Unheard Voices: The Burden Of Ischemia With No Obstructive Coronary Artery Disease In Women

Marah Maayah

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Unheard Voices:
The Burden of Ischemia with No Obstructive Coronary Artery Disease in Women

A Thesis Submitted to the Yale University School of Medicine
in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by

Marah Maayah, Class of 2024
Abstract

UNHEARD VOICES: THE BURDEN OF ISCHEMIA WITH NO OBSTRUCTIVE CORONARY ARTERY DISEASE IN WOMEN

Marah Maayah, Nazar Chowdhury, Kristie Walenczyk, Carolyn M. Mazure, Matthew Burg, Erica S. Spatz, and Samit Shah. Section of Cardiology, Department of Internal Medicine, Yale University, School of Medicine, New Haven, CT

Background: Ischemic heart disease (IHD) is a leading cause of morbidity and mortality in women. Up to two-thirds of women with IHD suffer from ischemia with no obstructive coronary artery disease (INOCA), which includes endotypes such as microvascular dysfunction and vasospasm. Due to a lack of clear prognostic data, INOCA has historically been viewed as a benign condition and many women have been dismissed from cardiovascular care, despite refractory symptoms and a risk for adverse outcomes. The objective of this qualitative study is to utilize structured interviews to formally characterize the experience of women with INOCA diagnosed with invasive coronary function testing.

Methods: We enrolled 50 women with INOCA who underwent clinically-indicated invasive coronary function testing. Structured interviews were performed to elicit symptom characteristics, physical and functional limitation, and perception of illness. Data extracted from the interviews was analyzed using the constant comparison method to determine themes among women with INOCA.

Results: The most common symptoms in our sample included chest pain (n=47, 94%), radiation of chest pain to other areas (43, 86%), dyspnea (43, 86%), fatigue (40, 80%), and abnormal heart rhythms (33, 66%). Most participants experienced symptoms daily (29, 58%) and reported severe symptoms (40, 80%). They expressed limitation to
instrumental activities of daily living (35, 70%), social life (33, 66%), hobbies (30, 60%), work (24, 48%), and travel (11, 22%). Many reported feelings of anxiety (47, 94%), depression (41, 82%), and frustration (25, 50%), a sense of foreshortened future (33, 66%), a feeling of invalidation by providers and loved ones (33, 66%), and difficulty finding a diagnosis (40, 80%). After receiving a diagnosis, participants reported positive outcomes such as reduced stress and better understanding of disease management.

**Conclusion**: Women with INOCA have significant impairment in quality of life due to frequent anginal symptoms. Feelings of invalidation were common, and many participants reported multiple incorrect diagnoses. After receiving a diagnosis, they reported reduced stress, improvement in illness perception, and hope for improved health in the future. These findings demonstrate the importance of recognizing INOCA and incorporating advances such as physiology-guided medical therapy into routine practice.
Acknowledgements

Personal acknowledgements

Words cannot express the gratitude I have to Dr. Shah for being the most incredible mentor I could have asked for. Under his guidance, I discovered my love for research and I saw myself grow into a confident researcher and aspiring clinician. Most importantly, I am deeply appreciative of his unwavering support, patience, and kindness. He is a reflection of everything I hope to be as a doctor, and I am so grateful to have had the opportunity to work with him. I would also like to acknowledge the other mentors I’ve met along the way, from residents to fellows and attendings, who helped me discover that internal medicine and cardiology are the path I want to follow.

I would like to thank the other members of the team for their support with this project. I am especially grateful to Nazar Chowdhury for the many hours he spent on this project and for the friendship we built along the way.

I could not have completed this work without the endless support and unconditional love of my family. For as long as I can remember, they have supported me in all my endeavors and have always reminded me that I am bigger than the challenges I face. Mama, Baba, and Jad - none of this would have been possible without you.

I am also grateful for my friends who have supported me through the lows and highs of college and medical school. A special thank you goes to Giuliana, Kacey, Farah, Aseel, Christina, Jafar, and Dana. I am forever grateful for their friendship.
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Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in women, affecting nearly half (44.4%) of women ≥ 20 years of age in the United States. The most common form of cardiovascular disease in women is ischemic heart disease (IHD). Every year, 190,000 women in the United States die of IHD, and that number is projected to rise in the coming years as the population ages. IHD encompasses atherosclerotic coronary artery disease (CAD) and ischemia with no obstructive coronary artery disease (INOCA). Whereas CAD refers to obstruction in epicardial or conduit coronary arteries, INOCA is characterized by nonatherosclerotic coronary vasomotor disorders such as coronary microvascular dysfunction (CMD), coronary vasospasm (VA), and symptomatic myocardial bridging (MB). Subtypes of INOCA may occur in isolation or as mixed syndromes, and they may be comorbid with obstructive CAD.

Evaluation of women with suspected IHD can be challenging because women tend to have greater symptom burden, more significant functional limitation, and a higher risk for adverse outcomes from IHD, yet they are more likely to have no obstructive CAD on coronary angiography when compared to men. Instead, up to two-thirds of women undergoing coronary angiography for suspected IHD are found to have INOCA. In the Women’s Ischemia Syndrome Evaluation (WISE) study, which initially recruited 323 women undergoing clinically-indicated coronary angiography for chest pain symptoms or suspected IHD, only 31% of women had significant coronary artery stenosis (defined as ≥50% obstruction), while 69% had either non-obstructive CAD (20-49% stenosis) or no CAD (<20% stenosis).
The pathophysiology behind the greater prevalence of INOCA compared to obstructive CAD in women is not well understood. It has been hypothesized that although women and men have equal rates of traditional cardiovascular risk factors that contribute to INOCA, there are sex-specific differences that may explain the different presentations of IHD in each group.\textsuperscript{10,11} Specifically, estrogen in women affects fat distribution and metabolism, insulin resistance, coagulation, and inflammation, and these differences may contribute to the greater prevalence of vascular dysfunction in women. Endogenous estrogen in premenopausal women protects against the development of atherosclerosis and thus CAD, and this protective role may explain the lower incidence of CAD in younger women.\textsuperscript{6} On the other hand, estrogen deficiency, especially estrogen deficiency in premenopausal women, may precipitate endothelial dysfunction, which can subsequently lead to development of VA or CMD.\textsuperscript{11,12} Furthermore, epicardial artery lumina in women are smaller than those in men, adding to the consequences of impaired vasodilation or endothelial dysfunction.\textsuperscript{6,8,13}

Patients with INOCA often experience typical anginal symptoms, including chest discomfort and dyspnea. Although these symptoms may be exertional as they typically are in CAD, they can also occur at rest, with emotional stress, or without any identifiable triggers.\textsuperscript{14–16} Subtypes of INOCA can present with various symptoms. Patients with CMD may have exertional or post-exertional fatigue, persistent chest pain not relieved by rest, and other symptoms like shortness of breath, jaw pain, and weakness.\textsuperscript{15} Patients with VA may experience sudden-onset chest tightness that either resolves quickly or persists at a lower intensity throughout the day and commonly occurs between night and early morning, often during rest.\textsuperscript{17} Patients with MB are typically asymptomatic but some may
experience symptoms such as exertional angina, episodic chest pain related to endothelial dysfunction or vasospasm, and less commonly, arrhythmias.\textsuperscript{18–20}

With emerging diagnostic techniques, INOCA is increasingly recognized but remains understudied with few consensus guidelines for diagnosis and treatment. Current guidelines for the diagnosis and management of IHD are based on evaluation of atherosclerotic disease as a first-line approach.\textsuperscript{4} According to the 2021 American Heart Association and American College of Cardiology Guideline for the Evaluation and Diagnosis of Chest Pain, a diagnosis of INOCA should be considered only after obstructive CAD has been excluded.\textsuperscript{21} Patients with stable chest pain and suspected INOCA in whom obstructive CAD has been ruled out may undergo assessment for INOCA either through non-invasive testing or invasive coronary function testing. Non-invasive testing includes stress positron emission tomography (PET), stress coronary magnetic resonance (CMR) imaging with myocardial blood flow reserve, or stress echocardiography with coronary flow velocity reserve. Invasive testing includes angiography with acetylcholine provocation testing and assessment of coronary flow reserve/the index of microcirculatory resistance.\textsuperscript{21} Findings from the randomized Coronary Microvascular Angina (CorMicA) trial demonstrated that stratified medical therapy based on a diagnosis with invasive coronary functional angiography led to greater symptom relief and improved quality of life.\textsuperscript{22,23} However, there are no consensus guidelines for the diagnosis of INOCA and available diagnostic testing is not accessible to most clinicians, resulting in misdiagnosis, delays in diagnosis, and persistent symptoms in patients with INOCA.\textsuperscript{6,24}
Although INOCA was historically viewed as a benign disorder, several studies have shown that INOCA has prognostic consequences. Patients with INOCA have an elevated risk for major adverse cardiovascular events.\(^{25-27}\) In a study comparing 540 patients from the WISE study (which included symptomatic women undergoing clinically-indicated coronary angiography) and 1,000 asymptomatic women in the community, women with 0-49% stenosis on angiography had a 5-fold increase in the 5-year cardiovascular event rate after adjusting for CAD risk factors.\(^{25}\) INOCA may also increase the risk for heart failure with preserved ejection fraction (HFpEF), as women with INOCA are more likely to have elevated left ventricular end-diastolic pressure,\(^ {28}\) and 75-81% of patients with HFpEF have CMD without obstructive CAD.\(^ {29,30}\) Compared to the general population of women aged 50-59, women without obstructive CAD on coronary angiography also have higher 10-year mortality rates (13% vs. 2.8%).\(^ 3\) Furthermore, they are more likely to experience recurrent hospitalizations, repeated procedures, and decreased satisfaction with medical care.\(^ {31,32}\)

In addition to impaired prognosis, INOCA is associated with reduced quality of life. In one study comparing patients with INOCA and patients with stable CAD, patients with INOCA were found to have worse quality of life, lower exercise capacity, greater physical and functional limitation, and more frequent angina.\(^ 8,33\) In a subsequent study of 297 patients (91% women) with a self-reported diagnosis of INOCA, participants reported that their symptoms had a negative impact on their functional capacity, home life, social life, mental health, outlook on life, intimate relationships, and work.\(^ {34}\) Another qualitative study of 29 participants with INOCA found that these women experience
significant distress from their symptoms (especially prior to receiving a diagnosis), emotional stress, and feelings of threat to their personal and professional identities.\(^{35}\)

Although INOCA has been shown to increase the risk of adverse events and decrease patients’ quality of life, it remains understudied, underdiagnosed, and poorly understood by many practicing clinicians, and patients with INOCA or suspected INOCA are often reassured and dismissed from cardiovascular care.\(^{7,31,32,36}\) For example, several studies have found that patients with INOCA are more likely to be dismissed from cardiovascular care and less likely to receive medical therapy compared to patients with stable CAD.\(^{32,37-39}\) Patients with INOCA are also more likely to experience difficulties in receiving a diagnosis. In the aforementioned study of 297 patients, 34.4% of patients experienced symptoms for \(\geq 3\) years prior to receiving a diagnosis, and 77.8% reported being told that their symptoms were not cardiac in nature.\(^{34}\) In the qualitative study of 29 women, many participants felt invalidated by healthcare professionals and reported a difficult journey towards diagnosis.\(^{35}\) Improving knowledge of INOCA and its management is important because patients have reported that a diagnosis can lead to better symptom control, improved quality of life, and feelings of empowerment.\(^{35}\)

Fewer than half of INOCA patients are treated with evidence-based therapies.\(^{26,40,41}\) Due to a lack of specific guidelines, the presence of no obstructive CAD or INOCA on angiography results in diagnostic and therapeutic uncertainty for clinicians, leading to lower rates of primary and secondary treatment.\(^{26}\) However, studies have shown that medical treatment for INOCA can result in improved symptoms and functional and exercise capacity. In general, medications that may be used in INOCA include calcium-channel blockers, nitrates, aspirin, statins, beta blockers, ACE inhibitors,
angiotensin receptor blockers, ranolazine, ivabradine, and nicorandil.\textsuperscript{10,26,42} However, because INOCA subtypes have different pathophysiologies, stratified therapy is necessary. In the CorMicA trial, stratified medical therapy based on results from invasive coronary function testing resulted in improved angina and improved quality of life in participants with no obstructive CAD.\textsuperscript{43} Despite the observed benefit of stratified therapy in CorMicA, there are no specific clinical practice guidelines for treatment of INOCA.\textsuperscript{26}

Although recognition of INOCA is growing, there remains a lack of validated standardized patient-reported outcome measures (PROM) for INOCA. Currently, the most commonly used PROM for IHD is the Seattle Angina Questionnaire, which was developed based on symptoms of obstructive CAD in men. However, women with INOCA present with symptoms and functional limitation that may not be captured in this PROM, making it difficult to clinically evaluate the course of illness or the effectiveness of medications or devices. As such, development of a disease-specific PROM is crucial for improving management in patients with INOCA and should be based on an accurate description of the symptom burden that these patients experience.
Statement of Purpose

We hypothesize that women with INOCA have a high burden of symptoms and significant functional limitation that are not adequately described in existing literature. The objective of our study is to formally characterize the experience of women with INOCA using structured interviews, which could lead to the development of a disease-specific, novel PROM in the future.

Specific Aims

1. To determine common themes in the symptoms, functional limitation, psychological toll, and illness perception in women diagnosed with INOCA by using structured interviews

2. To describe differences in the symptom burden, functional limitation, psychological toll, and illness perception of patients with INOCA endotypes including coronary microvascular dysfunction, coronary vasospasm, and myocardial bridging
Methods

Student Contributions

Study design, Institutional Review Board (IRB) approval, participant identification, and development of the standardized interview guide were completed by Dr. Samit Shah (principal investigator). Thereafter, the student, Marah Maayah, contributed to all steps of the research project under the supervision and guidance of Dr. Shah. Specific steps of this research process included conducting interviews with participants diagnosed with INOCA, transcribing and proofreading interview recordings, making iterative revisions to the structured interview guide, coding interviews to extract key concepts and ideas, analyzing the data using qualitative research software (Atlas.ti), and writing scientific material on the project, including presentations at the American Heart Association Scientific Sessions and Connecticut American College of Cardiology, and on a monthly basis with the Food and Drug Administration Office of Women’s Health. Nazar Chowdhury (medical student) and Kristie Walenczyk, PhD, assisted with coding and data analysis. Other contributors to this project include Carolyn M. Mazure, Matthew Burg, Erica S. Spatz, Michelle Bernabeo, Jessica Ritchie, and Madeline DiGiovanni.

Ethics Statement

This study was performed under the highest ethical standards. The potential risks to participants were minimal and were disclosed prior to initiation of the interview. There were no direct benefits for participants and no compensation was provided. However, the aim of the project is to improve diagnosis and management of women with INOCA, which is relevant to all study participants.
Human Subjects Research

This study was approved by the Yale Institutional Review Board (IRB protocol # 2000032984). Participants voluntarily provided informed consent prior to initiating the interview and were free to discontinue participation at any time. Participant privacy was maintained by removing all identifiers from interview transcripts, including name, age, place of residence, and place of work, and storing the data in the Yale OneDrive, which is safeguard-protected by Yale Information Technology Services and approved for storage of protected health information.

Methods Description

Study Sample

We enrolled 50 women from an active registry of women who underwent clinically-indicated invasive coronary function testing at Yale New Haven Hospital in New Haven, CT. All enrolled participants were English-speaking, greater than 18 years old, assigned female sex at birth, able to provide informed consent, and diagnosed with an INOCA endotype (coronary microvascular dysfunction, coronary vasospasm, myocardial bridge, or other disorder of coronary physiology). The coronary function testing protocol includes guidewire-based testing with coronary thermodilution using the PressureWire X (Abbott Vascular, Santa Clara, CA) and provocation testing with intracoronary acetylcholine administration (Appendix A).

Data Collection

Eligible participants were contacted by phone or text message and were provided with a description of the project and an explanation of their potential role. Participants
who agreed to enroll selected a mutually agreeable date and time for a Zoom interview. The interviewer obtained verbal informed consent prior to starting the interview. Interviews were conducted using a standardized interview guide, eliciting 5 main domains: frequency/stability of symptoms, physical limitation, functional limitation, psychological toll, and perception of illness. Interviews were conducted and recorded using HIPAA-compliant Zoom access, provided by the Yale School of Medicine. Interviews were de-identified and transcribed by two team members (Michelle Bernabeo and Madeline DiGiovanni) and stored in the Yale OneDrive. On average, interviews lasted 42 minutes. Additional participant data (age, racial and ethnic background, insurance type, and INOCA diagnosis) was obtained from the electronic medical records.

Data Analysis

The data collected during the interviews was coded by two researchers (Marah Maayah and Nazar Chowdhury) using ATLAS.ti Scientific Software (ATLAS.ti, Berlin, Germany). Data was analyzed using the constant comparison method, in which essential concepts from interview data were coded and compared over successive participant interviews to extract recurrent themes. The two researchers coded the data simultaneously and independently, extracting and coding essential concepts in interview transcripts. They met on a weekly basis to discuss observations, reconcile differences in coding, and incorporate emerging ideas into new codes. Coded transcripts were reviewed by Dr. Shah and Dr. Walenczyk at regular intervals. During the initial phase of coding the first 20 interviews, code structures were periodically reviewed and refined until no new concepts emerged, and the standardized interview guide was adjusted to incorporate emerging concepts. The final version of the interview guide, notated with modifications to the
original version, can be found in Appendix B. Thematic saturation was reached after 30 interviews. Finally, after all 50 interviews were coded, data was examined to determine common themes among women with INOCA, as well as to identify distinctions in coded themes between women with each specific INOCA endotype.

**Statistical Methods**

Data coded on Atlas.ti software was tabulated to determine the frequency of individual codes in the total cohort and stratified by the underlying INOCA diagnostic phenotype (CMD, VA, and MB). Tabulated data included reported symptoms, symptom-alleviating and symptom-aggravating factors, symptom frequency and severity; physical limitation; limitation to instrumental activities of daily living, social life, hobbies, work, and travel; psychological toll including anxiety, depression, frustration, sense of altered self-identity, and feelings of invalidation by others; and perception of illness, response to illness and diagnosis, and burden of illness.
Results

Participant Characteristics

Among a group of 69 women diagnosed with INOCA using coronary function testing, 50 women consented to enroll in the study and completed the interview. Of those who were not included, 16 could not be reached, and 3 declined to participate. On average, interviews lasted 42 minutes (range: 20-71 minutes), with a total 35.25 hours of interviews.

The mean age of participants was 58 years (range 37-82 years). Further demographic and insurance data are described in Table 1. Of the 50 participants, 34 (68%) had VA, 25 (50%) had CMD, and 3 (6%) had MB, with 11 (22%) having concurrent VA and CMD, and 1 (2%) having concurrent VA and MB.

Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>50</td>
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Race

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<td>Black</td>
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<tr>
<td>Asian</td>
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Ethnicity

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<tr>
<td>Non-Hispanic</td>
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Insurance Type

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<tr>
<td>Public Insurance</td>
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<tr>
<td>No Insurance</td>
<td>1 (2)</td>
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Diagnosis

<table>
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<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasospastic Angina</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Coronary Microvascular Dysfunction</td>
<td>34 (68)</td>
</tr>
<tr>
<td>Myocardial Bridging</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>
Symptom Characteristics

Symptom Types

Among the entire cohort of 50 participants, the most common symptoms were chest pain (n=47, 94%), radiation of symptoms into non-chest regions (43, 86%), dyspnea (43, 86%), fatigue (40, 80%), and abnormal heartbeats (33, 66%). Other reported symptoms included gastrointestinal symptoms (25, 50%), lightheadedness or dizziness (25, 50%), and excessive sweating (12, 24%). Findings are summarized in Figure 1.

Figure 1. Most common symptoms reported by participants, with percentages reflecting the frequency at which these symptoms were reported among all participants interviewed.

Chest pain was the most common symptom, with the character of the chest pain varying among participants. Among the 47 participants who reported chest pain, the most common descriptors for the chest pain were tightness (15, 32%), a sharp or stabbing
sensation (14, 30%), or a pressure-like sensation (13, 28%). Less commonly, participants reported their chest pain felt like a burning sensation (6, 13%) or a dull ache (4, 9%). Additionally, 43 participants reported that their chest pain radiated to areas outside the chest, most commonly the jaw or neck (25, 58%), arms (21, 49%), back (20, 47%), and shoulder (18, 42%). Rarely, participants reported radiation into their head or face (3, 7%) or abdomen (2, 5%). Additionally, some participants reported that their chest symptoms radiated into their arms or hands as numbness (4, 9%), tingling (3, 7%), or weakness (1, 2%).

Among the 33 participants who reported abnormal heartbeats, palpitations were the most common symptom (28, 85%), but some participants also reported skipped beats (4, 12%), an irregular rhythm (2, 6%), or extra beats (1, 2%). In the 25 participants with gastrointestinal symptoms, nausea was the most common (21, 84%), followed by acid reflux (11, 44%) and abdominal pain (3, 12%).

Symptoms in the VA subgroup (n=34) were similar to those in the entire cohort of participants, with the most common symptoms being chest pain (33, 97%), radiation of symptoms into non-chest regions (31, 91%), dyspnea (28, 82%), fatigue (28, 82%), abnormal heart rhythms (21, 62%), and gastrointestinal symptoms (20, 59%). Other reported symptoms included lightheadedness or dizziness (16, 47%) and excessive sweating (12, 35%). Chest pain was most commonly described as sharp, stabbing, or pinching (12, 36%), pressure-like (9, 27%), and tight or squeezing (7, 21%). Less common descriptors included “burning” (4, 12%) and “aching” (2, 6%). Participants reported radiation of their chest pain symptoms to the jaw or neck (19, 61%), back (17, 55%), arms (15, 48%), shoulders (14, 45%), head (3, 10%), and abdomen (1, 3%).
Among the 21 who reported abnormal heartbeats, most had palpitations (17, 81%), while fewer had skipped beats (3, 14%), extra beats (1, 5%), or irregular rhythms (1, 5%). In terms of gastrointestinal symptoms (n=20), most had nausea (17, 85%) or reflux (9, 45%), and a few had abdominal pain (3, 15%).

Among the CMD subgroup (n=25), symptoms were also similar to those of the overall group. The most common symptoms were dyspnea (23, 92%), chest pain (22, 88%), fatigue (21, 84%), radiation of chest symptoms into non-chest regions (20, 80%), and abnormal heart rhythms (18, 72%). Other reported symptoms included gastrointestinal symptoms (10, 40%), lightheadedness or dizziness (11, 44%), and excessive sweating (3, 12%). Chest pain was most commonly described as tight (9, 41%) or pressure-like (7, 32%). Less common descriptors included burning (4, 16%), sharpness (1, 4%), and aching or dullness (2, 8%). Chest symptoms commonly radiated to the jaw or neck (11, 44%), back (9, 36%), arm (9, 36%), or shoulder (6, 24%), and less commonly to the head (3, 10%) and abdomen (1, 4%). Among the 18 who reported abnormal heartbeats, most had palpitations (15, 83%), and a few had skipped beats (2, 11%), irregular rhythms beats (2, 11%), or extra beats (1, 6%). In those with gastrointestinal symptoms (n=10), most had nausea (8, 80%) or reflux (4, 40%), and one had abdominal pain (10%).

A summary of the most common symptoms reported by patients can be found in Table 2. A computer-generated word cloud of the most common words used by participants to describe the types of symptoms they experience can be seen in Figure 2A.
Table 2. Most Common Symptoms Reported by Participants

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort (n=50)</th>
<th>VA (n=34)</th>
<th>CMD (n=25)</th>
<th>MB (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Pain</td>
<td>47 (94)</td>
<td>33 (97)</td>
<td>22 (88)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>43 (86)</td>
<td>28 (82)</td>
<td>23 (92)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Abnormal Heartbeats</td>
<td>33 (66)</td>
<td>21 (62)</td>
<td>18 (72)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Radiating Pain</td>
<td>43 (86)</td>
<td>31 (91)</td>
<td>20 (80)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Gastrointestinal Symptoms</td>
<td>25 (50)</td>
<td>20 (59)</td>
<td>10 (40)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40 (80)</td>
<td>28 (82)</td>
<td>21 (84)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>25 (50)</td>
<td>16 (47)</td>
<td>11 (44)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>Sweating</td>
<td>12 (24)</td>
<td>12 (35)</td>
<td>3 (12)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Figure 2. Word clouds of the most common words used by participants to describe A) the types of symptoms they experience, B) physical limitation, C) functional limitation, and D) psychological toll of illness. Larger fonts represent more commonly used words.
Symptom Frequency and Severity

Many participants reported that their symptoms fluctuated in frequency and severity. However, at their worst, most participants experienced symptoms daily (29, 58%) and reported severe symptoms (40, 80%). Others experienced symptoms multiple times per week (10, 20%), multiple times per month (4, 8%), monthly (2, 4%), or less than monthly (5, 10%) and reported moderate (6, 12%) or mild (4, 8%) symptoms.

Results were similar among participants with VA or CMD. Most participants with VA experienced symptoms daily (21, 62%) or multiple times per week (6, 18%), and most (29, 85%) reported severe symptoms, while fewer reported moderate (4, 12%) or mild (1, 3%) symptoms. Similarly, among those with CMD, most experienced symptoms daily (15, 60%) or multiple times per week (5, 20%), and most (18, 72%) reported severe symptoms, with fewer reporting moderate (4, 16%) or mild (3, 12%) symptoms.

Figure 2 continued. Word clouds of the most common words used by participants to describe A) the types of symptoms they experience, B) physical limitation, C) functional limitation, and D) psychological toll of illness. Larger fonts represent more commonly used words.
Participants reported that symptoms occurred at various times throughout the day. In the general cohort, 26 (52%) participants reported that symptoms occurred only during the day, most commonly either situationally or randomly (20, 77%) rather than during a particular time of day (6, 23%). For other participants, symptoms occurred both during the day and during sleep (18, 36%) or only during sleep (6, 12%). In the VA subgroup, symptoms occurred during the daytime only in 44% of participants, during both the day and sleep in 41% of participants, and during sleep only in 15% of participants. In the CMD subgroup, symptoms occurred during the daytime only in 60% of participants, during both the day and sleep in 32% of participants, and during sleep only in 8% of participants.

A summary of symptom severity, frequency, and timing can be found in Table 3.

Table 3. Symptom Severity, Frequency, and Timing

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort (n=50)</th>
<th>VA (n=34)</th>
<th>CMD (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity of Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>40 (80)</td>
<td>29 (85)</td>
<td>18 (72)</td>
</tr>
<tr>
<td>Moderate</td>
<td>6 (12)</td>
<td>4 (12)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Mild</td>
<td>4 (8)</td>
<td>1 (3)</td>
<td>3 (12)</td>
</tr>
<tr>
<td><strong>Frequency of Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>29 (58)</td>
<td>21 (62)</td>
<td>15 (60)</td>
</tr>
<tr>
<td>Multiple times per week</td>
<td>11 (22)</td>
<td>7 (21)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Once or multiple times per month</td>
<td>5 (10)</td>
<td>4 (12)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Less than monthly</td>
<td>5 (10)</td>
<td>2 (8)</td>
<td>4 (16)</td>
</tr>
</tbody>
</table>
**Aggravating and Alleviating Factors**

Most participants (37, 74%) reported that their symptoms were induced by physical stressors, most commonly exertion and illnesses such as the common cold. Of those participants, 22 (61%) reported that symptoms also occurred during rest. Many participants (33, 66%) identified psychological stressors such as stress or anxiety as symptom-triggering. A few (11, 22%) reported no identifiable triggers, with symptom onset occurring randomly and unpredictably.

Within the VA subgroup, 23 (68%) reported physical triggers for their symptoms, and 13 of those 23 participants (57%) reported that symptoms also occurred during rest. 23 (68%) reported psychological stressors, and 7 (21%) reported no identifiable triggers. Among participants with CMD, 20 (80%) reported physical triggers, including 14 (56%) who also had symptoms during rest, 15 (60%) reported psychological stressors, and 3 (12%) reported no identifiable triggers.

Participants most commonly reported alleviation of symptoms with medications (42, 84%), typically nitrates and calcium-channel blockers, and rest (37, 74%).

---

**Table 3. Symptom Severity, Frequency, and Timing**

<table>
<thead>
<tr>
<th>Time of Symptoms</th>
<th>Entire cohort (n=50)</th>
<th>VA (n=34)</th>
<th>CMD (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime only</td>
<td>26 (52)</td>
<td>15 (44)</td>
<td>15 (60)</td>
</tr>
<tr>
<td>During sleep only</td>
<td>6 (12)</td>
<td>5 (15)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Daytime and during sleep</td>
<td>18 (36)</td>
<td>14 (41)</td>
<td>8 (32)</td>
</tr>
</tbody>
</table>
reported symptom relief with stress reduction techniques (21, 42%) such as prayer, therapy, and meditation, and a few reported that exercise programs like cardiac rehabilitation were helpful (12, 24%).

Results were similar among the VA and CMD subgroups. Participants found relief with medications (VA 88%, CMD 88%), rest (VA 74%, CMD 80%), stress reduction (VA 44%, CMD 48%), and exercise programs (VA 21%, CMD 28%).

A summary of symptom triggers and symptom alleviating factors can be found in Table 4.

**Table 4. Symptom Triggers and Alleviating Factors**

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort (n=50)</th>
<th>VA (n=34)</th>
<th>CMD (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom Triggers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exertion or illness</td>
<td>37 (74)</td>
<td>23 (68)</td>
<td>20 (80)</td>
</tr>
<tr>
<td>Psychological triggers</td>
<td>33 (66)</td>
<td>23 (68)</td>
<td>15 (60)</td>
</tr>
<tr>
<td>No identifiable triggers</td>
<td>11 (22)</td>
<td>7 (21)</td>
<td>3 (12)</td>
</tr>
<tr>
<td><strong>Symptom Alleviating Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td>42 (84)</td>
<td>30 (88)</td>
<td>22 (88)</td>
</tr>
<tr>
<td>Rest</td>
<td>37 (74)</td>
<td>25 (74)</td>
<td>20 (80)</td>
</tr>
<tr>
<td>Stress reduction</td>
<td>21 (42)</td>
<td>15 (44)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Cardiac rehabilitation or graded exercise program</td>
<td>12 (24)</td>
<td>7 (21)</td>
<td>7 (28)</td>
</tr>
</tbody>
</table>
Physical and Functional Limitation

Most participants expressed limitation to physical activity, reported by 41 (82%) of the entire cohort. 30 (60%) of participants reported difficulty climbing stairs or going up inclines, and 16 (32%) reported difficulty with carrying or moving objects, such as grocery bags and laundry baskets. In general, participants reported being limited by both their symptom burden and anxiety about triggering symptoms. Physical limitation was reported by 28 (82%) of the VA subgroup and 19 (76%) of the CMD subgroup. Figure 2B shows a computer-generated word cloud of the most common words used by participants to describe their physical limitation.

In terms of functional limitation, participants expressed limitation to instrumental activities of daily living (IADL) (35, 70%), most commonly mentioning household chores such as vacuuming or cooking, laundry, and grocery shopping, though a few participants also reported limitation to activities of daily living like showering (n=4) and getting dressed (n=2). Participants also reported limitation to social life (33, 66%), hobbies (30, 60%), work (24, 48%), and travel (11, 22%). Within the subgroups of VA and CMD, limitation was reported by 65% and 76% to IADLs, 71% and 60% to social life, 56% and 72% to hobbies, 41% and 48% to work, and 32% and 32% to travel, respectively. Figure 2C shows a computer-generated word cloud of the most common words used by participants to describe their functional limitation.

A summary of the physical and functional limitation expressed by participants can be found in Table 5.
Table 5. Physical and Functional Limitation

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort (n=50)</th>
<th>VA (n=34)</th>
<th>CMD (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Limitation</td>
<td>41 (82)</td>
<td>28 (82)</td>
<td>19 (76)</td>
</tr>
<tr>
<td>Functional Limitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent activities</td>
<td>35 (70)</td>
<td>22 (65)</td>
<td>19 (76)</td>
</tr>
<tr>
<td>Social life</td>
<td>33 (66)</td>
<td>24 (71)</td>
<td>15 (60)</td>
</tr>
<tr>
<td>Hobbies</td>
<td>30 (60)</td>
<td>19 (56)</td>
<td>18 (72)</td>
</tr>
<tr>
<td>Work</td>
<td>24 (48)</td>
<td>14 (41)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Travel</td>
<td>11 (22)</td>
<td>11 (32)</td>
<td>8 (32)</td>
</tr>
</tbody>
</table>

Psychological Toll

Participants with INOCA report significant psychological burden. Many participants reported that their symptoms or diagnosis caused anxiety or fear (47, 94%) depression or feelings of hopelessness or discouragement (41, 82%), and frustration or anger (25, 50%). Participants expressed that these feelings were due to not only symptom burden, but also uncertainty regarding the etiology of their symptoms prior to receiving a diagnosis. In addition, many participants reported a sense of altered self-identity, or a feeling that they are no longer the person they were prior to their symptom onset (31, 62%). Finally, most participants expressed that they felt invalidated by clinicians and loved ones (33, 66%) and that they had difficulty receiving a diagnosis, with multiple incorrect diagnoses or dismissal from cardiovascular care (40, 80%). Figure 2D shows a computer-generated word cloud of the most common words used by participants to describe the psychological toll of their illness.
Similar results were found in the CMD and VA subgroups. Within the VA and CMD subgroups, respectively, participants reported feelings of anxiety (91%, 92%), depression (85%, 76%), and frustration (47%, 48%). Additionally, participants reported a sense of altered self-identity (65%, 56%), difficulty receiving a diagnosis (82%, 72%), and feelings of invalidation by others (65%, 60%).

A summary of the psychological toll of illness reported by participants can be found in Table 6.

**Table 6. Psychological Toll**

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort (n=50)</th>
<th>VA (n=34)</th>
<th>CMD (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>47 (94)</td>
<td>31 (91)</td>
<td>23 (92)</td>
</tr>
<tr>
<td>Depression</td>
<td>41 (82)</td>
<td>29 (85)</td>
<td>19 (76)</td>
</tr>
<tr>
<td>Frustration</td>
<td>25 (50)</td>
<td>16 (47)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Altered self-identity</td>
<td>31 (62)</td>
<td>22 (65)</td>
<td>14 (56)</td>
</tr>
<tr>
<td>Difficulty Receiving</td>
<td>40 (80)</td>
<td>28 (82)</td>
<td>18 (72)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invalidation by Others</td>
<td>33 (66)</td>
<td>22 (65)</td>
<td>15 (60)</td>
</tr>
</tbody>
</table>

**Illness Perception**

*Patient Perception of Illness and Health*

In the general cohort of participants, most participants (47, 94%) believed that their symptoms or illness negatively impacted their life, due to factors such as general restrictions to their activities, burdensome symptoms, a sense of a changed identity, or needing to give up or limit certain activities. Of those participants, 13 (28%) said that
their illness was extremely burdensome or had significant impact on their life. Some participants (7, 14%) reported feeling that their illness does not currently significantly impact their life, though 4 of those participants reported that their illness was negatively impactful prior to receiving appropriate management. Additionally, 33 (66%) of participants reported feeling a sense of foreshortened future, or that their lives would be shortened due to their symptoms or diagnosis. In the VA and CMD subgroups, 79% and 52% of participants reported this sense of foreshortened future, respectively. When asked about their perception of their current state of health, most participants reported feeling healthy or moderately healthy (33, 66%), including 8 participants who said they felt healthy except for their heart health. 8 (16%) participants reported that they felt healthy prior to their symptom onset but now felt less healthy, and 9 (18%) reported feeling unhealthy in general.

*Patient Understanding of Illness*

Participants reported variable degrees of confidence in their understanding of their illness. 11 (22%) felt confident, 26 (52%) felt somewhat confident (26, 52%), and 13 (26%) felt unconfident. Participants used various resources to learn about their illness, most commonly relying on clinicians (18, 36%), general internet searches (13, 26%), scientific literature (7, 14%), specific internet links provided by clinicians (7, 14%), patient-oriented websites such as WebMD (6, 12%), and patient forums or communities (5, 10%). Some reported using no resources as of the time of the interview (11, 22%), though many of these participants had been diagnosed only a few days prior to the interview. In general, participants did not feel completely confident in their understanding of why they developed their illness (26, 52%), though many provided
hypotheses such as genetics (19, 38%), traditional cardiovascular risk factors like smoking, age, or weight (11, 22%), vaccines or viral illnesses, typically COVID-19 (9, 18%), psychological stressors (8, 16%), other health problems, mostly autoimmune rheumatologic disease (5, 10%), and menopause or premature menopause (4, 8%).

A summary of the common themes and sample quotations from each interview domain is shown in Table 7.

Table 7. Common themes and sample quotations from interview domains

<table>
<thead>
<tr>
<th>Domain</th>
<th>Common Themes</th>
<th>Sample Quotation</th>
</tr>
</thead>
</table>
| Frequency and stability of symptoms | ● Anginal symptoms such as chest pain, radiation of chest pain, shortness of breath, and palpitations  
   ● Severe, frequent symptoms | “I had this pain, like this pain pressure in my chest. I started sweating profusely. I started shaking. The pain was going across my back, down my arms. And I was like, something is wrong here.” |
| Physical limitation           | ● Limitation to exercise and physical activity                               | “I was less active. I was resting more. I was really trying to baby myself, not do anything that would put me, you know, into feeling like my heart was overtaxed.” |
| Functional limitation         | ● Difficulty with IADLs, work, hobbies, and travel                           | “It was horrible. I could barely do my job. My house was a mess. I couldn't do anything in the house. You know, I felt like I couldn't do anything” |
| Psychological toll            | ● Depression, anxiety, and frustration  
   ● Sense of altered identity  
   ● Difficulty with receiving diagnosis and feelings of invalidation by others | “It was really frustrating because you’re going around with something – you know it’s something wrong, but it’s unknown. And if it’s unknown to somebody but you know it’s real, it’s just like – it messes with your emotions,” |
Table 7. Common themes and sample quotations from interview domains

<table>
<thead>
<tr>
<th>Domain</th>
<th>Common Themes</th>
<th>Sample Quotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perception of illness</td>
<td>● Negative impact on life and health due to illness</td>
<td>“I feel better now than I felt in a long, long time and I know a lot of it’s just because I know what it is.”</td>
</tr>
<tr>
<td></td>
<td>● Inadequate understanding of illness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Positive effects after receiving diagnosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>because I know what I’m going through, but other people don’t believe what I’m going through.”</td>
<td></td>
</tr>
</tbody>
</table>

Effects of Receiving a Diagnosis

After receiving a diagnosis, participants reported positive outcomes (Figure 3). Many (17, 34%) explained that the knowledge that came with a diagnosis was both empowering and reassuring because they better understood the etiology behind their symptoms and were able to more confidently seek medical care. Many reported improved mental health and lower stress levels (15, 30%), better medical management of their symptoms (9, 18%), and improved symptom control (6, 12%). Some (5, 10%) still felt limited even with a diagnosis. Additionally, participants reported making several lifestyle changes in response to either their symptoms or their diagnosis, with varying impact on their symptom burden. For example, participants made changes to their diet (22, 44%), exercise routine (18, 36%), and smoking or alcohol consumption habits (4, 8%). They also reported adjusting or pacing their activities to make them achievable (12, 24%) and changing their outlook on life by choosing to “live in the day” or reducing daily stressors (12, 24%).
Figure 3. In general, participants reported positive outcomes after receiving a diagnosis, including improved medical management and symptom control, better knowledge of effective lifestyle changes, and improved mental health.
Discussion

IHD is a leading cause of morbidity and mortality in women in the United States, and over half of women with IHD have INOCA. Although INOCA is common and has been shown to decrease quality of life and increase the rate of adverse events, the burden of symptoms remains poorly characterized and many patients are misdiagnosed, undertreated, or dismissed from cardiovascular care under the incorrect assumption that INOCA is a benign illness. In this study of 50 women with INOCA, we used structured interviews to characterize the symptoms, physical and functional limitation, mental wellbeing, and perception of illness and health. We found that participants experienced debilitating anginal symptoms that negatively impacted physical capabilities, daily activities, and mental health. Yet, most participants felt their experience was invalidated by clinicians and many experienced symptoms for years prior to receiving the correct diagnosis. Receiving a diagnosis helped participants feel reassured and empowered and allowed them to have more control over their symptoms, mental health, and daily living.

Symptoms in patients with INOCA are typical cardiac symptoms, with a few notable differences. In this study, the majority of participants reported chest pain, often with radiation to the arms, shoulders, jaw, neck, and back, shortness of breath, and changes in heart rhythms such as palpitations. Participants often used anginal descriptors, such as tightness or pressure, to characterize their chest pain, though they also used descriptors less commonly associated with anginal chest pain, such as sharp or burning. Additionally, participants reported symptoms that are not traditionally associated with cardiac etiologies, such as fatigue and gastrointestinal symptoms like nausea or reflux.
Furthermore, in our study, participants with INOCA reported symptom triggers and symptom-alleviating factors that are classically associated with angina. Specifically, most participants expressed that physical stressors, such as exertion or illness, and emotional stressors were likely to elicit their symptoms, and that medications like calcium-channel blockers or nitrates, rest or slowing down activities, and general stress reduction reduced the frequency or severity of their symptoms. However, participants with INOCA commonly reported that symptoms often occurred randomly or without an identifiable trigger, which differentiates these symptoms from patients with CAD. Cardiac rehabilitation or graded exercise programs were only helpful for a fraction of participants.

Most participants expressed that their symptom burden was high and that INOCA had a negative impact on their life. Overall, 94% of participants expressed that INOCA had a negative impact on their life in some way, and 28% reported that their illness was extremely burdensome. Only 6% felt that their symptoms or illness never significantly impacted their life. In our study, most participants experienced severe symptoms that occurred daily or multiple times per week. Participants commonly reported physical limitation, such as difficulty walking, climbing stairs, carrying heavy objects, or exercising, and functional limitation to their IADLs, social life, hobbies, work, and travel. The psychological toll of INOCA was high. Participants commonly reported feelings of depression, anxiety, and frustration due their symptom burden or diagnosis, and many expressed that they felt their identity had changed due to their symptoms preventing them from pursuing certain activities. Finally, many participants felt that their lives would be shortened by their illness.
Overall, VA and CMD have similar presentations and limitations, though a few differences were noted in our study. Most symptoms occurred at relatively similar frequencies, but participants in the VA subgroup were more likely to report gastrointestinal symptoms and radiation of chest pain into other areas, and participants in the CMD subgroup were more likely to report shortness of breath and abnormal heartbeats. When describing their chest pain, participants with VA most commonly characterized it as sharp or pressure-like, while participants with CMD characterized it as tight or pressure-like, and only 4% described it as sharp. Symptom frequency and severity were similar overall, but participants with VA more commonly reported severe symptoms and were more likely to have nocturnal symptoms. In terms of symptom triggers, physical triggers like exertion were slightly less common in the VA subgroup, and symptoms that occurred randomly without an identifiable trigger were slightly more common in the VA subgroup. Overall, the psychological toll of INOCA was similar in both subgroups, but participants with VA were more likely to report a sense of foreshortened future.

Despite having burdensome anginal symptoms, patients with INOCA face difficulties in receiving a correct diagnosis and experience feelings of invalidation by their clinicians and loved ones. Many participants experienced symptoms for years and were misdiagnosed with anxiety, gastrointestinal reflux, or musculoskeletal pain or simply dismissed from cardiovascular care prior to receiving the correct diagnosis through coronary function testing. Additionally, they reported that their symptoms were often invalidated or dismissed by multiple clinicians and loved ones. These findings are in line with previous studies on patients with INOCA, which have shown that women
with INOCA are less likely to receive appropriate cardiovascular care compared to patients with obstructive CAD and that many patients with INOCA experience symptoms for years prior to receiving a diagnosis.\textsuperscript{34,35}

Making a diagnosis in patients with INOCA is important because a diagnosis brings positive changes to the lives of these patients. In our study, many participants expressed that a diagnosis was both reassuring and empowering. With a diagnosis, they had a better understanding of the etiology behind their symptoms, thus reducing anxiety, frustration, and feelings of hopelessness. They also felt more empowered to seek medical care when needed because they were able to present to clinicians with a diagnosis in hand, making them less worried about their symptoms being invalidated or being dismissed from care without appropriate treatment. Many participants also reported that after a diagnosis was made, the resulting medication changes led to better symptom control. Overall, the reduced symptom burden and knowledge of the underlying cause of their symptoms led to improved mental health and less stress in our participants. Finally, a diagnosis motivated many of the participants in our study to implement lifestyle changes to diet and exercise, make an effort to reduce stressors in their lives, and positively change their outlook on life.

However, even with a diagnosis, many participants reported feeling that their understanding of their illness is inadequate or incomplete. Participants in our study were motivated to learn more about their illness, using resources like their clinicians, internet searches, and scientific literature. Despite these efforts, only a few participants (22\%) felt completely confident in their understanding of their illness, while most felt either somewhat confident or not confident at all. Although participants cited many reasons for
their lack of confidence in their understanding of their illness, such as not knowing the pathophysiology or the treatment, the most common reason was not understanding why they developed their illness. Over half of our participants were unsure about the underlying cause of their illness, while some provided potential explanations such as genetics, viral illness or vaccine triggers, and emotional stressors. These gaps in patient knowledge are reflective of the larger gaps in the medical community’s understanding of INOCA, the lack of consensus guidelines on its diagnosis and management, and the lack of awareness of INOCA among clinicians.

In order to improve the diagnosis and management of patients with INOCA, it is imperative to expand existing research, develop consensus guidelines, and improve cardiology training to encompass education on sex-based differences in cardiac presentations. Currently, the approach to ischemic chest pain is predominantly based on evaluation for obstructive CAD first, and INOCA is only considered if no flow-limiting stenosis is found. However, compared to men, women with chest pain have a lower pre-test probability of having obstructive CAD. Thus, the standard approach to chest pain based on evaluation for obstructive CAD may not be appropriate for women, and more research is needed to evaluate whether a sex-based approach would be beneficial in avoiding incorrect diagnoses and delays in diagnosis in patients with INOCA. Additionally, there should be efforts to improve clinician awareness of the pathophysiology, diagnosis, management, and prognosis of INOCA and to incorporate training on the impact of sex differences on heart health into cardiology fellowship training.
Patients with INOCA experience debilitating symptoms that are anginal in nature and impact many aspects of their life, including daily activities, social interactions, mental health, and work. Left unmanaged, these symptoms decrease quality of life and increase the risk for adverse events, including MACE and mortality. Despite these adverse outcomes, there is poor clinician awareness of INOCA, and many providers incorrectly presume the condition to be benign. As a result, many patients with INOCA are dismissed from cardiovascular care when presenting to medical providers with anginal symptoms. Patients remain underdiagnosed or misdiagnosed, and most are inadequately treated even after a correct diagnosis is made, resulting in persistent decreases in quality of life and increases in risk for cardiovascular events. Although awareness of INOCA has been increasing with the advent of new diagnostic techniques, further work is needed to develop evidence-based guidelines and increase clinician awareness on the diagnosis and management. The findings from this work are currently being used to develop a disease and sex-specific PROM based on the symptoms and experiences of women with INOCA, a crucial step in improving the care of these patients.
Challenges and Limitations

There are several limitations to our study. First, our study sample of 50 participants included 34 participants with VA and 25 participants with CMD, and the relatively small sample sizes were insufficient for determining statistical significance of differences in presentation between the subgroups. Additionally, no significant conclusions can be made about the MB subgroup, which only contained 3 participants.

Second, our sample may not be representative of the larger population of participants with INOCA. Our sample included only participants diagnosed at one institution. Additionally, all participants included in this sample had already undergone invasive coronary function testing, raising the possibility that these were highly symptomatic patients who may have been more afflicted than women with no obstructive CAD who did not undergo invasive testing. Finally, most of our participants (70%) had private insurance, thus possibly selecting for a higher-than-average socioeconomic class, though this percentage is close to the national percentage of participants with private insurance.

Third, there was potential for recall bias, as the interviews were based on participants’ recollection of their experiences with INOCA rather than objective data.
Dissemination

Preliminary versions of this work were presented at local and national meetings: an oral presentation at the Connecticut Chapter of the American College of Cardiology Annual Meeting 2023, a poster presentation at the 2023 Yale School of Medicine Student Research Day, and a modified digital poster presentation at the American Heart Association Scientific Sessions 2023.
References


Appendix A: Yale Protocol for Invasive Coronary Function Testing

Electrocardiogram leads and a blood pressure cuff will be placed for hemodynamic monitoring. The patient will be assisted onto the cardiac catheterization table. Moderate sedation will be maintained with intravenous fentanyl, diphenhydramine, and midazolam. Arterial access will be obtained and therapeutic anticoagulation will be maintained per the standard of care. A coronary angiogram will be performed under moderate sedation per the laboratory protocol and digital fluorescent images will be obtained and stored per standard procedure. Symptoms of pain or anxiety will be assessed by the circulating nurse throughout the procedure and additional anxiolytics or sedation administered as necessary. Patients who are found to have obstructive coronary artery disease defined as either a left main coronary stenosis > 50% by angiography, non-left main stenosis > 70%, or fractional flow reserve (FFR) < 0.80 for a target stenosis will proceed with usual care which may include revascularization and the patient would be excluded from the research protocol, but will be followed via an intention to treat model.

If a subject is found to have either angiographically normal coronary arteries or non-obstructive CAD they will either undergo no further invasive testing or proceed with further physiologic evaluation per the Yale Angina Assessment Protocol per the discretion of the treating interventional cardiologist. Subjects will be informed of the potential for additional physiological testing prior to the procedure and again during the procedure if testing is performed. This protocol has been used clinically for > 1 year and is based on the CorMicA trial protocol. This protocol has been reviewed and approved locally by the Yale New Haven Hospital pharmacy and catheterization laboratory physician and nursing leadership.

Evaluation of Coronary Flow Reserve and Non-Endothelial Independent Microvascular Function

Intracoronary nitroglycerin 200 mcg will be administered per standard practice to relieve wire-induced vasospasm and control for any epicardial vasodilation that occurs with adenosine hyperemia. A PressureWire-X coronary pressure wire will be advanced beyond the stenosis of interest into the distal coronary artery, approximately 6 cm from the guide catheter. A baseline thermodilution measurement will be obtained to evaluate coronary flow. Briefly, 3 mL of room temperature saline will be injected into the coronary artery and a thermodilution curve obtained, which is used to calculate the mean transit time (Tmn) from the proximal wire to a distal thermistor. The Radi-analyzer software (Abbott, Illinois) derived Tmn will be recorded for each saline injection. The Tmn inversely correlates with measured coronary flow velocity and is obtained at rest as well as with hyperemia to estimate the coronary flow reserve (CFR). Maximal hyperemia will be achieved with an intravenous adenosine infusion (140 mg/kg/min) for a maximum of four minutes via a peripheral intravenous catheter. The hyperemic Tmn will then be obtained with serial intra-coronary injections of 3 mL room temperature saline to calculate the CFR (baseline Tmn / hyperemic Tmn) and index of microcirculatory resistance (distal coronary pressure Pd x hyperemic Tmn). The adenosine infusion will be discontinued after these measurements are obtained (typically within two minutes).

Coronary Vasoreactivity Testing for Endothelial Dependent Vasomotor Function

After a 10-minute washout period acetylcholine provocation is performed to assess
endothelium-dependent vasomotor function. A microcatheter is advanced into the left main coronary artery and sequential intracoronary infusions are performed with 2 mL acetylcholine at 2 mg, 20 mg, and 100 mg (or 50 mg for the right coronary artery). The patient is continuously monitored for symptoms such as chest pain, hemodynamic changes, arrhythmias, and electrocardiographic signs of ischemia. A coronary cine angiogram is performed after each dose of acetylcholine to evaluate for epicardial vasospasm. Following acetylcholine administration, 200 to 400 mg of intracoronary nitroglycerin is administered to demonstrate reversal of any epicardial vasospasm, symptoms, or electrocardiographic changes, confirming an endothelial-dependent mechanism.

Based on the information obtained during coronary physiological assessment the patient will be diagnosed with either non-cardiac symptoms, coronary microvascular dysfunction, vasospastic angina, or mixed microvascular dysfunction/vasospastic angina.
Appendix B: Standardized interview guide. Changes to the original interview guide are marked according to the legend below.

- Added
- Removed
- Amended (original version)

Opening Statement:
[Insert greeting] My name is ___________ (interviewer name) and I am a research associate working with Dr. Samit Shah from the Yale School of Medicine on a project regarding women’s heart health. Is this a good time to speak?

[If yes, proceed to Research Introduction. If no, ask if there is a better time for the researcher to call back.]

Research Introduction:
You underwent a heart catheterization in [insert month and year of procedure] and I am contacting you to ask if you would consider participating in a research study related to your heart health. The purpose of this research study is to improve our understanding of your symptoms and heart condition, and eventually develop a questionnaire or survey that can be used as a standard tool for describing similar heart conditions in women. This would involve a 45-minute phone or video interview, whichever you prefer, regarding the cardiac symptoms that you have experienced and the impact of these symptoms on your quality of life.

Would you like to hear more about the study?

[If Yes, proceed to Research Study Summary. If No, thank the participant for her time and ask if another time is better. Indicate that she can contact _____________ (research associate name and phone number) or Dr. Shah at 203-785-4129 if she changes her mind.]

Research Study Summary:
During the 45-minute interview, I will ask you questions about your symptoms, your experience with your condition, the effects of your condition on your mental health and well-being, and the overall effect on your quality of life.

Our interview will be recorded and later confidentially transcribed, at which point the recording will be securely deleted. We will also review your electronic medical record to collect information on the results of your heart catheterization. If your name or other personal information is shared during the interview it will be removed from the transcript to protect your privacy.

If you are interested in participating in the study, I can read the consent information to you, and if it provides the information you need, we can document consent over the phone. If you prefer, I can share this information with you by email for you to read.

[If Yes, proceed to Consent Information. If No, thank the participant for her time and indicate that she can contact _____________ (research associate name and phone number) or Dr. Shah at 203-785-4129 if she changes her mind.]
Consent Information:
You are invited to participate in a research study regarding heart disease in women because you underwent a heart catheterization procedure with advanced testing. There is no cost to you for participating in this study. The only cost to you will be time spent participating in the interview, which we expect to last 45 minutes. You will not be paid for participating in this study and your participation is voluntary.

Any information that you share will be confidential. Your name and other identifying information will be removed from study records, and you will be assigned a participant ID number that is not based on any information that could be used to identify you. The link between names and ID numbers will be secured and kept separate from all study data and only accessible to our research team and those responsible for research oversight.

There may be minor risks associated with participation in this study, including feeling uneasy about having your video or voice recorded. We may also ask about symptoms, health experiences, and mental health that could be upsetting. There are no direct benefits to you from participation in this study. However, your participation will advance our understanding and care of women with heart conditions like yours.

Participating in this study is voluntary. This means it is your choice. You may agree to participate or decline participation, or you may agree today and change your mind at a later date. Regardless, participation in this study does not have any effect on your relationship with Yale New Haven Health or any of your healthcare providers.

We encourage you to ask questions about anything that is not clear so far. If you have questions related to this research study, you also can contact Dr. Samit Shah, the principal investigator, at 203-785-4129, or the Yale Institutional Review Board at 203-785-4688.

Would you like to give your permission to participate in this study?

[If Yes, proceed to Introduction. If No, thank participant for her time and indicate that she can contact Dr. Shah if she changes her mind]

Introduction
Thank you for agreeing to participate, would you like to continue the interview now or schedule the interview for a later date?

[If Yes, proceed to Media Question. If No, document preferred date and time for interview: _______________ and proceed to Media Question]

Media Question
We can perform the interview with video and sound, or sound only. What is the format that would be most convenient for you?

[If Video and Sound, send Zoom link to patient via email or text message. If Sound only turn on recorder. Notify participant that we will begin recording.]
Now, we will begin the interview for the study.

**Symptom Assessment**

**Question:** Tell me about the time you first noticed symptoms related to your heart, and how you came to be diagnosed.

**Question:** When you have symptoms related to your heart, what physical sensations do you feel?

**Question:** Do you experience any of the following?
- Pain, Discomfort, or Pressure in your:
  - Chest
  - Shoulders
  - Jaw
  - Back
- Shortness of Breath
- Abnormal heartbeat (palpitations, slow heartbeat, skipped or extra beats)
- Fatigue
- Nausea
- Heartburn
- Dizziness or lightheadedness
- Sweating
- Is there anything else that you experience that I did not mention?

**Question:** How long have you experienced these symptoms?

**Question:** How would you describe the intensity or severity of your heart symptoms?
- Has the intensity of your symptoms changed over time?

**Question:** How often do you experience symptoms related to your heart?
- Every day?
- Every week?
- Every month?
- Less than once per month?
- Has this changed over time?

**Question:** Is there anything that makes your heart condition feel worse?
- Certain emotions, like feeling stressed, upset, or angry?
- Exercise or activity?
- Medications?
- Time: Over the course of the day? Over the course of a month?

**Question:** Is there anything that has made your heart condition better?
- Medications?
- Exercise or activity?
- Rest?
- Cardiac Rehabilitation?
Perception of Illness
Question: Do you have a diagnosis for your heart condition?
Question: What is the name of the diagnosis for your heart condition?
Question: How knowledgeable do you feel about your condition?

How confident are you in your understanding of your condition?

Question: How do you describe your condition to other people? (How do you describe your condition to family and friends? How do you describe your condition to doctors or other healthcare providers?)

- Family and friends?
- Healthcare providers?

Question: Why do you have this heart condition?

Question: What is different about your heart compared to other people who don’t have your condition?

Question: What resources have you used to learn about your heart condition?

Psychological Impact
Question: How has your heart condition impacted your physical health, such as how your body feels or how active you are?

- Stairs
- Inclines
- Carrying things

Question: How has your condition affected your concentration, memory, or other thinking or mental abilities?

Question: How has your condition impacted your social life, such as relationships or ability to participate in social engagements?

Question: When you have symptoms related to your heart, what emotions do you feel? Do certain thoughts go through your mind?

Question: How has your condition impacted your emotional and mental health, such as your mood, mental well-being, or outlook on life?

Question: Does your heart condition make you worry? What do you worry about?

Question: Does your condition make you feel discouraged?

Question: What emotions have you felt during the process of getting a diagnosis?

- Have you felt dismissed or invalidated?
Question: Have you sought mental health care because of your heart condition?
  ● Talk therapy?
  ● Medications?

Question: Has your condition changed the way you think about yourself or your future?

Functional Status Limitation

Question: How has your condition limited your ability to participate in routine activities, like household chores or grocery shopping? (How has your condition limited your ability to participate in routine activities?)

Question: What activities would be easier for you to accomplish if you did not have your heart condition?

Question: What changes have you made to prevent your symptoms from getting worse?

Question: Have you missed out on any aspects of your life because of your condition? Please elaborate.

Question: Has your condition affected your ability to sleep?

Question: How has your condition affected your ability to participate in:
  ● Hobbies or recreational activities?
  ● Work?
  ● Household chores?
  ● Traveling outside of your home? (Visiting family or friends?)
  ● Intimate relationships with loved ones?

Overall Health Status

Question: How healthy do you think you are?

Question: Has there been a time in the last year that you have felt disabled by your condition?
  ● If so, do you still feel disabled?
  ● If not, did you ever feel disabled? What changed?

Question: How does your condition affect your life?

This concludes the structured interview. Is there anything else about your heart health that you would like to share?

Do you have any questions for me before we end the call?

End recording. Thank the participant for her time and insights. If there are additional concerns related to their heart condition, the participant should contact Dr. Samit Shah at 203-785-4129.