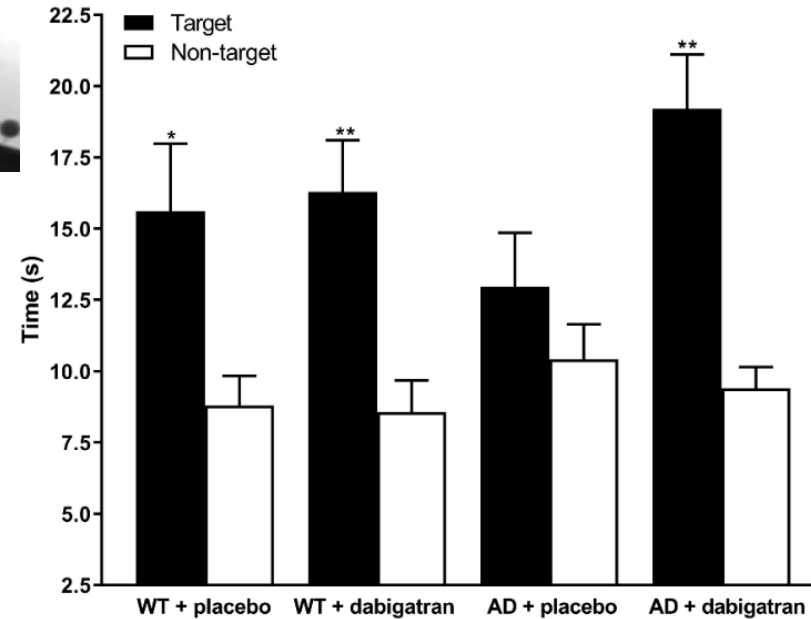
Long-term dabigatran treatment ameliorates amyloid burden, neuroinflammation and BBB damage in AD mice.

Dabigatran delays Alzheimer's disease pathogenesis

Memory Task - Barnes Maze



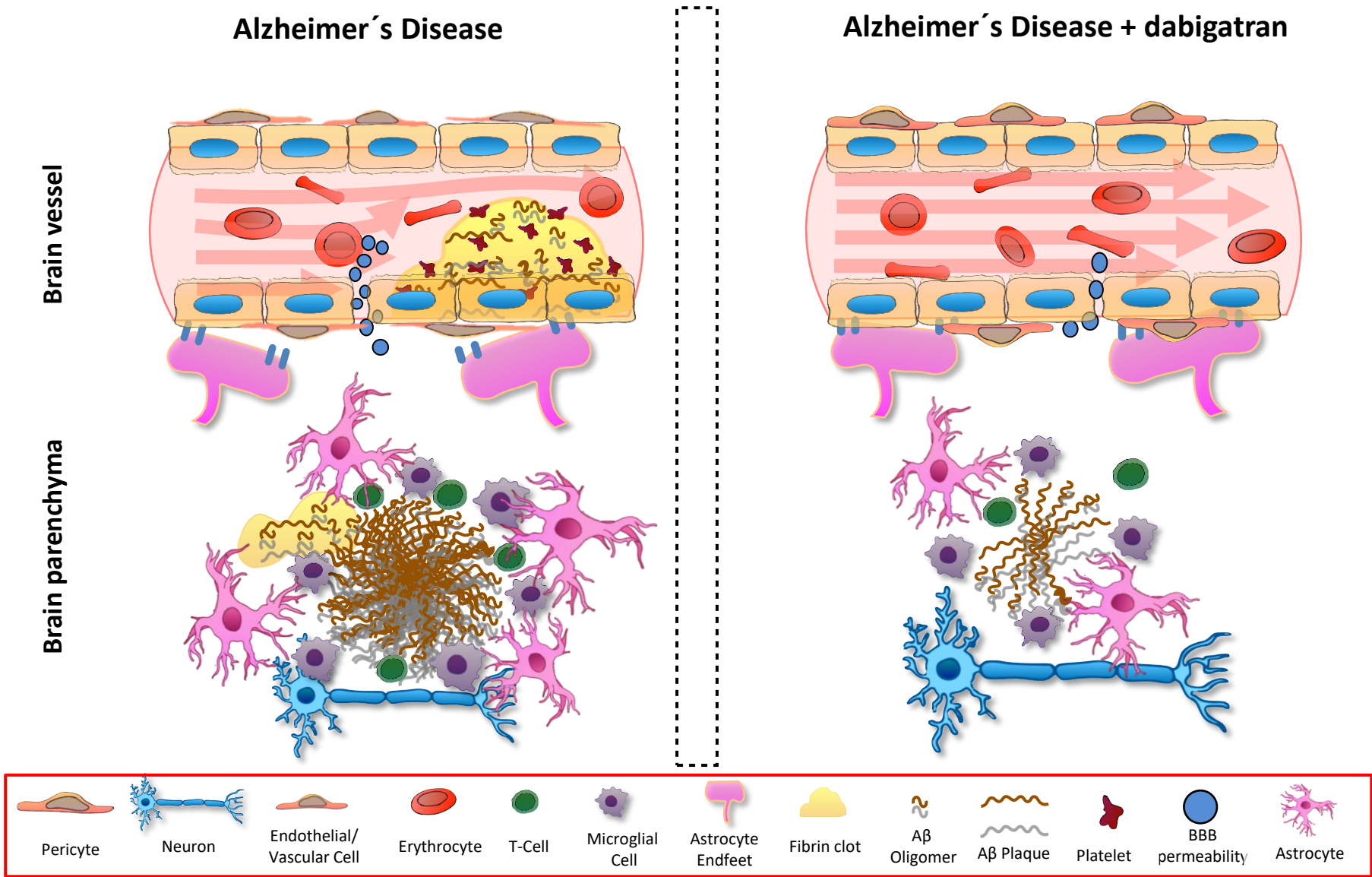
Barnes Maze 24h ProbeTrial



Anticoagulation with dabigatran prevents memory decline in AD mice.

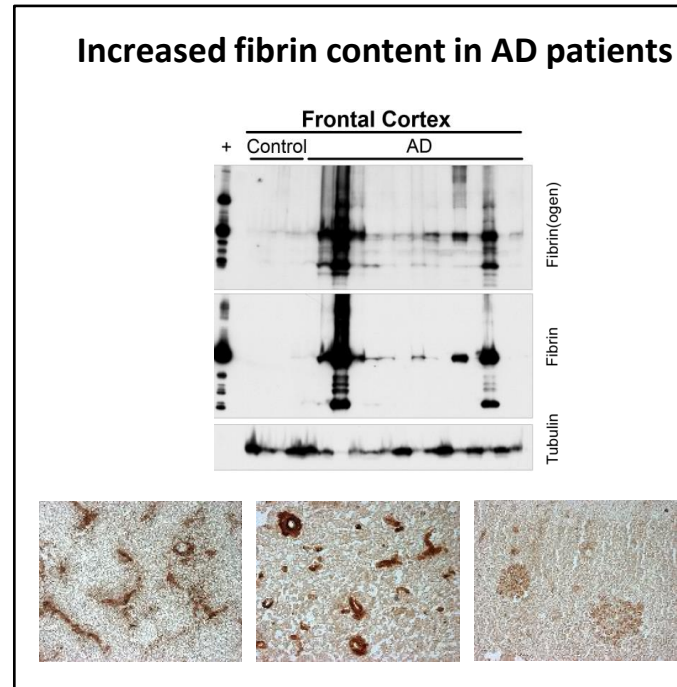
CENTRAL ILLUSTRATION: Long-Term Anticoagulation With Dabigatran Prevents Fibrin Deposition In The Alzheimer's Disease Brain, Ameliorating Amyloid Pathology And Neuroinflammation And Preserving Blood Brain Barrier Integrity and Cerebral Blood Flow.

Cortes-Canteli* et al. *J. Am. Coll. Cardiol.* (2019)



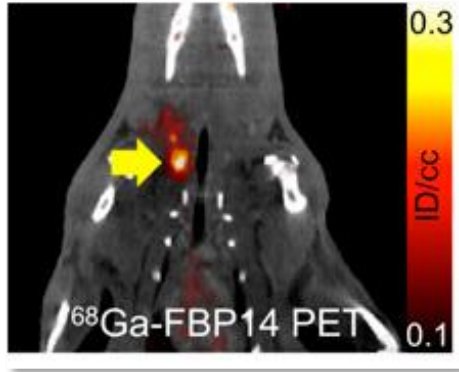
Pro-coagulant state in AD

Would a diagnostic approach aimed at localizing the thrombosis in AD be useful?



*AD is a multifactorial disease.
Individualized diagnostic and therapeutic strategies are needed!!*

In vivo imaging to detect the cerebral occlusions present in the vasculature of the AD brain.



Oliveira et al. J. Nucl. Med. 2015

Positron Emission Tomography – Molecular Imaging

FIBRIN

Fibrin Binding Probe (P. Caravan. MGH)

BioClotAD Study



Cortes-Canteli
Coordinator
Spain



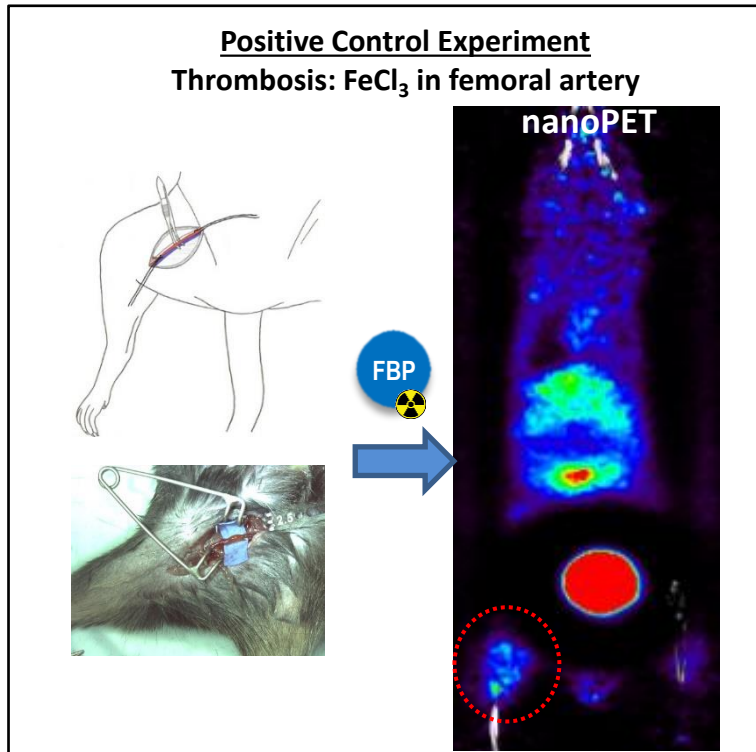
Desco
Partner
Spain



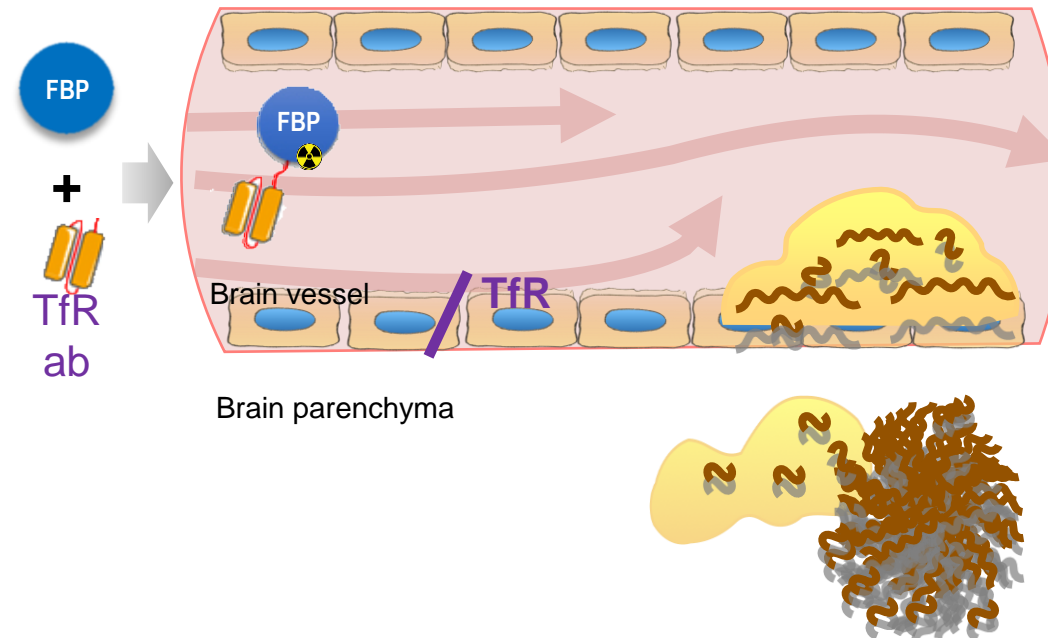
Sehlin
Partner
Sweden



Kossatz
Partner
Germany



Vascular + parenchymal fibrin PET imaging in AD mice



Take-Home Messages

There is a pro-coagulant state in AD contributing to disease onset & progression

A diagnostic approach would be fundamental to develop individualized therapeutic strategies

Thank you!



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