

# Give a Leg Up: Screening for Peripheral Artery Disease after Acute Myocardial Infarction

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Peripheral artery disease (PAD) is the atherosclerotic obstruction of the arteries supplying the limbs, especially the lower extremities. PAD affects approximately 230 million people worldwide, and the number of patients has been suggested to be increasing in the aged population<sup>1</sup>. A typical symptom of PAD is intermittent claudication, which is pain in the legs that worsens with walking and improves at rest; however, it has been reported that most patients with PAD are asymptomatic<sup>1</sup>. PAD has been shown to be an indicator of systemic atherosclerosis, including the coronary, carotid, and cerebrovascular arteries<sup>2</sup>. In addition, accumulating evidence have suggested that PAD is a predictor of future cardiovascular outcomes, such as myocardial infarction (MI), stroke, and death<sup>3</sup>. Thus, it has been suggested that the diagnosis of PAD in its asymptomatic stage might help improve clinical outcomes in atherosclerotic cardiovascular diseases.

The ankle-brachial index (ABI) is the ratio of the ankle to brachial systolic blood pressure. A value < 0.90 indicates the presence of flow-limiting arterial disease affecting the limb. The ABI is used in the diagnosis of PAD as a simple and noninvasive test that can be performed in the office or clinic. Although low ABI has been used as a surrogate marker for PAD, it remains controversial whether routine screening with the ABI in generally asymptomatic adults reduces morbidity and mortality from PAD or cardiovascular disease<sup>4</sup>. In primary care, several studies did not show the benefit of daily aspirin therapy or exercise therapy

in unselected population with low ABI<sup>4</sup>. In addition, it is largely unknown whether patients with other cardiovascular disease than PAD, including MI, would have benefit from screening with the ABI for detecting PAD. Collectively, identifying the subpopulation in which screening with the ABI would help improve the prognosis is one of the important topics in cardiovascular medicine.

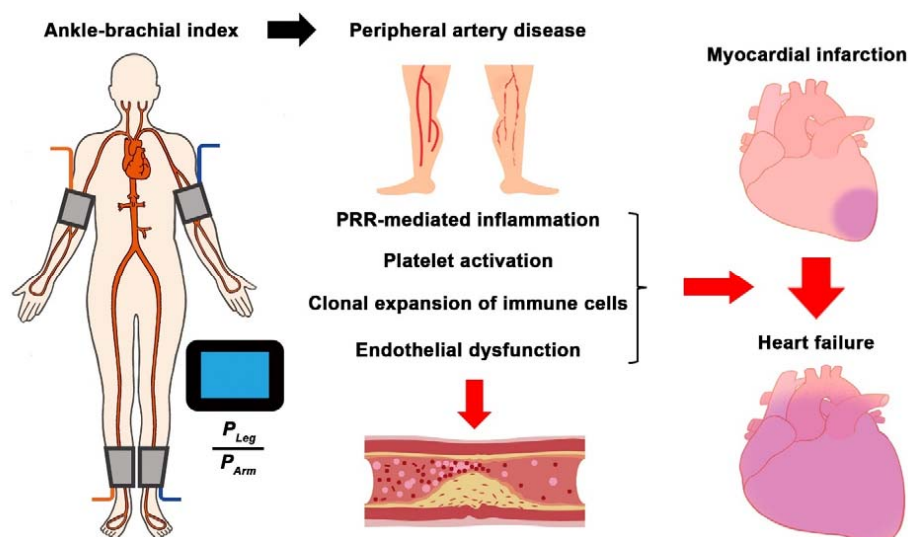
In this issue of the Journal of Atherosclerosis and Thrombosis, Ban *et al.* added important information on the usefulness of screening with the ABI in post-acute MI patients without treatment history of PAD<sup>5</sup>. In this retrospective study, the authors found that major adverse cardiovascular events (MACE), such as all-cause death, non-fatal MI, and readmission for heart failure (HF), were more frequently observed in post-acute MI patients with reduced ABI than in those with preserved ABI over the median follow-up period of 497 days (42.2% versus 15.0%). The multivariate Cox proportional hazard regression analysis demonstrated that low ABI was significantly associated with MACE with a hazard ratio of 2.046 in the study population after adjustment with multiple confounding factors, including cardiovascular risk factors, biomarkers, cardiac function, severity of coronary artery disease, medication, and PCI procedure. Among MACE, readmission for HF is the major contributor to poor clinical outcomes in asymptomatic low ABI patients after acute MI with an adjusted hazard ratio of 2.660. Although several pieces of information that might affect long-term outcomes, including residual ischemia at discharge and the rate of revascularization, are lacking, this study suggests that asymptomatic low ABI might be an independent

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**Fig. 1.** The ABI is used for the diagnosis of PAD as a simple and noninvasive test

PAD and HF share common pathogenic mechanisms, including pattern recognition receptor (PRR)-mediated inflammation, platelet activation, clonal expansion of immune cells, and endothelial dysfunction. The ABI could be a useful biomarker for the treatment of cardiac remodeling and HF after acute MI.

risk factor for cardiac remodeling and HF after MI.

As many good studies do, this study raises new questions and ideas for further studies. What would the ABI reflect in the pathophysiology of HF after MI? Systemic atherosclerosis, which is indicated by low ABI, shares various interacting pathogenic mechanisms with cardiac remodeling and HF, including pattern recognition receptor-mediated inflammation, platelet activation, clonal expansion of immune cells, and endothelial dysfunction (Fig. 1)<sup>6-9</sup>. Pattern recognition receptor signaling stimulated by endogenous molecules, termed danger-associated molecular patterns, in both immune and non-immune cells, and platelet activation initiate proinflammatory cytokine production and immune cell recruitment in cardiovascular disease<sup>6, 7</sup>. Clonal expansion of immune cells with proinflammatory phenotype accelerates immune responses<sup>8</sup>. Vascular endothelial cells protect the heart against oxidative stress and hypoxia *via* the release of antioxidant molecules and angiogenesis during cardiac injury and stress<sup>9</sup>. In addition, endothelial cells produce antiinflammatory and antithrombotic factors, including nitric oxide, prostacyclin, thrombomodulin, activated protein C, tissue factor pathway inhibitor, and antithrombin III<sup>10</sup>. Thus, endothelial dysfunction deteriorates oxidative stress and leads to impaired angiogenesis and vasodilation, as well as promotes proinflammatory responses and platelet activation. Collectively, low ABI

might indicate activities of pathological responses in the background of post-acute MI patients even without PAD symptoms.

To clarify the contributions of these mechanisms to clinical outcomes in this subpopulation, more information might be needed. For example, assessment of detailed immunological and inflammatory profiles, including proinflammatory cytokine levels, immune cell profiles, and platelet function, might provide a better understanding of the relationship between low ABI and inflammatory responses in post-acute MI patients. Myocardial blush grade could provide a simple visual angiographic assessment of myocardial perfusion and endothelial function. The presence of collateral flow even in acute MI might reflect angiogenic potentials. Comparison between PAD patients, diagnosed by imaging modalities, with reduced and preserved ABI might clarify whether functional assessment with the ABI could provide more important information than anatomical evaluation in post-acute MI patients.

Patients after acute MI usually receive optimal medical therapy that also targets PAD and its underlying pathogenic mechanisms. What difference would the ABI make in clinical decision-making? Recent advances in cardiovascular medicine have provided various therapeutic options, including antiinterleukin drugs, neprilysin inhibitors, sodium-glucose cotransporter 2 inhibitors, and phosphodiesterase

type 5 inhibitors. These drugs might have additional benefit, specifically in post-acute MI patients with asymptomatic PAD. The ABI might help stratify post-acute MI patients for optimal medical combination therapies.

In conclusion, screening with the ABI for PAD might provide significant benefits to post-acute MI patients. Further basic and clinical knowledge will be necessary for the ABI to be used as a standard biomarker for the treatment of MI in clinical practice.

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### Conflicts of Interest

M.S. has received speaking honoraria from Bayer Yakuhin, Ltd., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Company, Ltd., Daiichi Sankyo Company, Ltd., and Nippon Boehringer Ingelheim Company, Ltd., clinical research funding from Bayer Yakuhin, Ltd., and scholarship grants from Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Company, Ltd., and Daiichi Sankyo Company, Ltd. M.S. is involved with the Department of Cardio-Diabetes Medicine funded partly by Boehringer Ingelheim Company, Ltd. The other authors declare no conflicts of interest.

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