EVERIST HEALTH

ANGIODEFENDER™

"A man is as old as his arteries"

Dr. Thomas Sydenham, British physician (1624-1689) known as the "English Hippocrates"

Since the dawn of modern clinical medicine, when patient observation and accurate recording keeping became routine, the cardiovascular (CV) system has been recognized as key to one's health and longevity [1].

CARDIOVASCULAR DISEASE (CVD)

CVDs are a group of disorders of the heart and blood vessels that include coronary heart disease, cerebrovascular and peripheral arterial diseases, deep vein thrombosis and pulmonary embolism. More people throughout the world die from CVDs than from any other cause. Behavioral risk factors are responsible for an estimated 80% of CVDs, i.e., they are largely reversible with directed interventions [2]. Atherosclerosis, now considered a chronic immunoinflammatory disease of medium- and large-diameter arteries, often begins in childhood and adolescence and frequently remains clinically silent until plaque rupture or erosion leads to abrupt thrombosis and acute clinical sequelae **(Figure 1)** [3]. Therefore, prevention and early detection of CVD risk factors hold great promise for decreasing the mortality, morbidity, and costs of CVD.

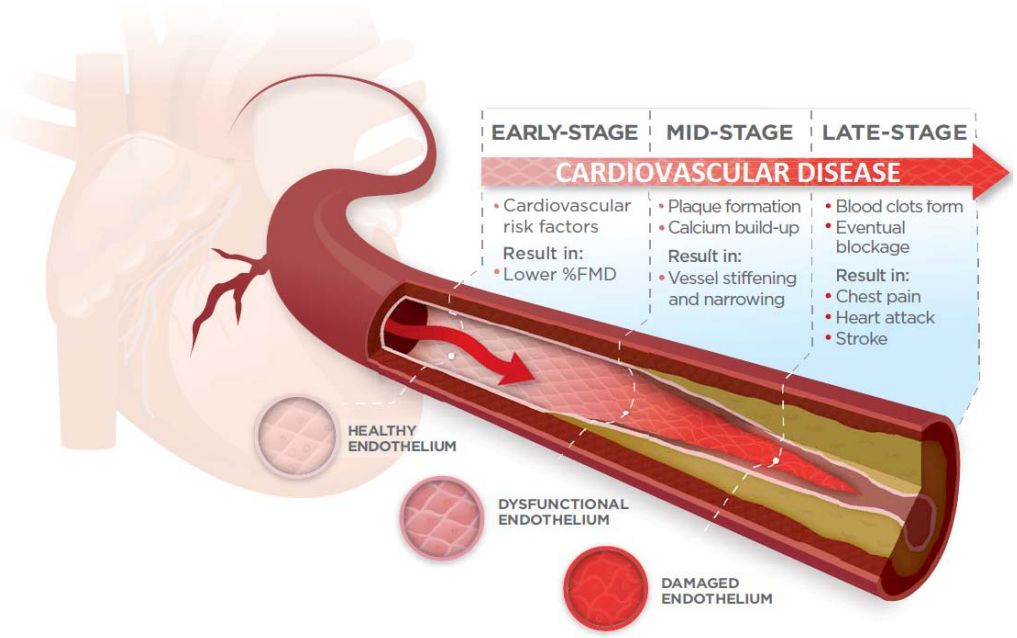


Figure 1. Progressive stages of CVD and corresponding endothelial cell health

ENDOTHELIAL DYSFUNCTION (EDF)

Defining an individual's CVD risk before the development of atherosclerotic plaque focuses on detecting the earliest evidence of dysfunction of the endothelium, the single-cell thick interior lining of all blood vessels in the body that plays a critical role in regulating blood flow and the passage of materials into and out of the bloodstream. EDF, consequent to the onslaught of multiple CVD risk factors (e.g., high blood pressure, smoking, obesity, diabetes, etc), initiates a vascular inflammatory process that leads to not only heart disease but a variety of other cardiovascular-related conditions, including peripheral artery disease, diabetic vasculopathy, chronic kidney disease, and vascular dementia, including Alzheimer's disease [4,5,6,7,8]. Being a systemic condition, EDF in peripheral arteries is closely related to EDF in coronary arteries [9]. These numerous consequences of EDF and the noted improvement in endothelial function (EF) seen with adoption of healthy lifestyles, diet, and/or pharmacologic intervention, support EF's moniker as a 'barometer of cardiovascular health' [3,10].

FLOW-MEDIATED DILATION (FMD)

In 1992, Celermajer *et al* introduced a non-invasive procedure for detecting EDF by measuring FMD of the brachial artery (BA) using high resolution continuous vascular B-mode (2D) ultrasound imaging during reactive hyperemia (a transient increase in tissue blood flow following brief BA occlusion), called brachial artery ultrasound imaging (BAUI). The degree to which the BA subsequently dilates (% increase in diameter relative to baseline) is directly related to the health of the endothelium and its synthesis and release of a variety of vasodilators, especially nitric oxide [11]. FMD impairment is positively correlated with coronary artery disease and the future occurrence of CVD events beyond that achievable using traditional risk factor assessment, e.g., the Framingham Risk Score [12,13,14] (**Figure 2**).

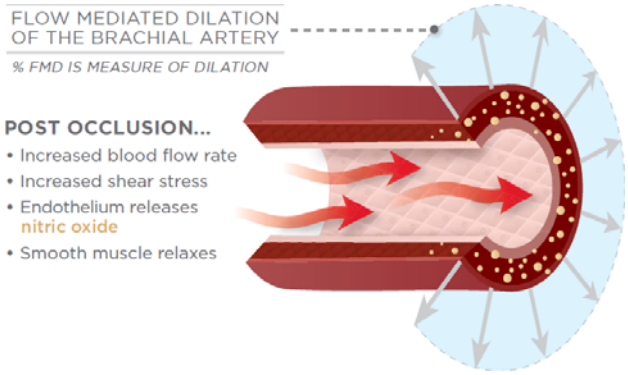
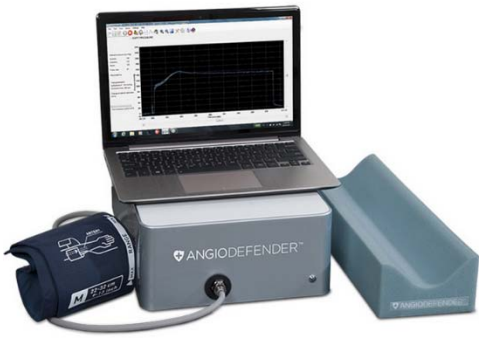


Figure 2. Flow-mediated dilation (FMD)

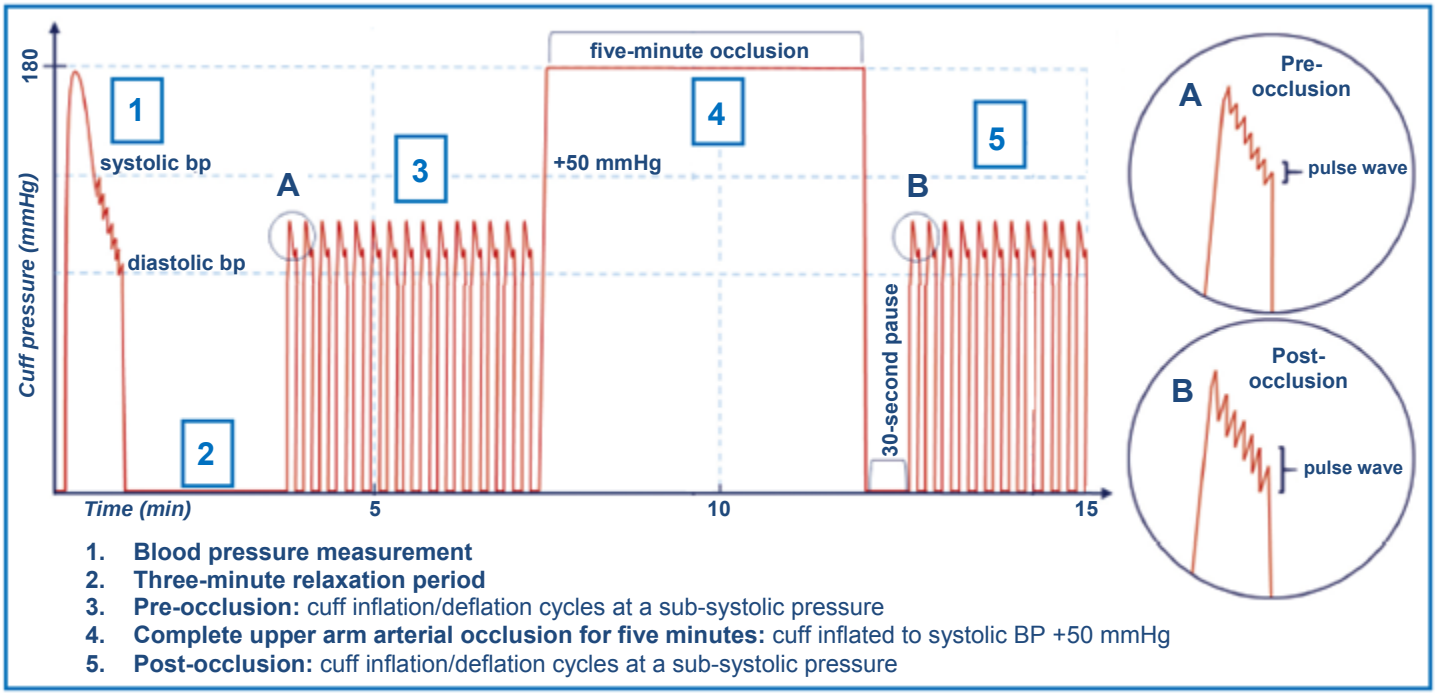
Although thousands of studies over the past two decades have documented the ability to predict future CV health using BAUI, the method is technically challenging, requiring highly skilled operators using expensive equipment to capture the consistently high quality images needed for subsequent analysis. Consequently, despite its reputation as the "gold standard" for measuring FMD, BAUI has not gained widespread clinical use in the general population and remains predominantly a research tool.

ANGIODEFENDER (AD): Technology & Testing Procedure



To address these inherent BAUI obstacles, Everist Health has developed AD to measure FMD. AD is a patented non-invasive technology platform that, rather than using vascular ultrasound, directly measures changes in BA pulse wave amplitudes consequent to reactive hyperemia using an upper arm BP cuff. The AD procedure is almost entirely automated, thereby significantly reducing operator-dependent error and permitting the test to be performed by a wide range of health care personnel, including technicians, nurses, and physicians. So that AD results can be interpreted in the context of the vast existent BAUI literature, they are presented as 'equivalent AD %FMD' units, i.e., equivalent to what one would get if using BAUI (**Figures 3 & 4**).

Figure 3. AngioDefender technology platform



1. **Blood pressure measurement**
2. **Three-minute relaxation period**
3. **Pre-occlusion:** cuff inflation/deflation cycles at a sub-systolic pressure
4. **Complete upper arm arterial occlusion for five minutes:** cuff inflated to systolic BP +50 mmHg
5. **Post-occlusion:** cuff inflation/deflation cycles at a sub-systolic pressure

Figure 4. AngioDefender test components (example based on an individual with a BP of 130/90)

ANGIODEFENDER (AD): Clinical Validation

A pilot study (n=29) conducted at Yale University (Jun-Aug 2014; Dr. David Katz, Principal Investigator) using individuals with a wide range of CV risk factors (16M/13F; median age 49, range 21-78) compared single BA %FMD determinations using AD vs BAUI. BAUI %FMD data was derived from duplicate scan readings by a central reader and allometrically scaled per Atkinson and Batterham [15]. AD %FMD scores were calculated using an algorithm that differentially weighted adjustments to pulse wave amplitudes using a variety of anthropomorphic and hemodynamic parameters.

Results:

1) Pearson's correlation coefficient, **r = 0.75** (95% CI: 0.53 to 0.88, p<0.0001)
2) Deming regression analysis showed no systematic differences between AD and BAUI (**Figure 5**):
3) A multiple regression model showed that AD %FMD provided statistically significant prediction of allometrically scaled BAUI %FMD beyond that of the anthropomorphic and hemodynamic parameter inputs to the algorithm (p<0.0015).

Conclusion: AD and BAUI are comparable in their abilities to quantify %FMD of the BA

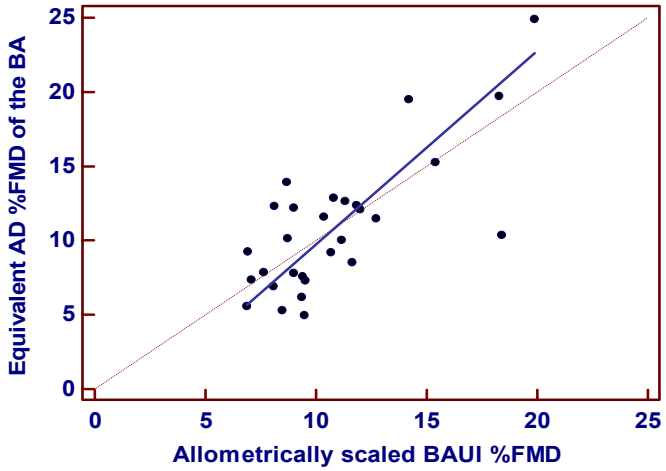


Figure 5. Deming regression analysis (n=29)

ANGIODEFENDER VASCULAR AGE CALCULATOR (AD VAC)

"People who know their 'heart age' make greater improvements to their heart health" – so read the headlines announcing the publication of a landmark 2014 Spanish study (n = 3,153) that convincingly showed that informing men and women about their CVD risk expressed in the format of a vascular age calculator (VAC; 'Heart Age') resulted in CVD risk reductions greater than those achieved after either conventional medical advice was given or a Framingham Heart Study-derived risk score ('REGICOR') was used [16,17]. Most notably, the quitting rate for smokers was four times greater in the VAC group compared to smokers who only received the traditional percentage risk scores.

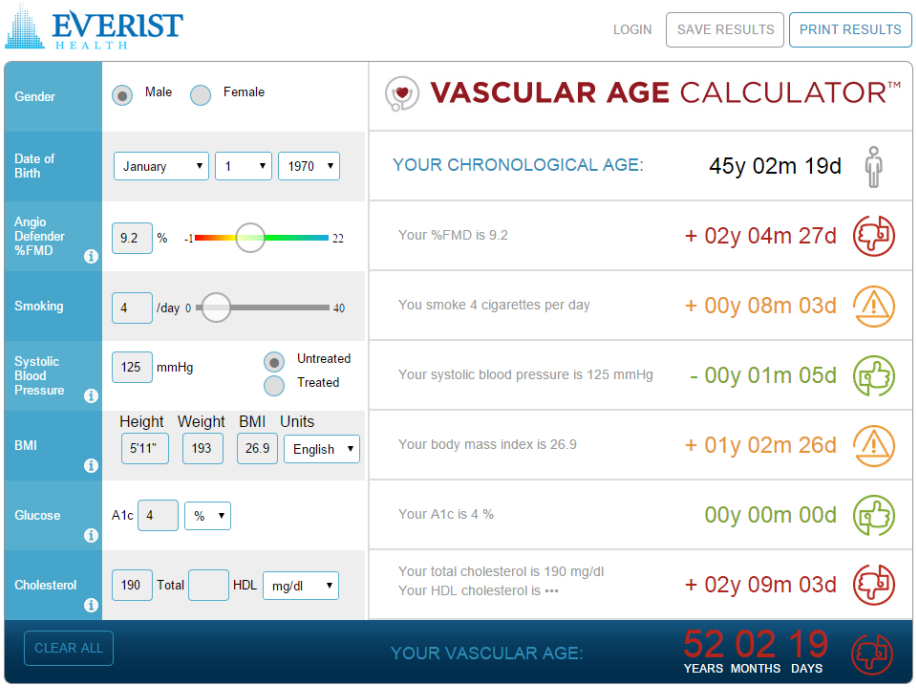


Figure 6. Example of data input and results using the AD VAC

Employing similar anthropomorphic and metabolic parameters as were used in the Spanish study's VAC, the **AD VAC** [**Fig 6;** http://everisthealth.com/tools/calculator/] also aims to promote behavioral changes resulting in reduced CV risk. The AD VAC trumps other similar tools by uniquely incorporating '%FMD' and additional measures of CVD risk supported by the medical literature, making it more engaging and sensitive to the underlying causes of CVD.

CONCLUSIONS

- **Endothelial function is a barometer of CV health and can be non-invasively quantified by measuring flow-mediated dilation (FMD) of the brachial artery (BA)**
- **AngioDefender (AD) is a patented, CE Mark-certified, automated technology that accurately measures FMD without the expensive ultrasound equipment and operator expertise needed to assess FMD using BA ultrasound imaging (BAUI)**
- **AD and BAUI are comparable in their abilities to determine %FMD**
- **Vascular Age Calculators (VACs) promote heart-healthy behaviors**
- **The on-line AD VAC uniquely incorporates %FMD into the mix of anthropomorphic and metabolic parameters used to determine vascular age, making it the most engaging and sensitive VAC available**
- **Studies employing AD and its VAC are underway in cardiac rehabilitation, rheumatology and commercial wellness programs and are planned for vascular dementia, kidney disease, and many other conditions linked to endothelial dysfunction**

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