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Anticoagulant Therapy for Alzheimer's Disease: A Review of Recent Research

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative, vascular, and hemostatic disease characterized by cerebral-amyloid angiopathy (CAA). Thrombin, fibrin, and amyloid-(Aβ) toxic proteins are important initiators of vascular anomalies and resulting neurodegeneration in AD, which can be managed with anticoagulants, as this article reviews. Recent research suggests that the pathophysiology of AD is influenced by risk factors for cardiovascular disease, dysregulated intrinsic coagulation, and cerebrovascular damage. Anticoagulants may be a viable treatment option for AD patients with vascular condition cognitive impairment. This article provides a thorough analysis of recent research, demonstrating that anticoagulant-particularly those of the direct oral anticoagulants (DOAC) type-may be able to combat the vascular-driven progression of AD-related neuroinflammation and CAA, given complete cerebral perfusion and a decreased milieu that accumulates fibrin and Aβ. When administered early, either therapeutically or prophylactically, DOAC may be more effectively utilized to reduce inflammation and vascular dysfunction due to pharmacological reasons. Preclinical research in AD animal models will be the first step in determining whether this treatment strategy can actually effectively combat the cerebral-vascular dysfunction that are a component of AD etiology.

Keywords: Alzheimer's disease, anticoagulant, brain perfusion, cerebral amyloid–Angiopathy, fibrin, neuroinflammation, thrombin, vascular dysfunction.

INTRODUCTION

Neocortical and hippocampus brain regions are the primary sites of neurodegenerative, vascular, and hemostatic changes that culminate in a complicated condition known as AD. AD pathogenesis culminates in the gradual disappearance of a person's known personality along with memory, cognition, behavioural, and motor functions. Over 40 million individuals globally, with one million residing in Germany alone, are afflicted by this illness, which is becoming more common as the number of older people who are affected by it rises. In the case of early-onset AD, less than 10% of these patients have symptoms because of a genetic and inherited predisposition long before they turn 65.1

For over 25 years, cholinesterase inhibitors, including galantamine, rivastigmine, and donepezil, have been the cornerstone of treatment for AD in its early, mild, or moderate phases. Cholinesterase inhibitors are frequently used in conjunction with glutamate antagonists like memantine in later, more severe phases.2 Additionally thought to have a preventative and delaying effect are dietary and lifestyle modifications, as well as the avoidance of cardiovascular risk factors.3 Novel medications that are either in the research pipeline or currently available for clinical use are what are still lacking after decades of rigorous study and expenditure.4 Because they address the underlying causes of the disease, disease-modifying drugs are especially desirable for efficiently combating it. Symptomatic drugs, which solely address the disease's symptoms, are less significant.2, 5, 6 although the exact cause of this is yet unknown, the accumulation of toxic amyloid-β-proteins (Aβ) in the afflicted brain is

thought to play a significant role in AD development. Recently, aducanumab, an anti-Aβ antibody, was approved by the U.S. Food and Drug Administration (FDA) to treat a new condition.5, 6 In order to counteract this causal component, aducanumab targets Aβ and clears these peptides. However, the approval of aducanumab for the treatment of mild AD has prompted a contentious debate about whether the scientific trials that were filed to support this treatment can indeed prevent memory loss and cognitive decline with this antibody.2, 5, 6

Anticoagulant therapy appeared to have a beneficial impact on the development of senile dementia symptoms in early clinical trials involving small groups of patients .7 The notion that AD is partly caused by cerebrovascular dysfunction has been reinforced by the findings of basic research conducted over the past several years.8,9 Thrombin, fibrin, and amyloid-(Aβ) toxic proteins are important initiators of vascular anomalies and resulting neurodegenerative alterations in AD, which can be managed with anticoagulants, as this article reviews. Given this, anticoagulants may be a viable treatment option for AD patients' hemostatic and cerebrovascular dysfunctions as well as related neurodegenerative processes.9-12 Recent research suggests that the pathophysiology of AD is influenced by risk factors for cardiovascular disease, dysregulated intrinsic coagulation and cerebrovascular damage. This has led to the renaissance of anticoagulative therapy, which was first evaluated clinically over 55 years ago.10,13,14 Dysregulation of blood flow has also been revealed by quantitative transcriptome profiling of major vascular and perivascular cell types from hippocampal and cortical brain tissues of AD patients. It is interesting to note that gene expression patterns connected the vasculature to 30 of the top 45 genes for AD risk.15 In instance, it was discovered that toxic Aβ accumulations, in addition to elevated thrombin and fibrinogen accumulations, are directly responsible for cerebrovascular and blood–brain barrier (BBB) dysfunction. Anticoagulants may be used to treat these alterations mechanistically by addressing their root causes.10, 12, 16 This article provides a thorough analysis of recent research, demonstrating that anticoagulants-particularly those of the DOAC type-may be a viable treatment option for AD patients with vascular conditioned cognitive impairment.

DEPRESSICE IMPACT ON THROMBOSIS AND CLOTTING

The multi-stage process of hemostasis prevents excessive blood loss in the organism in the event of blood vessel damage.[17] the blood clotting (coagulation) phase, which leads to wound closure and healing, is when the soluble blood protein fibrinogen changes into insoluble fibrin. Following that, a fibrin clot (thrombus) is created, which is a fibrin fiber network with integrated erythrocytes and platelets. Numerous tissue and coagulation factors, such as factor Xa, cascade-like to induce the manufacture of the main core enzyme, the serine protease thrombin. A process depending on vitamin K activates several of these factors. The overproduction of fibrin clots is inhibited by endogenous inhibitors. One example is the conversion of plasminogen to the proteolytic enzyme plasmin, which is induced by the tissue plasminogen activator (t-PA). During the fibrinolysis process, plasmin breaks down fibrin, dissolve fibrin clots. [17] Large wound areas after surgeries and injuries, genetic variations in certain coagulation factors or inhibitors, and slowing blood flow (e.g., through atrial fibrillation, changes in blood vessels due to atherosclerosis, surgeries, limited movement) can all contribute to increased blood clotting with the formation of thrombin. When these thrombi detach and move through the circulatory system, they can cause brain infarction or pulmonary embolism. Alternatively, they can close blood channels throughout the thrombosis process.[18] Anticoagulant drugs are used either preventatively or therapeutically to stop blood clotting, which minimizes the risk of emboli or thrombosis developing. Different mechanisms exist for anticoagulants to prevent blood clotting.[19]

i. Indirectly, as in the case of heparins (e.g., enoxaparin), heparinoid dana paroid sodium and fondaparinux (with parenteral action), and vitamin K antagonists (VKAs, e.g., warfarin, phenprocoumon, acenocoumarol, with oral impact);

ii. Directly, for instance, in the case of blood clotting factor inhibitors (e.g., factor Xa inhibitors, such as apixaban, rivaroxaban, edoxaban, betrixaban with oral effect; otamixaban, with parenteral effect); thrombin inhibitors (e.g., dabigatran texilate, ximelagatran, with oral effect; hirudin, bivalirudin, argatroban, with parenteral effect). DOACs are the combination of factor Xa and direct thrombin inhibitors.

HISTORICAL MARKS AND CURRENT THERAPEUTIC MEDICATIONS FOR ALZHEIMER'S DISEASE

The medications now on the market for the treatment of AD, such as glutamate antagonists like memantine and cholinesterase inhibitors like donepezil, galantamine, and rivastigmine, can only postpone the onset of dementia symptoms for a limited amount of time.[20] Therefore, a pressing goal of pharmaceutical research is to find new, more potent medications.[21]

According to recent studies, the pathogenesis of AD is mostly initiated by toxic accumulations of misfolded amyloid-(Aβ) proteins in brain tissue.[21, 22] enzymatic release of amyloid-protein precursor (APP) Aβ is facilitated by secretases. Fission products of varying lengths, known as secreted APP, are delivered by APP, which is anchored in the cell membrane of neurons and is crucial for the performance of synapses.[23] On the other hand, poisonous Aβ builds up as insoluble fibrils that are deposited and as soluble dimers and oligomers (Aβ plaques). Aβ plaques and oligomers are found around and in cerebral blood vessels (specifically Aβ 40) as well as between neurons in specific parenchymal tissue sections of the brain, particularly in the

neocortex and hippocampus (Aβ42 and Aβ43). An intricate equilibrium exists between the soluble and insoluble forms of Aβ. Aβ is actively transported into the circulatory system via the blood-brain barrier, which is the vascular interface of the brain (BBB).[24] Aβ causal role of these Aβ accumulations in early AD pathogenesis suggests that 1) Synapses and neurons were damaged due to hyperactivation caused by soluble Aβ aggregates[22, 25] 2) The production of Aβ plaques is linked to all key gene changes that are associated with an elevated risk of AD, and 3) Early administration of Aducanumab, an anti-Aβ antibody, to AD patients may enhance cognitive function even with decreased Aβ accumulation.[26] Furthermore, the development of AD pathogenesis is characterized by the spread of tau-protein fibrils and intraneural deposits, abnormalities in the blood-brain barrier, neural inflammatory processes that result in the production of reactive oxygen species (ROS), and the loss of synapses and neurons. Consequently, there is a great deal of therapeutic research focused on these mechanisms.[25, 27–30] Specifically, the development and dissemination of cerebral Aβ deposits are facilitated by inflammatory processes originating from activated microglia cells, which produce interleukins and ASC (apoptosis associated speck-like protein containing a CARD) protein complexes during microgliosis.[31, 32] Conversely, early in the disease, active microglia cells caused the cerebral Aβ deposits to break down. Thus, mutations in the microglia cell activating gene TREM2 enhanced the risk of AD by increasing the production of Aβ plaques.[33] Estimates suggest that cerebral Aβ accumulates in AD patients 10–20 years prior to the onset of symptoms. Similarly, 16 years before symptoms appeared, the blood levels of people with known AD showed a rise in neurofilament light chain protein (Nfl), an indicator protein for the loss of brain neurons.[34]

ANTICOAGULANTS PREVENT THE FORMATION OF THROMBIN AND FIBRIN IN HAEMOSTASIS

When the blood vessel system is injured, the multi-stage process of hemostasis keeps the body from losing too much blood.[35]To seal and mend a wound, a soluble blood protein called fibrinogen is changed into an insoluble fibrin during the blood clotting (coagulation) process. A fibrin clot, or thrombus, is formed when platelets and erythrocytes are integrated into a fibrin network. Numerous tissue and coagulation factors, including factor Xa, regulate the generation of the causative enzyme, thrombin, which is released from its precursor protein prothrombin. This process occurs in a cascade. A procedure that depends on vitamin K is used to activate some of these in advance.[36] However, during the fibrinolysis process, the proteolytic enzyme plasmin breaks down fibrin, dissolving fibrin clots.[35] In cases where there is a genetic alteration in coagulation factors, large wounds from surgery or injuries, slower blood flow from incidents like atrial fibrillation, damaged blood vessels from atherosclerosis, and limited physical exercise, the risk of forming harmful thrombi increases as blood clotting is stimulated. When these thrombi detach, they can travel through the circulatory system to organs and induce conditions like brain infarction or pulmonary embolism. Alternatively, they might cause obstruction of blood vessels during the thrombosis process.[37] Anticoagulants inhibit blood clotting to stop thromboembolism from happening, either therapeutically or preventively. Short-term anticoagulation is advised for the prophylaxis of thrombosis and for the acute treatment of venous thrombosis in risk scenarios, such as following surgery. For example, individuals with cardiac arrhythmias such atrial fibrillation, elevated cardiovascular risk, or mechanical heart valve replacement are prescribed persistent anticoagulation as a preventive measure against thromboembolism,[36] medications with an alternative mode of action are available for the antithrombotic effect; these medications might indirectly affect blood coagulation in parenteral heparins (enoxaparin), heparinoid danaparoid sodium, Fonda parinux, and in oral active VKAs (warfarin, phenprocoumon, and acenocoumarol). Parenteral thrombin-inhibiting drugs such as hirudin, bivalirudin, and argatroban, as well as oral active thrombin inhibitors like dabigatran and factor Xa inhibitors like apixaban, betrixaban, edoxaban, and rivaroxaban, all directly suppress blood clotting .[37] DOACs include many drugs and factor Xa inhibitors. In Germany, DOACs are prescribed to around two million patients, the majority of whom are over 70 years old, in accordance with anticoagulant indications.[16] In contrast, the number of patients in Germany who are currently receiving VKA prescriptions has fallen over the past few years to about one million.[38] In susceptible people, the treatment significantly lowers the chance of a deadly heart attack or stroke. But the antithrombotic action also raises the chance of bleeding.[37] There is now debate regarding the medicinal repositioning of anticoagulants for the treatment of brain amyloidosis because AD involves vascular and haemostatic alterations in the etiology.[1, 39]

ALZHEIMER'S DISEASE: TRIGGERED NEUROPATHOGENIC PHENOMENA AND TOXIC AMYLOID PROTEINS

A neuropathologist alois Alzheimer made the first identification and description of protein deposits in the brain tissue of a deceased dementia patient.[40] In fact, misfolded, toxic Aβ build-up in brain tissue has been shown to be a critical driver of AD pathogenesis. To try to halt the progression of the illness, this notion today serves as the main treatment foundation.[41, 42] by working in succession, and-secretes liberate Aβ from the amyloid-protein precursor (APP). APP produces fission products of varying lengths and is attached in the membrane of the neuron. (Secreted APP). Aβ may have functions in the healthy brain that include controlling hippocampal synaptic activity, sealing blood-brain barrier leakage, and warding off infections.[43] A complicated equilibrium of soluble dimers and oligomers is formed in the AD brain when toxic Aβ are released from APP and aggregate into insoluble fibrils that are deposited (Aβ plaques). Neuritic plaques of Aβ and oligomeric Aβ, specifically Aβ42 and Aβ43, are found between neuron cells in the brain parenchyma, while Aβ oligomers of shorter subtype, specifically Aβ40,

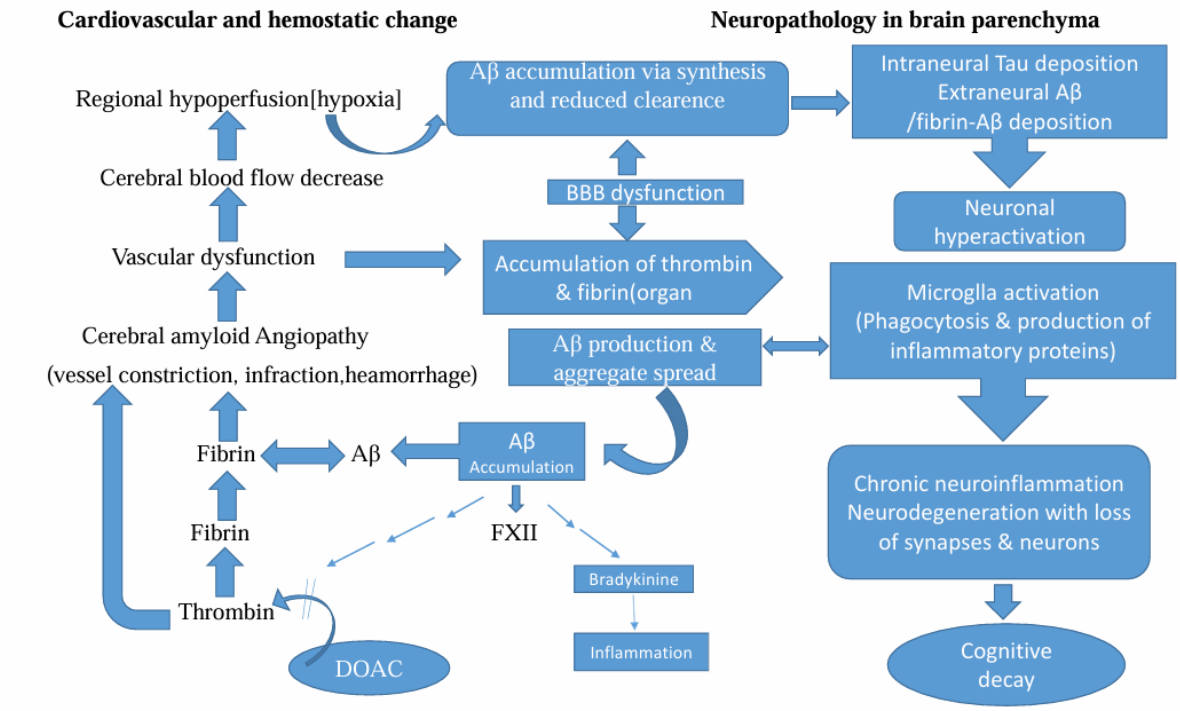
are found in and around the blood vessels of leptomeningeal and cortical arteries as well as occasionally veins. Particularly in the neocortical and hippocampus regions of the brain, both activities occur Excessive neuronal activity, malfunction, and synaptic loss in these particular brain regions have been linked, in a substantial way, to progressive cognitive impairment in the early stages of AD.[42, 44] The brain's vascular interface, or BBB, actively facilitates the entry of Aβ into the bloodstream.[45] The following arguments point to these Aβ accumulations' potential causative role in early AD. Glutamatergic neurons and synapses can be hyper activated and damaged by soluble Aβ dimers and oligomers.[42, 46] Furthermore, Aβ production, aggregation and clearance, and microglia responses are linked to every major gene alteration that has been found to date to be associated with an elevated risk of AD. Additionally, when individuals are treated with anti-Aβ antibodies relatively early in the disease, aducanumab[47] and donanemab[48] have demonstrated potential to prevent cognitive decline by lowering brain Aβ load. Clinical research is presently being conducted on these and additional anti-Aβ antibodies, including gantenerumab and BAN2401.[47, 48] Additional features of the progressive pathogenesis of AD include intraneural deposits of tau protein aggregates, which are toxic to neurons and spread from one to another. Neurofibrillary tangles (NFT), which are commonly seen in AD, are created when the microtubule-associated tau protein is phosphorylated under pathological circumstances. These insoluble, filamentous tau aggregates result from this process. The illness known as tau opathies may be exacerbated by filamentous and oligomeric tau aggregates and fragments, which can lead to synaptic dysfunction and neuronal cell death.[49] Perhaps via stimulating cyclic-dependent kinase activity for tau Hyperphosphorylation and aggregation, Aβ enhances tau-seeded diseases in AD.[50, 51] Hyperphosphorylation of soluble tau has been linked to both the rise in Aβ oligomers and the decrease in cerebral blood flow (CBF) in AD. Soluble tau gets transferred from axonal micro tubules to dendrites. Cognitive decline may result from the myelin breakdown and ensuing synapse disruption.[49, 51]

ALZHEIMER'S DISEASE, CEREBRAL AMYLOID ANGIOPATHY, AND NEUROLOGICAL DISORDERS

Although cerebral-amyloid angiopathy (CAA; Figure 1), a condition well-known and typical of AD, has only recently attracted more attention in therapeutic research due to pathogenic alterations in cerebral blood vessels linked to Aβ. Cerebrovascular abnormalities are identified very early in the etiology. CAA mostly affects the neocortical and hippocampal brain areas. Aβ aggregates collect and deposit in and around the walls of brain arteries, arterioles, and capillaries, interfering with their function.[52, 53, 54, 55] Aβ is derived from neurons and can spread out from their original site to accumulate in the cerebral vasculature. Therefore, cerebral blood flow and perfusion are impaired in the Aβ-loaded, diseased brain, reducing the amount of blood and its components that reach the tissue, such as oxygen, nutrients (including glucose, ions, and amino acids), hormones, proteins, and cellular components.[56,57,58–60] Aβ is initially deposited in the brains of AD patients around the edges of arterioles, at the location of purported interstitial fluid drainage pathways, because blood capillaries damaged by CAA also prevent the release of proteins, such as Aβ, into the bloodstream from the interstitial brain fluid (ISF).[61, 62] 65This impairs the blood's capacity to distribute and eliminate parenchymal Aβ (perivascular Aβ clearance), leading to an increasing accumulation of Aβ in the brain parenchyma.[61,63] Transgenic mouse lines are gaining popularity as a model for investigating the role of CAA-induced vascular dysfunction in AD, in addition to investigations on AD patients. Transgenic mouse lines are gaining popularity as a model for investigating the role of CAA-induced vascular dysfunction in AD, in addition to investigations on AD patients.[64, 65] Vascular Aβ build-up, mainly in neocortical and hippocampal brain areas, is the primary trigger for CAA, according to recent studies on AD patients and rodent models.[52, 66–69] However, this tau buildup is typically not a characteristic that distinguishes CAA disease.68 A reduction in CBF, a progressive loss of vascular function, hypoperfusion, and insufficient oxygen and nutrition reaching the brain (hypoxia) are all related to the degree of Aβ deposition in CAA.[56,69,70] (Figure 1). Experiments employing in vivo AD mice models and living human brain biopsy tissue, as well as mechanistic experiments involving the addition of medications and Aβ to rat cortical slice capillaries, have exemplarily proven the vascular involvement to AD. A close relationship has been observed between the deposition of Aβ in cortical capillaries and the expansion of their pericytes on the walls of the outer vessels.[70] Venules and arterioles, on the other hand, did not change. The Aβ-mediated mechanism for pericyte contraction appears to be based on endothelin-1 release induced by ROS. [71] Pericyte contraction lowered capillary diameter, resulting in vasoconstriction, or constriction of the capillaries, and decreased blood flow within the vessels. As a result, the impacted brain regions experienced prolonged hypoperfusion (ischemia), which resulted in hypoxia-a well-known occurrence in the early stages of AD.[70] Both in AD mice and AD patients, vascular dysfunction, and a simultaneous reduction in CBF, measured within a 25% range, have been noted.[69, 71] Research has also demonstrated that brain hypoxia/ischemia conditions cause the neural precursor APP to produce Aβ through activation of secretases and up-regulation of the gene expression for secretase1 (BACE1), which essentially happens in a self-amplifying process [72–74]. This promotes degenerative and inflammatory changes that impair cognition.[73, 74] Additional clinical investigations demonstrated that 82–98% of AD patients have both CAA and AD disease co-occurring in their brains. [75] Consequently, vascular function restriction in CAA, along with the ensuing drop in CBF and hypoperfusion, are thought to constitute an early and important pathophysiological mechanism in AD [54,72,76] which takes its origin from cerebrovascular Aβ deposition and evoked vasculopathies. In addition to the constriction of vessels caused by Aβ, they also involve micro infarction (occlusion) and micro-haemorrhagic (bleeding) events that damage the blood-brain barrier and generate inflammatory and degenerative changes in brain tissue [52,76,77] (Figure 1). It is interesting to note that exercise, which increases CBF and brain perfusion, has

been shown to slow down neuropathological processes in AD rodent models [79] and in those with a hereditary susceptibility to the disease.[78]

Figure 1: *Mechanism of action of DOACs, in AD.*



Mechanism of action of DOACs, a major factor in AD, in the therapeutic treatment of vascular abnormalities produced by thrombin. Early and distinctive characteristics of AD include Aβ-containing fibrinogen clots that are hard to break down, an inflammatory milieu, elevated thrombin generation in the blood that leads to fibrin formation, and the accumulation of toxic tau and Aβ proteins in the brain parenchyma. Particularly in the neocortical and hippocampal parenchyma, the release of Aβ into the blood causes the formation of thrombin and proinflammatory bradykinin. In the plasma contact system, Aβ causes blood coagulation factor XII to become activated, producing FXIIa. It is made easier for thrombin to be produced from prothrombin by factor Xa (FXa). Thrombin catalyzes the conversion of fibrinogen to fibrin and stimulates platelet aggregation in conjunction with fibrinogen, both of which can result in vessel obstruction. Amyloid plaque build-up in the brain and vascular constriction is brought on by the deposition of oligomeric Aβ and fibrin clots containing Aβ (CAA). Aβ-induced brain vasculopathies and related lesions, like (Figure 1), are primarily caused by CAA. Mechanism of action of DOACs, a major factor in AD, in the therapeutic treatment of vascular anomalies produced by thrombin. Early and distinctive characteristics of AD include Aβ-containing fibrinogen clots that are hard to break down, an inflammatory milieu, elevated thrombin generation in the blood that leads to fibrin formation, and the accumulation of toxic tau and Aβ proteins in the brain parenchyma. The release of Aβ into the blood causes the synthesis of thrombin and proinflammatory bradykinin. This is particularly true in the neocortical and hippocampal parenchyma in the plasma contact system, where Aβ stimulates blood coagulation factor XII to create FXIIa. It is made easier for thrombin to be produced from prothrombin by factor Xa (FXa). Thrombin catalyzes the conversion of fibrinogen to fibrin and stimulates platelet aggregation in association with fibrinogen, both of which can result in vessel obstruction. The deposition of fibrin clots containing Aβ and oligomeric Aβ cause vessel constriction and cerebral amyloid angiopathy (CAA). The deposition of fibrin clots containing Aβ and oligomeric Aβ cause vessel constriction and cerebral amyloid angiopathy (CAA). This leads to a decrease in cerebral blood flow (CBF) and perfusion, as well as a decrease in the amount of oxygen and nutrients that reach brain tissue (hypoxia). Simultaneously, perivascular Aβ clearance is impeded by the BBB, leading to Aβ accumulation and aggregates spreading in the parenchymal tissue due to hypoxia-induced Aβ synthesis. The self-amplifying build-up of Aβ leads to neurotoxic tau diseases by causing synaptic disruption and neuronal hyperactivation. Furthermore, when the blood-brain barrier is compromised, vascular thrombin and fibrinogen can permeate into the parenchymal tissue and stimulate glial cells in conjunction with Aβ. This results in persistent inflammation and increased production of Aβ. Cognitive decline is also a result of increasing brain injury, which results in the loss of neurons and synapses. The primary mediator in this vicious cycle, thrombin, is the goal of DOAC intervention. DOAC and FXa inhibitors, such rivaroxaban, can block thrombin's activity or synthesis. Early thrombin inhibition in AD patients may preserve vascular and blood-brain barrier integrity for full brain perfusion and function. In this manner, blood vessel-induced neurotoxicity and inflammation that result in cognitive decline could be prevented or at least modified.[90] as bleeding and

blockage of vessels, which ultimately result in vascular and blood-brain barrier (BBB) dysfunction. As a result, there is a drop in cerebral blood flow (CBF) and perfusion as well as a reduction in the nutrition and oxygen supplied to brain tissue (hypoxia). At the same time, hypoxia-induced Aβ synthesis and poor perivascular Aβ clearance via the BBB lead to an increased accumulation and dissemination of Aβ aggregates in the parenchymal tissue. The self-amplifying build-up of Aβ leads to neurotoxic tau diseases by causing synaptic disruption and neuronal hyperactivation. Furthermore, when the blood-brain barrier is compromised, vascular thrombin and fibrinogen can permeate into the parenchymal tissue and stimulate glial cells in conjunction with Aβ. This results in persistent inflammation and increased production of Aβ. Cognitive decline is also a result of increasing brain injury, which results in the loss of neurons and synapses. The primary mediator thrombin is the goal of DOAC intervention into this vicious cycle. DOAC and FXa-inhibitors can block thrombin's activity or synthesis. For complete brain perfusion and function, early thrombin inhibition in AD patients may maintain vascular and blood-brain barrier integrity. In this way, neurodegeneration and inflammation caused by blood vessels that lead to cognitive loss could be avoided.[90]

ALZHEIMER'S ILLNESS, THE FUNCTIONS OF THROMBIN, FIBRIN, AND AMYLOID IN FIBRIN-CONTAINING CLOTS

Recent research has demonstrated that the brains of individuals with hereditary and sporadic AD, as well as AD mice, exhibit co-occurring accumulations of toxic Aβ, thrombin, and fibrin/fibrinogen.[53, 54, 80–84] It has been discovered that fibrinogen and Aβ co-colonize the walls of cerebral vessels and the parenchyma of the nervous system[54, 80,84] neuro-inflammatory processes are initiated by thrombin and fibrinogen, and fibrinogen can also interact with Aβ [54,80,82–84] (Figure 1). Because of the developing vascular dysfunction in CAA, the BBB becomes increasingly leaky for plasma proteins, which leads to an accumulation of fibrinogen and thrombin in parenchymal tissue. [77, 85, 86] it is possible for fibrinogen to enter parenchymal tissue from blood vessels. Here, after vascular disruption, it is transformed into fibrin by thrombin, extra perivascular tissue factor, and procoagulant proteins, which are also widely distributed in this tissue.[77,85,86] The breakdown of pericytes in capillary walls, which disrupts connections between neighbouring endothelial cells, causes haemorrhage and infarction damage, which cause the blood-brain barrier to leak.[86] In general, increased Aβ synthesis, microglia activation, and malfunctioning and loss of synapses and neurons are linked to BBB disruption and the processes that follow[57] (Figure 1). Fascinatingly, recent studies have revealed that, in accordance with Aβ42, fibrinogen can bind to Aβ through its central region, while Aβ binds the C section of fibrinogen[81, 83] Aβ-containing fibrin-Aβ clots are created when fibrinogen and Aβ combine to promote Aβ oligomerization.[80, 83, 87] Compared to normal clots, these fibrin-Aβ clots are more resistant to the plasmin fibrinolysis enzyme-degrading enzymes because of an aberrant fibrin mesh structure.[80, 83, 87] Compared to normal clots, these fibrin-Aβ clots are more resistant to the plasmin fibrinolysis enzyme-degrading enzymes because of an aberrant fibrin mesh structure. It has been found that these fibrin clots containing Aβ are deposited in the cerebral blood vessels of the neocortical and hippocampal brain areas of CAA. Additionally, they accumulate in parenchymal brain regions of dystrophic neuritis along with Aβ oligomers and plaques.[80, 81, 83–85] Fibrin-Aβ clot deposition in blood arteries impairs blood flow in CAA regions and disrupts BBB and vascular function. Blood flow in CAA regions is impeded by fibrin-Aβ clot formation in blood vessels, which also compromises BBB and vascular function.[54] Aβ mutations that facilitate the production and deposition of cerebral fibrin-Aβ clots in the pathophysiology of AD have been found in patients with hereditary CAA.[87] Conversely, RU-505, which binds directly to Aβ, and other pharmacological inhibitors of the fibrinogen-Aβ interaction can stop fibrin-Aβ clots from forming.[54,88] As a result, RU-505 treatment for an extended period of time dramatically decreased cerebral microgliosis, vascular amyloid deposition, vessel blockage, and cognitive impairment in an AD animal model.[54,88] Interestingly, the amide side chain portion of RU-505,[87] which may be involved in the fibrinogen-Aβ interaction, shares some structural similarities with the pharmacophore for thrombin binding of the DOAC.[89] Beyond its well-known ability to inhibit thrombin and may also be able to interfere with the production of fibrin-Aβ clots, which is something worth looking into.

NEW THERAPEUTIC METHODS INCLUDING ANTICOAGULANTS

The treatment strategy is predicted on the theory that anticoagulants impact the development of critical drivers in AD-related neuroinflammation and CAA. Anticoagulants work by blocking thrombin's ability to create fibrin, which prevents the build-up of fibrin clots that contain Aβ and are resistant to breakdown, as well as thrombin that promotes inflammation and microglia activation. In regions of CAA, these fibrin-Aβ clots are seen in the cerebral blood vessels and brain parenchyma, which disrupts cerebral blood flow. As a result, anticoagulant therapy can compensate for hypoperfusion and limited oxygen and nutrition delivery to brain tissue. Simultaneously, it is possible to mitigate hypoperfusion-enhanced neurodegenerative processes, including synapse and neuron cell death, neuroinflammation, and increasing accumulation of Aβ through production and decreased clearance (Fig. 1). When administered early in the process, anticoagulants may be able to slow the vascular-driven progression of the neurodegenerative and cognitive abnormalities associated with AD, given complete cerebral perfusion and a decreased milieu that accumulates fibrin and Aβ. Consequently, administration of the indirect heparin-type thrombin inhibitor enoxaparin decreased cortical Aβ formation, as demonstrated by earlier research using AD mice models.[91, 92] Moreover, administration of the direct thrombin inhibitor such as DOAC resulted in a reduction in the production of ROS and

vascular inflammatory proteins[93] as well as in the activation of microglia.[94] Thrombin inhibitors have been proposed as a potential treatment for AD symptoms due to their inhibitory action on vascular pro-inflammatory thrombin.[95] The drawbacks of heparin infusion therapy are as follows: 1) non-specific plasma protein binding can alter anticoagulation unpredictable; 2) thrombocytopenia can be caused; and 3) fibrin-bound thrombin, a significant stimulant of fibrin clot development, is not inactivated.[1, 96] In contrast, oral anticoagulants offer advantages for treating vascular dysfunction in AD due to their broad application and unique mode of action. On the other hand, bleeding difficulties and the impact of vitamin K insufficiency on vital proteins of the neurological and circulatory systems are un favourable side effects of oral anticoagulants of the VKA type, such warfarin[1, 97] The particular acting DOACs, such as the blood clotting factor Xa-inhibitors rivaroxaban (Xarelto®), apixaban (Eliquis®), edoxaban (Lixiana®), and betrixaban (Bevyxxa®), and the direct thrombin inhibitor etexilate (Pradaxa®), are far more appropriate. For the following reasons, commercial choice when treating vascular dysfunction in AD patients. The prodrug version of some drugs is the one that releases the active ingredient in vivo. Thrombin is the enzyme that directly converts fibrinogen into insoluble fibrin at the end of the blood clotting cascade. This enzyme is specifically inhibited by DOAC.[98] Certain these have been associated with a decreased risk of ischemic stroke, a 66% reduction in cerebral hemorrhage, and a decreased risk of death in elderly patients with atrial fibrillation. These drugs have a shorter half-life in humans than the VKA warfarin.[99, 100] In a research FDA, it was shown that taking DOAC reduced the incidence rate of cerebral haemorrhage per 1000 person-years to 3.3 (0.33%), whereas taking warfarin increased the rate to 9.6 (0.96%) [100] Thus, in the AD mouse model, DOAC did not result in an increase in cerebral micro bleed.[101] And also has no effects on vitamin K insufficiency or nutritional interactions with anticoagulation because of its mode of action. The substance produces anticoagulation that is efficient, dependable, and predictable.[98] additionally, the trade antibody idarucizumab offers a particular counteragent that instantly negates the effects of DOAC, effectively reducing the danger of bleeding.[102] A modified recombinant inactive form of human factor Xa, and the reversal agent have made this option available for factor Xa-inhibiting DOACs as of late.[103] However, considering the correlation between vascular fragility and CAA, the use of DOAC or other antithrombotic medicines to AD patients who are at higher risk of bleeding needs to be carefully assessed for bleeding risk.[104]

CONCLUSION

Theoretically, anticoagulants of the DOAC type, in particular, such as the direct thrombin inhibitor and the indirect thrombin impacting factor Xa inhibitors, are suitable for treating the cerebrovascular changes associated with AD. Anticoagulants have the potential to inhibit the production of inflammatory thrombin and fibrin, as well as the deposition of fibrin clots containing Aβ that are resistant to breakdown in cerebral blood arteries of CAA and brain parenchyma. When administered early, either therapeutically or prophylactically, DOAC may be more effectively utilized to reduce inflammation and vascular dysfunction due to pharmacological reasons Anticoagulant therapy may lessen the disruption of cerebral blood flow, brain perfusion and supply with oxygen and nutrients, and enhanced advancement of neurodegenerative processes, all of which contribute to cognitive loss (Figs. 1). The therapeutic translation to this novel illness indication is likely to be accomplished more quickly and at a lower cost because DOAC a medication that has been clinically approved, given for many years, and has a recognized safety profile. Preclinical research in AD animal models will be the first step in determining whether this treatment strategy can actually effectively combat the cerebrovascular dysfunction that is a component of AD etiology. Interestingly, Cortes-Canteli and colleagues (2019) have revealed results in the AD mouse model that support the idea that was put forth.[90] over time, brain fibrin build-up, hypo perfusion, and memory loss were prevented by DOAC therapy. In parallel, there was a decrease in the amount of Aβ plaques and oligomers as well as neuroinflammatory activity, which was typified by T cells infiltrating and phagocytic microglia. In addition, the absence of astrogliosis and changes in pericytes showed that BBB function was maintained. There were no signs of intracranial bleeding or haemorrhages Sub-sequently, extensive clinical trials of This-type anticoagulants on their therapeutic efficacy in AD would be strongly advised if these findings are validated by more research in AD animal models. When conducting clinical trials to test the theory, position emission tomography (PET) and magnetic resonance imaging (MRI) approaches can be used to visualize brain biomarkers such as micro bleeds, CBF dynamics, and plaques of Aβ in order to study the effects of DOAC on early AD and CAA progression in patients[4, 52, 89, 91] Furthermore, evaluations of cognitive function and biochemical assays, namely for blood biomarkers that indicate neurodegenerative[31] and haemostatic (e.g., fibrin clot formation) alterations, can supplement the analysis. However, before to study, the desired methodologies' cost/benefit should be evaluated [91] Despite this, every attempt should be taken, as there is presently no recognized potential medication on the horizon for the successful treatment of this horrible illness, which is estimated to affect over 40 million people globally [92, 93] Of these, 5% are thought to have early-onset AD (hereditary AD susceptibility), which causes symptoms to typically appear well before the age of 65.[94]

ABBREVIATIONS

Abbreviation	*Full Form*
AD	Alzheimer Disease
AÎ²	Amyloid
APP	Amyloid-protein precursor
ASC	Apoptosis associated speck-like protein containing a CARD
BBB	Bloodâ€“brain barrier
PET	Position emission tomography
CAA	Cerebral-amyloid angiopathy
CBF	Cerebral blood flow
DOAC	Direct oral anticoagulants
FDA	Food and Drug Administration
ISF	Interstitial brain fluid
NFL	Neurofilament light chain protein
NFT	Neurofibrillary tangles
ROS	Reactive oxygen species
T-PA	Tissue plasminogen activator
TREM2	Triggering receptor expressed on myeloid cell 2

ETHICAL DECLARATION

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