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.

Cilostazol (Pletal)

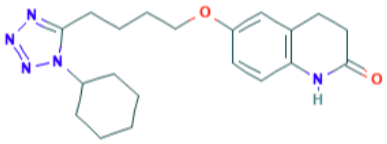
Evidence Summary

There is some evidence from poorly designed studies suggesting cilostazol may be beneficial for Alzheimer's disease (especially with a vascular component), but these will have to be confirmed in larger studies.

Neuroprotective Benefit: Poorly designed clinical studies lower the potential evidence in Alzheimer's disease; however, it is a promising therapeutic, especially if there is evidence of small vessel disease.

Aging and related health concerns: Some evidence suggest cilostazol may be beneficial in vascular diseases.

Safety: Multiple clinical studies suggest that cilostazol may be associated with some moderate side-effects, but it appears safer than other anti-platelet therapies.

Availability: Available as a generic drug with prescription as a tablet at 100mg and 50mg	**Dose**: 100-200mg per day	**Chemical formula**: $C_{20}H_{27}N_5O_2$; **Molecular Weight:** 369.46g/mol  **Source:** PubChem
Half life: 11-13 hours	**BBB**: Yes	
Clinical trials: 25 ongoing including trials for atherosclerosis in type 2 diabetics, patients with MCI, small vessel disease, and stroke.	**Observational studies**: Multiple observational studies looking at risk for dementia	

What is it?

Phosphodiesterases (PDEs) hydrolyze the phosphodiesteric bond of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), important secondary messengers that perform many functions. PDEs are classified into 11 families (PDE 1-11), and certain PDEs have different tissue distribution and preference for breaking down cAMP, cGMP or both. Different classes have different gene products and splice variants, and it is estimated that more than 100 human PDEs exist (Prickaerts et al, 2017).

Cilostazol is an anti-platelet and vasodilation drug that is a phosphodiesterase 3 (PDE3) inhibitor used primarily to treat intermittent claudication in individuals with peripheral artery disease. In East Asian countries (Japan, Korea, China), it is often used for secondary prevention of stroke. PDE3 breaks down cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), important secondary messengers, therefore cilostazol may increase signaling through these pathways.

Neuroprotective Benefit: Poorly designed clinical studies lower the potential evidence in Alzheimer's disease; however, it is a promising therapeutic, especially if there is evidence of small vessel disease.

Types of evidence:

- 1 pilot RCT in patients with possible Alzheimer's and confirmed cardiovascular lesions
- 1 single-arm open label pilot study in Alzheimer's patients
- 3 observational studies in Alzheimer's patients
- 2 observational studies for dementia prevention
- Multiple meta-analyses for secondary prevention of stroke
- Multiple preclinical laboratory studies on possible mechanisms of action

Human research to suggest that cilostazol can prevent dementia:
A small retrospective observational study reported that cilostazol (mean 130mg/day) prevented cognitive decline in patients with MCI vs. controls but not in patients with normal cognition or dementia. There are many caveats to this study: 1) controls were individuals who had previously taken cilostazol but stopped due to side-effects, 2) the study was very small, especially for an observational study (n=40), 3) most patients had cardiovascular risk factors (hypertension, hyperlipidemia, diabetes) (Taguchi et al, 2013).

In a cohort study using Taiwan's National Health Insurance Research Database examining patients 40-90 who had taken cilostazol for at least 3 months, long-term cilostazol (at least 217 days) was associated with a reduced incidence of dementia (HR = 0.53; 95%CI 0.37-0.76). These results were primarily driven by individuals over 65, males (no significant effect in females), and patients with cerebral vascular disease (HR = 0.34; 95%CI 0.21-0.54) (Tai et al, 2017).

Human research to suggest that cilostazol can benefit patients with Alzheimer's disease or dementia:
Three studies (a pilot open-label study, a small retrospective observational study, and a pilot RCT) examined cilostazol as an add-on to donepezil treatment in patients with Alzheimer's disease, dementia, or possible Alzheimer's disease with confirmed cardiovascular disease. Overall the studies reported that cilostazol (100mg/day) + donepezil was superior to donepezil alone in slowing cognitive decline in mild dementia patients but not severe dementia patients. Cilostazol tended to stabilize cognition during the time period analyzed and increased cerebral blood flow. Given the small numbers (between 10 and 40 in treatment arms) and nature of the studies, larger, controlled trials will be required to determine whether cilostazol is a good treatment for dementia or prevention of dementia (Arai et al, 2009; Ihara et al, 2014; Sakurai et al, 2013).

Tai et al (2017) performed a case control study in 30 Alzheimer's patients taking an acetylcholine esterase (AChE) inhibitor and 30 patients taking an AChE inhibitor + cilostazol (50mg 2x per day). They reported favorable outcomes in a greater percentage of patients for those taking cilostazol (defined as improvement in cognition) over one year (50% favorable for cilostazol vs. 20% for placebo). However, the average decline in cognition was the same between the groups suggesting that some of the cilostazol patients may have declined to a greater extent than controls.

Another retrospective study compared the effects of galantamine (an AChE inhibitor) monotherapy followed by cilostazol + galantamine dual therapy and vice versa. Analysis started in patients taking a monotherapy (they could have been taking the monotherapy for up to a year, but measures started at -3 months), the add-on therapy was then given at baseline, and measurements made at +3 months and +6 months. In both groups, cognition and activities of daily living improved with monotherapy and dual therapy provided additional benefits. However, these effects could have been transient, as at 6 months patients had started to decline (Hishikawa et al, 2017).

Human research to suggest that cilostazol benefits patients in secondary prevention of stroke:
Cilostazol is widely used for secondary prevention of stroke in East Asian countries, and there are currently at least 12 clinical trials as well as six meta-analyses based on these trials. Although cilostazol has only gone head-to-head in clinical trials against aspirin, placebo and clopidogrel, meta-analyses suggest that cilostazol may be more effective than low-dose aspirin at secondary stroke prevention.

In a meta-analysis of 9 studies for prevention of stroke recurrence compared to placebo, aspirin, or clopidogrel, cilostazol treatment (200mg/day) was associated with a reduced risk of stroke recurrence (RR 0.63; 95%CI 0.52-0.76 – 5.3% vs 8.3% of patients), intracranial hemorrhage (RR 0.36; 95%CI 0.21-0.63), extracranial bleeding complications (RR 0.62; 95%CI 0.46-0.83) with no significant differences in cerebrovascular events or cardiac adverse events (Tan et al, 2015).

Compared to aspirin: Cilostazol is associated with a significant reduction in serious vascular events (OR 0.69; 0.55-0.86) (Niu et al, 2016), hemorrhagic stroke (RR 0.27; 0.13-0.54), hemorrhagic events (RR 0.52; 0.34-0.79), with trends for a reduction in ischemic stroke (RR 0.81; 0.62-1.06), all-cause mortality (RR 0.87; 0.46-1.66), and gastrointestinal bleeding (RR 0.60; 0.34-1.06) (Dinicolatonio et al, 2013).

Long-term secondary prevention of stroke (>1 year): Of 11 anti-platelet therapies, cilostazol was most effective at reducing stroke recurrence, composite vascular events, intracranial hemorrhage, and major bleeding (Xie et al, 2015).

Network Meta-analyses: One network meta-analysis reported that cilostazol ranked highest for prevention of overall stroke risk and hemorrhagic stroke risk, and second for fatal stroke risk (Wang et al, 2016). Another ranked cilostazol highest compared to other anti-platelet therapies (n=10) for reduced risk of composite vascular events and major bleeding, second for all-cause death and ischemic stroke, and sixth for intracranial hemorrhage (Huang et al, 2016).

Mechanisms of action for neuroprotection:

PDE3 degrades cAMP and cGMP – two secondary messengers responsible for the propagation of signals to many protein kinases in cells. As a PDE3 inhibitor, cilostazol increases levels of cAMP and cGMP, which can prevent platelet aggregation and promote vasodilation. But cilostazol may have other effects that could explain its benefits to cognition and secondary prevention of stroke.

cAMP signaling through cAMP response element-binding protein (CREB) is important for synaptic plasticity and memory formation, and, in fact, treatment of healthy adult mice with cilostazol was reported to improve hippocampal-dependent memory (Yanai et al, 2014). In SAMP8 mice, long-term treatment with cilostazol increased the number of pCREB+ cells in the hippocampus (Yanai et al, 2017).

cAMP-independent activation of AMP-activated protein kinase (AMPK) by cilostazol in cell culture and rat diabetes models was reported to increase NO production and lower VCAM-1 expression (a marker of vascular inflammation) via inhibition of nuclear factor-kB (Suzuki et al, 2008; Gao et al, 2006)

Additional preclinical Alzheimer's disease studies suggest that cilostazol may prevent memory deficits, reduce amyloid beta and phospho-tau levels, reduce lipid peroxidation, and increase expression of SIRT 1 (Hiramatsu et al, 2010; Lee et al, 2014; Park et al, 2011). Its benefit in Alzheimer's mouse models, however, appears to be only preventative (Park et al, 2011). In mouse models of vascular dementia, cilostazol also prevents cognitive deficits, lowers levels of inflammation, protects cerebral white matter, prevents endothelial dysfunction, and increases vascular NO production (Kumar et al, 2015; Choi et al, 2016).

Cilostazol may also have beneficial effects on blood-brain barrier integrity. In a SAMP8 model, long-term cilostazol treatment improved blood-brain barrier integrity (as measured by extravasation of a blood-brain barrier impermeable dye) and increased expression of BBB proteins (Yanai et al, 2017).

In a rotenone-induced Parkinson's model, daily oral treatment of cilostazol improved motor function and reduced inflammatory mediators and cytokines NF-kB, TNFα, and IL-1β by a little more than half. It also increased the expression of SIRT1, increased autophagy, and decreased apoptosis (Hedya et al, 2018). In cell culture studies, cilostazol transiently increased AMPK phosphorylation and decreased mTOR phosphorylation. This led to an increase in autophagy and a decrease in intracellular Aβ accumulation through SIRT1 activation (Park et al, 2016; Lee et al, 2015).

APOE4 interactions:
None reported.

Aging and related health concerns: Some evidence suggest cilostazol may be beneficial in vascular diseases.

Types of evidence:

- 2 meta-analyses of atherosclerosis
- 3 RCT of change in lipid profiles and vasculature
- A few preclinical studies looking at age-related diseases

Details: In one meta-analysis of 2 RCTs, cilostazol (200mg/day) or cilostazol + aspirin (1 study) was superior to aspirin preventing the *progression* of intracranial artery stenosis (OR 0.21; 0.09-0.47) but not in promoting the *regression* of intracranial artery stenosis (Zhang et al, 2015). In another meta-analysis of 5 RCTs (most patients with type 2 diabetes), cilostazol monotherapy was superior to placebo, aspirin, and dual anti-platelet therapy in preventing the progression of carotid intima-media thickness (Geng et al, 2012).

In addition to its anti-inflammatory effects and vaso-protective effects (see above), its benefits on atherosclerotic progression may also have to do with its effects on plasma lipoproteins. In an RCT of patients with intermittent claudication, 12 weeks of cilostazol at 100mg twice per day decreased plasma triglycerides (15% p<0.001), increased HDL-c (10%, p<0.001) and increased ApoA1 (5.7%, p<0.01) (Elam et al, 1998). Chao et al (2016) reported that 12-week treatment of cilostazol (200mg) in patients at high

risk of cardiovascular disease (at least one risk factor) decreased triglycerides (-10% vs. +18% for placebo), increased HDL (8.7% vs. -2.4%), increased endothelial progenitor cells (149% vs. 72%), and improved flow mediated dilation (FMD) (232% vs. -47%); however, it also increased heart rate (9.5% vs. -2%). Two caveats of the previous study are that more patients in the cilostazol group were also taking aspirin (51% vs. 18%) and had slightly lower flow mediated dilation to begin with (2.3% vs. 5.3%). Another study reported that 6-9 months of 100mg/day cilostazol treatment did not improved FMD compared to placebo but did improve the rate of change from baseline to maximal brachial artery diameter (Mori et al, 2016).

A small pilot study reported no improvements in diabetic neuropathy with cilostazol, however, 100mg/day over 12 weeks improved walking speed (Rosales et al, 2011).

Preclinical studies suggest that cilostazol may decrease atherosclerotic lesions in mouse models and that these beneficial effects on lipids and atherosclerosis may be due to an increase expression of low-density lipid receptor protein 1 (LRP1) and an increase in macrophage-mediated reverse cholesterol transport, possibly through increased expression of ABCA1 (Kim et al, 2014; Jeon et al, 2015; Nakaya et al, 2010; Takase et al, 2007).

Because other PDE3 inhibitors, such as milrinone, have been associated with an increased mortality rate in patients with congestive heart failure (CHF), cilostazol carries a warning that it should not be used in this patient population. However, a recent study that analyzed its use over the last 18 years in patients in the Stanford clinical data warehouse (232 patients with peripheral artery disease taking cilostazol) reported that there is no increased risk of mortality compared to control patients, even in those with CHF (Leeper et al, 2013).

Safety: Multiple clinical studies suggest that cilostazol may be associated with some moderate side-effects, but it appears safer than other anti-platelet therapies.

Types of evidence:

- Multiple meta-analyses of 12 clinical trials in secondary prevention of stroke in East Asian populations

Although cilostazol appears to have a better safety profile than other anti-platelet drugs for major adverse events such as hemorrhagic events and bleeding, it can lead to a greater risk of headache,

diarrhea, dizziness, palpitations, and tachycardia (Tan et al, 2015). Drugs.com list side effects such as fast or irregular heartbeat and fever (more common). It is not recommended in patients with heart failure because other PDE3 inhibitors have decreased survival in this patient population (Rogers et al, 2015). Cilostazol is associated with 83 major drug interactions, including other anti-thrombotic drugs, which can be found at drugs.com.

Sources and dosing:
Cilostazol is available from Otsuka Pharmaceuticals and as a generic. Typical doses are oral administration of 100mg twice/day, though if there are side effects it can be reduced to 50mg/day.

Research underway:
Cilostazol is currently in Phase II clinical trials for patients with mild cognitive impairment (NCT02491268), cerebral small vessel disease (NCT02481323 and NCT01932293), and lacunar stroke (NCT03451591). Importantly, the cerebral small vessel disease study is completed and is in the UK, so we should get some of our first cognition data in non-Asian populations. Unfortunately, it is an open-label study.

Search terms:
Pubmed:
Cilostozal + dementia, longevity, aging, stroke, atherosclerosis (meta-analysis), neuropathy, hypotension

Clinicaltrials.gov: cilostazol + dementia, stroke