

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

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SANITARIA
FUNDACIÓN JIMÉNEZ DÍAZ

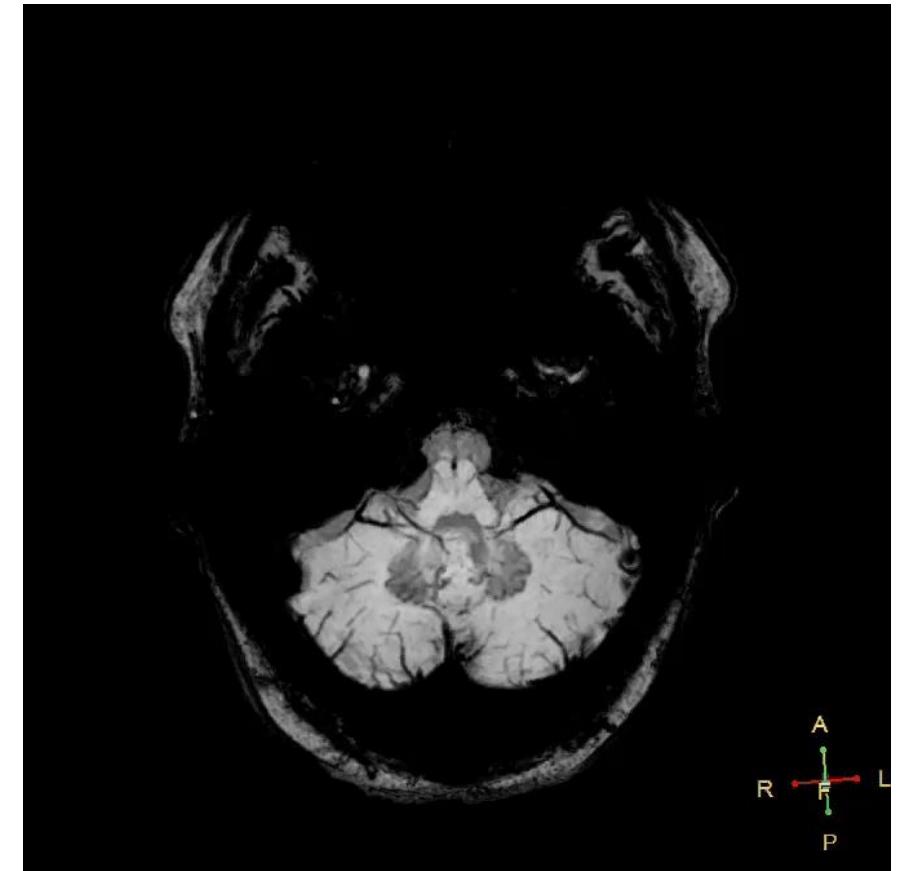
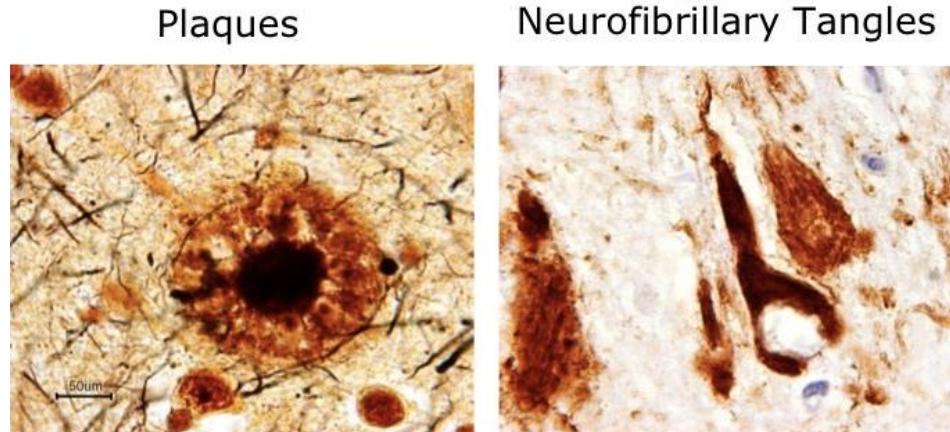
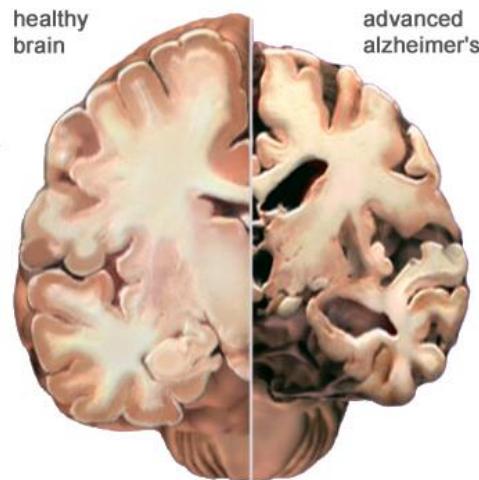


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Alzheimer's disease

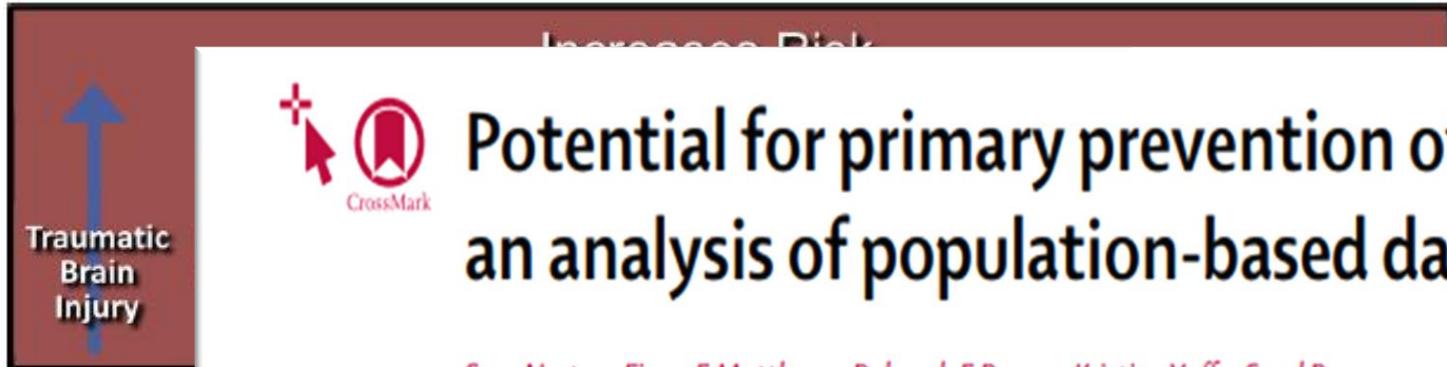
- ✓ Complex and multifactorial neurodegenerative disease.
- ✓ 35 million people affected (100 by 2050).
- ✓ Main pathological hallmarks: amyloid plaques & tau tangles.
- ✓ Treatment: Only symptomatic agents.
- ✓ Pharmacological & non-pharmacological approaches under development.



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.



Potential for primary prevention of Alzheimer's disease: an analysis of population-based data

Sam Norton, Fiona E Matthews, Deborah E Barnes, Kristine Yaffe, Carol Brayne

Lancet Neurol 2014; 13: 788–94

Interpretation After accounting for non-independence between risk factors, around a third of Alzheimer's diseases cases worldwide might be attributable to potentially modifiable risk factors. Alzheimer's disease incidence might be reduced through improved access to education and use of effective methods targeted at reducing the prevalence of vascular risk factors (eg, physical inactivity, smoking, midlife hypertension, midlife obesity, and diabetes) and depression.

Decreases Risk



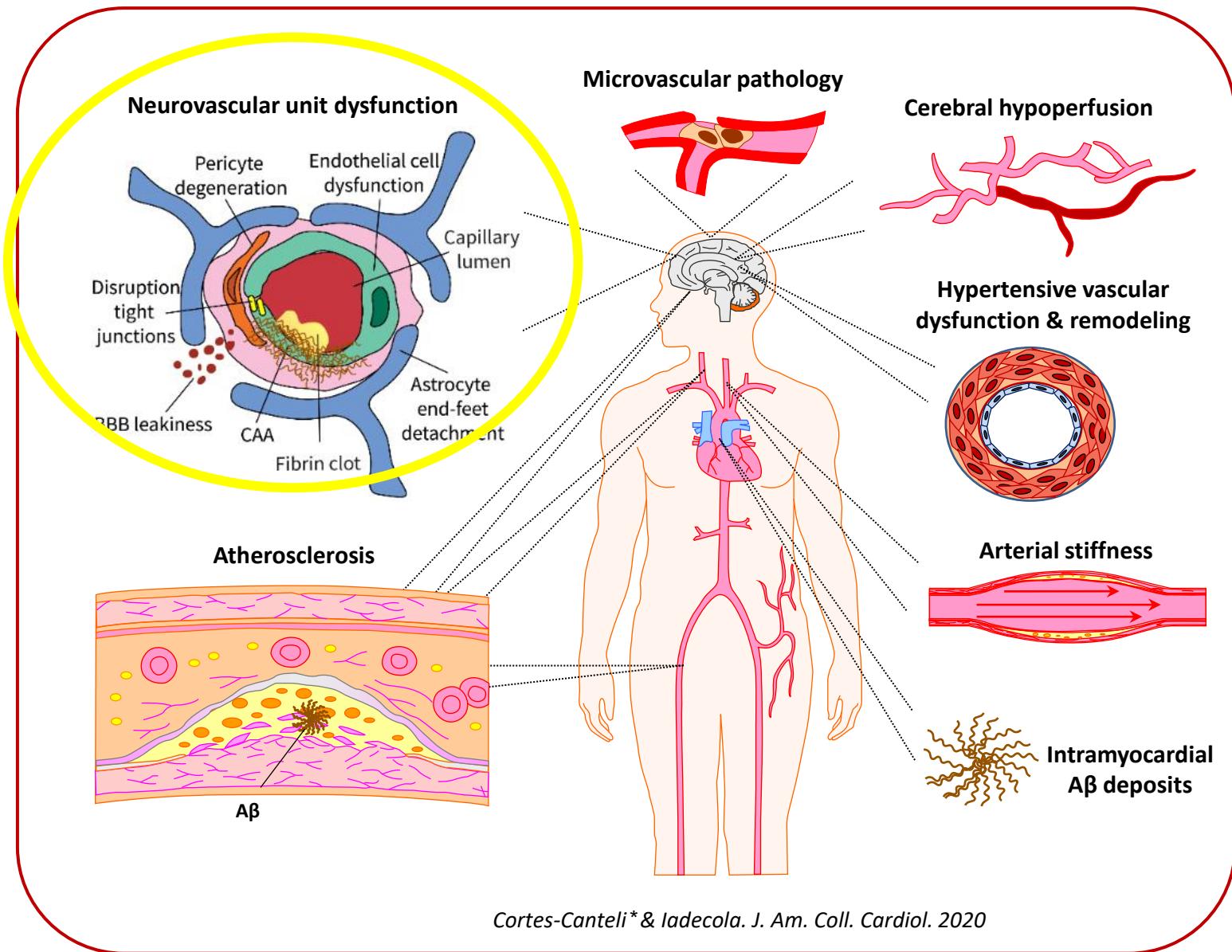
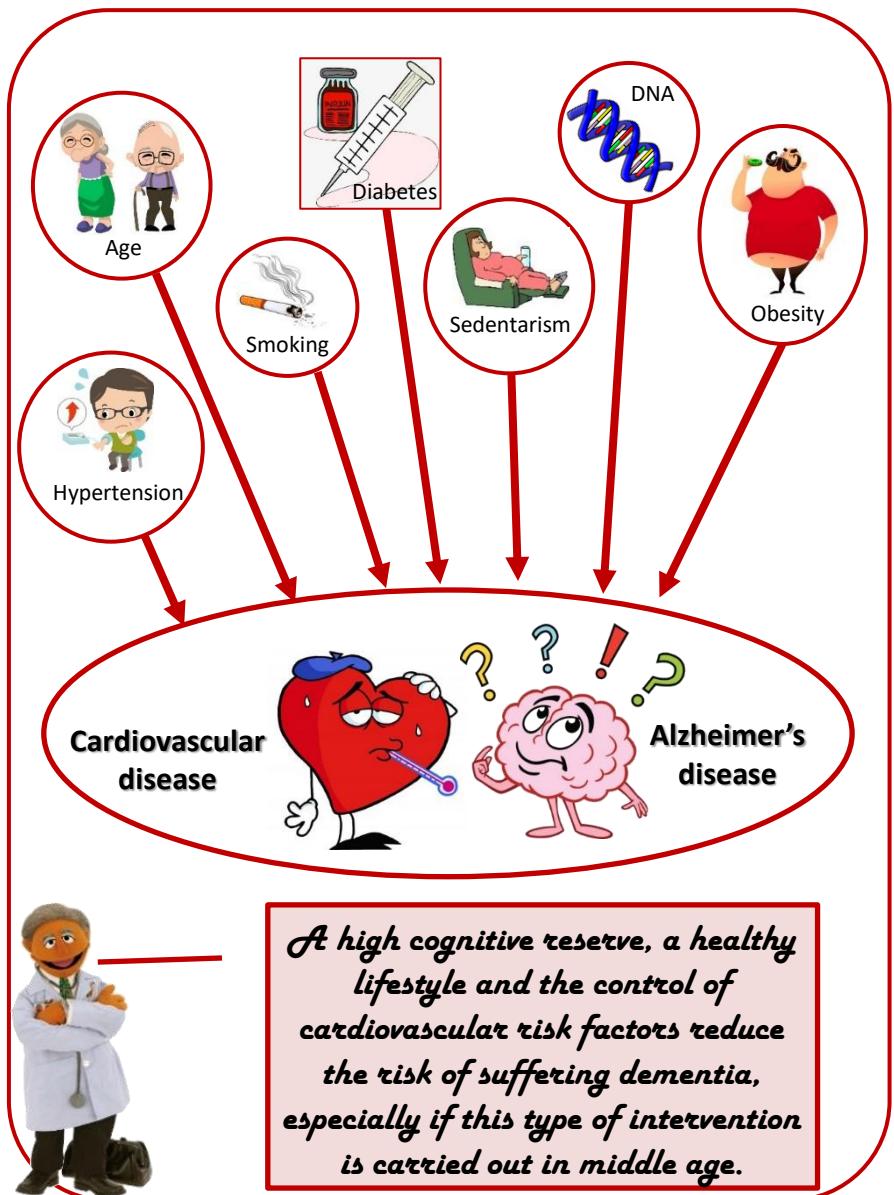
Fig. 1. Strength of evidence on risk factors for cognitive decline.

Baumgart et al. Alz & Dem. 2015.

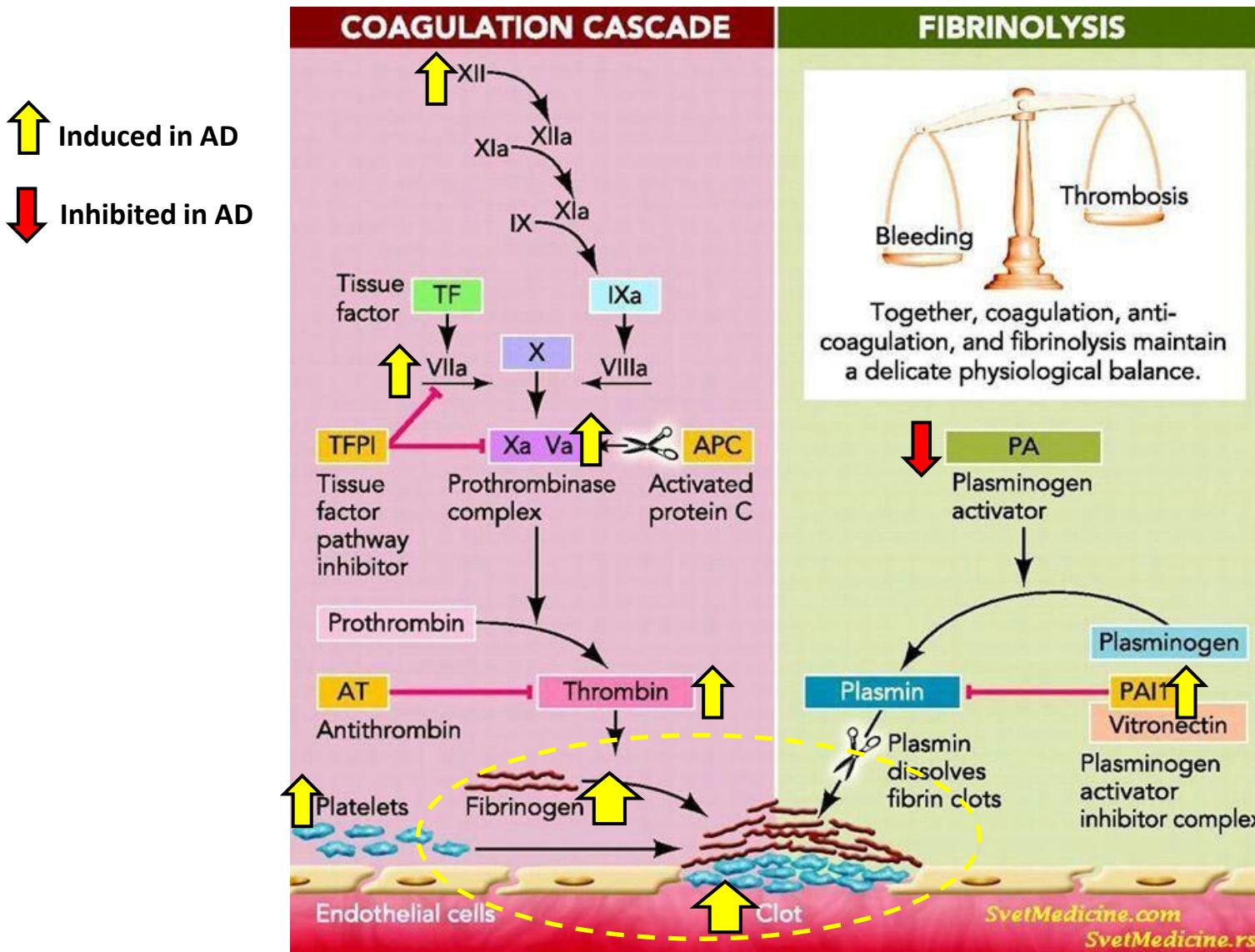
Concomitant clinical vascular disease	frailty		
	stroke		
	coronary artery disease		
	atrial fibrillation		
	peripheral arterial disease		
	chronic kidney disease		
	low cardiac output		
	depression		

Iadecola et al. J. Am. Coll. Cardiol. 2019

The Heart-Brain Axis in Alzheimer's Disease



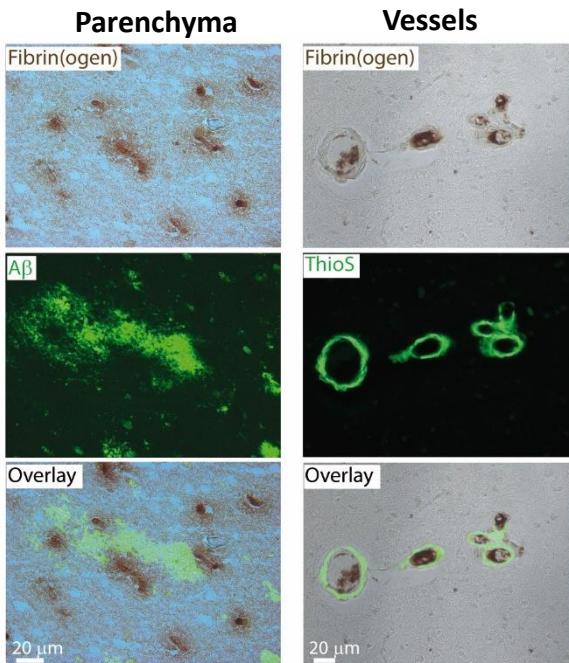
Pro-coagulant state in Alzheimer's disease



Fibrin(ogen) accumulation in AD?

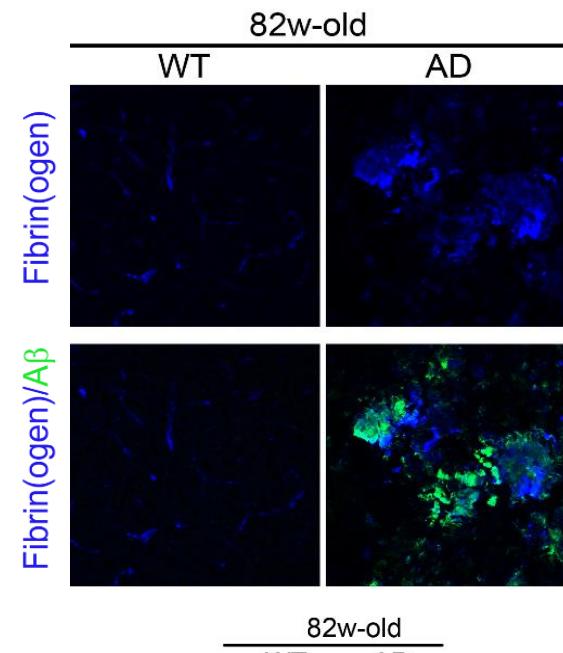
Pro-coagulant state in Alzheimer's disease

Human AD Brain



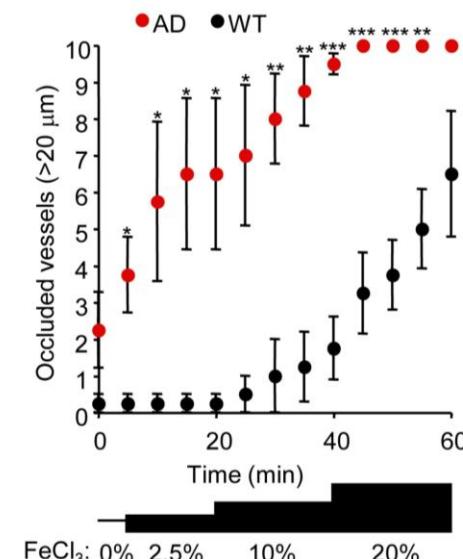
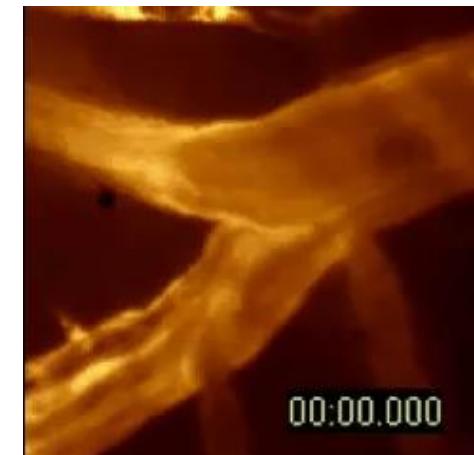
Cortes-Canteli et al. *J. Alz. Dis.* (2012)

Mouse AD Brain



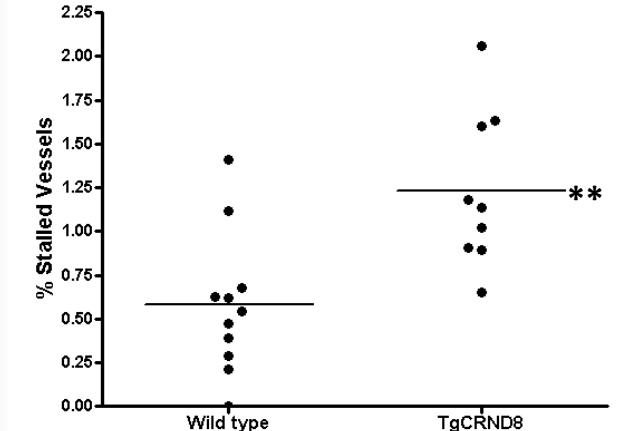
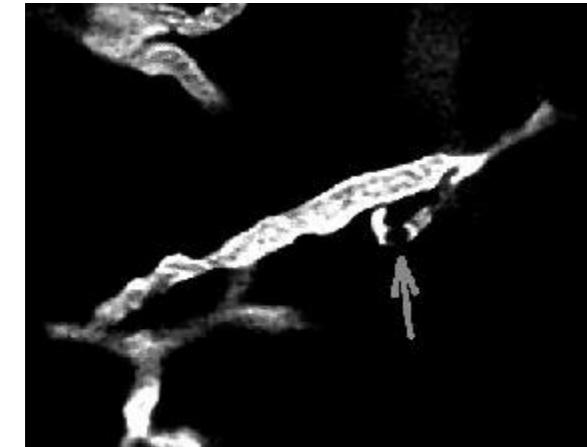
Cortes-Canteli et al. *Neurobiol. Aging* (2015)

Thrombosis & Fibrinolysis in AD mice



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

Increased Stalled Brain Capillaries in AD mice



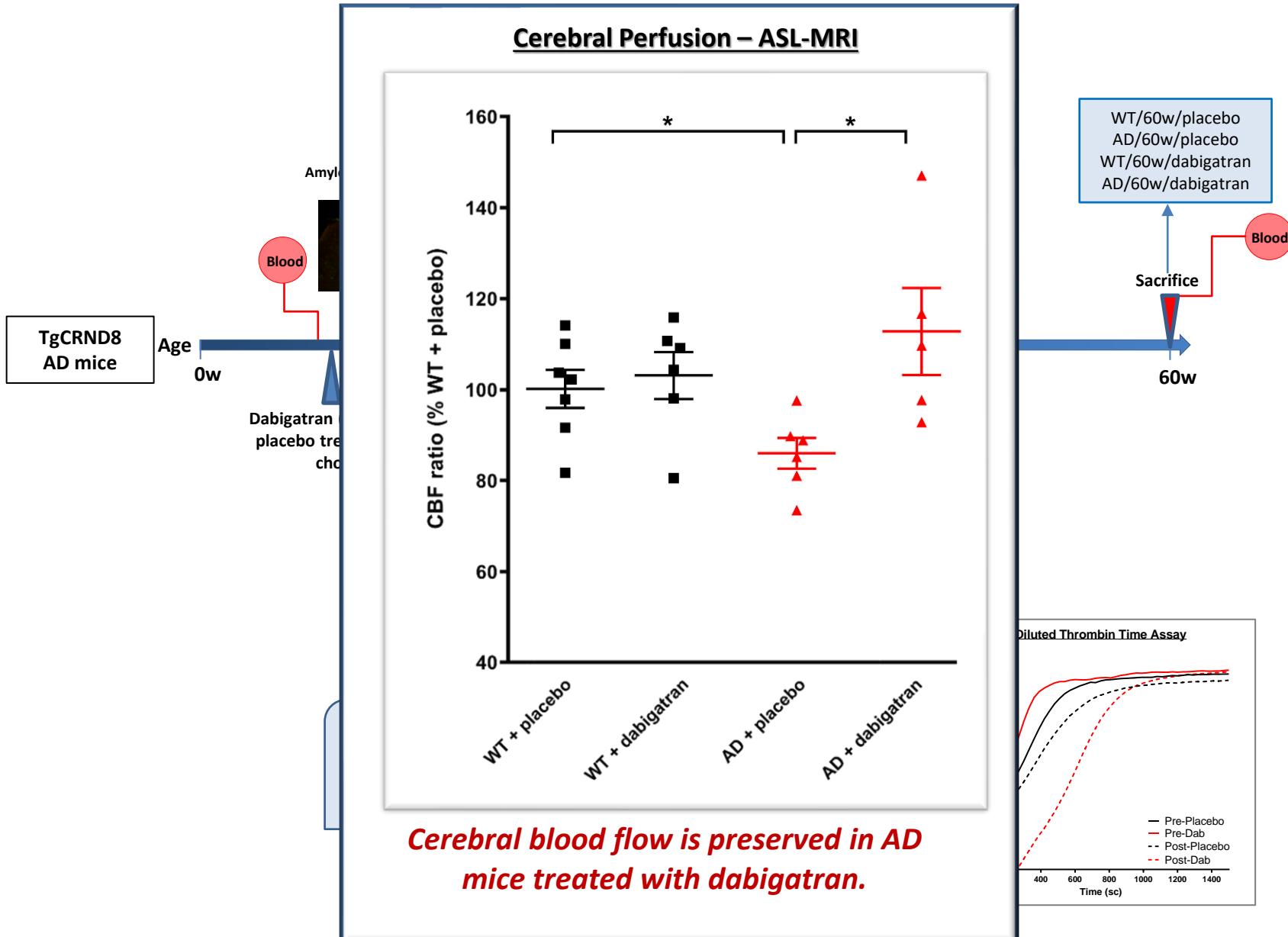
Cruz Hernandez; Bracko; Kersbergen; Muse; Haft-Javaherian; Berg; Park; Vinarcik; Ivasyk; Kang; Cortes-Canteli, et al. *Nat. Neuroscience*. (2019)

Pro-coagulant state in AD

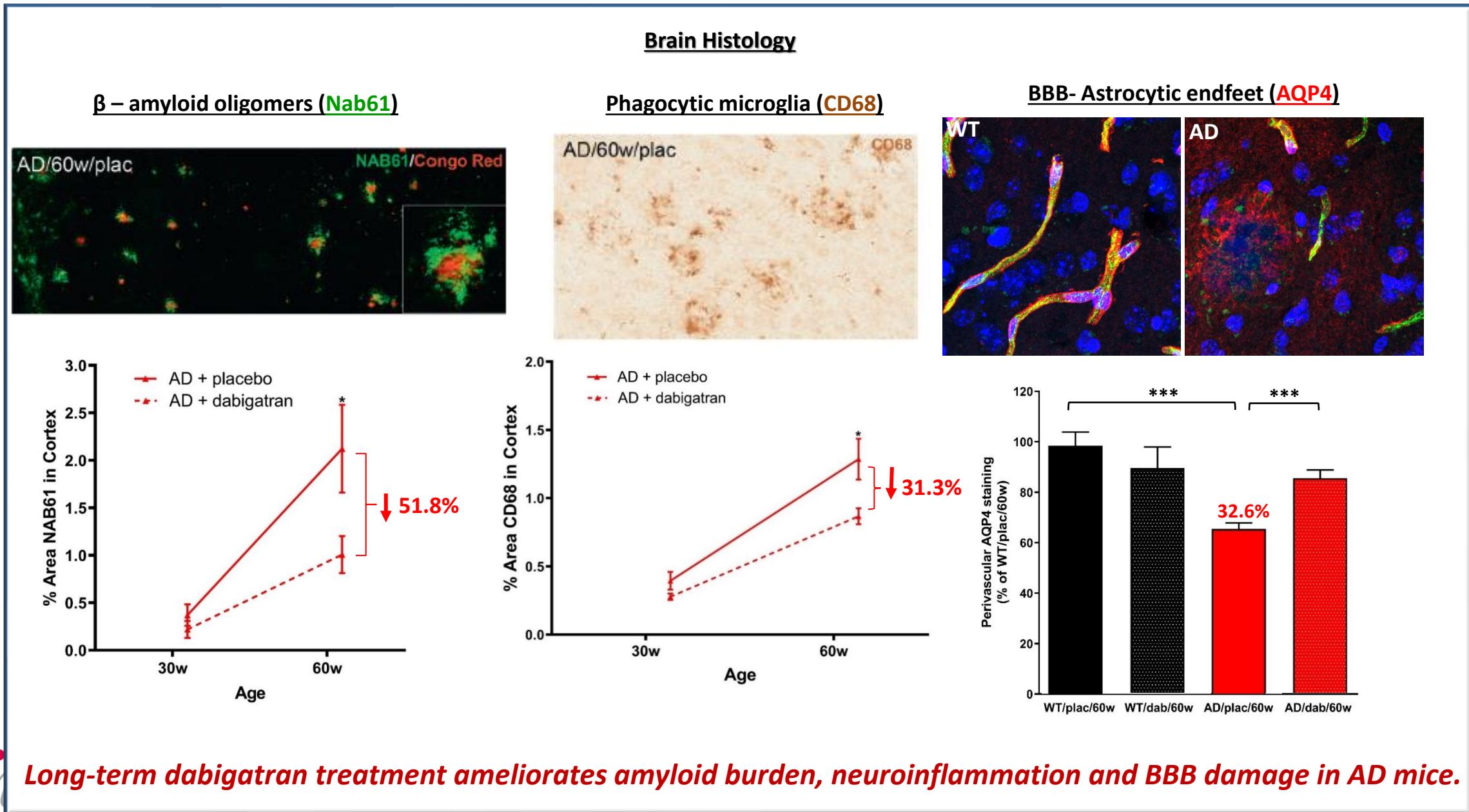


Would a therapeutic approach
aimed at normalizing the
thrombosis in AD be beneficial?

Dabigatran delays Alzheimer's disease pathogenesis

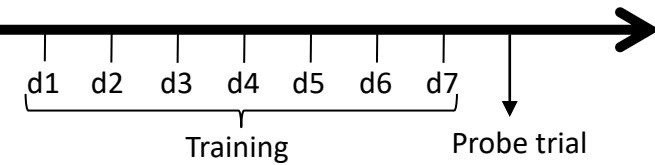
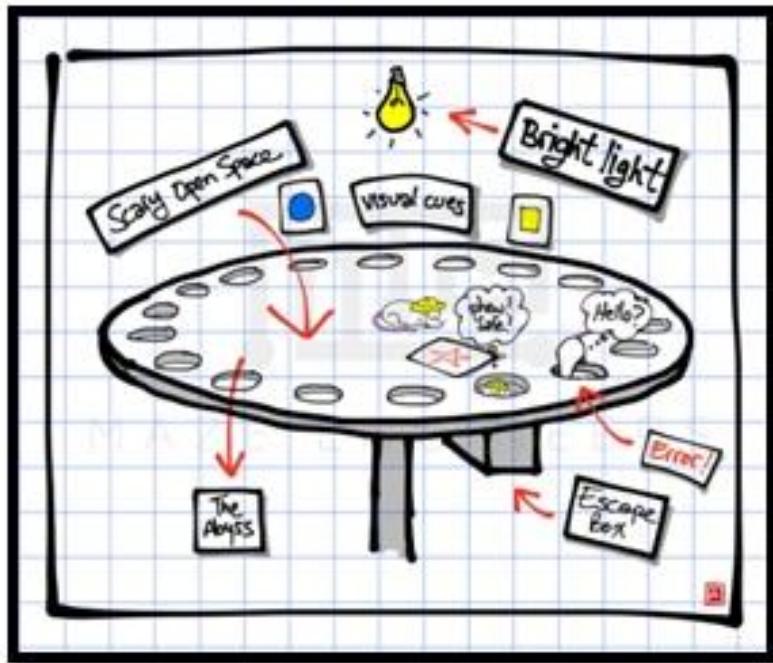


Dabigatran delays Alzheimer's disease pathogenesis

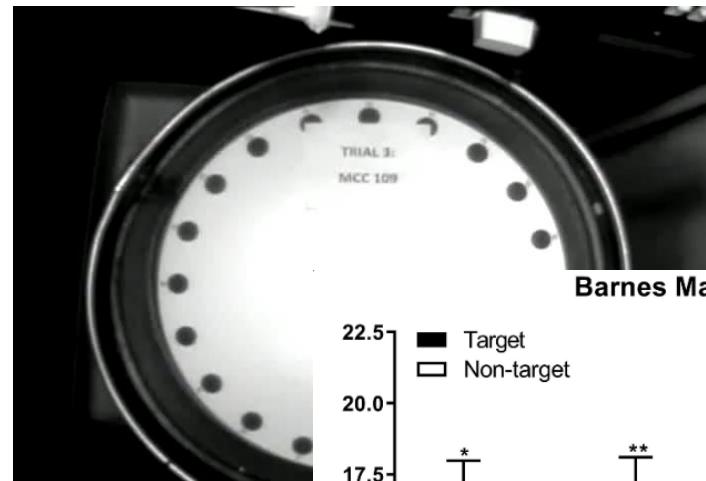


Dabigatran delays Alzheimer's disease pathogenesis

Memory Task - Barnes Maze



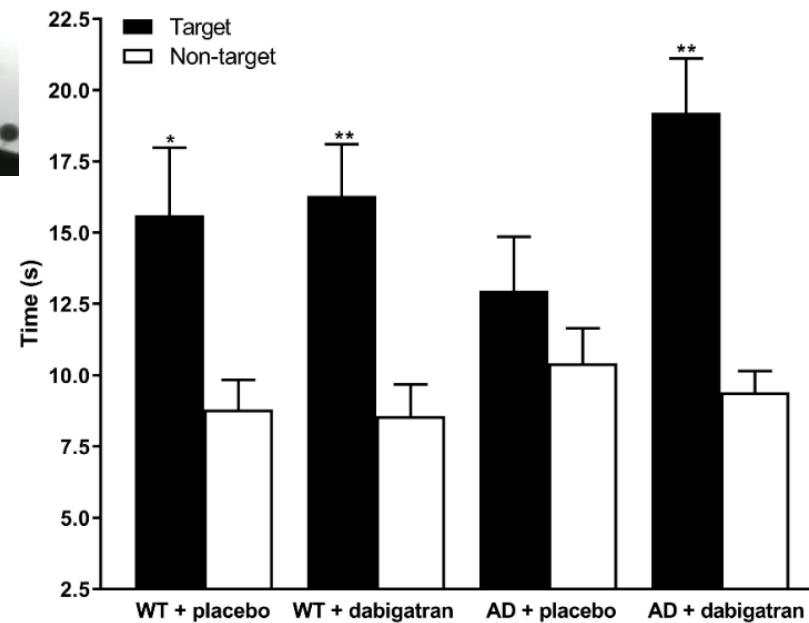
WT



Probe Trial



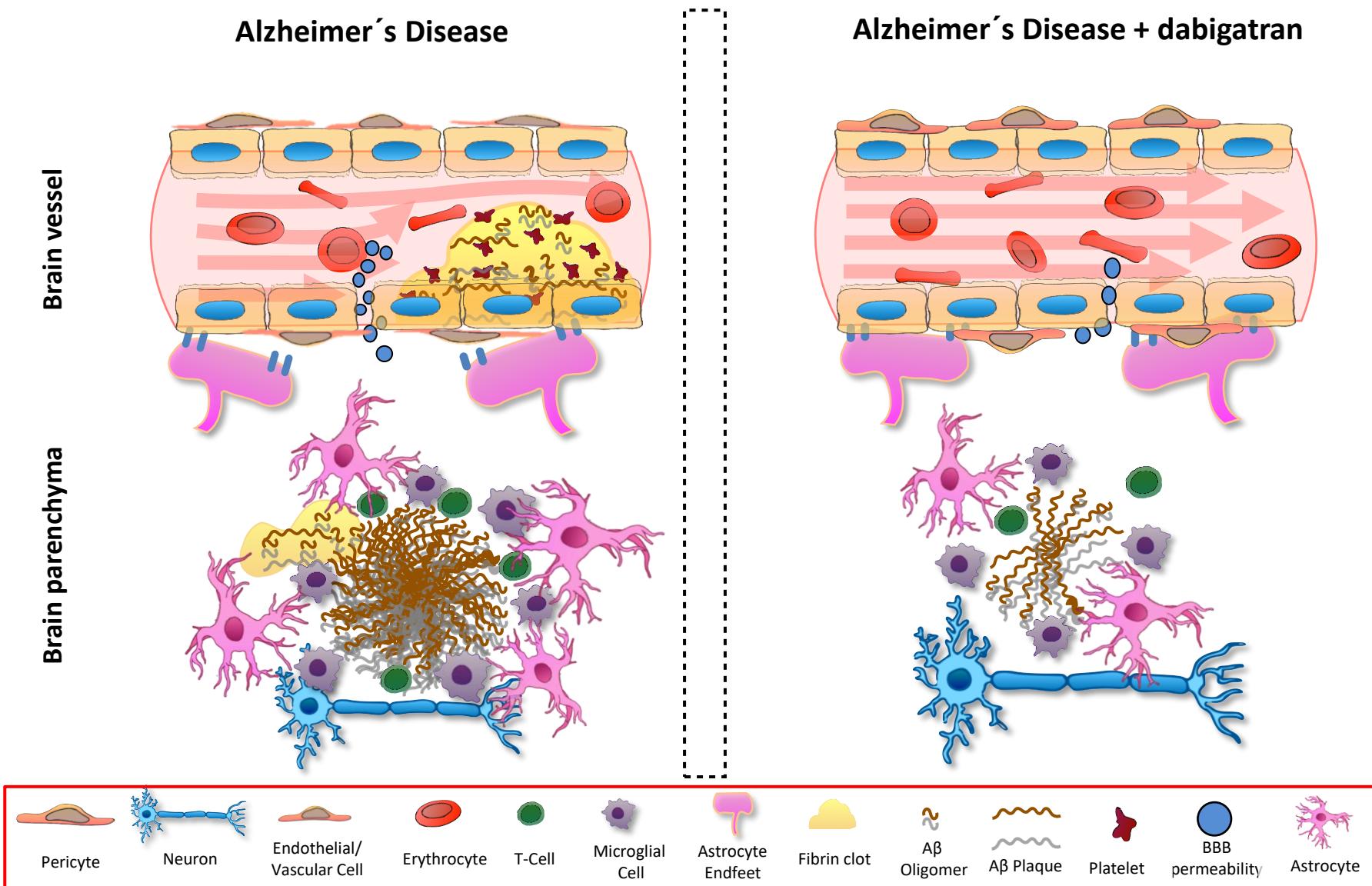
AD



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.

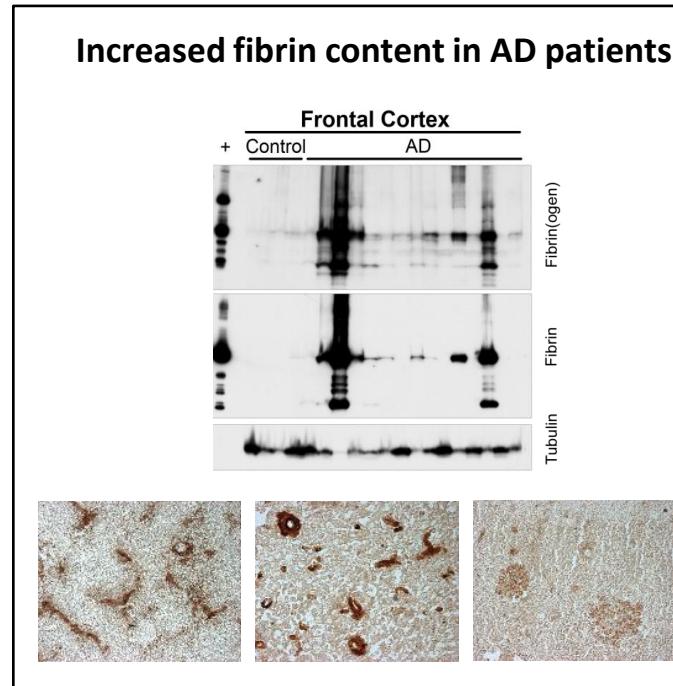
Cortes-Canteli* et al. *J. Am. Coll. Cardiol.* (2019)



Pro-coagulant state in AD

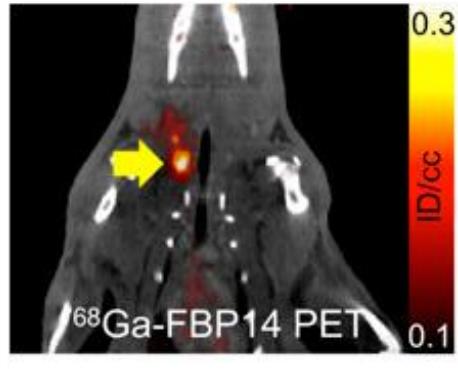


Would a diagnostic approach aimed at localizing the thrombosis in AD be useful?



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



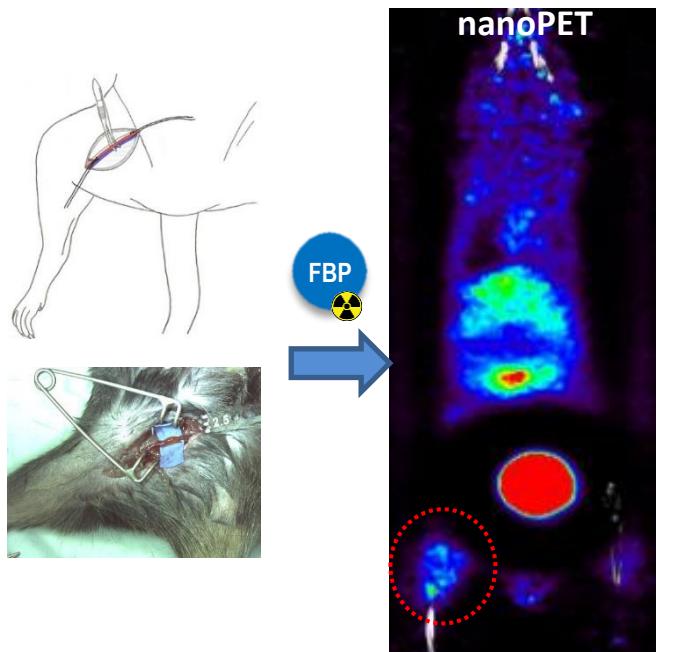
Sehlin
Partner
Sweden



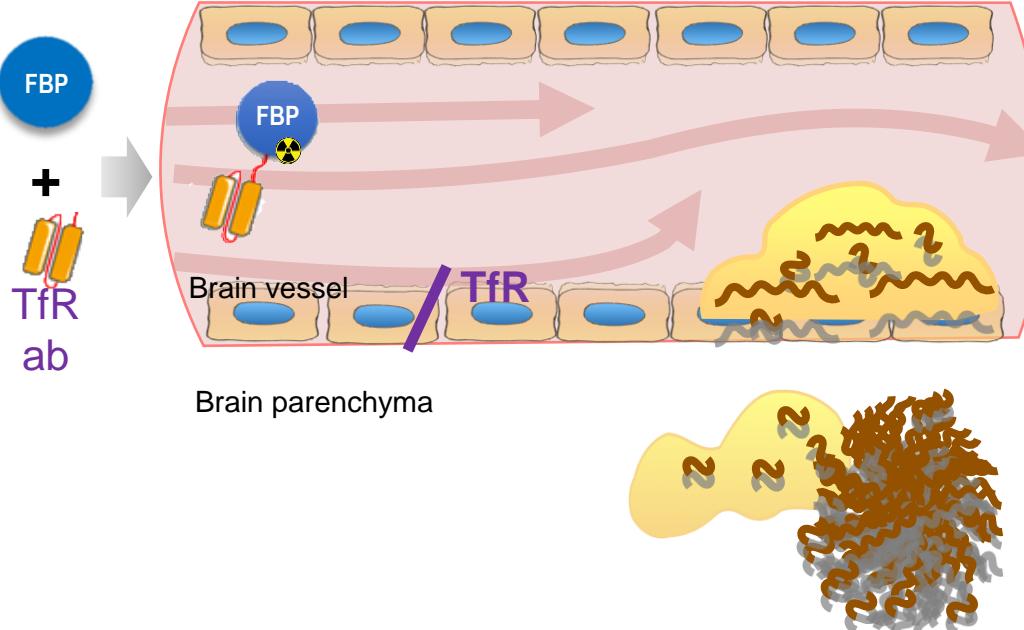
Kossatz
Partner
Germany



Positive Control Experiment Thrombosis: FeCl_3 in femoral artery



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



Colaboradores



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