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Vascular Cognitive Impairment and Cilosazol

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Vascular cognitive impairment (VCI) includes post-stroke cognitive impairment (PSCI) and VCI related to cerebral small vessel disease (SVD) which are progressive vascular lesions. The PSCI includes post-stroke dementia (PSD) and post-stroke cognitive impairment with no dementia (PSCIND). The VCI related to cerebral SVD included subcortical vascular dementia (SVaD) and subcortical vascular MCI (svMCI). About 30% of patients with SVaD or svMCI had amyloid deposition on amyloid PET in Korean studies. Stroke may induce cognitive impairment through several mechanisms as follows; vascular brain lesions by themselves, previous silent vascular lesions, accelerated evolution of pre-existing degenerative lesions through hypoxia, direct induction of neurodegeneration, synergistic effect of amyloid pathology, induction of neuroinflammation, or impairment of endothelium function and blood–brain barrier leakage.

Cilostazol is a selective inhibitor of phosphodiesterase type 3 with therapeutic focus on increasing cAMP. An increase in cAMP results in an increase in the active form of protein kinase A (PKA), which is related with an inhibition in platelet aggregation. PKA also prevents the activation of myosin light-chain kinase, thereby exerting its vasodilatory effect. Cilostazol also induces the activation of endothelial nitric oxide synthase, thereby resulting in an angiogenic effect. Cilostazol was non-inferior, and might have been superior, to aspirin for secondary prevention of stroke, and was associated with fewer hemorrhagic events in the cilostazol for prevention of secondary stroke (CSPS-2), in which the stroke subtype was a lacunar infarction in more than half of the participants. Cilostazol also decreased Aβ levels, pTau and neuroinflammatory responses in $A\beta_{25-35}$ injected mouse.

Early-onset PSD results from a complex interplay between stroke lesion features and brain resilience. Delayed-onset PSD is associated mainly with the presence of severe sporadic SVD, and to a lesser extent with AD pathology or recurrent stroke. Cilostazol may be more effective than aspirin for the prevention of progression of cerebral SVD, and reduce Aβ accumulation and Tau phosphorylation. Therefore, cilostazol may be effective to prevent delayed-onset PSD and progression of VCI related to cerebral SVD. These findings should be examined further in randomized clinical trials.