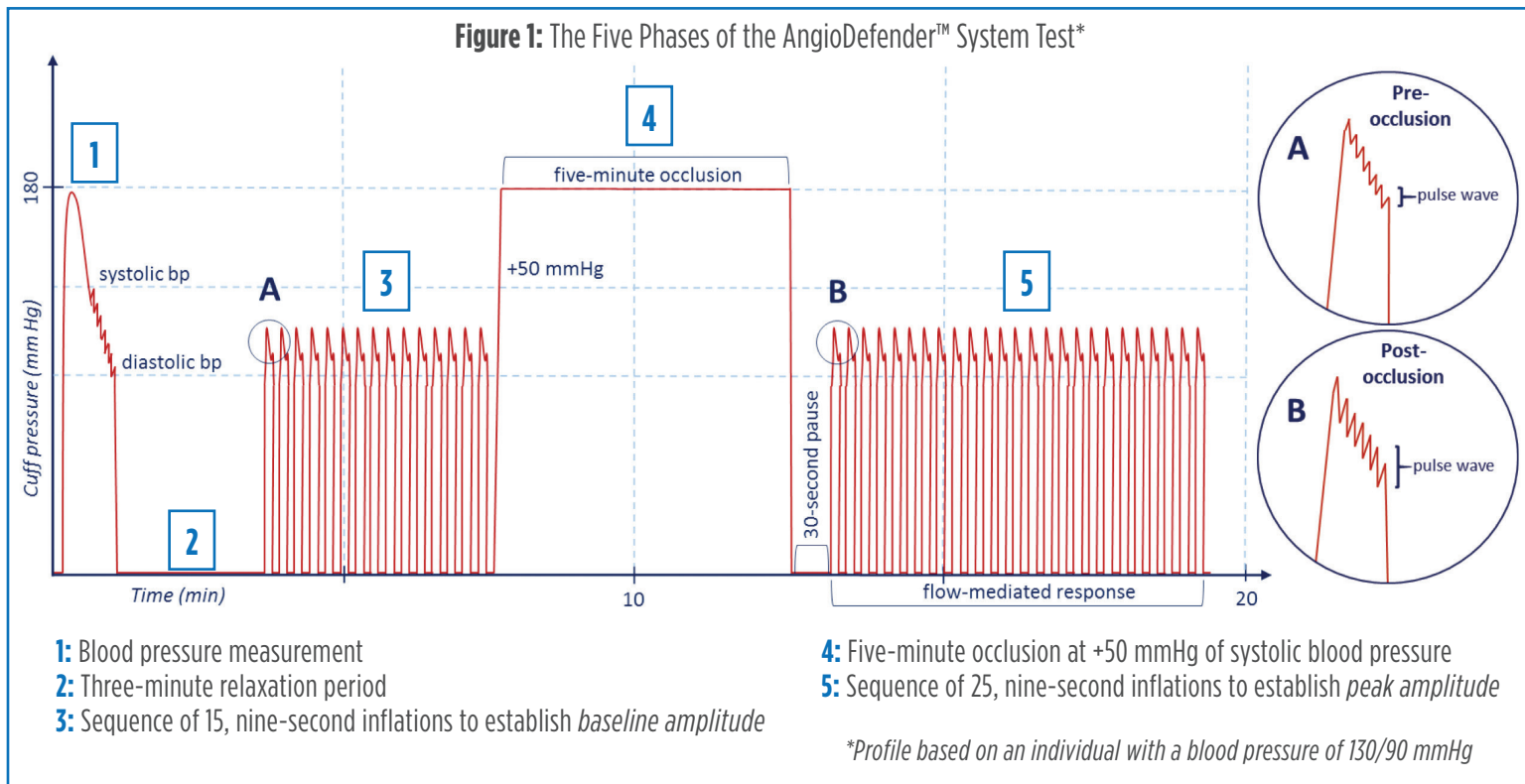


THE TEST OVERVIEW

OVERVIEW: The **AngioDefender™** system conducts an operator-independent analysis of the brachial artery’s dilation response to increased blood flow in under 20 minutes. It can be administered in either an office or hospital setting. First, a standard blood pressure cuff is secured on the arm above the patient’s elbow. After a resting period of ten minutes, the operator presses the “Start Test” button and the system begins five automated phases described in Figure 1 below. After the test is completed, a report is instantly generated.



INDICATION: The **AngioDefender™** System is a CE-marked, non-invasive device for the diagnostic of percentage flow-mediated dilation (%FMD) of the brachial artery.

VALIDATION STUDIES: EQUIVALENCE TO BRACHIAL ARTERY ULTRASOUND IMAGING

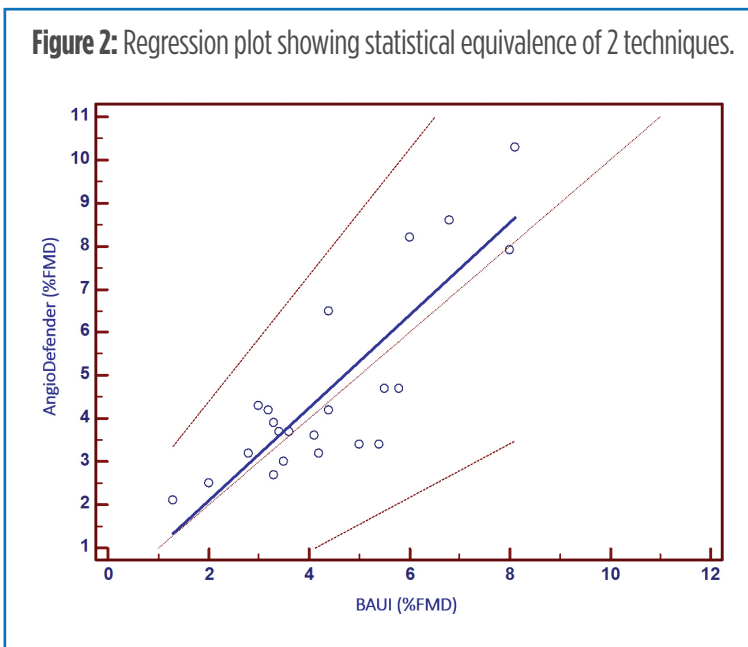
The following comparison studies reveal that the AngioDefender™ system is statistically equivalent to the gold standard brachial artery ultrasound imaging (BAUI) technique as used to measure %FMD.

1. Moscow Medical Academy, Moscow, Russia. 2010.

Each of twenty-two subjects with a range of CVD risk factors underwent testing with both procedures, separated by a one-hour interval, with each test administered in random order. Figure 2 illustrates a Passing-Bablok regression of the data, showing a close matching of the regression line with the line-of-identity (Pearson correlation coefficient = 0.84, $p < 0.0001$). No significant adverse events were reported.

2. Medanta Heart Institute, New Delhi, India. 2011.

Each of thirty-three subjects underwent FMD testing using BAUI and the AngioDefender™ system, with the two tests being performed on consecutive days for each individual. A Passing-Bablok regression of the data also showed statistical equivalence. No significant adverse events were reported. Graph not shown.



ENDOTHELIAL DYSFUNCTION PREDICTS EARLY-STAGE CARDIOVASCULAR DISEASE

“Extensive literature documents that endothelial dysfunction is associated with almost every condition predisposing to atherosclerosis and cardiovascular disease.”¹

Studies have long demonstrated a correlation between endothelial dysfunction and conditions predisposing to CVD, including: arterial hypertension⁴, normotensive subjects with a family history of hypertension⁵, smoking⁶, dyslipidemia⁷, ageing⁸, diabetes mellitus⁹, and obesity⁹. Table 1 highlights some of the most significant studies from the last twenty years.

Table 1: Significant studies support endothelial dysfunction’s association with the pathogenesis of early atherosclerosis

Study	Authors & Publication	Size	Conclusions
Impairment of endothelium-dependent dilation is an early event in children with familial hypercholesterolemia and is related to the lipoprotein (a) level.	Sorensen KE, Celermajer DS, Georgakopoulos D, <i>et al. Journal of Clinical Investigation</i> 1994; 93:50-55.	Children with and without familial hyper-cholesterolemia (n=60)	Impaired endothelium-dependent dilation is present in children with familial hypercholesterolemia as young as 7 yrs. of age and the degree of impairment is related to the lipoprotein (a) level.
Comparable prognostic value of vasodilator response to acetylcholine in brachial and coronary arteries for predicting long-term cardiovascular events in suspected CAD.	Takase B, Hamabe A, Satomura K, <i>et al. Circulation</i> 2006; 70:49-56	Patient suspected of having coronary artery disease (n=70)	The brachial artery vasodilator response to optimal ACh dosage can be used as a surrogate prognostic predictor for coronary endothelial function tests in patients with suspected CAD.
Coronary endothelial dysfunction in patient with early coronary artery disease is associated with the increase in intravascular lipid core plaque.	Choi B-J, Prasad A, Gulati R, <i>et al. European Heart Journal</i> 2013; 34:2047-2054	Patients with chest pain who had diameter stenosis (n=32)	Patients with early coronary artery disease and endothelial dysfunction had a higher lipid content in the vascular wall than patients with normal endothelial function.

Further reading: Comprehensive review papers summarize the substantial research linking endothelial dysfunction with CVD^{2,3}

FLOW-MEDIATED DILATION ACCURATELY MEASURES ENDOTHELIAL DYSFUNCTION

Table 2 summarizes longitudinal studies using the gold standard — brachial artery ultrasound imaging — to measure %FMD. In these large population studies, the correlation between overall CVD risk and %FMD is apparent.

Table 2: Large longitudinal studies reveal FMD as a strong predictor of endothelial dysfunction

Study	Authors & Publication	Size	Conclusions
Flow-mediated dilation and cardiovascular risk prediction: A systematic review with meta-analysis	Ras RT, Streppel MT, Draijer R, Zock PL, <i>et al. Intl Journal of Cardiology</i> 2012; 168:344-351	23 studies involving nearly 15,000 subjects	For studies reporting continuous risk estimates, the pooled overall CVD risk was 0.92 (95%CI: 0.88; 0.95) per 1% higher FMD. A higher association was observed in diseased populations.
Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study the Multi-Ethnic Study of Atherosclerosis (MESA)	Yeboah J, Folsom AR, Burke GL, <i>et al. Circulation</i> 2009; 120:502-509	6 clinical sites with over 3,000 subjects free of clinical CVD	Brachial FMD is a predictor of incident cardiovascular events in population-based adults and improved the classification of subjects as low, intermediate, and high CVD risk compared with the FRS.
Long-term association of brachial artery flow-mediated vasodilation and cardiovascular events in middle-aged subjects with no apparent heart disease	Shechter M, Issacher A, Marai I, <i>et al. Intl Journal of Cardiology</i> 2008; 134:52-58	435 healthy subjects	Demonstrated in 435 healthy subjects that, in a multivariate analysis that included conventional CVD risk factors, %FMD by BAUI independently predicted CVD risk with an odds ratio of 2.70.

1. Flammer AJ, *et al.* The Assessment of Endothelial Function: From Research Into Clinical Practice. *Circulation* 2012; 126:753-767.
2. Widlansky ME, *et al.* The Clinical Implications of Endothelial Dysfunction. *J Am Coll. Cardiol* 2003; 42:1149-1160.
3. Esper RJ, *et al.* Endothelial dysfunction: a comprehensive appraisal. *Cardiovasc Diabetology* 2006; 5:4.
4. Panza JA, *et al.* Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. *N Eng J Med* 1990; 323:22-27.
5. Taddei S, *et al.* Defective L-arginine-nitric oxide pathway in offspring of essential hypertensive patients. *Circulation* 1996; 94(6):1298-303.

6. Celermajer DS, *et al.* Cigarette smoking is associated with dose related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation* 1993; 88:2149-2155.
7. Spieker LE, *et al.* High-density lipoprotein restores endothelial function in hypercholesterolemic men. *Circulation* 2002;105:1399-1402.
8. Linder L, *et al.* Indirect evidence for release of endothelium-derived relaxing factor in human forearm circulation in vivo: blunted response in essential hypertension. *Circulation* 1990; 81:1762-1767.
9. Steinberg HO, *et al.* Obesity/insulin resistance is associated with endothelial dysfunction: implications for the syndrome of insulin resistance. *J Clin Invest* 1996; 97:2601-2610.

The AngioDefender™ system is not commercially available in the United States.

REF:110004