Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Dabigatran (Pradaxa)

Evidence Summary

Vascular activation is a promising theory as a contributing factor for Alzheimer's disease and atherosclerosis. There is little evidence that dabigatran is beneficial, and it is associated with adverse effects which may limit its use.

Neuroprotective Benefit: Biomarker data suggest the involvement of thrombin in Alzheimer's pathology, but there is no evidence that dabigatran itself would prevent dementia or if thrombin is the primary mediator of vascular activation.

Aging and related health concerns: In certain conditions, such as venous thromboembolism or stroke prevention in patients with atrial fibrillation, dabigatran reduces the risk of bleeding compared to other drugs, such as warfarin. Pre-clinical data suggests prevention of atherosclerosis.

Safety: Clinical evidence suggests an increased risk of bleeding and dyspepsia, and clinical trials suggest almost 3% risk of a serious adverse events.

What is it?

In response to tissue damage, tissue factor initiates a cascade of events that leads to the formation of thrombin from prothrombin. Thrombin cleaves fibrinogen to create fibrin. Molecules of fibrin aggregate to form a blood clot at the damaged tissue to prevent excessive bleeding.

Thrombin has many other effects beyond coagulation via the protease-activated receptors I-IV (PARs), including changes in vascular tone, endothelial dysfunction, endothelial permeability, angiogenesis, and inflammation. Most of this we know through *in vitro* studies, and the exact mechanisms by which thrombin activation of PARs causes these effects is not clear (Borissoff et al, 2009). Thombin may also be directly toxic to neurons (Tripathy et al, 2013). Regardless, studies suggest that thrombin may be involved in the pathophysiology of Alzheimer's disease, atherosclerosis and stroke, suggesting thrombin inhibition as a potential therapeutic option.

Vascular activation is the first step in the process of angiogenesis. Endothelial cells are activated (and the release of pro-inflammatory cytokines); extracellular matrix is degraded, and endothelial cells proliferate and migrate. However, due to pathologies in the Alzheimer's brain (such as amyloid beta peptides), the process of angiogenesis may be unable to resolve, leaving endothelial cells in an activated state (thus releasing inflammatory cytokines). Thrombin is thought to be one mediator of vascular activation (Grammas et al, 2014).

Dabigatran is a direct thrombin inhibitor that is approved for the prevention of stroke in patients with non-valvular atrial fibrillation and to treat patients with deep vein thrombosis and pulmonary embolism.

Neuroprotective Benefit: Biomarker data suggest the involvement of thrombin in Alzheimer's pathology, but there is no evidence that dabigatran itself would prevent dementia or if thrombin is the primary mediator of vascular activation.

Types of evidence:

- One observational study on stroke/transient ischemia attack/dementia prevention
- Biomarker studies suggesting that thrombin is associated with Alzheimer's pathology
- *In vitro* data suggesting that exposure of plasma to amyloid beta increases thrombin levels
- Pre-clinical studies suggesting that thrombin induces cell death in mouse brains
- One pre-clinical mouse study suggesting that dabigatran improves vascular pathology in a mouse model of Alzheimer's disease

Human research to suggest prevention of dementia, prevention of cognitive decline, or improved cognitive function?

One observational study of 5,254 patients comparing direct oral anti-coagulants (DOAC) (rivaroxaban, apixaban, and dabigatran) vs warfarin for thromboembolism prevention reported a reduced risk of long-term incident dementia (p=0.03). A few caveats: although the observational study was over 4 years, the median patient follow up was 243 days, so it is not clear what 'long-term incident dementia' means; the paper is unclear whether this result is dementia, per se, or a composite of stroke/transient ischemic attack/dementia. Also, this is a composite of three direct oral anti-coagulants and not dabigatran specifically, and the absolute reduction in dementia was only 0.4% (0.7% for warfarin, 0.3% for DOAC, equivalent to about 18 and 8 patients, respectively) (Jacobs et al, 2016).

Human research to suggest benefits to patients with dementia:

Microvessels isolated from human Alzheimer's patients were reported to have increased expression of thrombin (Grammas et al, 2006; Yin et al, 2010) and reduced expression of the protease nexin-1, an endogenous thrombin inhibitor (Vaughan et al, 1994). However, another autopsy study suggested that human blood vessels of both control patients and Alzheimer's patients had increased thrombin expression while Alzheimer's patients had increased levels of thrombin around amyloid plaques (Akiyama et al, 1992). Thrombin was also reported to be increased in the CSF of Alzheimer's patients (Yin et al, 2010). In a non-blinded study of 84 patients with possible or probable Alzheimer's disease taking donepezil or donepezil + hirudin (a direct thrombin inhibitor isolated from the salivary gland of medicinal leeches), patients taking donepezil + hirudin showed statistically significant (though probably not clinically significant) improvements in cognition (ADAS-Cog) and in activities of daily living, though no changes in the neuropsychiatric inventory scale over 16 weeks. However, a subgroup analysis of patients with vascular risk factors did see improvements in all measures that were attenuated after a four week washout period (Li et al, 2012).

Additionally, exposing the plasma from healthy volunteers to amyloid beta increased expression of thrombin which may be a positive feedback loop both increasing toxicity and thrombin expression in blood (Zamolodchik et al, 2016).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

In vitro experiments suggest that thrombin can increase the expression of reactive oxygen species and matrix metalloproteinases in glia cells (Choi et al, 2005; Choi et al, 2008). In addition, *in vitro* data suggests that thrombin and PAR-I and PAR-4 agonists increase phosphorylated tau in mouse hippocampal neurons (Suo et al, 2003). Intra-cerebral infusion of thrombin in mice causes cell death and

the release of pro-inflammatory cytokines (IL-6, TNFα, IL-1β, iNOS) (Lee et al, 2006). In rats, intra-cerebral infusion of thrombin impairs cognition, and increases cell death, inflammation and ApoE. When thrombin was co-infused with hirudin, there were no deficits in cognition (Mhatre et al, 2004). Finally, in a mouse model of Alzheimer's disease, 34-week treatment with dabigatran reduced frontal cortex microvasculature levels of HIF-1a (a hypoxia-response protein), IL-6, MCP-1, MMP2, and thrombin. It also reduced levels of HIF-1a, thrombin, MCP-1, and MMP2 in control animals (Tripathy et al, 2013).

APOE4 interactions:
None reported

Aging and related health concerns: In certain conditions, such as venous thromboembolism or stroke prevention in patients with atrial fibrillation, dabigatran reduces the risk of bleeding compared to other drugs, such as warfarin. Pre-clinical data suggests prevention of atherosclerosis.

Types of evidence:

- RCTs, observational studies and meta-analyses for venous thromboembolism or stroke prevention in patients with atrial fibrillation
- Multiple preclinical studies in mouse models of atherosclerosis

Longevity
None.

Stroke in patients with atrial fibrillation
Typical doses of dabigatran are either 110mg or 150mg two times per day. An RCT of 18,113 patients reported that 110mg of dabigatran over 2 years was associated with a similar risk of stroke and systemic embolism compared to warfarin with lower rates of major hemorrhage. 150mg of dabigatran was associated with a decreased risk of stroke and systemic embolism compared to warfarin and a similar risk of hemorrhage (note that all of these risks are in the 1-3% range – it may be due to the drug or underling atrial fibrillation) (Connolly et al, 2009). A meta-analysis of observational studies of 348,750 patients reported that both doses were non-inferior to warfarin in preventing stroke and had a decreased risk of intracranial bleeding. The 150mg dose had a greater risk of gastrointestinal bleeding, but this was specifically due to the patients >75 years of age (Romanelli et al, 2016).

Venous thromboembolism

A network meta-analysis of patients with venous thromboembolism comparing different anti-coagulant drugs reported that dabigatran was associated with a reduced risk of bleeding but no difference in mortality (Cohen et al, 2015). A Cochrane meta-analysis reported no difference between dabigatran and standard anti-coagulant therapy (vitamin K antagonists such as warfarin) in preventing pulmonary embolism, recurrent venous thromboembolism, deep vein thrombosis, or major bleeding (Roberson et al, 2015). Just as in the stroke studies, risk of these adverse events is in the 1-3% range, and it may be due to the drug or underlying condition.

In a mouse model of venous thromboembolism, dabigatran treatment did not change thrombus size but increased embolic events and pulmonary embolism load. The researchers speculated that thrombin inhibition caused pieces of the clot to break off while adding pieces back on. They suggested caution in patients with thromboembolism (Shaya et al, 2016).

Atherosclerosis

Due to its effects on the vasculature, dabigatran was tested in a number of atherosclerosis mouse studies (ApoE-/-). It was reported to reduce atherosclerotic lesion size (up to 31% in one study), reduce plaque burden, reduce the size of the necrotic core, reduce monocyte infiltration, increase or not change the fibrotic cap, reduce intima/media ratio, decrease aortic oxidative stress, and improve endothelial function (Pingel et al, 2014; Preusch et al, 2015; Borissoff et al, 2013). However, one study reported that there was no effect when lesions were already established in the later stages of the disease (Preusch et al, 2015).

Safety: Clinical evidence suggests an increased risk of bleeding and dyspepsia, and clinical trials suggest almost 3% risk of a serious adverse events.

Types of evidence:

- Multiple RCTs

Dabigatran is an anti-coagulant and is associated with an increased risk of bleeding (up to 16% of patients per year; although it is generally superior to other anti-coagulants such as warfarin) (drugs.com). It also requires a low pH for absorption, and the capsules have an acidic core which might be why it is associated with an increased risk of gastrointestinal bleeding and dyspepsia (up to 12% of patients) (Connolly et al, 2009). There were reports that dabigatran is associated with an increased risk

of acute coronary syndrome compared to warfarin or placebo (increased risk of 54% and 87% [n.s.], respectively) (Locke et al, 2014). A meta-analysis of RCTs reported a significant 33% increased relative risk of myocardial infarction or acute coronary syndrome compared to the control group (other anti-coagulants or placebo); however, the absolute risk was only increased 0.27% (Uchino and Hernandez, 2012).

Idarucizumab is an antibody that binds to thrombin at the same site as dabigatran and has recently been approved as a first-line agent for the reversal of dabigatran-associated intracranial hemorrhage; however it is still new and evidence of its effectiveness is limited (Gottlieb and Khishfe, 2017).

Drug Interactions:
Dabigatran is an anti-coagulant with an increased risk of bleeding so should not be taken with other drugs that may also increase risk of bleeding. It is also a substrate for P-glycoprotein, so care should be taken if taking other P-gp substrates. Drugs.com lists 113 major drug interactions and 252 moderate drug interaction (drugs.com).

Sources and dosing:
Dabigatran (Pradaxa) is available with prescription from Boehringer Ingelheim. Typical doses are 110mg or 150mg twice/day. Higher doses are more efficacious for stroke prevention but come with increased risk of bleeding.

Research underway:
There are currently 82 open clinical trials for dabigatran (clinicaltrials.gov) mostly for various cardiovascular complications.

Search terms:
Pubmed:

- Dabigatran + Alzheimer, dementia, cerebrovascular, atherosclerosis
- Thrombin + Alzheimer
- systematic reviews from https://www.ncbi.nlm.nih.gov/pubmedhealth/

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.