Clinical Investigation Protocol

Simultaneous Measurement of EpicArdial and Microvascular ResisTance via Angiographic FLOW (SMARTFLOW) Study

Validation study of an AI-driven Angiogram-based Physiological Assessment

Protocol number:	CSP-001
Revision:	A
Date:	11 May 2026
Sponsor:	AngioInsight, Inc.
Grant Giver:	AngioInsight, Inc.
Principal Investigators:	Todd C. Villines, MD and Carlos Collet, MD, PhD

Protocol approval page

We, the undersigned, have read and approved the protocol specified above and agree upon the contents:

Todd C. Villines, MD Professor of Medicine (Cardiology) University of Virginia, Charlottesville, USA *Co-Principal Investigator*	Date
Carlos Collet, MD, PhD Interventional Cardiologist OLV Aalst *Co-Principal Investigator*	Date

Table of Contents

Table of Figures

1. PROTOCOL SYNOPSIS

Study title	Simultaneous Measurement of EpicArdial and Microvascular ResisTance via Angiographic Flow
Short title	SMARTFLOW
Prepared by	Todd C. Villines MD and Carlos Collet MD, PhD
Study phase	Pre-market
Patient population	Patients with acute or chronic coronary artery disease
Aims	To establish the diagnostic performance of the AngioAI+ System (AngioInsight, Inc, USA) for: 1. Fractional flow reserve (FFR) 2. Detection of coronary microvascular disease (CMD)
Design	Prospective, single-arm, observational multicenter study of patients with suspected coronary artery disease (CAD) undergoing clinically indicated invasive coronary angiography with physiological assessment. The study is designed to evaluate performance of the AngioAI+ software using the subject's acquired imaging and ground truth data in a retrospective manner. As such, the investigational AngioAI+ device will not inform clinical decisions amid the study; subjects will follow standard of care (SoC) for their indicated reference procedures.
Study endpoint(s)	<u>Primary endpoints 1 - FFR:</u> Per-vessel diagnostic performance (i.e., sensitivity and specificity) of AngioAI+ FFR for identifying flow-limiting lesions, using measured FFR as the reference standard <u>Primary endpoints 2- CMD:</u> Diagnostic performance (i.e., sensitivity and specificity) of AngioAI+ for detecting CMD in patients with non-obstructive

CAD (NOCAD) using invasive coronary flow reserve (CFR) derived from continuous thermodilution as reference.

Secondary endpoints:

1. Agreement between continuously measured AngioAI+ FFR and invasive FFR.

2. Agreement between continuously measured AngioAI+ pullback pressure gradients (PPG) and invasive PPG.

3. Agreement between continuously measured AngioAI+ CFR and invasive CFR

4. Diagnostic performance of AngioAI+ using resting angiograms for detecting CMD in patients with NOCAD using invasive CFR (<2.5) derived from continuous thermodilution as reference.

5. Diagnostic performance of AngioAI+ for detecting CMD in patients with NOCAD using invasive CFR (< 2.5) derived from bolus thermodilution as reference.

6. Diagnostic performance of AngioAI+ for detecting CMD in patients with NOCAD using invasive IMR (> 25) derived from bolus thermodilution.

7. Diagnostic performance of AngioAI+ for detecting CMD in patients with NOCAD using invasive CFR (< 2.5) and IMR (> 25) derived from bolus thermodilution as reference.

8. Negative predictive value of AngioAI+ for detecting CMD in patients with NOCAD compared with invasive CFR (< 2.5) derived from continuous thermodilution as reference.

9. Negative predictive value of AngioAI+ for detecting CMD in patients with NOCAD compared with invasive

CFR (< 2.5) derived from bolus thermodilution as reference.

10. Negative predictive value of AngioAI+ for detecting CMD in patients with NOCAD compared with invasive CFR (< 2.5) and IMR (> 25) derived from bolus thermodilution as reference.

11. Agreement between AngioAI+ derived luminal dimensions (diameter stenosis, reference vessel diameter, and minimal lumen diameter) and quantitative coronary angiography (QCA) as reference.

12. Test reproducibility and repeatability of the AngioAI+ FFR and CMD outputs.

13. Device rejection rate (%). The ratio of produced AngioAI+ FFR & CMD values from all AngioAI+ measurements that were attempted.

14. Any adverse events from performing the image or invasive assessments.

15. Time for invasive FFR, thermodilution CMD assessment and time for performance of AngioAI+ FFR and CMD analyses

Clinical Sites	Approximately 24 clinical sites in the United States and Europe.
Investigational technology	AngioAI+ System (AngioInsight, Inc, USA)
Eligibility and Cohorts	Adult patients with acute or chronic coronary syndromes referred for invasive coronary angiography with clinically indicated physiologic assessment. Two prospective cohorts will be included:

1. Cohort 1. Patients with intermediate coronary artery stenosis (30-90% diameter stenosis) with clinically indicated FFR assessment.
2. Cohort 2. Symptomatic patients with NOCAD (<30% stenosis) with clinically indicated microvascular assessment.

Key exclusion criteria

Clinical Exclusion Criteria

1. Patients presenting with ST-elevation acute coronary syndrome
2. Prior myocardial infarction in the target vessel
3. Stent implantation in the target vessel within the last 12 months
4. Previous coronary artery bypass grafting (CABG)
5. Previous heart valve surgery
6. Previous heart transplantation
7. Moderate-to-severe valvular disease
8. Left ventricular ejection fraction (EF) ≤45%
9. Hemodynamic instability or cardiogenic shock

Angiographic Exclusion Criteria

1. Left main stenosis ≥50%
2. Chronic total occlusion in target vessel
3. CTO in a non-target vessel
4. Less than thrombolysis in myocardial infarction (TIMI) 3 flow in target vessel
5. Target vessel receiving collaterals
6. Inadequate coronary angiographic images
7. Ostial lesions
8. Severe tortuosity