Supplemental Material
Data S1.

Heart Trends Device

The regulatory status: The previous software version was cleared for marketing in the USA under 510k number K012825. The cleared intended use was for the analysis, summary and reporting of up to 3 channels of prerecorded ambulatory ECG data. It was also intended to provide measurements of MPW (Multipole Parameter Weighted) HRV.

Cleared Device description: The HeartTrends® software was employed as a measuring tool to present Heart Rate Variability (HRV) to qualified clinician review, edit and assessment. It provides measurements of the MPW HRV. Heart rate variability is a known method for analyzing the changes in heart rate over the recorded duration. Subjects with a low variability were suggested to be at increased risk for cardiac events. The HeartTrends device is based on a novel algorithm for analyzing heart rate variability, which is constructed from the Multipole method, based on a physical-mathematical description of complex time series. The Multipole method generates several parameters, multipoles, where every single one describes the HRV. The HeartTrends device received CE mark (0344) on 17 July 2013 and valid through 2024, for the product category: Software based medical devices for diagnostics-aid of ischemic heart diseases using Heart Rate Variability analysis. The DyDx indicator value can be used as a prognostic score to assist in diagnosis of coronary artery disease for which the physician renders their own opinion. HeartTrends does not offer a diagnostic opinion to the user. HeartTrends is intended to be used by qualified personnel in evaluating the subject in conjunction with the subject's clinical history, symptoms, other diagnostic tests, as well as the professional's clinical judgment.
The changes between the FDA-cleared software version and the version to be tested in this study were minimal; the base algorithm did not change, changes were made in the GUI dividing the software into a Client-Server base application, and adaptation to more recent operating systems. Additionally, there was a change in the intended use of the HeartTrends device, while used before for ECG data recording, storing and analysis, it is now investigated for the diagnosis of ischemic heart disease:

The software underwent full software validation and verification that complies with international regulatory requirements.
Table S1. Inclusion and exclusion criteria for study participation.

**Inclusion Criteria:**

- Age ≥ 21
- Referral for EST in a subjects without known CAD due to either one of the following two indications:
  1. Chest pain syndrome or equivocal angina in subjects with low to intermediate pretest probability of CAD
  2. At least one CAD risk factor (diabetes mellitus, hypertension, smoking, positive family history, and/or dyslipidemia) in asymptomatic subjects referred for cardiovascular risk assessment.
- Willing and able to provide written informed consent

**Exclusion Criteria:**

- Acute Coronary Syndrome
- Established CAD
- Atrial fibrillation or flutter
- Cardiac Pacemaker
- Clinical diagnosis of heart failure
- Severe COPD (FEV1 < 50% predicted value)
- Active myocarditis, constrictive pericarditis, any cardiomyopathy, cardiac or systemic amyloidosis
- Known drug or alcohol dependence or any other factors which will interfere with the study conduct or interpretation of the results or in the opinion of the investigator are not suitable to participate;
- Any illness that might reduce life expectancy to less than 1 year from screening
- Left bundle branch block (LBBB), significant intraventricular conduction delay (IVCD) or significant (>1mm) ST deviations on baseline ECG
- Inability to perform an exercise stress test (i.e. orthopedic or neurological limitations)
- Any significant valvular disease defined as:
  Established valvular regurgitation or stenosis abnormality above moderate severity
  - BMI >35 kg/m²
  - Recent (< 6 months) history of pulmonary embolism
Figure S1. Bland-Altman analysis of the Holter ECG comparing HeartTrends results from 1-hour recordings with data derived from 20 minute recordings.*

*The graph tracks the P-Value over 10-minute time intervals. Results of the analysis also yielded statistically significant P-Values of: 0.000297, 0.000303, 0.000284, 0.000248, 0.000127 for all the 10 to 50-minute intervals analyzed.