Structured Measurement of Coronary Microvascular Function and Ranolazine Therapy for INOCA (SMART): Rationale and Design of a Prospective Multicenter Randomized Study

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Abstract

Background: Ischemia with non-obstructive coronary arteries (INOCA) is increasingly recognized as a major contributor to angina, impaired quality of life, and adverse cardiovascular outcomes despite the absence of obstructive epicardial coronary artery disease. Contemporary guidelines recommend invasive coronary functional testing, including coronary flow reserve (CFR), index of microcirculatory resistance (IMR), and vasospasm provocation testing, to identify underlying coronary microvascular dysfunction (CMD) or coronary artery spasm (CAS). However, prospective evidence demonstrating the clinical benefit of a structured physiology-guided diagnostic strategy remains limited.

Objectives: The SMART (Structured Measurement of Coronary Microvascular Function and Ranolazine Therapy for INOCA) trial aims to evaluate whether a structured coronary functional assessment strategy improves angina burden and quality of life compared with conventional angiography-guided management in patients with INOCA. In addition, the study investigates whether ranolazine-based therapy can improve symptoms in patients with confirmed CMD.

Methods: The SMART trial is a prospective, multicenter, randomized controlled trial enrolling patients with suspected INOCA from multiple tertiary referral centers in Taiwan. Eligible patients presenting with angina symptoms and non-obstructive coronary arteries will

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be randomized 1:1 to either a coronary functional testing group or a conventional care group. Patients assigned to the coronary functional testing group will undergo invasive CFR, IMR and intracoronary methylergonovine provocation testing. Based on physiological findings, patients will be categorized into CMD, CAS, combined CMD/CAS, functional angina, or non-cardiac chest pain phenotypes. Patients with CMD or combined CMD/CAS will undergo a second randomization to ranolazine-based therapy or conventional endotype-guided therapy. The primary endpoint is the difference in Seattle Angina Questionnaire (SAQ) Summary score at 12 months. Secondary endpoints include serial SAQ changes, EQ-5D quality-of-life assessment, angina-related hospitalization, and hierarchical win-ratio analysis.

Conclusions: The SMART trial is designed to evaluate the clinical value of a structured physiology-guided diagnostic and therapeutic strategy for INOCA. The study may provide important evidence supporting personalized treatment approaches for coronary microvascular and vasospastic disorders.

Keywords: INOCA, coronary microvascular dysfunction, coronary vasospasm, ranolazine, coronary physiology

Introduction

Ischemia with non-obstructive coronary arteries (INOCA) represents a prevalent yet under-recognized clinical syndrome among patients undergoing coronary angiography for angina symptoms[1]. Approximately 40-50% of patients referred for invasive coronary angiography are found to have non-obstructive coronary artery disease despite persistent ischemic symptoms. Although traditionally considered a benign condition, accumulating evidence demonstrates that INOCA is associated with recurrent angina, impaired quality of life, repeated hospitalizations, and increased long-term cardiovascular risk[2,3].

The pathophysiology of INOCA is heterogeneous and includes coronary microvascular dysfunction (CMD), epicardial coronary spasm, microvascular spasm, and overlapping endotypes [4-7]. Conventional coronary angiography is unable to adequately evaluate coronary vasomotor function or microvascular physiology. Accordingly, invasive coronary functional testing using coronary flow reserve (CFR), index of microcirculatory resistance (IMR), and vasoreactivity testing has emerged as an important diagnostic strategy to identify underlying mechanisms of ischemia[4,8].

Recent international guidelines and expert consensus documents strongly support invasive coronary functional assessment in patients with suspected INOCA. The 2023 Japanese Circulation Society/Coronary Vasomotion Disorders International Study Group guideline recommends coronary vasomotor testing as a Class I indication in selected patients with angina and non-obstructive coronary arteries[9]. Similarly, the European Association of Percutaneous Cardiovascular Interventions (EAPCI) consensus document emphasizes the importance of mechanism-based diagnosis and personalized treatment in INOCA[10].

The recently published AID-ANGIO study proposes a structured diagnostic strategy integrating angiographic evaluation with invasive coronary physiology and vasospasm provocation testing[11]. This approach significantly improves diagnostic yield compared with conventional angiography alone and influences downstream clinical management.

Ranolazine is a late sodium current inhibitor that improves myocardial relaxation and reduces intracellular calcium overload. Prior studies suggest potential benefits of ranolazine in patients with microvascular angina and INOCA, particularly in improving exercise tolerance and

angina-related quality of life[12]. Nevertheless, large prospective studies evaluating ranolazine in physiologically characterized CMD populations are still unavailable.

Although previous studies have suggested that invasive coronary functional testing combined with stratified medical therapy may improve symptoms and quality of life in patients with INOCA[13,14], prospective evidence from Asian populations remains limited. Furthermore, the clinical utility of a structured diagnostic strategy incorporating CFR, IMR, and methylergonovine provocation testing has not been prospectively evaluated in a Taiwanese multicenter cohort. The incremental therapeutic benefit of ranolazine in patients with physiologically confirmed CMD or combined CMD and CAS also remains uncertain. Therefore, the SMART trial has been designed to evaluate both the diagnostic performance of a structured physiology-guided strategy and the therapeutic efficacy of ranolazine in Taiwanese patients with INOCA.

Methods

Study Design

SMART is a prospective, multicenter, randomized controlled study conducted across tertiary cardiovascular centers in Taiwan. The study is designed to compare a structured physiology-guided diagnostic strategy with conventional management of patients with INOCA.

Study Population

Inclusion Criteria

Eligible participants must fulfill the following criteria:

- Age ≥20 years
- Presence of angina or angina-equivalent symptoms
- Evidence of myocardial ischemia on non-invasive testing, or persistent Canadian Cardiovascular Society (CCS) class II–IV angina, despite negative non-invasive testing
- Clinical indication for coronary angiography
- Non-obstructive coronary arteries with <50% left main stenosis and <70% epicardial stenosis
- Intermediate lesions (50-70%) with negative FFR (>0.80)

Exclusion Criteria

Major exclusion criteria include:

- Acute coronary syndrome
- Prior coronary artery bypass graft surgery
- Severe valvular heart disease
- Left ventricular ejection fraction <30%
- Severe chronic kidney disease or dialysis
- Hypertrophic cardiomyopathy
- Severe pulmonary hypertension
- Significant obstructive coronary artery disease

Randomization and Study Groups

The study flow is shown in Figure 1. The study population will be enrolled and randomized in a 1:1 ratio using a centralized web-based randomization platform. Participant enrollment is planned from July 2026 to December 2028.

Coronary Functional Testing Group

Patients randomized to the coronary functional testing (CFT) group will undergo testing for:

- Coronary flow reserve (CFR)
- Index of microcirculatory resistance (IMR)
- Intracoronary methylergonovine provocation testing

Based on the test results, patients will be classified into the following endotypes:

1. Coronary microvascular dysfunction (CMD)
2. Coronary artery spasm (CAS)
3. Combined CMD/CAS
4. Functional angina
5. Non-cardiac chest pain

Patients diagnosed with CMD or mixed CMD/CAS following invasive coronary function testing will subsequently undergo a second-stage 1:1 randomization to receive either ranolazine-

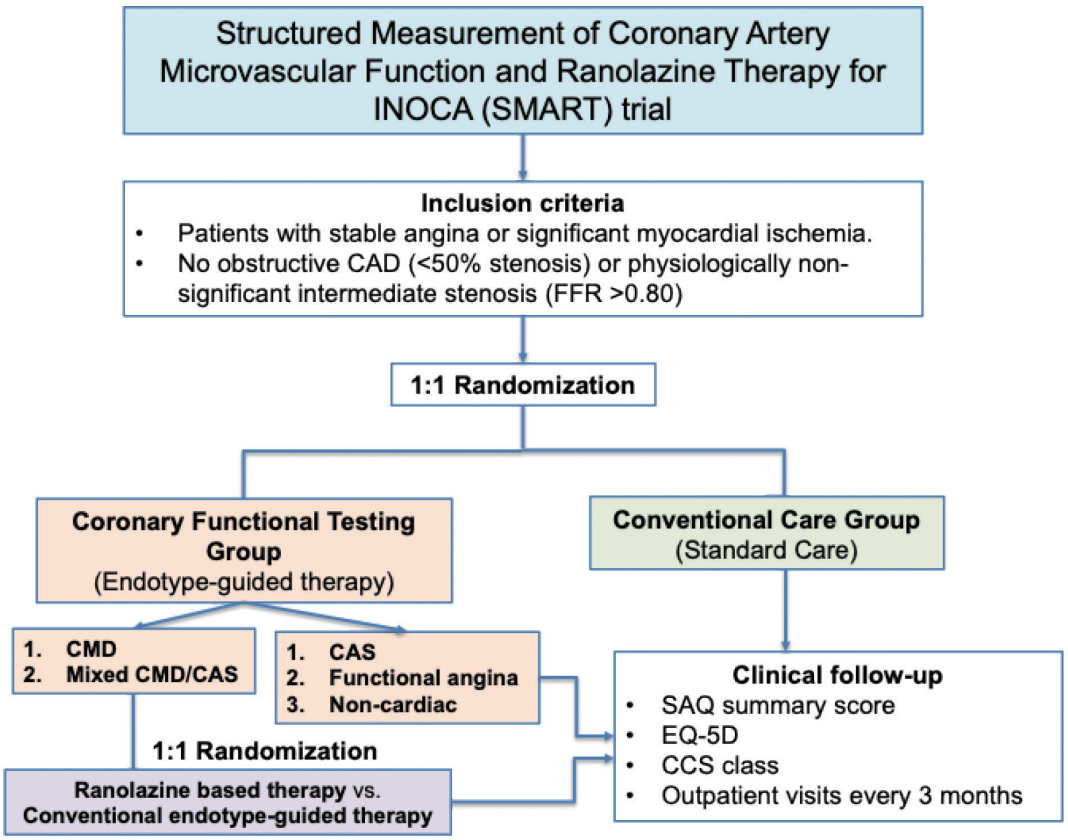

Figure 1. Study Flow.
CAS: Coronary Artery Spasm, CCS: Canadian Cardiovascular Society, CMD: Coronary Microvascular Dysfunction, FFR: fractional flow reserve, SAQ: Seattle Angina Questionnaire.

based therapy in addition to guideline-directed medical therapy or conventional antianginal therapy alone.

Conventional Care Group

Patients randomized to the control group will receive standard medical therapy without additional invasive coronary functional testing.

Coronary Microvascular Testing

Coronary physiological assessment will be performed using a pressure-temperature sensor guidewire (PressureWire X, Abbott Vascular, Santa Clara, CA, USA) according to standard invasive coronary function testing protocols. Following intracoronary administration of nitroglycerin (100-200 μg), the pressure wire will be calibrated, equalized, and advanced to the distal segment of the target coronary artery. CFT will be performed in the left anterior descending artery in all patients as the mandatory target vessel because of its large myocardial territory and established role as the standard vessel for invasive physiological assessment. When clinically indicated or technically feasible, physiological assessment may additionally be performed in the left circumflex or right coronary artery at the operator's discretion.

Maximal hyperemia will be induced by continuous intravenous adenosine infusion at 140 μg/kg/min via a large peripheral or central vein. CFR will be determined using the thermodilution technique by obtaining three consecutive injections of 3 mL room-temperature

saline at rest and during steady-state hyperemia. The mean transit time (Tmn) will be calculated automatically as the average of three reproducible measurements, and CFR will be calculated as the ratio of resting to hyperemic mean transit time. IMR will be calculated as the product of distal coronary pressure (Pd) and hyperemic mean transit time. All physiological measurements will be analyzed using the CoroFlow software platform (Coroventis Research AB, Uppsala, Sweden).

Vasospasm Provocation Testing

Before vasospasm provocation testing, vasoactive medications, including calcium-channel blockers, long-acting nitrates, nicorandil, and other antianginal agents, will be withheld for 24 hours where clinically feasible, in accordance with a pre-specified protocol washout period. Intracoronary methylergonovine will be administered in incremental doses (5, 10 and 30 μg) under continuous electrocardiographic, hemodynamic and angiographic monitoring[6]. Coronary angiography will be performed 1-2 minutes after each methylergonovine injection. If chest pain or ischemic electrocardiographic changes occur before the scheduled angiographic assessment, coronary angiography will be performed immediately. If no coronary spasm is identified in the left coronary artery, methylergonovine provocation testing will subsequently be conducted in the right coronary artery after a 5-minute interval. The test will be terminated immediately if severe chest pain, significant ischemic ECG changes, severe epicardial spasm, hemodynamic instability, or clinically significant arrhythmia occurs. Intracoronary nitrates will be administered immediately after a positive test or when clinically indicated to reverse coronary spasm. Contraindications, rescue medications, and emergency management procedures are predefined in the study protocol.

INOCA Endotype Definitions

Patients in the functional assessment group will be classified into pre-specified coronary functional endotype groups according to CFR, IMR and vasospasm provocation testing. CMD is defined by a reduced CFR (<2.0) or elevated IMR (≥ 25). Patients with CMD can subsequently be stratified into functional CMD (CFR <2.0 with IMR <25), structural CMD (CFR <2.0 with IMR ≥ 25) and discordant structural CMD (CFR ≥ 2.0 with IMR ≥ 25)[15]. Epicardial coronary spasm will be defined as $\geq 90\%$ epicardial vasoconstriction accompanied by reproduction of symptoms and ischemic ECG changes during methylergonovine provocation. Microvascular spasm will be defined as reproduction of angina symptoms and ischemic ECG changes during provocation testing in the absence of $\geq 90\%$ epicardial vasoconstriction. Mixed CMD/CAS will be defined as the coexistence of CMD and either epicardial or microvascular spasm. Patients with typical anginal symptoms who do not fulfil the diagnostic criteria for either CMD or CAS will be classified as having functional angina[16]. Patients without obstructive coronary artery disease and with entirely normal coronary functional test results will be classified as having no demonstrable coronary functional disorder, and alternative non-cardiac causes of symptoms should be considered.

Medical Therapy

In the coronary functional testing group, treatment strategies will be guided by the underlying coronary functional endotype. Patients will receive targeted lifestyle counselling, endotype-specific anti-anginal therapy, and, where appropriate, additional evaluation for non-cardiac causes of symptoms (Table 1). Patients diagnosed with CMD or combined CMD/CAS will subsequently undergo secondary randomization to: Ranolazine-based treatment or conventional antianginal therapy. Patients assigned to the conventional care group will receive standard medical therapy at the discretion of the treating physician according to contemporary guideline recommendations. Antianginal therapy may include beta-blockers, calcium-channel blockers, nitrates, nicorandil or other agents as clinically indicated. Cardiovascular risk factor modification,

Table 1. Coronary Functional Endotypes and Recommended Treatment

Clinical Endotype	Diagnostic Criteria for Functional Abnormalities	Recommended Treatment Strategy
Coronary Microvascular Dysfunction (CMD)	**Functional CMD** CFR < 2.0, IMR < 25 **Structural CMD** CFR < 2.0, IMR ≥ 25 **Discordant structural CMD** CFR ≥ 2.0, IMR ≥ 25	**Baseline:** Lifestyle modification, cardiovascular risk factor control, and preventive pharmacotherapy according to clinical indication (including statins, ACEI/ARB, or antiplatelet therapy when appropriate). **First-line:** Group A1: Ranolazine based therapy; Group A2: Conventional endotype-guided therapy.
Coronary Artery Spasm (CAS)	Based on COVADIS criteria, provocation testing identifies: • **Epicardial Spasm:** Angina symptoms, Ischemic ECG changes, and Angiographic stenosis ≥ 90%. • **Microvascular Spasm:** Angina symptoms, Ischemic ECG changes, and Angiographic stenosis < 90%.	**First-line:** Non-DHP CCB. **Second-line:** Nitrate / Nicorandil. **Third-line:** DHP-CCB.
Mixed CMD/CAS	Concurrent presence of both CMD and CAS abnormalities (impaired vasodilator function and positive spasm provocation).	**First-line:** Group A1: Ranolazine based therapy; Group A2: Conventional endotype-guided therapy.
Functional Angina	Patients with typical anginal symptoms who do not fulfil the diagnostic criteria for either CMD or CAS.	**Baseline:** Lifestyle modification, cardiovascular risk factor control, and preventive pharmacotherapy according to clinical indication (including statins, ACEI/ARB, or antiplatelet therapy when appropriate). **First-line:** Conventional endotype-guided therapy.
Non-cardiac Chest Pain	Exclusion of significant epicardial stenosis and absence of any functional abnormalities or coronary spasm.	**Action:** Refer to appropriate specialty (e.g., Gastroenterology) after ruling out cardiac etiology.

including lipid-lowering therapy, antihypertensive therapy, diabetes management, smoking cessation, and lifestyle counseling, will be provided according to individual clinical indications. Coronary functional testing will not be performed to guide treatment in this group.

CMD or Combined CMD/CAS

Patients assigned to ranolazine-based therapy will receive ranolazine 500 mg twice daily, with titration to 1000 mg twice daily depending on symptom response and tolerability. Baseline and follow-up electrocardiography will be performed to monitor QT interval prolongation. Renal function, hepatic function, adverse events, drug interactions, and treatment adherence will be assessed at each follow-up visit. Ranolazine will be discontinued or the dose reduced in cases of significant QT prolongation, intolerable adverse effects, clinically relevant drug interactions, severe renal/hepatic dysfunction, or at the discretion of the treating physician.

CAS or Functional Angina

Patients diagnosed with epicardial or microvascular spasm will receive endotype-guided antianginal therapy. Non-dihydropyridine calcium-channel blockers (e.g., diltiazem or verapamil) will be considered for first-line therapy because of their established efficacy in preventing coronary vasospasm. If symptoms remain uncontrolled or calcium-channel blockers are contraindicated or not tolerated, long-acting nitrates or nicorandil will be considered as second-line therapy. For patients with refractory symptoms, combination therapy with calcium-channel blockers and long-acting nitrates or nicorandil may be prescribed at the discretion of the treating physician.

Patients classified as having functional angina will receive conventional antianginal therapy according to current clinical practice, with individualized treatment based on symptom burden, cardiovascular risk profile, and the physician's judgment. Lifestyle modification and optimization of cardiovascular risk factors will be recommended for all patients.

Study Endpoints

Primary Endpoint

The primary endpoint will be the difference in the SAQ Summary Score at 12 months between the CFT group and the conventional care group. Other individual SAQ domains, including physical limitation, angina frequency, angina stability, treatment satisfaction, and quality of life, will be analyzed as secondary endpoints.

Secondary Endpoints

- Serial SAQ Summary Score changes at 3, 6, 9 and 12 months
- Individual SAQ domains changes at 3, 6, 9 and 12 months
- EQ-5D quality-of-life assessment
- Angina-related emergency department visits or hospitalization
- Hierarchical win-ratio analysis
- Clinical safety outcomes

Exploratory secondary endpoints for the ranolazine sub-study

Among patients with CMD or mixed CMD/CAS who undergo second-stage randomization, exploratory secondary endpoints will compare ranolazine-based therapy with conventional endotype-guided antianginal therapy. These endpoints will include:

- Change in SAQ Summary Score from baseline to 12 months
- Serial changes in SAQ Summary Score at 3, 6, 9 and 12 months
- Changes in individual SAQ domains, including angina frequency, physical limitation, treatment satisfaction, and quality of life.
- Change in CCS angina class from baseline to follow-up
- EQ-5D quality-of-life score at 12 months
- Proportion of patients achieving a clinically meaningful improvement in SAQ Summary Score, defined as an increase of ≥ 10 points

- Angina-related emergency department visits or hospitalizations
- Treatment discontinuation, dose reduction, QT prolongation, and other adverse events related to ranolazine

Hierarchical Win-Ratio Analysis

In addition to the primary and secondary endpoint analyses, a hierarchical win-ratio analysis will be performed to provide a comprehensive assessment of the overall clinical benefit of the physiology-guided strategy. Patients will be compared in matched pairs according to a pre-specified hierarchy of clinically important outcomes. Pairwise comparisons will proceed sequentially through the hierarchy until a winner is identified. If no difference is observed for a higher-priority endpoint, the comparison will continue to the next endpoint. A tie will be declared only if all hierarchical endpoints are equivalent between the paired patients.

The hierarchy of outcomes will be:

- Angina-related hospitalization or emergency department visit
- Worsening of CCS angina class from baseline to 12 months
- Change in SAQ Summary Score from baseline to 12 months
- Change in EQ-5D health-related quality-of-life score from baseline to 12 months

The overall treatment effect will be summarized using the win ratio with corresponding 95% confidence intervals. A win ratio greater than 1 will indicate a favorable outcome for the coronary function testing strategy compared with conventional angiography-guided care.

Sample size calculation

The sample size calculation is based on the primary comparison between the functional assessment group and the conventional angiography-guided care group. Assuming a standard deviation of 20 points in the SAQ Summary Score, a clinically meaningful inter-group difference of 10 points, 80% power, a two-sided alpha level of 0.05, and a 10% attrition rate, a total sample of 144 patients will be enrolled. The secondary randomization of patients with CMD or mixed CMD/CAS to ranolazine-based therapy, as opposed to conventional therapy, will be treated as an exploratory analysis, as this sub-group comparison may not be adequately powered for definitive conclusions about efficacy.

Blinding

Although treatment allocation cannot be fully blinded due to the nature of the invasive intervention, SAQ and EQ-5D assessments will be collected using standardized questionnaires by trained study personnel who will be blinded to treatment allocation whenever feasible. Clinical events, including angina-related emergency department visits and hospitalizations, will be adjudicated by an independent clinical events committee blinded to group assignment.

Statistical Analysis

All efficacy analyses will be performed according to the intention-to-treat principle. Continuous variables will be presented as mean ± standard deviation or median (interquartile range), as appropriate, and compared using Student's t-test or the Mann–Whitney U test. Categorical variables will be expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate.

The primary endpoint, the inter-group difference in the SAQ Summary Scores at 12 months, will be analyzed using an analysis of covariance (ANCOVA) model adjusting for baseline SAQ Summary Score. Serial changes in SAQ Summary Score, individual SAQ domains, CCS angina class, and EQ-5D over time will be analyzed using linear mixed-effects models to account for repeated measurements within individuals.

Time-to-event outcomes, including angina-related hospitalization and emergency department visits, will be analyzed using the Kaplan–Meier method and compared using the log-rank test. Hazard ratios with 95% confidence intervals will be estimated using Cox proportional hazards

regression, when appropriate.

A pre-specified hierarchical win-ratio analysis will be performed as a supportive secondary analysis to evaluate the overall clinical benefit of the physiology-guided strategy. Pairwise comparisons will be conducted according to the predefined hierarchical endpoint structure, and the overall treatment effect will be summarized as the win ratio with corresponding 95% confidence intervals.

The exploratory comparison between ranolazine-based therapy and conventional endotype-guided therapy will be analyzed using the same statistical methods but will be considered hypothesis-generating, as the second-stage randomization is not sufficiently powered to detect definitive differences in efficacy.

All statistical tests will be two-sided, and a P value <0.05 will be considered statistically significant. Statistical analyses will be performed using R (R Foundation for Statistical Computing, Vienna, Austria).

Discussion

INOCA has emerged as a clinically important syndrome associated with substantial symptom burden and adverse long-term outcomes despite the absence of obstructive epicardial coronary artery disease. However, the optimal diagnostic and therapeutic strategy for these patients remains incompletely defined.

The SMART trial addresses several important unmet clinical needs. Although invasive coronary function testing is increasingly recommended by international guidelines for patients with INOCA, robust prospective evidence demonstrating that physiology-guided diagnosis translates into improved patient-centered outcomes remains limited, particularly in Asian populations. The SMART trial is one of the first prospective randomized studies to evaluate whether a structured physiology-guided diagnostic and therapeutic strategy can improve angina burden, health-related quality of life, and clinical outcomes, when compared with conventional angiography-guided care in Taiwanese patients with INOCA.

Second, the SMART trial incorporates comprehensive endotype-based classification of INOCA, including CMD, epicardial spasm, microvascular spasm, and mixed phenotypes. This approach reflects the contemporary understanding that INOCA represents a heterogeneous disorder requiring individualized treatment strategies rather than empiric antianginal therapy.

Third, the study evaluates the role of ranolazine in physiologically confirmed CMD populations. Although prior studies and meta-analyses suggest potential symptomatic benefits of ranolazine, existing evidence has been limited by small sample sizes and inconsistent phenotyping. By enrolling patients with objectively documented coronary microvascular dysfunction, SMART may provide more definitive evidence regarding the role of ranolazine in precision medicine for INOCA.

Another important feature of the SMART trial is the use of methylergonovine for coronary spasm provocation testing. While acetylcholine is more commonly used in contemporary coronary function testing studies, ergonovine and methylergonovine are also recognized pharmacological agents for vasospasm provocation. Nevertheless, evidence regarding their use within a comprehensive INOCA diagnostic strategy remains less extensive than that for acetylcholine. The SMART trial therefore has the potential to generate clinically relevant data on the diagnostic performance and procedural safety of methylergonovine-based provocation testing when integrated with invasive assessment of CFR and IMR.

An additional strength of the study is the incorporation of hierarchical win-ratio analysis, which allows simultaneous evaluation of symptom burden, hospitalization and quality-of-life outcomes. This design better reflects the multidimensional clinical impact of INOCA beyond traditional hard cardiovascular endpoints.

Several limitations should be acknowledged. The sample size is relatively modest and powered primarily for quality-of-life endpoints rather than major adverse cardiovascular events. In addition, the ranolazine comparison is exploratory and may be underpowered for definitive conclusions about efficacy. Nevertheless, the SMART trial represents an important step toward mechanism-guided management of INOCA.

In conclusion, the SMART trial is designed to evaluate whether structured invasive coronary functional assessment and physiology-guided therapy can improve symptoms and quality of life in patients with INOCA. The study may provide clinically relevant evidence supporting personalized diagnostic and therapeutic strategies for coronary microvascular and vasospastic disorders.

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