

## Subclinical Disease as Surrogate Endpoint of Cardiovascular Disease Events: Ankle-brachial Index as an Example

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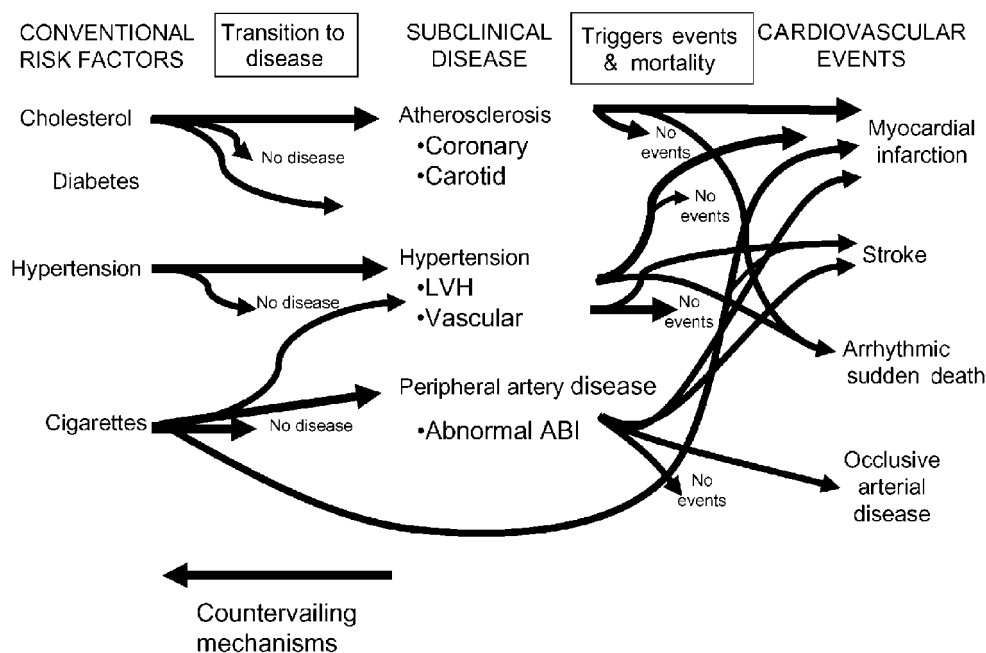
Screening of subclinical diseases and atherosclerotic high risk groups is mandatory for asymptomatic atherosclerotic patients. Although there are many options for screening of occlusive peripheral artery disease, such as flow velocity, Doppler wave analysis or Duplex imaging and flow velocity, the segmental blood pressure ratio, ankle-brachial index (ABI), is considered as the best screening tool for peripheral artery disease, because ABI measurement is relatively easy and the pathogenesis duration is shorter time to follow-up, compared with hard endpoint events of occlusive events.<sup>1</sup> Although intermittent claudication is the major symptom for occlusive arterial disease, ABI provides a useful screening tool for occlusive peripheral artery disease. The characteristics of screening tool by ABI are high case detection, minimal false positives, and effective treatment available for positive cases. The standardized procedure for ABI measure is by supine position at rest, with a 12-cm cuff at the ankle and 6 systolic blood pressures measured over left and right arms, two left and right ankle sites. Also, hand-held Doppler can be used over the brachial artery and posterior tibial artery at the ankle sites. The definition of abnormal ABI is less than 0.90 (or 0.95-0.80, depending on various populations). In the paper of this issue, Dr. Su and colleagues report an automated oscillometric method to measure ABI, stratifying the subjects by ABI for clinical comparison.<sup>2</sup> The authors argued that low ABI was an independent predictor for hard cardiovascular events among coronary heart disease patients.

There is much literatures about ABI as a surrogate endpoint for peripheral artery disease. ABI was highly correlated with angiographically determined peripheral artery disease, and the risk factors associated with abnormal ABI were cigarette smoking, blood pressure, low HDL cholesterol, triglyceride, homocysteine, fibrinogen and blood viscosity.<sup>3</sup> Among diabetic Taiwanese, lipo-

protein (a) was reported to be associated with abnormal ABI.<sup>4</sup> More important, the ABI was associated with cardiovascular morbidity and there was dose-response gradient for cardiovascular mortality.<sup>5</sup> In the paper, the authors also demonstrate that ABI less than 0.9 can be an independent factor for cardiovascular events in the setting of outpatient clinic.

The limitations of ABI as a useful marker are twofold. First, the prevalence of abnormal ABI in general population was relatively low, only 2-3% in middle age.<sup>6</sup> Second, low sensitivity rate was found to detect small-vessel lesions in diabetes mellitus, for which toe-brachial index might be more applicable. But the toe-brachial index is highly sensitive to room temperature, and blanket covering is necessary for the measurement.

When clinicians apply subclinical diseases such as ABI in their daily care, several scenarios are mentioned. First, no guidelines for routine examination in general population are constructed now. It is still not cost-effective to apply the ABI screening on general population. Only selected high-risk groups such as elderly or hypertension are suggested to undertake the screening. Second, the presence of subclinical disease such as abnormal ABI is a better predictor for morbid events than the conventional risk factors. Stratification by subclinical disease can provide an effective way to implement a preventive program. The prevention strategy begins with the identification of preclinical disease in those at a minimal threshold of risk based on the conventional risk factors. Finally, subclinical disease is useful for monitoring drug effects, and some large-scale clinical trial studies were designed to evaluate the efficacy on ABI progress. There are benefits of sample size and power for ABI as endpoints due to easy measurement and progress, compared with clinical hard endpoints of myocardial infarction or death. Pharmacological therapies of antiplatelets, angiotensin-converting enzyme inhibitors and hypolipidemic drugs are targeted on



**Figure 1.** Diagram of relationship of subclinical diseases to conventional risk factors and hard cardiovascular events. The presence of subclinical diseases can be viewed as a better predictor of hard events than the conventional risk factors.

ABI regression slowing.<sup>1</sup>

In conclusion, ABI can be considered an important screening tool for subclinical disease endpoints, and the clinicians should consider the strengths and limitations of its application. If subclinical disease is present, traditional risk factors such as hypertension, hyperlipidemia, diabetes and smoking will be treated and the effect on progression of preclinical disease will be monitored carefully. If preclinical disease such as abnormal ABI progresses, more aggressive treatment of the conventional and/or the new risk factors is indicated (Figure 1).

## REFERENCES

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