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VISIBLE: Women's heart disease revealed

One out of every three women dies of cardiovascular disease[1]. It is the number one cause of death for women. Approximately 100 million* women, globally, live with stable chest pain†. Each year, a subset of these women — an estimated 700,000 women in the United States and Europe alone — undergo invasive coronary angiography and leave without a diagnosis. They are told their arteries look "normal." That their hearts are healthy. That it might be anxiety.

These women, in addition to having debilitating symptoms, carry an up to 4-fold higher risk of major cardiovascular events including cardiovascular death, heart attack, stroke, or hospitalization for heart failure, than women without these symptoms[2]. The condition they have is increasingly recognized as angina, the clinical term for chest pain, with no obstructive coronary arteries (ANOCA)‡.

Of the women with stable angina who undergo coronary angiography, two out of three do not have a blockage in their heart arteries[3-5] — the cause of heart disease medicine has spent decades learning to find and fix. In most of ANOCA, the underlying abnormality lies in coronary function, which remains largely invisible to current diagnostic pathways. This includes dysfunction of the coronary microvasculature, vasospasm of the larger coronary arteries, or a combination of both. The most common abnormality, present in up to 70% of patients, is coronary microvascular dysfunction[6,7].

The coronary microvasculature consists of the smallest blood vessels of the heart, typically only hundreds of microns or less in diameter. Although invisible on coronary angiography, these vessels comprise the vast majority of the vascular network and, under normal conditions, control more than 80% of the blood flow to the heart muscle[8]. Coronary microvascular disease reflects failure of this regulatory system, leading to restricted or abnormal blood flow that can result in a mismatch between oxygen supply and demand (ischemia) even in the absence of upstream blockages.

Importantly, most women with ANOCA do not have "normal" arteries. When intravascular imaging is used rather than visual assessment of the angiogram alone, up to about 80% are found to have atherosclerotic plaque[9], not as focal obstructions, but as a diffuse, non-obstructive disease pattern that conventional tests are not designed to detect. The interaction between diffuse plaque and microvascular dysfunction may be a key driver of adverse outcomes, yet remains poorly understood.

The result of a system optimized to find focal blockages is a diagnostic odyssey and a population, predominantly women, left unseen. Many, in search of answers, endure years of repeated stress tests, repeated angiograms, and repeated dismissals before anyone names what is wrong.

The consequences are profound. Seven in ten women with ANOCA report adverse effects on work, with at least half reducing hours or retiring early; approximately 40% apply for disability, and 30% move into lower-paid roles[10]. Seven in ten report adverse effects on mental health, and eight in ten report impacts on their social lives[10].

The economic cost is equally staggering. Healthcare systems spend thousands of dollars per patient on tests designed to detect a disease pattern that is not present. Lifetime healthcare costs associated with ANOCA are estimated at $750,000 per patient[11]. For women themselves, out-of-pocket expenses, travel, and lost productivity consume nearly 10% of household income[11].

What are the limits of current practice?

Diagnosing coronary microvascular disease in ANOCA patients faces multiple technical challenges. Unlike the larger heart arteries that run along the surface of the heart (epicardial coronary arteries), the coronary microvasculature consists of vessels mostly embedded within the heart muscle itself. These vessels are difficult to assess not only because of their small size, but also because they are in constant motion with each heartbeat.

As a result, evaluation of microvascular function relies on indirect measurements of coronary blood flow and vascular resistance in upstream vessels. This requires an invasive approach similar to coronary angiography, but with specialized equipment, pharmacologic agents (such as acetylcholine), and expertise that is not available in most catheterization laboratories. In addition, coronary microvascular disease arises from heterogeneous, partly overlapping pathophysiological mechanisms, which limits the utility of single-modality testing and renders currently available non-invasive tests insufficient for comprehensive evaluation.

The limitations of existing practice are not only technical, but also systemic. Clinical guidelines for stable ischemic heart disease, built on decades of research conducted predominantly in male populations, often with fewer than 30% women enrolled, have historically centered diagnosis on obstructive coronary artery disease. Although coronary function testing is included in most recent guidelines, the recommendations are based on the weakest level of evidence, reflecting the lack of robust clinical research[12,13]. Patients with ANOCA continue to be framed as a "specific" or "special"

group, despite representing the majority of women undergoing coronary angiography for stable angina.

> **The result is a diagnostic gap for millions of women globally — estimates suggest that fewer than 1% of women with ANOCA undergo coronary function testing.**

Even for the small number of women who receive a diagnosis of coronary microvascular disease, robust evidence to guide treatment pathways and improve long-term outcomes is absent. Significant deficits in knowledge persist regarding the detailed mechanisms of coronary microvascular disease and how they relate to clinical manifestations. Although measures of coronary microvascular function, such as coronary flow reserve, have been consistently associated with cardiovascular death and other adverse events[14,15], it remains unclear whether the underlying microvascular abnormalities are causally related to these outcomes. As an example, interest has recently been directed towards a potential causal relationship between coronary microvascular disease and heart failure with preserved ejection fraction, a condition that affects approximately 30 million people worldwide, half to two-thirds of whom are women[16]. Coronary microvascular dysfunction has been demonstrated in up to three-quarters of these patients, supporting a potential mechanistic link[17].

Given the complexity of blood flow regulation by the coronary microvasculature, multiple mechanisms have been investigated in an effort to identify treatment targets. However, attempts to selectively target individual pathways, such as endothelin-1-mediated vasoconstriction, have yielded inconsistent improvements in coronary microvascular function or symptoms[18,19]. While these largely negative findings may in part reflect heterogeneous study populations and inconsistent outcome assessment, they also point to a deeper problem: coronary microvascular disease represents dysfunction of a complex regulatory system with multiple, partially redundant pathways, such that targeting a single component in isolation may be insufficient.

More fundamentally, the microvasculature is unlikely to become dysfunctional spontaneously but rather is driven toward dysfunction by upstream processes that should be considered important treatment targets. Current clinical management targets traditional cardiovascular risk factors such as diabetes and high cholesterol, which have been shown in experimental studies to contribute to coronary microvascular dysfunction and remain important treatment targets given the prevalence of non-obstructive plaque in these patients. However, at least within ANOCA populations, traditional risk factors have explained only a limited proportion of coronary microvascular dysfunction variability, and some studies have failed to predict its presence altogether[20,21]. These observations raise critical questions about additional upstream drivers of coronary microvascular disease that must be identified to advance treatment and improve care.

Why women?

Coronary microvascular structure and function are shaped by adaptation to changing physiological demands. In women, this adaptation is uniquely dynamic across the life course[22]. The microvasculature continuously responds to hormonal fluctuations and to profound physiological transitions, such as pregnancy, during which blood volume increases by up to 50%[23,24]. Such demands require extensive remodeling of the microvascular network.

The requirement for a highly adaptive regulatory system and/or the cumulative effects of repeated microvascular remodeling may increase susceptibility to dysregulation, injury, and maladaptive structural change. Adverse pregnancy outcomes, such as preeclampsia, are increasingly recognized as early markers of vascular vulnerability, with arterial stiffness and endothelial dysfunction proposed as potential links to future cardiovascular risk[25,26]. Whether preeclampsia acts as a vascular stressor, represents 'demasking' of inherent risk, or both, remains unknown.

Importantly, the menopausal transition represents a major inflection point in vascular biology. Declining estrogen levels have been linked to adverse changes in endothelial function, arterial elasticity, autonomic regulation, and inflammatory signaling that appear to extend beyond the effects of chronological aging alone[27]. Experimental and clinical data suggest that altered estrogen receptor signaling in endothelial cells, with downstream effects on vascular smooth muscle tone, may contribute to impaired microvascular flow regulation during this stage of life[28].

Sex-specific coronary anatomy and flow dynamics may also contribute to differential disease phenotyping. Because women generally have smaller coronary vessel diameters, even modest structural thickening or loss of elasticity in upstream vessels may have a proportionally greater impact on the transmission of pulsatile pressure to the microcirculation, potentially predisposing to microvascular injury.

Understanding these sex-specific mechanisms is essential to developing diagnostic strategies, mechanistic models, and treatments informed by the true disease biology.

Why now?

Progress in coronary microvascular disease has historically been limited by the lack of scalable diagnostic approaches, tractable mechanistic models, and sufficiently well-characterized patient cohorts, collectively impeding both causal inference and therapeutic development. These barriers are now lifting.

Advances in data-rich clinical diagnostics and artificial intelligence make it increasingly feasible to extract clinically meaningful signatures of coronary microvascular dysfunction from routinely acquired data and non-invasive testing[29,30], creating a realistic pathway toward earlier and more scalable identification of patients with coronary microvascular disease beyond specialized centers. In parallel, the emergence of human-based experimental and computational models create the opportunity to develop experimental systems capable of controlled interrogation of coronary microvascular mechanisms under conditions that more closely reflect human physiology, including bioengineered human cardiac tissues designed to integrate multiscale vascular architecture, patient-specific genetics, and biochemical, mechanical, and immune cues, an approach intended to overcome long-standing limitations of animal and reductionist *in vitro* models[31-35].

At the same time, growing recognition of coronary microvascular disease as part of a systemic microvascular disorder expands the investigative landscape, creating new opportunities to leverage information from other microvascular beds and integrative physiological signals, complementing coronary-specific assessment[36,37].

The emergence of cohorts with comprehensive evaluation of coronary microvascular disease provides further opportunity to define disease endotypes and to explore differences in underlying mechanisms and potential treatment strategies.

Goal of the program

The goal of VISIBLE is to increase the proportion of women presenting with stable angina who receive effective diagnosis and treatment for coronary microvascular disease from less than 1% to more than 80%. In so doing, the program aims to demonstrate advances capable of reducing the burden of cardiovascular disease for millions of women worldwide.

All approaches must incorporate clinically deployable implementation strategies that expand effective care for coronary microvascular disease without increasing the risk of missed diagnosis or treatment of obstructive coronary heart disease.

VISIBLE aims to achieve this goal by:

(1) developing scalable approaches for diagnosis and monitoring of coronary microvascular disease;

(2) identifying risk factors and evaluating prognosis of coronary microvascular disease endotypes;

(3) building and validating multiscale, human-relevant models of the coronary microvasculature to interrogate causal mechanisms of coronary microvascular disease; and

(4) developing treatment strategies that improve both coronary microvascular function and patient-centered outcomes by testing existing therapies in well-characterized populations that most likely will benefit.

Central to the program is the recognition that coronary microvascular disease encompasses multiple endotypes with distinct, yet overlapping, pathophysiological mechanisms, including functional (e.g., endothelial dysfunction, smooth muscle dysfunction) and structural (e.g., vascular rarefaction) abnormalities. By refining and validating these endotypes, anchored in measures currently derived from invasive coronary function testing, the program aims to move beyond empiric care toward mechanism-informed diagnosis and treatment. All approaches supported by the program should be designed and evaluated to ensure generalizability and equitable impact across diverse populations of women.

The VISIBLE program is soliciting abstracts and proposals across four (4) thrust areas, each contributing to the program goals, and as described in detail below. Individual teams are not expected to address all facets of the program. Progress will be driven by multiple focused, collaborative efforts that integrate at the program level toward shared, measurable outcomes. Across selected projects, definitions and performance metrics (including measures of coronary microvascular function, reference standards, and endpoints) will be harmonized to enable comparison, integration, and validation. Wellcome Leap will enable cross-collaboration between thrusts, which will be integral to the success of the program — proposals will be expected to articulate clear strategies for data sharing, integration, and coordination across projects.

Thrust 1: Develop scalable approaches for diagnosis and monitoring of coronary microvascular disease.

Current gold standard testing is invasive, costly, and requires specialized operator expertise, which makes it impractical for population-scale diagnosis and monitoring of treatment response in both clinical and research settings. While non-invasive tests exist, they detect only certain disease endotypes and remain constrained by cost, limited availability, and technical or patient-specific factors. None are currently suitable for monitoring disease activity deemed critical to advancing treatment options. Thrust 1 aims to develop scalable diagnostics to detect coronary microvascular disease with >80% sensitivity and >80% specificity as benchmarked against current gold standard invasive coronary function testing (including acetylcholine challenge).

Considering that coronary microvascular disease is at least as prevalent as obstructive coronary artery disease among women presenting with stable angina, proposed diagnostic approaches must be deployable early in the diagnostic workup at a scale comparable to current non-invasive testing for obstructive coronary artery disease. In practice, this implies a testing volume on the order of cardiac stress testing, which in the United States alone accounts for roughly 10 million tests per year.

To enable mechanism-informed treatment, approaches must also, either as a single test or in combination, be able to differentiate between coronary microvascular disease endotypes, as currently derived from invasive coronary function testing. All proposals must describe validation strategies to assess whether the approach is able to achieve statistically significant discrimination beyond chance and adequate reliability across repeated measurements (e.g., via appropriate permutation-based testing and/or consistency metrics). Diagnostic approaches that provide continuous quantification of disease severity will be prioritized over binary classifications based on threshold crossings of continuous measures (e.g., coronary flow reserve).

Examples of novel approaches that hold promise to support increased scalability include strategies using artificial intelligence or machine learning to identify signatures of coronary microvascular disease from data already acquired in routine care, such as electrocardiograms, or those leveraging the concept of coronary microvascular disease as a systemic disease and thus accessing microvascular beds outside of the heart (e.g., retina) to obtain markers of the disease. Proposals that identify biomarkers and other patient characteristics (e.g., symptom patterns) linked to coronary microvascular disease will also be considered, but only if the proposal can clearly define how they support risk stratification, diagnosis, or monitoring of disease activity and treatment response.

Any diagnostic approach must complement and ideally facilitate the existing workup for obstructive coronary artery disease (e.g., integrate testing for coronary microvascular disease into current stress testing modalities and/or leverage AI approaches to both detect signatures of coronary microvascular disease and enhance the sensitivity/specificity of obstructive coronary artery disease detection). Specifically, new approaches must not increase the risk of missed obstructive coronary artery disease. Detection of and differentiation from epicardial vasospasm is desirable.

Proposals should either (i) describe concrete partnership plans for accessing the patient populations required for diagnostic validation — specifying whether validation will leverage existing cohorts/datasets or involve prospective enrollment, and outlining relevant regulatory, ethical, and data-access considerations; or (ii) request to be paired with teams that have access to large datasets suitable for validating diagnostic approaches.

Thrust 2: Identify risk factors and evaluate prognosis of coronary microvascular disease endotypes.

Thrust 2 seeks to identify upstream risk factors for coronary microvascular disease and define the prognostic significance of distinct endotypes. These findings will inform diagnostic prioritization (Thrust 1) and treatment strategies (Thrust 4).

2A: Identify risk factors for coronary microvascular disease (effect sizes ≥1.5) to define treatment targets.

Altering the disease trajectory of coronary microvascular disease will require targeting upstream drivers rather than focusing solely on downstream mechanisms of the disease. Current practice is limited to targeting traditional cardiovascular risk factors, although it remains unclear what their contribution to disease development in women is and whether other determinants play a role. To better characterize upstream drivers of coronary microvascular disease in women, Thrust 2 seeks to identify risk factors (including sex-specific risk factors) using clinical and biological data. Associations should be quantified using adjusted odds ratios, hazard ratios, or relative risks, with effect sizes ≥1.5 considered indicative of a meaningful impact on risk.

Proposed studies may leverage existing cohorts in which information on coronary microvascular function is available or readily obtainable. We are particularly interested in studies that link factors to not only coronary microvascular disease, but to specific coronary microvascular disease endotypes. Therefore, large cohorts with comprehensive invasive coronary function testing, including acetylcholine challenge, will be prioritized. Well-characterized cohorts using non-invasive measures of coronary microvascular function, such as coronary flow reserve or quantitative myocardial perfusion indices, are also acceptable if they are applied in populations of specific interest (e.g., those enriched for a history of adverse pregnancy outcomes or the menopausal transition).

Studies must support deep phenotyping of female-specific vascular stressors across the reproductive life course (such as pregnancy and the menopausal transition), including characterization of biological, molecular, or physiological markers that reflect adaptive or maladaptive vascular responses (e.g., preeclampsia), together with cardiometabolic trajectories across the life course, rather than relying solely on binary exposure histories or single time-point hormone measurements.

Where studies are anchored in ANOCA populations, proposals should explain reference group selection and describe strategies to mitigate selection bias. Studies must allow for subgroup analysis based on disease endotypes and teams may therefore have to combine their datasets with others to achieve sufficient sample size. Proposals should clearly describe the feasibility of such data integration approaches. In population-based or community cohorts, coronary microvascular function may be studied as a continuum, enabling examination of risk factor associations across the full spectrum of microvascular function, including before symptoms emerge. In such settings, non-invasive testing, preferably without radiation exposure, is acceptable and may enable adequately powered analyses even in smaller populations, as analyses will include measures of coronary microvascular function (e.g., coronary flow reserve) as a continuous metric. Across all study designs, approaches must explicitly address temporal ordering and confounding to support an upstream role of identified factors. The specific approach to cohort construction and comparison may vary by setting, and innovation in design and bias mitigation is encouraged.

Proposals leveraging large existing cohorts or prospective studies should explicitly state whether there is willingness and feasibility to use these cohorts for validation of diagnostic approaches developed in Thrust 1.

2B: Define prognosis of coronary microvascular disease endotypes.

In parallel with identifying upstream risk factors, the program seeks to leverage existing ANOCA datasets with comprehensive invasive coronary function testing (including acetylcholine challenge) and follow-up of at least one year, with longer follow-up preferred for evaluation of major adverse cardiovascular events, to define the prognostic significance of distinct coronary microvascular disease endotypes. These cohorts may overlap with those used in Thrust 2A.

Outcomes of interest include, but are not limited to, angina burden and quality of life (e.g., Seattle Angina Questionnaire domains) and major adverse cardiovascular events, including cardiovascular death, myocardial infarction, stroke, and heart failure (differentiated as heart failure with preserved ejection fraction versus heart failure with reduced ejection fraction where feasible).

Studies should compare outcomes across coronary microvascular disease endotypes and against appropriate comparators (e.g., ANOCA patients with normal coronary function testing, asymptomatic individuals) to characterize the prognostic profile of each endotype with respect to both symptom burden and major adverse cardiovascular events. Where data are available, analyses should explore the role of epicardial

non-obstructive plaque burden and whether it mediates or modifies the prognosis associated with certain endotypes.

Analyses must report absolute event rates and (adjusted) risk estimates (e.g., hazard ratios) for each endotype, with $p<0.05$ indicating statistical significance. Proposals should explicitly address overlap between coronary microvascular function abnormalities. Inclusion of epicardial vasospasm as a comparator, alone and in combination with coronary microvascular disease endotypes, is encouraged.

Proposals should specify the number of endotypes to be compared and provide justification that the available sample size and event rates are sufficient to detect clinically meaningful differences in outcomes across groups. Proposals must describe how datasets can be combined with other teams' datasets for analysis and outline relevant regulatory, ethical, and data-access considerations.

Thrust 3: Build and validate multiscale human-relevant models of the coronary microvasculature to interrogate causal mechanisms of coronary microvascular disease.

Definitive pathophysiological causes of coronary microvascular dysfunction remain poorly understood, in part because existing experimental systems do not permit controlled, causal interrogation of microvascular function in a human-relevant environment. Recent advances in biomedical engineering provide new opportunities to address these gaps. For example, microphysiological systems, particularly vessel-on-a-chip platforms within the broader organ-on-a-chip framework, have enabled controlled modeling of flow-mediated endothelial dysfunction under coronary-relevant mechanical conditions, with quantitative characterization of endothelial structural, barrier, and inflammatory responses to defined mechanical perturbations[33]. In parallel, integrative approaches that combine *in vitro* microvascular networks with *in silico* modeling have been applied to simulate hemodynamic changes and perfusion impairment in coronary microvascular disease, providing a framework for linking local microvascular perturbations to tissue- and organ-level functional consequences[34].

Thrust 3 seeks to develop and apply integrated, multiscale models, coupling human cell-based systems with computational frameworks, to establish causal relationships between upstream drivers, proposed disease mechanisms, and resulting changes in coronary microvascular function. Proposals must demonstrate a clear strategy for bridging biological data from the cellular and mesoscale (e.g., vessel-on-a-chip) to the physiological level (e.g., blood flow, vascular resistance).

Proposals must describe how their models will recapitulate key features of coronary microvascular physiology directly relevant to function, including endothelial–smooth muscle cell interactions and flow-dependent regulation of vascular behavior. Critically, proposals should explain their strategy for taking female-specific biology into account in their models. Approaches must incorporate quantitative methods to assess microvascular function or downstream functional consequences (e.g., blood flow, vascular resistance, vasoreactivity, or perfusion) in response to standardized mechanical and/or biochemical challenges.

Studies will be expected to manipulate candidate factors within the developed models (increase, decrease, and, where feasible, rescue) to demonstrate reproducible and interpretable changes in prespecified functional endpoints. Experimental designs must be powered to detect physiologically meaningful within-model effects; proposals should justify the smallest effect size considered meaningful for mechanistic inference (e.g., standardized effect size ≥0.2).

Modeling studies of interest include (i) those that manipulate upstream drivers relevant to coronary microvascular disease (e.g., metabolic stress, inflammatory signaling, or altered flow and pressure dynamics) and quantify their impact on coronary microvascular function, and (ii) those that directly model previously proposed disease mechanisms at the cellular or vessel-wall level and establish their causal relationship with coronary microvascular dysfunction.

Thrust 4: Develop treatment strategies that improve both coronary microvascular function and patient-centered outcomes.

To date, studies of interventions intended to improve symptoms and/or coronary microvascular function have yielded inconsistent results. However, many of these studies enrolled heterogeneous populations without accounting for disease endotypes or incorporating coronary microvascular function testing at all[18]. To overcome this limitation, it is essential that studies move beyond the use of umbrella diagnoses such as ANOCA or coronary microvascular disease and instead use coronary function testing to explicitly match distinct disease endotypes to specific treatments. Thrust 4, therefore, focuses on proof-of-concept studies testing existing interventions in well-characterized patient populations that most likely will benefit. These studies will be restricted to therapies approved by major regulatory authorities (e.g., FDA, MHRA, EMA) or otherwise supported by established human safety data. Development of entirely novel

therapeutic agents requiring de novo safety evaluation is outside the scope of this program.

Preference will be given to proposal teams capable of using invasive coronary function testing (including acetylcholine challenge) to establish the diagnosis of coronary microvascular disease (including disease endotypes) and to assess treatment effects. Coronary microvascular disease endotypes must be prospectively characterized and incorporated into study design, endpoint selection, and prespecified analyses. Successful interventions are expected to demonstrate statistically significant improvement ($p < 0.05$) in prespecified coronary microvascular function domains, with effect sizes appropriate to the targeted mechanism.

Specific treatment targets must be met for the following outcomes:

i) Coronary microvascular function: Coronary flow reserve (CFR) is the most prognostically validated measure of coronary microvascular function. Prior studies have shown that lower CFR is associated with a higher risk of major adverse cardiovascular events, with an up to 20% increase in risk per 10% decrease in CFR[14]. Accordingly, a ≥20% relative improvement in CFR from baseline, or restoration of CFR to the normal range, will be used to define a clinically meaningful improvement in coronary microvascular function for those with impaired CFR at baseline.

ii) Patient-centered outcomes: A minimum ≥10-point improvement in the Seattle Angina Questionnaire Summary Score should be considered clinically meaningful, consistent with established thresholds for clinically important change in angina-related health status. Additional patient-reported outcome measures are encouraged, including objective measures of angina burden, quality of life, and exercise capacity.

Concordance between improvement in coronary microvascular function and symptoms will provide internal validation of treatment effect, particularly in uncontrolled study designs. Where feasible, inclusion of endpoints relevant to downstream consequences of coronary microvascular disease, including myocardial ischemia or markers associated with heart failure with preserved ejection fraction (e.g., diastolic function, myocardial strain, circulating biomarkers), is desirable to support a disease-modifying interpretation of treatment effects. Proposals must clearly describe the study design (e.g., comparisons of outcomes before and after intervention within participants, or treated versus untreated comparisons), sample size, and the minimum detectable treatment effect with ≥80% power at a significance level of $\alpha = 0.05$.

Intervention candidates (single or combination therapies) should be supported by mechanistic rationale or preliminary clinical signals, including therapies that produced

inconclusive or inconsistent results in earlier studies due to heterogeneous study populations and/or inadequate disease endotyping. Therapies of particular interest are those that target multiple interconnected cardiometabolic pathways and have the potential to modify disease biology (e.g., SGLT-2 inhibitors). Studies of menopausal hormone therapy are also of interest, given advances in understanding of the timing hypothesis, formulation, route of administration, and risk stratification that now enable rigorous testing in carefully selected women with coronary microvascular disease.

The target population is based on the following COVADIS criteria for microvascular angina[38]: Eligible participants must have symptoms suggestive of myocardial ischemia (criterion 1) and absence of obstructive coronary artery disease (criterion 2), together with evidence of impaired coronary microvascular function (criterion 4). Objective evidence of myocardial ischemia (criterion 3) is not required but will be considered supportive when present.

We expect insights emerging from Thrusts 2 and 3 during the program to inform studies conducted in Thrust 4. Study designs that allow for multiple intervention arms are desirable.

*Estimates range from 60-140 million[39,40].

†Stable chest pain is the most common symptom of ischemic heart disease, a condition caused by reduced blood flow to the heart muscle.

‡ or ischemia with no obstructive coronary artery disease (INOCA), when objective evidence of ischemia is present

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