Oral anticoagulants: A plausible new treatment for Alzheimer's disease?

Running Title: Anticoagulation and Alzheimer´s disease

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Abstract

Alzheimer's disease (AD) and cardiovascular disease (CVD) are strongly associated. Both are multifactorial disorders with long asymptomatic phases and similar risk factors. Indeed, CVD signatures such as cerebral microbleeds, micro-infarcts, atherosclerosis, cerebral amyloid angiopathy and a procoagulant state are highly associated to AD. However, AD and CVD co-development and the molecular mechanisms underlying such association are not understood.

Here, we review the evidence regarding the vascular component of AD and the clinical studies using anticoagulants that specifically evaluated the development of AD and other dementias. Most studies reported a compelling decreased incidence of composite dementia in anticoagulated atrial fibrillation individuals, with the highest benefit for direct oral anticoagulants. However, sub-analyses by differential dementia diagnosis were scarce and inconclusive.

We finally discuss whether anticoagulation could be a plausible preventive/therapeutic approach for AD and, if so, which would be the best drug and strategy to maximize clinical benefit and minimize potential risks.

Keywords

Cardiovascular risk factors; Cerebrovascular disease; Cerebral blood flow; Dementia; Intracranial hemorrhages; Thrombosis.

Abbreviations

AD, Alzheimer's disease

Aβ, amyloid-β

APOE, Apolipoprotein-E

ASL, arterial spin labeling

AF, atrial fibrillation

CVD, cardiovascular disease

CVRFs, cardiovascular risk factors

CAA, cerebral amyloid angiopathy

CBF, cerebral blood flow

DOACs, direct oral anticoagulants

FDG, 2-[18F]fluoro-2-Deoxy-D-glucose

tPA, tissue plasminogen activator

VKA, vitamin K antagonists

WMHs, white matter hyperintensities

Introduction

Worldwide, around 55 million people have dementia. Upon the many forms of dementia, 60-70% of cases are diagnosed as Alzheimer's disease (AD) (WHO, 2021). As aging is the strongest risk factor, and the proportion of elderly population is increasing every year, it is expected that 139 million people will develop dementia in 2050, which in terms of AD implies 84-97 million patients. Moreover, the derived costs of dementia globally have been estimated to be $1.3 trillion in 2019 (WHO, 2021), thus the social and economic impact for upcoming years will be tremendous, unless we find new effective treatments to prevent this pathology.

Alois Alzheimer was the first clinician to report the pathological and clinical features of this cerebral disease. Interestingly, he described the pathology as an "arteriosclerotic brain atrophy" (Drouin & Drouin, 2017), already reporting the presence of vascular pathology in AD. However, the cognitive deterioration and neuropathological hallmarks kept practically all the researchers' attention to decipher the etiology of the disease. Thanks to these investigations, the pathological hallmarks of AD have been well characterized: amyloid-β (Aβ) plaques and Tau-tangles, both required to diagnose this disorder (DeTure & Dickson, 2019). However, AD is a multifactorial and heterogeneous disease also characterized by brain atrophy, blood-brain barrier (BBB) dysfunction, neuronal death, neuroinflammation, synaptic decline, glucose hypometabolism in parieto-temporal cortex, and vascular dysfunction (DeTure & Dickson, 2019; Sweeney et al., 2019). Moreover, other forms of dementia may be confounding or even coexisting with AD. Vascular dementia is the second most common type and shares pathophysiology, symptomatology and risk factors with AD (Rizzi et al., 2014). Vascular dementia results from ischemic, hemorrhagic or hypoxic brain damage, being its main characteristics small vessel disease and impaired cerebral blood flow (CBF) (Shabir et al., 2018). Though AD etiology is less clear, it may be triggered by vascular dysfunction through mechanisms that include reduced CBF together with BBB and neurovascular unit damage, leading to Aβ aggregation in the brain parenchyma and vessels (Zlokovic, 2011). AD and vascular dementia are not easily distinguished, with overlapping lesions in both entities such as high incidence of vascular lesions and white matter alterations, suggesting additive or synergistic effects of both pathologies on cognitive deterioration (Attems & Jellinger, 2014). The amount, location and extent of such lesions (Palesi et al., 2018) and identifying the specific neuropsychological domain impaired (Reed et al., 2007) may help distinguishing AD from vascular dementia. However, experimental and clinical evidence point to the majority of dementia cases presenting a mixed pathology (Fierini, 2020; Langa et al., 2004) and vascular dysfunction is becoming to be recognized as a prominent feature of the Alzheimer's clinical syndrome (Sweeney et al., 2019).

Despite the fact that the overall number of people affected by dementia will increase in the coming years due to population aging, recent epidemiological studies point towards a declining in the incidence of dementia (Gao et al., 2019), which has been attributed to better management of cardiovascular risk factors (CVRFs) (Pase et al., 2017). Indeed, the vast majority (~ 80%) of patients diagnosed with AD present CVD signatures such as cerebral microbleeds, lacunar-, cortical- and micro-infarcts as indicators of small vessel disease, intracranial atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy (CAA) and an important procoagulant state featured by the abnormal presence of the blood clotting protein fibrin(ogen) in the brains of AD patients and AD mice (Cortes-Canteli & Iadecola, 2020; Sweeney et al., 2019). AD and cardiovascular disease (CVD) are enhanced by traditional CVRFs, such as aging, obesity, hypertension, sedentarism, alcohol and tobacco consumption, diabetes, and elevated serum levels of cholesterol (Baumgart et al., 2015) (**Figure 1**). Furthermore, both disorders share key

pathological features as a prolonged subclinical phase, similar age-dependence, Aβ accumulation, and parallel Apolipoprotein-E (APOE) genetic-predisposition (Lathe et al., 2014). ApoE is a glycoprotein found in brain and blood involved mainly in lipid transport and metabolism, but also in neuronal plasticity and synaptogenesis among other functions (Marais, 2019; Yamazaki et al., 2019). There are three APOE alleles in the human population, APOE-ε2, APOE-ε3, and APOE-ε4, with different properties for binding lipoproteins depending on their structure. APOE-ε2 and APOE-ε3 bind predominantly high-density lipoproteins (HDL), while APOE-ε4 binds preferentially very-low and low-density lipoproteins (VLDL and LDL). These binding differences have been associated with changes in blood cholesterol levels. The combination of the three APOE alleles give rise to three homozygous (ε2/ε2, ε3/ε3, ε4/ε4) and three heterozygous genotypes (ε2/ε3, ε2/ε4, ε3/ε4) (Eichner et al., 2002; Strittmatter & Hill, 2002). The inheritance of the APOE-ε4 allele has been associated with elevated levels of LDL cholesterol, an increased risk of developing atherosclerosis and premature CVD (Eichner et al., 2002; Marais, 2019; Strittmatter & Hill, 2002), and is also considered the strongest genetic risk factor for late onset AD, decreasing the age of onset and tripling the risk [OR=3.68 (3.30-4.11)] (Yamazaki et al., 2019). On the contrary, individuals carrying the APOE-ε2 allele have lower levels of LDL cholesterol (Marais, 2019) and decreased risk for AD [OR=0.621 (0.456-0.85)] (Yamazaki et al., 2019).

Over the years, few drugs have been approved for the management of AD, all symptomatic-targeted agents, including cholinesterase inhibitors (donepezil, galantamine and rivastigmine) and N-methyl-D-aspartate receptor antagonists (memantine) (Cummings et al., 2017). However, the growing AD population is in urgent need of new therapies to prevent, delay the onset of disease and slow its progression. Improvements in disease-modifying drugs and combination therapy are accelerating the development of new options (Cummings et al., 2017). Indeed, in 2021 aducanumab was the first FDA-approved anti-amyloid therapy. Currently, over 140 agents are being assessed as AD treatments, 68% of which are also disease-modifying targeting mechanisms such as Aβ plaques, tau tangles, neuroinflammation, synaptic plasticity, oxidative stress and brain vasculature (Cummings et al., 2022). While AD remains one of the least well-served disease in terms of treatment options, biomarkers are now playing greater roles as outcomes of disease-modifying clinical trials for its ability to confirm AD-type pathology (Cummings et al., 2022).

The aim of this work is to gather evidence regarding the vascular components of AD, review the clinical studies using anticoagulants as potential AD therapies and discuss the best intervention strategy in a hypothetical clinical trial targeting the procoagulant state observed in AD.

Vascular dysfunction in AD.

Despite all the evidence pointing to a strong association between AD and CVD, their interrelation, which is the cause and which the consequence, and the molecular mechanisms underlying their co-development are still not clearly understood. A vast amount of AD patients presents vascular abnormalities as intracranial atherosclerosis, CAA, and microvessel alterations as microbleeds, white matter hyperintensities (WMHs), increased perivascular spaces and lacunar infarctions. Since cross-sectional postmortem analysis revealed a prevalent atherosclerosis in the Circle of Willis brain vessels of AD patients (Hofman et al., 1997), intracranial atherosclerosis has been widely associated with AD (**Figure 2**). The Circle of Willis and connected arteries protect from hemodynamic stress preserving BBB function (Ritz et al., 2014), which is also commonly altered

during the asymptomatic phases of AD (Fisher et al., 2022) . Indeed, alterations of Circle of Willis directly affect CBF.

In line with this, studies in prodromal AD have shown changes in CBF measured by transcranial doppler or arterial spin labeling-magnetic resonance imaging (ASL-MRI) (**Figure 2**). The correct oxygenation of brain cells depends on CBF and, for this reason, hypoperfusion has been suggested a bona-fide *in vivo* predictor of future cognitive deterioration (Zhang et al., 2021). Another early *in vivo* biomarker of AD is an altered pattern in 2-[^{18}F]fluoro-2-Deoxy-D-glucose (FDG)-positron emission tomography (PET) imaging, which permits to detect glucose metabolism cerebral changes as consequence of synaptic decline (Aisen et al., 2017) (**Figure 2**). Accordingly, our group has recently demonstrated that CVRFs, and particularly hypertension, are strongly associated with brain hypometabolism in key cerebral AD areas in a middle-aged asymptomatic cohort (Cortes-Canteli et al., 2021). CBF changes have also been related with neurological dysfunction and cognitive function decline particularly in the posterior cingulated, precuneus, basal ganglia and temporal areas among some others, at early asymptomatic stages (Zhang et al., 2021). Thus, CBF and glucose metabolism may be intimately linked and prematurely altered prior to Aβ and Tau accumulation (Peretti et al., 2019). Moreover, intracranial atherosclerosis (Ritz et al., 2014) and hypoperfusion (Zhang et al., 2021) concomitantly may hinder brain clearance probably exacerbating Aβ deposition and enhancing Aβ-plaques formation in the brain parenchyma. Indeed, *in vivo* multiphoton microscopy experiments have shown that intravascular lesions alter the deposition/clearance rate of Aβ in AD mice (Zhang et al., 2020), further supporting the idea that reciprocal interactions between amyloid pathology and vascular function are present in this neurodegenerative disorder. In turn, Aβ aggregation in brain vessels alters even more CBF (Brenowitz et al., 2015) and enhances glucose hypometabolism in response to the increased metabolic demand due to amyloidosis (Fisher et al., 2022), inflammation and oxidative stress (**Figure 2**).

This deposition of Aβ in brain vessel walls is a common pathological finding in older people, it is the hallmark of CAA and has also been closely related with AD. *In vivo* multiphoton imaging in AD mice also showed that this vascular amyloid pathology occurs in an age-dependent manner (Dong et al., 2010) and is further accelerated by the presence of diabetes (Vargas-Soria et al., 2022). In fact, over 80-90% of AD patients present CAA (DeSimone et al., 2017a) which is indeed associated with the presence of APOE-ε4 allele, hypercholesterolemia and history of stroke (Brenowitz et al., 2015). Furthermore, CAA aggravates AD derived symptoms as cognitive impairment and vascular pathology. On the other hand, CAA has been linked to cognitive deterioration independently of AD, and has also been related with APOE-ε2, although this allele confers protection for AD (DeSimone et al., 2017a). As a consequence of Aβ accumulation, the vessel wall is progressively debilitated, thus CAA is an important cause of cerebral microbleeds, and lobar intracranial hemorrhages (Brenowitz et al., 2015) (**Figure 2**).

These vascular abnormalities are common in AD, even though they are also linked to age. Cerebral microbleeds are present in 20% of older adults (>60 years), its prevalence increases with age (DeSimone et al., 2017b), and with AD (Zhou et al., 2015). Interestingly, stroke is intimately related with aging and significantly increases the risk of cognitive decline and AD (Zhou et al., 2015; Zupanic et al., 2020), and dementia patients show three to seven times more chances to suffer a stroke (Zupanic et al., 2020). WMHs are another common finding within older population and AD patients and are easily detected by MRI (Habes et al., 2016) (**Figure 2)**. These cerebral lesions are multifactorial myelin and axonal loss mainly caused by ischemic conditions. Thus,

WMHs appear as consequence of cerebral small vessel disease and their presence has been linked to cognitive complaints, dementia and disability (Prins & Scheltens, 2015).

Additionally, systemic inflammation, which is known to contribute to CVD (Liberale et al., 2022), has been also suggested as an important component of AD (Heneka et al., 2015) and brain amyloid pathology (Tejera et al., 2019; Walker et al., 2018). Indeed, abnormalities have been reported in peripheral immune T cells in AD, including alterations in their total cell number, function, markers, activation and infiltration into the AD brain parenchyma (Dai & Shen, 2021). Interestingly, interleukin-17 seems to play a key role not only in promoting systemic inflammation, but also in cognitive impairment, peripheral vascular dysfunction and prothrombosis in AD mice (Cristiano et al., 2019; Vellecco et al., 2022). Moreover, neutrophils also contribute to AD pathophysiology (Zenaro et al., 2015), and have been found adhered to brain capillaries impacting CBF in AD mice (Cruz Hernández et al., 2019).

Hence, vascular dysfunction may be playing a key role from the silent onset towards the full clinical AD spectrum, being one of the mechanisms able to expedite the pathological development of the disease.

Procoagulant profile in AD.

In line with the vascular dysfunction, it has also been described a procoagulant state in AD patients (Cortes-Canteli & Iadecola, 2020). Fibrinogen is the main protein component of blood clots, which is converted by thrombin from its soluble form into fibrin, as the final step of the coagulation cascade (**Figure 3**). When fibrin accumulates, it forms a sticky insoluble net, which promotes the aggregation of activated platelets and other blood cells (**Figure 3**). Fibrin(ogen) is abnormally found in the brains of AD mouse models (Cortes-Canteli et al., 2015; Cortes-Canteli et al., 2010; Paul et al., 2007; Ryu & McLarnon, 2009) and in the human postmortem AD brain (Cortes-Canteli et al., 2015; Cortes-Canteli et al., 2010; Cullen et al., 2005; Fiala et al., 2002; Jantaratnotai et al., 2010; Lipinski & Sajdel-Sulkowska, 2006; Ryu & McLarnon, 2009; Viggars et al., 2011). Indeed, elevated serum levels of fibrinogen have been associated with cognitive decline (Xu et al., 2008) and increased risk of AD (van Oijen et al., 2005), and has even been proposed as a plausible blood or cerebral spinal fluid biomarker specific for AD (Chiam et al., 2015). Fibrin(ogen) has been also related to neuroinflammation, neurovascular damage, BBB permeability, neuronal degeneration and vascular amyloid deposition (Cortes-Canteli et al., 2015; Cortes-Canteli et al., 2010; Merlini et al., 2019; Paul et al., 2007; Ryu & McLarnon, 2009). Indeed, fibrin(ogen) interacts with Aβ (Ahn et al., 2010), which alters the structure of fibrin, impeding plasmin-mediated fibrin cleavage and interfering with the lysis of clots, further contributing to the pro-thrombotic scenario (Zamolodchikov, Berk-Rauch, et al., 2016; Zamolodchikov, Renne, et al., 2016).

Besides this strong evidence linking fibrin(ogen) and AD, a procoagulant state is further supported by the association of other coagulation factors with AD and cognitive deterioration (**Figure 3**). Thrombin has also been linked to Aβ and Tau and it is known to be elevated in AD brains, particularly in brain microvessels of AD patients (Grammas et al., 2006; Tripathy et al., 2013). As fibrinogen, thrombin has been related as well to neuroinflammation and neurodegeneration. In fact, AD is characterized by a chronic neuroinflammatory condition, and fibrinogen and thrombin are proinflammatory molecules capable of activating inflammatory cytokines, that, in turn, induce even further the coagulation process (Iannucci et al., 2020). Thus, coagulation and inflammation are processes intimately linked that regulate each other, and both

are affected not only in AD, but also in CVD. Furthermore, elevated levels of prothrombin fragment 1+2 and D-dimer induce thrombin production and are associated with increased rate of cognitive decline in older individuals (Stott et al., 2010). Prothrombin fragment 1+2 serum levels are increased in AD patients, as well as Factor VII (Gupta et al., 2005). In turn, Factor VII and other coagulation factors, such as Factor V, promote thrombin generation, hence further amplifying the coagulation process (**Figure 3**). Interestingly, carriers of the mutant form of Factor V Leiden present thrombotic propensity and higher risk of developing dementia (Bots et al., 1998). Additionally, plasma levels of the coagulation Factor XI (Begic et al., 2020) and Factor XIIa (Zamolodchikov et al., 2015) have been found also significantly increased in AD patients (**Figure 3**). Indeed, Factor XII, a procoagulant and pro-inflammatory serine protease that initiates the intrinsic coagulation pathway (**Figure 3**), is activated by Aβ itself (Zamolodchikov et al., 2015; Zamolodchikov, Renne, et al., 2016) and, hence, Factor XII and the contact activation pathway have been suggested as promising therapeutic targets for AD (Singh et al., 2021; Strickland, 2018).

Additionally, increased levels of von Willebrand factor have been detected in AD and other types of dementia (Gupta et al., 2005), and they are also considered a bona fide predictor of endothelial damage and CVD, due to its important role in platelets activation (Peyvandi et al., 2011). Platelets are another key player of hemostasis. In the absence of injuries or pathological conditions, they patrol the organism through the blood in an inactive form. The presence of fibrin and other damage signals, drive platelets activation and aggregation. Interestingly, activated platelets are present in AD mice (Canobbio et al., 2016; Jarre et al., 2014) and AD patients (Stellos et al., 2010) and are correlated with disease progression and severity (Prodan et al., 2011; Prodan et al., 2007, 2008). Platelets are the main source of Aβ in blood (Chen et al., 1995), and activated platelets from AD patients produce more Aβ in comparison to the ones from healthy individuals (Tang et al., 2006), hence further contributing to the pro-thrombotic milieu in AD (Cortes-Canteli et al., 2012).

Once coagulation cascade is initiated, the fibrinolytic system is also activated in order to counteract excessive clotting. Tissue plasminogen activator (tPA) is the main molecule responsible for the breakdown of clots, converting plasminogen into plasmin, the protease in charge of degrading cross-linked fibrin clots (Chapin & Hajjar, 2015) (**Figure 3**). This fibrinolysis pathway is also altered in AD. Plasminogen-tPA activity is greatly reduced in the frontal cortex of AD patients due to a significant increase in the levels of the tPA inhibitor neuroserpin (Fabbro & Seeds, 2009), and plasmin expression was found to be downregulated in cerebral tissue from AD patients (Ledesma et al., 2000). Furthermore, tPA-neuroserpin complexes were found co-localizing with Aβ plaques (Fabbro & Seeds, 2009), and *in vitro* (Kinston et al., 1995; Tucker et al., 2000) and *in vivo* (Melchor et al., 2003) studies showed that the tPA-plasmin system collaborated in Aβ clearance (**Figure 3**).

Anticoagulation and Dementia

The normalization of this procoagulant state in several studies using AD mouse models showed reduction in different pathological features, suggesting a contributing role in AD pathogenesis. For example, i) decreasing fibrinogen levels reduced neuroinflammation, neurodegeneration, synaptic dysfunction, BBB damage, CAA, Aβ burden and cognitive decline (Cortes-Canteli et al., 2015; Cortes-Canteli et al., 2010; Paul et al., 2007); ii) blocking the interaction between Aβ and fibrinogen reduced CAA and improved cognition (Ahn et al., 2014; Cortes-Canteli et al.,

2015); and iii) Factor XII depletion reduced fibrin(ogen) deposition, neuroinflammation, neurodegeneration and cognitive dysfunction (Chen et al., 2017).

If normalizing this prothrombotic state in AD halts disease progression in animal models, anticoagulation may be a plausible therapeutic approach for this neurodegenerative disorder (Grossmann, 2020). Anticoagulants are very-well known drugs that have been on clinical use for more than 60 years in order to avoid thrombus formation and embolism (Gómez-Outes et al., 2012). The classic prescribed anticoagulants indirectly inhibit clot formation as vitamin K antagonists (VKA) (e.g. warfarin, acenocoumarol,…) (**Figure 3**). During the last two decades, drug development has permitted the emergence of novel non-VKAs, direct oral anticoagulants (DOACs), which directly inhibit clotting factors as Factor Xa (apixaban, rivaroxaban, edoxaban and betrixaban) or thrombin (dabigatran, ximelagatran) leading to less adverse effects (**Figure 3**). Anticoagulation in AD animal models have indeed shown promising results. Peripheral treatment of AD mice with enoxaparin, a low molecular weight heparin, decreased Aβ pathology (Bergamaschini et al., 2004) and improved spatial memory performance (Timmer et al., 2010). More recently, long-term dabigatran treatment decreased oxidative stress and inflammation in 3xTgAD mice (Tripathy et al., 2013) and normalized cerebral perfusion together with amelioration of memory loss, amyloid load, neuroinflammation, and BBB dysfunction in the TgCRND8 mouse AD model (Cortes-Canteli et al., 2019). Similar results have been found in an AD mouse model with strong CAA treated with rivaroxaban, another DOAC (Bian et al., 2022), further supporting the beneficial effects of anticoagulation to prevent AD.

Another piece of evidence of the link between clot formation and dementia is the promising results obtained in studies using anticoagulant treatment in patients. Small-scale human studies performed several decades ago already showed that warfarin-treated patients did not worse (Ratner et al., 1972) or even presented with cognitive improvement compared to untreated patients (Walsh, 1996; Walsh et al., 1978). More recently, reduced risk of dementia has been also observed in patients undergoing long-term anticoagulation for atrial fibrillation (AF) (**Table 1**). AF is a cardiac arrythmia mostly present in elderly individuals that is linked to multiple comorbidities, including the development of dementia (Bunch, 2020). A possible mechanism behind the association between AF and dementia has been speculated to be the increased incidence of asymptomatic microstrokes (Dagres et al., 2018). Although through a different etiology, such mechanism resembles the above described impact of the procoagulant state on AD progression. Indeed, when looking at the development of AD specifically, Proietti et al calculated that an AF patient has a 30% increased chance of developing AD compared to an individual without AF (Proietti et al., 2020). Antithrombotic medication is one of the gold-standard treatments for AF, and, almost two decades ago, Barber et al found a trend towards warfarin use being independently associated with decreased incidence of dementia in AF individuals of the Coagulation Activation and Risk of Stroke in Atrial Fibrillation (CARSAF) study [OR=0.52 (0.26-1.07), p=0.08)] (Barber et al., 2004). Since then, compelling evidence from other population-based studies proved that anticoagulation in AF decreases significantly the incidence of dementia in these patients (Bezabhe et al., 2022; Ding et al., 2018; Friberg et al., 2019; Madhavan et al., 2018; Mongkhon et al., 2020). Many of these studies went one step forward and compared the efficacy of different antithrombotics (including both, antiplatelets and anticoagulants) (**Table 1**). In general terms, the use of DOACs was the one associated with a more pronounced reduced risk of dementia compared to other AF treatments, being the order DOACs>VKAs>antiplatelet therapy. However, some discrepancy with the net effect was found, with certain studies reporting a striking 50% reduction in the incidence of dementia when using DOACs versus other antithrombotics in AF (Bezabhe et

al., 2022; Jacobs et al., 2016), others a 20-30% decrease (Chen et al., 2018; Hsu et al., 2021) and in some cases no significant difference between antithrombotic regimens was found (Mongkhon et al., 2020; Søgaard et al., 2019). Some of these discrepancies may be explained by the different age range of the individuals included in the study, the follow-up time, or the diagnostic criteria used to define dementia.

Is an anticoagulant therapy plausible for AD?

We reviewed each of the AF studies with special focus on the dementia subtypes analyzed, in order to find a specific impact of anticoagulation on AD progression (**Table 1**). Unfortunately, most of them did not identify a specific diagnosis of AD but rather reported a composite dementia one. Two of the studies included a differential diagnosis of dementia subtypes in the Methods section but then used a composite when analyzing the impact of the use of anticoagulant drugs, so no conclusions regarding the impact on AD progression could be drawn from these two specific reports (Ding et al., 2018; Jacobs et al., 2016). The study performed by Søgaard et al included as secondary outcome specific dementia subtypes (i.e. AD, vascular dementia and other dementia), and observed a trend towards a 25% decrease in the incidence of AD in 70-79 years-of-age individuals taking DOACs versus those taking warfarin [HR=0.75 (0.54-1.04)] (Søgaard et al., 2019). Mongkhon et al also performed subgroup analysis and found that the use of warfarin/DOACs compared to no treatment was significantly associated with lower risk of vascular dementia [HR=0.89 (0.80–0.99); P=0.049] and unspecified dementia [HR=0.74; (0.66–0.83); p<0.001) but not of AD [HR=0.99 (0.86-1.14), p=0.86] (Mongkhon et al., 2020). A recent meta-analysis in 611,069 AF patients showed that DOACs were associated with a lower risk of composite dementia compared with warfarin use [OR=0.56 (0.34–0.94), p=0.03], although no significant difference was found when performing sub-analyses by dementia subtype (vascular dementia, AD, other cognitive disorder) (Lee et al., 2021). Hence, although the evidence reporting a decreased incidence of dementia with anticoagulation in AF individuals is compelling, more studies are needed to clarify the particular impact in each of the dementia subtypes.

Long-term anticoagulant treatment has been poorly addressed in dementia patients for several reasons that precluded its broad use in this population. The main one is that individuals with dementia present 41% more chances to develop cerebral hemorrhages due to the high prevalence of CAA (Zhou et al., 2015). Hence, the higher risk of intracranial bleeding associated with the use of antithrombotics has raised concerns in long-term anticoagulated AF patients who also present dementia symptoms, and these individuals are usually treated with antiplatelet therapy instead (Zupanic et al., 2020). Indeed, results from the The REstart or STop Antithrombotics Randomised Trial (RESTART) proved the safety of taking antiplatelet therapy after intracerebral hemorrhage that occurred while on antithrombotics (Al-Shahi Salman et al., 2021; RESTART Collaboration, 2019). However, antiplatelets are not as effective as anticoagulants at reducing dementia incidence in AF individuals (**Table 1**).

The development of DOACs tried to address some of the caveats associated with the use of the classic anticoagulants (i.e. VKAs and heparins), such as the need for routine coagulation monitoring and, more importantly, the increased incidence of hemorrhage. All the DOACs have proven to be non-inferior compared to VKAs at preventing stroke and systemic embolism, and superior to VKAs and aspirin in reducing the risk of life-threatening bleedings, especially in the lower dosage regime (Chan et al., 2020; López-López et al., 2017). Of particular interest, the use of certain DOACs was associated with an important reduction in the risk of intracranial bleeding compared to warfarin, with systematic reviews and meta-analysis reporting more than 50%

decrease with the use of DOACs as a class (Fanning et al., 2020; Gomez-Outes et al., 2013). The thrombin inhibitor dabigatran was the DOAC with the strongest reduction in intracranial bleeding compared to warfarin [HR=0.40 (0.27-0.60), p<0.001] (Connolly et al., 2009), followed by the Factor Xa inhibitors apixaban [HR=0.42 (0.30-0.58), p<0.001] (Granger et al., 2011), edoxaban [HR=0.47 (0.34-0.63), p<0.001] (Giugliano et al., 2013) and rivaroxaban [HR=0.67 (0.47-0.93), p=0.02] (Patel et al., 2011). Interestingly, a recent meta-analysis in anticoagulated octogenarians with non-valvular AF showed that, besides the significant reduction in all-cause mortality in those treated with DOACs versus those treated with warfarin, there was also a 43% reduction of intracranial bleeding (Bonanad et al., 2021), pointing to DOACs as a safe and effective alternative for the elderly. Additionally, the most widely used DOACs (i.e. dabigatran, apixaban and rivaroxaban) already have antidotes available in case severe or life-threatening bleeding occurs and anticoagulation needs to be reversed immediately (White et al., 2022).

In any case, anticoagulation in the frail elderly population with dementia needs to be evaluated very carefully in a one-to-one basis. Fanning et al recently analyzed the risks of embolic events, bleeding and mortality comparing DOACs with warfarin in 2399 individuals with AF and dementia (Fanning et al., 2020). They found that DOACs indeed presented reduced intracranial bleeding but increased gastrointestinal bleeding and all-cause mortality than warfarin users, although this last finding should be interpreted cautiously since DOACs are usually prescribed to sicker individuals (Fanning et al., 2020).

With all this evidence, and all the cautiousness in mind, we could argue that a DOAC might be a reasonable choice to normalize the procoagulant state in AD, especially since they have proven to be much safer than warfarin with respect to intracranial bleeding (Grossmann, 2020; Grossmann, 2021b). Which DOAC would be the best one? A systematic review including 94,656 patients across 23 randomized trials of oral anticoagulants concluded that apixaban ranked the highest in most of the outcomes (López-López et al., 2017). However, dabigatran, especially the 110 mg dose, is the one reported to have the lowest incidence of intracranial bleeding associated with its use, showing a 60% reduction compared to warfarin (Connolly et al., 2009) and its efficacy halting AD pathology has been demonstrated in AD mice (Cortes-Canteli et al., 2019). Hence, dabigatran has been suggested as the DOAC of choice for its repositioning as AD treatment (Grossmann, 2021a). Currently, there is one ongoing pilot clinical trial regarding the use of dabigatran in AD – the BEACON trial – that estimates to include 40-60 participants from 50-85 years old with the final aim of evaluating dabigatran efficacy in mild cognitive impairment and AD by measuring fluid-based biomarkers and cognitive performance (Santos et al., 2019). However, a systematic review recently performed by Lee et al in nine different studies showed no significant difference in the risk of composite dementia outcomes between the dabigatran and warfarin groups in AF patients [OR 0.97 (0.88–1.08), p=0.61]. In this same meta-analysis, apixaban [OR=0.58 (0.50–0.67), p<0.00001] and rivaroxaban [OR=0.67 (0.61–0.75), p<0.00001] use was linked to a significantly lower risk of dementia compared to warfarin use (Lee et al., 2021), pointing towards these two Factor Xa inhibitors as better candidates. Nevertheless, more studies are required to assure efficacy and safety, and further describe adverse reactions and mortality risk in the AD population. Additionally, trials to specifically adjust the DOAC doses would be helpful since lower doses present even more favorable bleeding profiles (Ruff et al., 2014).

Apart from DOACs, there are other promising anticoagulant drugs focused on inhibiting the intrinsic coagulation pathway that are of particular interest since, while having a key role in blocking thrombosis and inflammation, have little to no disruption of hemostasis and, hence,

present less bleeding (Fredenburgh & Weitz, 2021). Antisense oligonucleotides, monoclonal antibodies and small molecule inhibitors for Factor XI are already in phase II trials with promising results (Fredenburgh & Weitz, 2021). In the next years, phase III trials in larger populations will be needed to address if these new inhibitors are as effective as DOACs but safer in terms of bleeding, pointing them as potential therapeutic agents for AD.

Finally, since the procoagulant state is not present in 100% of the AD individuals (Cortes-Canteli et al., 2015), those patients that would benefit from anticoagulation should be carefully identified in order to minimize the risk-benefit ratio and avoid the exposure of AD patients with no prothrombotic state to anticoagulants. Besides specific AD biomarkers of preclinical AD, a hypothetical clinical trial to evaluate the effectiveness of a DOAC treatment in AD pathology should comprise certain inclusion criteria such as an altered coagulation profile (Suidan et al., 2018), APOE genotype (Bangen et al., 2013; Lathe et al., 2014), CBF assessment by ASL-MRI (Wierenga et al., 2014), family history of CVD and presence of CVRFs (Baumgart et al., 2015). Avoid intracranial bleeding must be another priority, hence, HAS-BLED score (Lip et al., 2011) and advance CAA should be used as exclusion criteria. HAS-BLED scheme can offer a good predictive outcome of bleeding risk and may be easy to apply. AD-related CAA is the most common cause of intracranial bleeding after traumatic injury (Charidimou et al., 2017). Additionally, the development of specific imaging and fluid biomarkers of the procoagulant state in AD would be of important value to be used as inclusion criteria in such a clinical trial. This strict selection of patients combined with a long follow up period with thorough characterization of blood flow changes (i.e. by ASL-MRI), intracranial atherosclerosis (i.e. by angiography, Time of Flight sequence) and carotid plaques by 3-dimensional-ultrasound, cerebral metabolism, presence of APOE-ε4 allele, hypertension, cognitive decline, coagulation profile, state of platelets and brain atrophy can help to achieve a positive outcome in a future clinical trial.

Conclusions

Due to the increasing prevalence of AD worldwide and the lack of existing treatments for the disease, alternative therapies are sorely needed. Over the past 20 years, we have seen the failure of treatments and drugs to reduce Aβ burden, so here we present a broader view and approach to AD, focused on the vascular component that accompanies the disease and is often disregarded. Vascular changes such as intracranial atherosclerosis, CAA, and microvascular alterations may lead to intracranial hypoperfusion, impede proper brain cell oxygenation and metabolism, make brain clearance difficult, aggravate Aβ deposition, and promote the formation of brain parenchyma Aβ plaques. A procoagulant state and changes in the coagulation cascade associated with vascular disease have been described also in AD patients. Fibrin(ogen) is abnormally present in AD mice and in human postmortem AD brains, co-depositing and interacting with Aβ, altering the structure of fibrin and interfering with plasmin-mediated clot lysis. A procoagulant milieu present in AD plays an essential role in disease progression from the beginning, pointing to be one of the mechanisms that exacerbates the pathological development of the disease that should be considered when diagnosing and treating this neurodegenerative disorder.

During the last two decades, drug development has allowed the emergence of novel anticoagulants (i.e. DOACs), which directly inhibit clotting factors leading to less adverse effects than the classic ones. The use of these drugs for the treatment of AF have shown a striking reduction in the incidence of dementia in these patients, shedding light about the possibility of prescribing this medication for dementia. Furthermore, our group has previously demonstrated that one of these DOACs, dabigatran, significantly preserved cerebral perfusion and prevented memory decline in AD mice, accompanied by inhibition of fibrin deposition, amelioration of amyloid burden and neuroinflammatory activity, and enhanced preservation of the BBB. Drug repositioning and repurposing is a highly valuable approach for AD, and as evidence indicates a change in the disease's coagulation state, anticoagulation therapy for AD patients worth formal discussion. Detailed analysis of individual´s risk and a combined therapy with other disease modifying compounds will be key to a successful therapeutic approach for AD.

Figure Legends

Figure 1. CVRFs predisposing to CVD & AD development. CVD and AD share a long subclinical phase during which the exposure to CVRFs as alcohol and tobacco consumption, high blood sugar levels, stressed- and sedentary-lifestyle, obesity and a high-fat diet could lead to disorders as diabetes, hypertension and high cholesterol (LDL) levels, which might evolve into a more serious pathological scenario as atherosclerosis. In turn, hypertension and atherosclerosis increase the likelihood of CVD and AD, as well as diabetes. Unhealthy habits are modifiable risk factors that can be redirect towards a healthy lifestyle that would prevent CVD and AD. Other CVRFs, such as the inheritance of genes associated with these pathologies (e.g. APOE-ε4 isoform) or the physiological aging process, are inevitable and also predispose to CVD and AD.

Figure 2. Schematic flow of pathological events that trigger cerebrovascular pathology and AD development. A poor vascular health might precipitate the beginning of cholesterol accumulation in brain vessels (intracranial atherosclerosis), a procoagulant state and Aβ accumulation, together with changes in cerebral perfusion and brain glucose metabolism. Aβ deposits increase, affecting brain vessels (cerebral amyloid angiopathy, CAA), driving neuroinflammation, blood brain barrier malfunctioning and reactive oxygen species accumulation, that lead to cell-oxidative stress. Aβ deposits are firmly aggregated into sticky plaques at the brain parenchyma, which along with neurofibrillary Tau-tangles (NFTs) formation, drive synaptic dysfunction and increase the risk of intracranial microbleeds. In a more advanced and severe stage, cerebrovascular alterations as white matter hyperintensities (WMH), neurodegeneration and other vascular abnormalities may contribute to mild cognitive impairment (MCI), and later to the development of the last stage of AD.

Figure 3. Coagulation cascade & fibrinolytic system in relation with anticoagulants & AD biomarkers. Coagulation is a complex physiological process that depends on three interrelated molecular pathways, the intrinsic (red), the extrinsic (blue), and the common (black) coagulation pathway, all ending up in the fibrinolysis (green) route. A signal of damage in a cell surface (intrinsic) or in a tissue (extrinsic) promotes the activation of the coagulation process. Both routes induce the activation of Factor IX, a step required to enhance thrombin formation. Fibrinogen is converted into fibrin by thrombin, and thrombin also activates platelets and Factor XIII, inducing the generation of cross-linked clots. The fibrinolytic system is key to hemostasis regulation since it is responsible of clot degradation through plasmin activity. At the same time coagulation is induced, fibrinolysis is likewise activated, however this process works slowly. Other inhibitors such as antithrombin III and α2-antiplasmin also play a crucial role in hemostasis equilibrium. Vitamin K and calcium are key molecules necessary for the correct functioning of many of the coagulation factors. Anticoagulant drugs (orange) block the coagulation process at different points. Heparin through activation of antithrombin III and warfarin/Acenocumarol through antagonizing with vitamin K. The new generation of anticoagulants are vitamin K-independent, which directly inhibit Factor Xa (Apixaban, Rivaroxaban, Edoxaban, and Betrixaban) or thrombin (Dabigatran, and Ximelagatran), known as direct oral anticoagulants (DOACs). Amyloid-β (Aβ) protein is capable to bind some of the coagulation factors (i.e. Factor XII, thrombin, fibrinogen, and Factor XIII) promoting a procoagulant state in AD. In addition, some procoagulant molecules are upregulated (thrombin, fibrinogen, vWF, FBP, D-dimer, …) or downregulated (plasmin and tPA/uPA) (purple arrows) in AD, contributing to this procoagulant state (gray squared). The "a" denotes activation of coagulation factors; PF1+2, prothrombin fragment 1+2; tPA, tissue plasminogen activator; vWF, von Willebrand factor; uPA, urokinase plasminogen activator; FBP, fibrinopeptide B.

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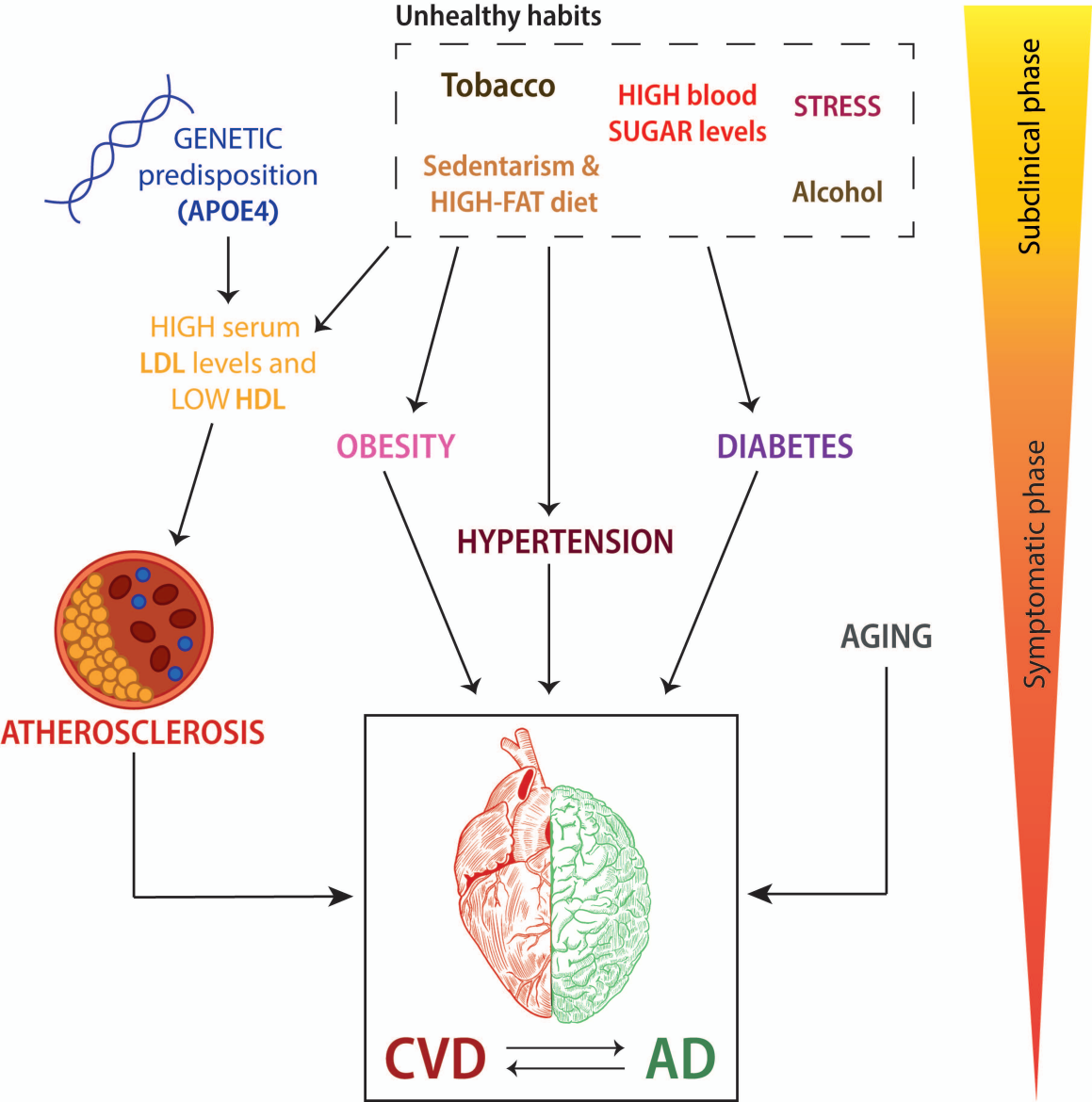
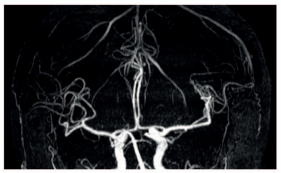
Drug/Study	Cognition Outcome	AF Patients	Age (years)	Follow-up (years)	Findings
Warfarin vs APT BAFTA (Mavaddat et al., 2014)	Cognitive impairment (by MMSE)	973	≥75	2.75±1.2	Non-significant differences in MMSE between people assigned to warfarin vs aspirin at 9-, 21- or 33-month follow-up.
Warfarin vs DOACs (Jacobs et al., 2016)	Dementia (AD, vascular, senile & unspecified dementia by ICD-9 codes)	5,254 (matched 1:1)	72.4 ±10.9	0.66	Patients taking DOACs had a 51% decreased risk of dementia vs those taking warfarin [HR=0.49 (0.35-0.69), p<0.0001). No difference in rate of dementia comparing DOACs.
VKAs vs APT SNAC-K (Ding et al., 2018)	Dementia (AD, vascular and mixed dementia by MMSE)	2,685	73.1 ±10.5	5.8±2.2	Use of VKAs significantly associated with a 60% reduced risk of dementia [HR=0.40 (0.18-0.92), p=0.031].
Warfarin vs DOACs MARKETSCAN +OPTUM (Chen et al., 2018)	Dementia (by ICD-9 codes)	468,445	67-73 ±12	0.7-2.2	Treatment with DOACs was associated with lower risk of dementia than warfarin: dabigatran [HR=0.85 (0.71-1.01)], rivaroxaban [HR=0.85 (0.76-0.94)] & apixaban [HR=0.80 (0.65-0.97)]. No difference in rate of dementia comparing DOACs.
Warfarin vs no treatment (Madhavan et al., 2018)	Dementia (by ICD-9 codes)	2,800	71.2 ±14.6	5±3.7	Warfarin therapy was associated with reduced incidence of dementia [HR=0.80 (0.64-0.99). p=0.04).
Rivaroxaban vs APT BRAIN-AF (Rivard et al., 2019)	Cognitive impairment (by MMSE & MoCA)	503	53.1 ±7	2-3	Ongoing, no results published.
VKAs/DOACs vs no treatment (Friberg et al., 2019)	Dementia (by ICD-10 codes)	47,492 (matched 1:1)	60.8 vs 61.5	4.7±2.8	Anticoagulation associated with lower risk of dementia [sHR=0.62 (0.48-0.81)].
Warfarin vs DOACs	Dementia	33,617	≥60	3.4	No significant difference between DOAC vs warfarin in dementia rates

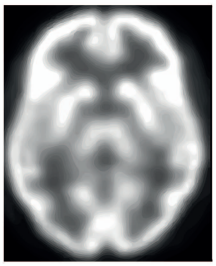
(Søgaard et al., 2019)	(AD, Vascular & other dementia by ICD-8 & ICD-10 codes)				in the 60-69- and 70-79-year-old groups. >80-year-old, DOACs use was significantly associated with increased rates of dementia vs warfarin use [HR=1.31 (1.07-1.59)].
Warfarin/DOACs vs APT vs no treatment (Mongkhon et al., 2020)	Dementia or cognitive impairment (AD, vascular & unspecified dementia)	84,521	>18	5.9	Anticoagulant treatment associated with a lower risk of dementia vs no treatment [HR=0.90 (0.85-0.95), p<0.001] or vs antiplatelets [HR=0.84 (0.79-0.90), p<0.001]. No significant difference in dementia risk observed for DOACs vs warfarin [HR=0.89 (0.70-1.14), p=0.37].
DOACs vs Warfarin (Hsu et al., 2021)	Dementia (by ICD-9 & ICD-10 codes)	12,068	70.3 ±11.7	3.08-3.27	Use of DOACs associated with lower risk of developing dementia vs warfarin use in individuals aged 65-74 years [HR=0.82 (0.73-0.92), p=0.0004].
DOACs vs VKA **(**Cadogan et al., 2021**)**	Dementia or MCI following Read codes for first clinical diagnosis	39,200	76	1.37	DOAC treatment was associated with a 16% reduction in incident dementia diagnosis than VKA treatment [HR=0.84 (0.73-0.98), p=0.02], after adjusting for all covariates DOACs were also found to be associated with a 26% reduction in MCI compared with VKAs [HR=0.74 (0.65-0.84), p=0.009].
DOACs vs Warfarin vs no treatment (Bezabhe et al., 2022)	Dementia	18,813	71.9 ±12.6	3.7±2	Incidence of dementia significantly lower in anticoagulant- vs non-treated individuals [HR=0.59 (0.44-0.80), p<0.001]. DOACs users had a lower incidence of dementia than non-users [HR=0.49 (0.33-0.73), p<0.001] or warfarin users [HR=0.46 (0.28-0.74), p=0.002]. No significant difference between warfarin- and non-treated individuals.

Table 1. Summary of studies reporting incidence of dementia in AF patients with antithrombotic treatment. Abbreviations: APT, Antiplatelet Therapy; DOACs, Direct Oral Anticoagulants; ICD9 and ICD10, 9th and 10th revisions of the International Classification of Diseases developed by the WHO; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; VKAs, Vitamin K Antagonists. Studies are shown in chronological order.

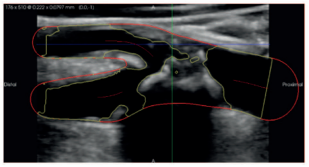

Unhealthy habits
Tobacco
HIGH blood SUGAR levels
STRESS
Sedentarism & HIGH-FAT diet
Alcohol
GENETIC predisposition (APOE4)
HIGH serum LDL levels and LOW HDL
OBESITY
DIABETES
HYPERTENSION
AGING
ATHEROSCLEROSIS
CVD
AD
Subclinical phase
Symptomatic phase



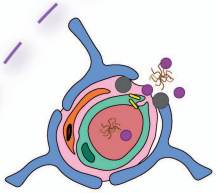
Vasculature Alterations
(TOF-MRI)



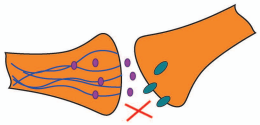
Hypometabolism
(FDG-PET)



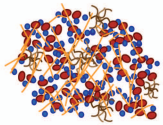
Carotid Atherosclerosis
(3D Ultrasound)



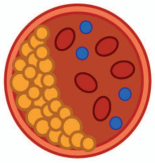
Blood Brain Barrier
Dysruption



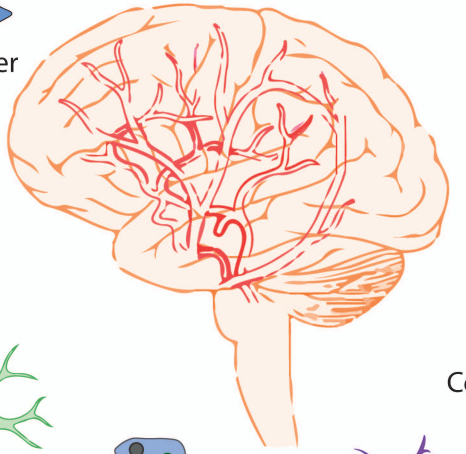
Synaptic Dysfunction



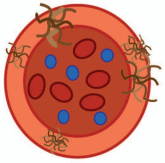
Procoagulant
State



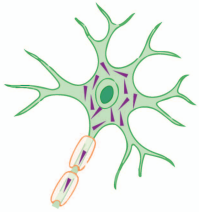
Intracraneal
Atherosclerosis



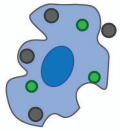
Aβ Accumulation



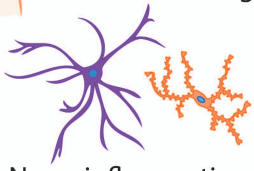
Cerebral Amyloid
Angiopathy



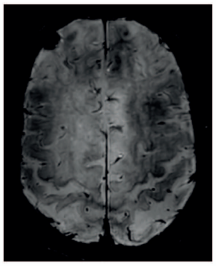
NFTs Formation



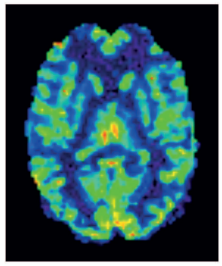
Cell-Oxidative
Stress



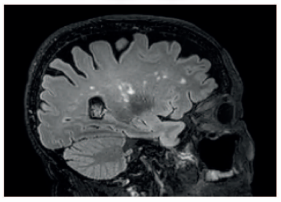
Neuroinflammation



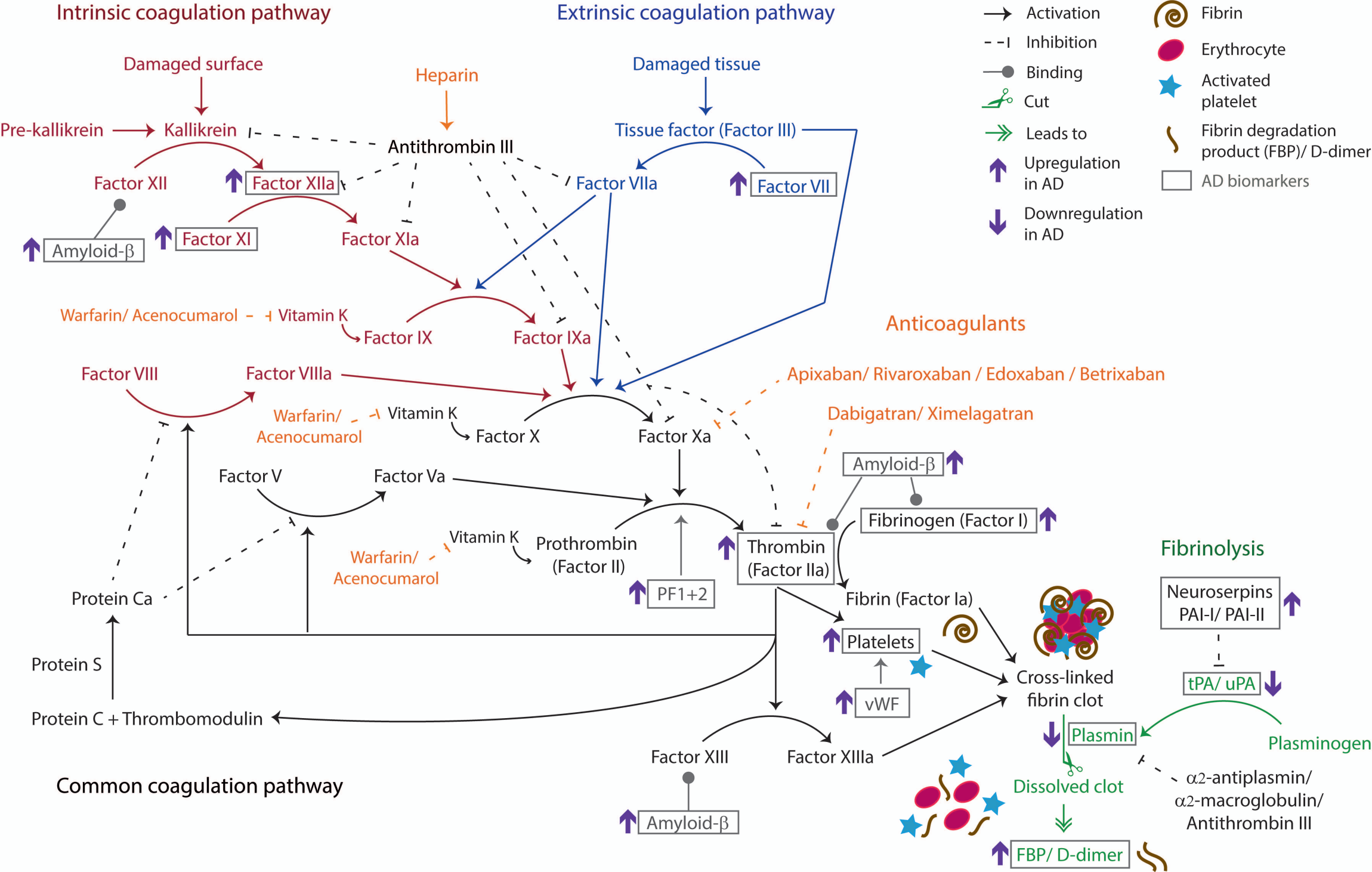
Microbleeds
(SWI-MRI)



Hypoperfusion
(ASL-MRI)



WMH
(FLAIR-MRI)


Intrinsic coagulation pathway
Extrinsic coagulation pathway
Damaged surface
Heparin
Damaged tissue
Pre-kallikrein
Kallikrein
Antithrombin III
Tissue factor (Factor III)
Factor XII
Factor XIIa
Factor VIIa
Factor VII
Amyloid-β
Factor XI
Factor XIa
Warfarin/ Acenocumarol
Vitamin K
Factor IX
Factor IXa
Anticoagulants
Factor VIII
Factor VIIIa
Apixaban/ Rivaroxaban / Edoxaban / Betrixaban
Warfarin/ Acenocumarol
Vitamin K
Factor X
Factor Xa
Dabigatran/ Ximelagatran
Amyloid-β
Factor V
Factor Va
Fibrinogen (Factor I)
Vitamin K
Warfarin/ Acenocumarol
Prothrombin (Factor II)
Thrombin (Factor IIa)
Fibrinolysis
Protein Ca
PF1+2
Fibrin (Factor Ia)
Neuroserpins PAI-I/ PAI-II
Platelets
Protein S
vWF
Cross-linked fibrin clot
tPA/ uPA
Protein C + Thrombomodulin
Plasmin
Plasminogen
Factor XIII
Factor XIIIa
Dissolved clot
α2-antiplasmin/ α2-macroglobulin/ Antithrombin III
Amyloid-β
FBP/ D-dimer
Common coagulation pathway
Activation
Inhibition
Binding
Cut
Leads to
Upregulation in AD
Downregulation in AD
Fibrin
Erythrocyte
Activated platelet
Fibrin degradation product (FBP)/ D-dimer
AD biomarkers