# 00028
# Whole-Brain Low-Intensity Pulsed Ultrasound Therapy For Early Stage Of Alzheimer's Disease (LIPUS-AD): A Randomized, Double-Blind, Placebo-Controlled Trial

## New therapies and clinical trials

**Biographies (1 for poster/oral communications & 4 for the symposium) / 200 words per bio**

Hiroaki Shimokawa graduated from Kyushu University in 1979 and obtained MD and PhD degrees at the University. He studied vascular biology at the Mayo Clinic in 1985-1987 and was appointed as an assistant professor of Kyushu University in 1991, and then associate professor in 1995. In 2005, he was appointed as the professor and chairman of the Department of Cardiovascular Medicine, Graduate School of Medicine, Tohoku University. In 2020, he was appointed as the Vice Dean of Graduate School, International University of Health and Welfare, while he also serves as a visiting professor at Tohoku University. He has performed a number of innovative translational research in both basic and clinical cardiovascular medicine, including coronary functional abnormalities (e.g. coronary vasospasm and microvascular angina), endothelial functions, development of innovative treatments with sound waves, and epidemiological studies on coronary artery disease and heart failure. He has received the society awards from the Japanese Circulation Society (JCS) in 1999, the American Heart Association (AHA) in 2006, and the European Society of Cardiology (ESC) in 2014. Currently, he serves as a Co-Editor of European Heart Journal (ESC), and an associate editor of Arteriosclerosis, Thrombosis, and Vascular Biology (AHA) and International Journal of Cardiology.

**Hiroaki Shimokawa [1, 2], Tomohiko Shindo [1], Aiko Ishiki [3], Naoki Tomita [3], Kumiko Eguchi [1], Takashi Shiroto [1], Jun Takahashi [1], Kentaro Shiratsuchi [4], Satoshi Yasuda [1], Hiroyuki Arai [3]**

**[1]Tohoku University Graduate School Of Medicine - Sendai (Japan), [2]International University of Health and Welfare - Narita (Japan), [3]Institute Of Development, Aging And Cancer, Tohoku University - Sendai (Japan), [4]Sound Wave Innovation, Co. - Tokyo (Japan)**

**Abstract:**

***Backgrounds:*** Along with society aging, the prevalence of Alzheimer's disease (AD) has been rapidly increasing worldwide. However, effective and safe treatment of AD remains to be developed. For the last decades, amyloid β (Aβ) cascade hypothesis has been in the center of the pathogenesis of the disorder. Based on the hypothesis, a number of pharmacological agents that inhibit Aβ synthesis or promote its degradation have been developed without convincing success. It is widely known that AD and vascular dementia (VaD) share common risk factors, such as hypertension, hypercholesterolemia, and diabetes mellitus. Long-term exposure to these risk factors result in common outcome, i.e. impairment of vascular endothelial functions. Indeed, endothelial dysfunction with reduced nitric oxide (NO) availability has been suggested to play an important role in the pathogenesis of AD. Furthermore, the combination of amyloid pathology (e.g. Aβ deposition and neurofibrillary change) and cerebral ischemic pathology has been found as major triggering mechanisms of dementia. Thus, vascular dysfunction, especially cerebral microcirculatory dysfunction, should also be regarded as an important pathology of AD. We have developed a low-intensity pulsed ultrasound (LIPUS) therapy that upregulates endothelial NO synthase (eNOS) with resultant therapeutic angiogenesis and suppression of chronic inflammation. We demonstrated that the LIPUS therapy is effective and safe in animal models of chronic myocardial ischemia, myocardial infarction, and left ventricular diastolic dysfunction. We also demonstrated that the LIPUS therapy ameliorates cognitive dysfunctions in mouse models of AD, VaD and cerebral infarction. The effects of the LIPUS therapy is mainly mediated by upregulation of eNOS as its beneficial effects are absent in eNOS-deficient mice. ***Objectives:*** We thus performed a pilot study to address the efficacy and safety of our LIPUS therapy in patients with AD. ***Methods:*** We performed two trials of the LIPUS therapy for AD (mild cognitive impairment due to AD and mild AD); a roll-in open trial for safety and a randomized, double-blind, placebo-controlled (RCT) trial in a 1:1 fashion for efficacy and safety. The LIPUS therapy was performed for whole brain through the bilateral temporal bones alternatively for one hour 3 times per week as one session under the special conditions (1.3MPa, 32 cycles, 5% duty cycle) that we identified. The LIPUS therapy was performed for one session in the roll-in trial (N=5), and 6 sessions with a 3-month interval in the RCT trial (N=22). The primary efficacy endpoint was the changes in ADAS-J cog scores from baseline at 72 weeks. ***Results:*** Roll-in Trial. The 5 patients (M/F 4/1) were 70.8±9.5 year-old with MCI due to AD in 4 and mild AD in one and had MMSE-J score 24.8±3.4. Twelve weeks after the therapy, no adverse effects or abnormal MRI findings were noted. RCT Trial. In this trial, although the planned number of patients was 40, due to the COVID-19 pandemic in Japan, the trial was terminated prematurely, upon approval by the Pharmaceuticals and Medical Device Agency of Japan (PMDA) with a final number of 22 patients. Among them, 4 did not complete the planned protocol (withdrawal of consent in 1, operation for cholelithiasis in 1, worsening of cognitive functions in 2). Another patient was found to receive prohibited concomitant medications and was excluded from the analysis. Another 2 patients completed 4 sessions due to the early termination of the trial. Thus, a total of 19 patients were analyzed for efficacy and 18 for safety. Among them, 9 had MCI due to AD and 10 had AD. There were no significant differences in baseline clinical characteristics or cognitive functions between the 2 groups. For the safety issue, there was no adverse effects of the

LIPUS therapy including brain MRI findings. For the efficacy issue, the changes in ADAS-J cog scores from baseline progressively worsened at 24, 48, and 72 weeks in the placebo group, whereas they remained unchanged in the LIPUS group. The difference in ADAS-J cog scores at 72 weeks between the 2 groups, which is the primary efficacy endpoint, did not reach a statistically significant level (P=0.257) due to a small number of patients. A number of 40~50 patients in each group would reach a statistically significant level. Importantly, the prevalence of responders with improvement or no worsening from baseline to 72 weeks was 50% (5/10) in the LIPUS group but 0% (0/5) in the placebo group. The prevalence of responders progressively increased only in the LIPUS group. There were no significant differences in other parameters between the 2 groups. ***Conclusion:*** These results suggest that the LIPUS therapy could suppress the progression of cognitive impairment in patients with AD. The present findings need to be confirmed in a next pivotal trial with a large number of patients.

**(Ref.)** Eguchi K, et al. Whole-brain low-intensity pulsed ultrasound therapy markedly improves cognitive dysfunctions in mouse models of dementia -Crucial roles of endothelial nitric oxide synthase- Brain Stim 2018;11:959-973.