Illness Perception And The Impact Of A Definitive Diagnosis On Women With Ischemia And No Obstructive Coronary Artery Disease: A Qualitative Study

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Illness Perception and the Impact of a Definitive Diagnosis on
Women With Ischemia and No Obstructive Coronary Artery Disease:
A Qualitative Study

A Thesis Submitted to the Yale University School of Medicine
In Partial Fulfillment of the Requirements for
the Joint Degree of Doctor of Medicine-Master of Health Science

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January 2024
TITLE: Illness Perception and the Impact of a Definitive Diagnosis on Women With Ischemia and No Obstructive Coronary Artery Disease: A Qualitative Study

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ABSTRACT

Background: Ischemia and no obstructive coronary artery disease (INOCA) disproportionately impacts women, yet the underlying pathologies are often not distinguished, contributing to adverse health care experiences and poor quality of life. Coronary function testing at the time of invasive coronary angiography allows for improved diagnostic accuracy. Despite increased recognition of INOCA and expanding access to testing, data lack on first-person perspectives and the impact of receiving a diagnosis in women with INOCA.

Methods: From 2020 to 2021, we conducted structured telephone interviews with 2 groups of women with INOCA who underwent invasive coronary angiography (n=29) at Yale New Haven Hospital, New Haven, CT: 1 group underwent coronary function testing (n=20, of whom 18 received a mechanism-based diagnosis) and the other group who did not undergo coronary function testing (n=9). The interviews were analyzed using the constant comparison method by a multidisciplinary team.

Results: The mean age was 59.7 years, and 79% and 3% were non-Hispanic White and non-Hispanic Black, respectively. Through iterative coding, 4 themes emerged and were further separated into subthemes that highlight disease experience aspects to be addressed in patient care: (1) distress from symptoms of uncertain cause: symptom constellation, struggle for sensemaking, emotional toll, threat to personal and professional identity; (2) a long journey to reach a definitive diagnosis: self-advocacy and fortitude, healthcare interactions brought about further uncertainty and trauma, therapeutic alliance, sources of information; (3) establishing a diagnosis enabled a path forward: relief and validation, empowerment; and (4) commitment to promoting awareness and supporting other women: recognition of sex and racial/ethnic disparities, support for other women.

Conclusions: Insights about how women experience the symptoms of INOCA and their interactions with clinicians and the healthcare system hold powerful lessons for more patient-centered care. A coronary function testing-informed diagnosis greatly influences the healthcare experiences, quality of life, and emotional states of women with INOCA.
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INTRODUCTION

Many women with chronic stable angina have no evidence of obstructive coronary artery disease (CAD) at the time of invasive coronary angiography. This presentation, referred to as ischemia and no obstructive CAD (INOCA), may occur in two-thirds of women who are referred for angiography for persistent symptoms and clinical signs of ischemia. INOCA encompasses several underlying pathologies that until recently, were difficult to detect. Specifically, 2 of the most common endotypes—coronary vasospasm and coronary microvascular dysfunction—require a high index of suspicion and specialized functional testing that is not widely available. These features amplify well-recognized disparities in women’s cardiovascular health, wherein cardiovascular symptoms are dismissed or attributed to noncardiac symptoms including anxiety, and are not rigorously evaluated. For example, there is persistent underrecognition of myocardial infarction in women and fewer referrals for stress testing and coronary angiography as compared with men.

INOCA disproportionately impacts women, is associated with increased risk for future cardiovascular events, and leads to worse outcomes than in men. Women with INOCA bear the double burden of persistent symptoms and lack of diagnosis, potentially contributing to adverse health care experiences and worse quality of life. Many women with INOCA have poor exercise tolerance and impaired functional status, resulting in repeat testing and hospitalizations that may not lead to a diagnosis yet incur costs similar to those for obstructive CAD. In the Coronary Microvascular Angina (CorMicA) trial, after invasive coronary function testing (CFT), patients with INOCA who were told of their diagnosis and received stratified therapy (compared with those
who were not treated empirically) reported improved angina and quality of life. It is possible that the psychological burden of medical uncertainty in the face of not feeling well portends worse cardiovascular outcomes, whereas a definitive diagnosis might promote a better understanding of disease physiology and greater control and agency.

The paradigm of care for women with chest pain syndromes is rapidly changing with greater recognition that ischemia may occur without obstructive CAD; accordingly, there is increased adoption of CFT at the time of angiography to assess the most common INOCA endotypes, such as coronary microvascular dysfunction, vasospastic angina, myocardial bridging, or a combination of these mechanisms. Understanding the experiences of women with INOCA, including the impact of receiving a diagnosis, is essential to caring for patients with INOCA and appropriately messaging information to women about heart disease. Accordingly, this qualitative study captured first-person narratives of 2 groups of women with INOCA who recently underwent coronary angiography, with and without CFT. We sought to identify the impact of a CFT-informed diagnosis on the healthcare experiences, quality of life, and emotional states of women, with the goal of improving patient-centered care for this population.
PURPOSE

INOCA poses a significant and disproportionate burden on women, impacting their healthcare experiences and overall quality of life. Despite increasing recognition, the underlying pathologies are often indistinct, leading to a lack of personalized care. To address this gap, this master's thesis aims to delve into the specific hypothesis and aims outlined in the abstract.

Hypothesis:

The study hypothesizes that a comprehensive understanding of the first-person perspectives of women with INOCA, particularly those who have received a definitive diagnosis after coronary function testing during invasive coronary angiography, will provide crucial insights into the intricacies of their disease experience. Furthermore, it is anticipated that a mechanism-based diagnosis, derived from coronary function testing, significantly influences the healthcare experiences, quality of life, and emotional states of women with INOCA.

Specific Aims:

1. Capture the diverse range of experiences related to symptom, quality of life, and seeking medical attention among women with INOCA.
2. Examine the various emotional, social, and financial factors influencing the diagnostic journey of women with INOCA.
3. Understand the implications of receiving (or not receiving) a diagnosis for women with INOCA.
4. Explore sex and racial/ethnic disparities in medical care and the broader narrative of surrounding the condition.
By employing structured telephone interviews and utilizing the constant comparison method, this study aims to provide a nuanced understanding of the experiences of women with INOCA, differentiating between those who undergo coronary function testing and those who do not. Rigorous qualitative analysis by a multidisciplinary team aims to gather data to derive meaningful insights that can inform more patient-centered and tailored approaches to care.

This research seeks to contribute to the broader goal of improving healthcare outcomes for women with INOCA, emphasizing the importance of personalized diagnosis and patient-centered care. The resulting knowledge will hopefully not only enhance our understanding of the disease but also pave the way for more effective strategies in addressing the unique challenges faced by women with INOCA.
METHODS

Student Contributions

L.Y. Tseng, S.M. Shah, and E.S. Spatz conceived the study and designed the study protocol. L. Curry and E. Cherlin provided feedback to the analysis mythology of the study protocol. L.Y. Tseng and E.S. Spatz applied for IRB approval. L.Y. Tseng applied for dedicated funding to support this study. L.Y. Tseng and S.M. Shah screened potential participants for eligibility. L.Y. Tseng invited and enrolled participants. L.Y. Tseng performed audiotaped virtual phone interviews. L.Y. Tseng and N. Goc transcribed the interviews. N. Goc verified the transcripts. L.Y. Tseng and N. Goc performed the initial qualitative analysis parallelly and individually and met for weekly discussion to develop the code structure. E.S. Spatz, L. Curry, and E. Cherlin verified the analytical methods and supervised the code structure. L.Y. Tseng, S.M. Shah, and E.S. Spatz prepared the abstracts summarizing the early results of the study. L.Y. Tseng created the posters and slides for the conference presentation under the guidance of E.S. Spatz and S.M. Shah. L.Y. Tseng and E.S. Spatz wrote the manuscript in consultation with S.M. Shah and L. Curry. L.Y. Tseng communicated the published results to the study participants.

Ethics Statement & Human Subjects Research

This study protocol, approved by the Yale University Institutional Review Board (ID: 2000028626), adheres to ethical guidelines and standards established by the Yale School of Medicine's Institutional Review Board. Informed consent was obtained from all participants, ensuring voluntary participation and understanding of rights. Confidentiality measures were implemented to protect participant privacy, and data were anonymized.
Participants were assured of their right to withdraw without consequences. The study aims to contribute valuable insights to the scientific community, with potential benefits outweighing minimal risks. Ongoing oversight ensures ethical conduct throughout the data collection, analysis, and reporting process. The research findings were transparently reported, acknowledging limitations and conducting the study with integrity and respect for participants.

**Methods Description**

Participants were selected from a local registry of women with known or suspected ischemic heart disease who underwent clinically indicated invasive coronary angiography at Yale New Haven Hospital, New Haven, CT, between October 2020 and July 2021 (Figure 1). All consecutive women who underwent CFT at the time of angiography to establish INOCA endotypes (referred to as angiography+CFT below) were eligible for inclusion. The CFT protocol included provocative testing with intracoronary acetylcholine administration and guidewire-based testing with coronary thermodilution using the PressureWire X (Abbott Vascular, Santa Clara, CA). From the same registry, we used a purposeful sampling approach\(^\text{20}\) to select a comparison group who did not undergo CFT (referred to as angiography alone below). Specifically, the characteristics of women in the angiography+CFT group who agreed to be interviewed were periodically reviewed to inform subsequent selection and enrollment of women in the angiography-alone group. Interviews with each group were performed in parallel to achieve a similar distribution of characteristics between the 2 groups. The size of both groups was determined based on the principle of thematic saturation, defined as the point at which
novel themes or information ceased to emerge after sequential interviews in each participant group.\textsuperscript{21,22}

Following permission from the treating primary care provider or cardiologist, eligible participants were enrolled by phone. Participants selected days and times that were convenient for phone interviews. A trained researcher obtained verbal informed consent and conducted interviews using a structured interview guide with open, nondirective questions and standard probes designed to elicit individual perceptions and experiences (Table 1).\textsuperscript{23} Participants were not compensated. Interviews were audiotaped using Health Insurance Portability and Accountability Act-compliant software and transcribed by research team members (L.Y.T. and N.G.). Additional patient data from the electronic medical records on demographics (age, racial and ethnic backgrounds, relationship status, and insurance type), cardiovascular diagnoses and procedures, and relevant comorbidities were collected to characterize the 2 groups.

The data collected for this study were analyzed using a grounded theory approach, specifically the constant comparison method.\textsuperscript{24,25} Two researchers (L.Y.T. and N.G.) with multidisciplinary backgrounds performed data analysis simultaneously and independently using the ATLAS.ti Scientific Software, version 8 (ATLAS.ti, Berlin, Germany). Essential concepts were extracted and coded, followed by comparison over successive interview transcripts to identify recurrent themes across all interviews. Researchers met on a weekly basis to discuss their observations, reconcile discrepancies in coding through negotiated consensus, and update the code book to capture emergent constructs. Additional team members (E.S.S. and L.A.C.) reviewed coded transcripts at regular intervals as the analysis progressed to inform subsequent data collection and analysis.
Researchers continued the process of refining code structures and detailing the recurring themes until no new concepts emerged. Additionally, themes were compared within and between the angiography+CFT and angiography alone groups to examine the concordance and discordance in coded themes.
RESULTS

Participant Characteristics

Among 26 women with INOCA and who underwent angiography+CFT, 22 women consented to enroll in the study. Another 26 women with INOCA who did not undergo CFT (and, therefore, did not have a definitive diagnosis) were selected as a purposeful sample for the angiography alone group, among whom 16 agreed to participate. In total, 16 patients declined to participate, citing reasons such as time constraints and having limited insights to share; 7 participants were unable to be reached by phone after 3 attempts on different days. The final sample included 20 patients who underwent coronary angiography and CFT and 9 underwent coronary angiography alone, which was sufficient to achieve thematic saturation.

The median time from angiography with or without CFT to interview was 1.9 months. Interviews lasted 31 minutes on average. Participant sociodemographic and clinical characteristics are described in Table 2. Four recurrent themes emerged (Table 3), characterizing the experiences of women with INOCA in their illness perception, diagnosis, and treatment. Finally, the Consolidated Criteria for Reporting Qualitative Studies (COREQ) checklist was completed to ensure comprehensive and standardized reporting, enhancing the transparency, credibility, and methodological rigor of the study's qualitative results (Table 4).

Theme 1: Distress From Symptoms of Uncertain Cause

Starting from the onset of their symptoms, participants from both groups recounted feeling distressed by new and unfamiliar physical symptoms. They reported struggling to
make sense of the symptoms and described the emotional toll and threat to their identity that the symptoms imposed.

**Symptom Constellation**

Women described a wide constellation of symptoms that varied in onset, duration, and presentation. Many participants experienced chest pain or pressure, palpitations, and shortness of breath that were described as debilitating. These symptoms raised concern for a potentially life-threatening cardiac illness that required immediate medical attention, but when the initial workup in the emergency setting came back negative for a heart attack, many women were perplexed. With ongoing symptoms, women sought out additional testing, which was often negative or inconclusive, which created uncertainty about whether or when to seek care. Some participants avoided seeking care altogether, whereas others felt they were left with no choice but to return to the emergency department, incurring substantial healthcare costs and stress.

*If I call acute care and say I’m having heart pain, it’s like, OK, go right to the E.R. I’m like, well, I don’t think it’s a heart attack because this feeling I’ve had it before. And every time they hook me up to the EKG, they’re like, it’s fine, but I know it’s not.* (Participant #12, angiography+CFT; coronary microvascular dysfunction)

**Struggle for Sensemaking**

Before receiving a diagnosis, women reported it was difficult for them to make sense of their symptoms especially since they were not informed about a plausible biological
mechanism to explain their symptoms. Many participants sifted through life events to understand what may have provoked their symptoms, hoping to identify causes or triggers, but many found no discernable pattern. Others scrutinized their lifestyle choices and wondered if they were responsible. Participants who had a family history of heart disease felt especially vulnerable after witnessing the devastating consequences of heart disease in family members.

*I went from being a very active person to basically staying in my apartment and not being able to do anything because I didn’t know what [would] provoke the chest pain. I didn’t know what would bring it on. I didn’t know what would make it better. I didn’t want to risk it happening, so I stopped doing anything. I really just want to get back to normal. (Participant #2, angiography+CFT; elevated resting flow)*

**Emotional Toll**

In response to questions about mental and emotional well-being, while navigating symptoms, participants in both groups described feeling shocked, fearful, stressed, frustrated, upset, depressed, and exhausted. Women reported feeling alone and invalidated, simultaneously doubting if their symptoms were legitimate and worried others would not understand if they could not make sense of it themselves.

*It made me think I was crazy, yet I knew I wasn’t. I had these conflicting talks. Every day I said, “I’m going to be OK. I’m better today. It’s not going to happen anymore because they [doctors] are not worried. And I’m not worried.” As soon as I said it, I wondered, “Is*
anything going to happen to me? Is my heart going to stop?” “No, no, you’re fine.” (Participant #5, angiography+CFT; vasospastic angina)

**Threat to Personal and Professional Identity**

For some women, the symptoms directly impacted their personal and professional identities. Some women feared that they could no longer continue in caregiver roles, whereas others reported being hesitant to ask family and friends for support, as they struggled to explain their illness. Lacking a clear diagnosis also made it difficult to request accommodations at the workplace.

*I have always been a strong, powerful woman. I don’t necessarily want people to go around thinking I have heart disease. I don’t think it’s necessary for me to be labeled that I have heart disease... I wouldn’t call it vanity, but I always prided myself on being really strong. Now I’m not so strong and I don’t know why. It’s a hard pill to swallow.* (Participant #3, angiography+CFT; coronary microvascular dysfunction)

**Theme 2: A Long Journey to Reach a Definitive Diagnosis**

In search of a definitive diagnosis for their symptoms, women depended on self-advocacy and fortitude. Some women experienced further uncertainty and trauma navigating the medical system, whereas others were able to form therapeutic alliances through their healthcare interactions. Women from both groups relied on a variety of sources to gather information about their condition.
Self-Advocacy and Fortitude

Nearly all participants reported that their illness was not well understood, and many felt delegitimized, with some participants describing the process of diagnosis as navigating a seemingly impermeable system. Already, many women were negotiating a transition from a previously healthy life to the day-to-day reality of unpredictable symptoms. When their condition was not recognized by the medical community, many women reported feeling that their symptoms reflected a weakness of character. To persist in seeking a diagnosis, they had to overcome self-doubt, occasional skepticism from loved ones, and even the reluctance of some clinicians.

When a medical doctor of that caliber says, “Oh, no, go be active, you’re going to be fine. You’re not going to have a heart episode.” Then you keep trying. Being the athlete that played college sports, you push through pain. I kept trying to push through the pain and thought I was crazy. (Participant #18, angiography+CFT; vasospastic angina)

Healthcare Interactions Brought About Further Uncertainty and Trauma

As women sought care for their symptoms, their interactions with the health system sometimes brought about further uncertainty and trauma. Many women reported that after the initial cardiac workup was negative, they were referred to other specialties for a noncardiac workup of their chest pain. However, this also did not reveal a specific pathology, leaving women to feel further dismissed and frustrated. Additionally, they
often received conflicting information from different specialists and were frequently told their symptoms were psychosomatic in nature.

    I just felt he wanted to push me out like someone else should deal with this. All of us have our blind spots, and no one has all the knowledge in the world, and I’m okay with that, as long as there is honesty... But there’s no awareness that they’re not infallible. I have a problem with that. (Participant #20, angiography+CFT; vasospastic angina)

Patients who managed to establish care in cardiology faced a long series of diagnostic testing. As many patients with INOCA are of low or immediate cardiovascular risk because of their relatively young age and lack of other risk factors, testing often returned negative or equivocal, leading to more testing. Participants reported additional burdens related to insurance coverage with prior authorizations and tiered formularies. Many reported long wait times and challenges with receiving test results. A few interviewees underwent multiple coronary angiograms before being referred for angiography with CFT.

    Even before my procedure, they said, we’re calculating your out-of-pocket expense to be $1,900 and we’re willing to take off 15% if you pay it now... so all those things play a role in my decision-making, whether [to let] insurance dictate [if I get] the answer I needed. (Participant #18, angiography+CFT; vasospastic angina)

    Therapeutic Alliance
Despite the difficult journey, many respondents in the angiography+CFT group considered themselves to be fortunate that they eventually found clinicians who listened to their symptoms and were willing to forge a therapeutic relationship despite uncertainty about the diagnosis. Participants valued clinicians who adopted active listening, provided validation, and encouraged questions. They welcomed honesty and transparency when clinicians did not have a perfect answer. This alliance helped them to feel empowered and have agency over their health, even when there was uncertainty about the diagnosis. Many participants recognized the role of the care team, including nurses and office staff, in shaping their healthcare experiences.

*I felt for the first time I talked to her, you know what, I’ve never talked to a doctor for [a] full 50 minutes, ever in my life. And she actually dedicated to me for 50 minutes and really listened to what I had to say and describe the pain.* (Participant #20, angiography+CFT; vasospastic angina)

*If you believe in a second opinion, go for it. I really don’t know what’s going on here. I can ask my colleagues, but I don’t know.* So at least he was open and transparent to me about not knowing. It made me feel that he was really honest, and that is somehow reassuring when your doctor tells you, as far as I know, we’re going to have to find answers somewhere else. (Participant #20, angiography+CFT; vasospastic angina)

**Sources of Information**
Participants relied on different sources of information in seeking a diagnosis. Some reported accessing peer-reviewed literature, citing their concern for abundant misinformation on the internet, but some found the study results difficult to interpret. Some trusted their clinicians to be the expert. Others noted that access to electronic medical records allowed them to review their conversation with their clinicians after their visits and organize their thoughts. Finally, a few interviewees mentioned cardiac rehabilitation or visits with dieticians had been good resources to learn how to take care of their new symptoms.

*I’m pretty skeptical, so I try not to Google too much. I try to read through legitimate publications, [but they are] too technical, so I pretty much stay in MyChart and then the links that they send.* (Participant #24, angiography alone; no obstructive CAD)

**Theme 3: Diagnosis Enabled a Path Forward**

A definitive diagnosis based on CFT brought relief, validation, and empowerment with a path forward for women in the angiography+CFT group. Participants in the angiography alone group were also relieved to receive a diagnosis of no CAD but had remaining questions.

**Relief and Validation**

Participants from both groups reported feeling relief upon hearing that they did not have coronary artery blockages. Women who underwent CFT shared a sense of validation that
there was another explanation for their symptoms. They reported that the risks of the procedure, stress, and time were worth it to receive a definitive diagnosis.

*I was relieved because I wasn’t crazy. I felt people were not believing me.* (Participant #10, angiography+CFT; vasospastic angina)

*I’ve been on this journey for a long time. For the last several years there is something that has been going on with my heart. So, it is a relief to have a name for what I’m experiencing.* (Participant #7, angiography+CFT; coronary microvascular dysfunction)

In the angiography-alone group, whereas most were relieved that they did not have CAD, not having a definitive diagnosis left them with a sense of unease. Some participants were offered a repeat coronary angiography with CFT yet they opted out.

*I have confidence in the outcome, but my concern is that I had this diagnostic imaging that showed a reversible perfusion defect. I still occasionally wonder what that means. The answer I’ve gotten is, diagnostic imaging isn’t perfect. But they don’t do invasive catheterization on a 59-year-old woman unless they have a significant level of concern. That is a hard thing to just let go of when they say, “Oh, never mind, [the imaging] might have been a false positive.” It leaves you with questions.* (Participant #29, angiography alone; no obstructive CAD)
Empowerment

The diagnosis provided insights into the pathophysiology behind day-to-day symptoms, which in turn promoted better therapeutic engagement between the care team and the patients. With the guidance of their clinicians, women could now make a plan for acute episodes. Women who underwent CFT reported feeling they were no longer at the mercy of their symptoms. Participants were able to safely resume activities they once enjoyed, build new dietary habits, and practice mindfulness activities to reduce stress. These actionable behaviors in turn allowed them to gain agency over their own health. Furthermore, the diagnosis provided women the tools to communicate about their illness, find support from a larger community, and reclaim their identities.

Now that I have a diagnosis and I have a doctor who’s comfortable with that diagnosis, there’s a trust factor. If he suggests a medication, I say, “hey, if you think it’s going to work, I’m going to try it”... We’re going to work on this together and find a solution. So, win-win.

(Participant #18, angiography+CFT; vasospastic angina)

Theme 4: Commitment to Promoting Awareness and Supporting Other Women

Women from both groups reported issues around sex and racial/ethnic disparities in heart health. They were also committed to promoting awareness of INOCA and support for others with the same condition.

Recognition of Sex and Racial/Ethnic Disparities
Although doing research for their diagnosis, many participants became aware of known disparities in women’s cardiovascular health. Many voiced concerns about how medical research prioritized the disease model for men, and what it meant in relation to their own healthcare experiences. They wondered if their symptoms would have been taken more seriously or if they would have received a diagnosis sooner if they were men. The disparity was felt particularly among women of color, immigrant women, and women with less financial or social resources. They spoke about how the intersectionality of their identities made them more vulnerable, and it took courage for them to persist on their journey to diagnosis.

*They look at my accent, they look at I’m a woman of color, and they treat me very differently... Once the nurse came to me when I was screaming in pain. She said it’s probably just an idea [in my head]. And I looked at her and said, “if I was a 42-year-old White male complaining of chest pain right now, you would not say that.” She was taken aback. We have the stats there, which tell us how symptoms in women are dismissed in a way that they don’t get dismissed in men. So please don’t tell me that it doesn’t happen. (Participant #27, angiography alone; no obstructive CAD, no definitive diagnosis)*

**Support for Other Women**

Women felt empowered by the diagnosis as they were now able to contribute to the science behind their not-so-well-known diagnosis. They shared solidarity with other women who have similar experiences. The connectivity provided by the internet also
allowed patients to meet in online support groups during the pandemic. Some interviewees were even able to connect with patients from different parts of the world. They also appreciated how these interviews would allow them to share their experiences and voices with the rest of the community. Many of them offered some advice to others who are undertaking the same journey and volunteered to be contacted again if their contributions might be needed in future studies.

It’s kind of surprising [when] I found out there are two really good Facebook groups. One is centered in Great Britain for patients with [INOCA] and the other focus solely on microvascular disease... The other thing is going to cardiac rehab, really fed my desire to have some structure around trying to get better. It helped my mind to be with other people, most of whom had cardiac conditions. (Participant #4, angiography+CFT; coronary microvascular dysfunction)
CHALLENGES & LIMITATIONS

Although our work provides important and novel insights into the experiences of women with INOCA, there are several limitations.

Participants were selected as a convenience sample from a single clinical center; the results from our interviews may not reflect the experiences of women treated at other clinical centers. This was a predominantly White population (79%) with private insurance (72%) which may have influenced the findings. Further work is necessary to ensure that all women suspected of INOCA have an opportunity to undergo further testing and are represented in studies. For example, referrals to subspecialists, advanced diagnostic imaging, and procedures can be challenging without comprehensive insurance coverage. Our interviews revealed that attending appointments required significant time and financial commitment, as well as psychosocial support from friends, families, and the workplace. Finally, women who are not native English speakers and women from historically underserved communities could face tremendous barriers to establishing a therapeutic relationship with their medical provider, which was key to arriving at a definitive diagnosis. Further work with greater representation of women from diverse backgrounds is needed to fully capture the range of experiences of all women with INOCA.

Second, selection bias may have influenced study findings. To mitigate selection bias we enrolled consecutive patients undergoing angiography+CFT. We also used a purposeful sampling of women who underwent angiography alone, selecting women who shared similar sociodemographic characteristics as women who underwent coronary angiography+CFT. Still, women who declined CFT may not have thought it was
necessary for their recovery. Not all contacted participants in either groups agreed to enroll. Participants in the angiography+CFT group had a higher enrollment rate (77%) than the angiography alone group (35%), potentially reflecting satisfaction with care. In addition, including a third group of women with suspected symptoms who did not undergo coronary angiography would further enrich our understanding of the experiences of women with INOCA, especially since most women with chest pain are not referred for coronary angiography, even when a stress test is abnormal. We did not include this group because it is difficult to identify individuals with INOCA (or suspected INOCA) in the medical record—a limitation of current diagnostic coding, and because the diagnosis of INOCA may not be certain.

Third, recall bias is possible because we interviewed participants after their angiography procedure; however, we sought to minimize this bias by conducting interviews within 6 months of the angiography and by adopting probing techniques to recall a spectrum of factors associated with participants’ experiences. In addition, we used several strategies to ensure data reliability, including consistent use of the interview guide, simultaneous double-coding, and analysis of the data using the software.
DISCUSSION

Our team identified 4 recurrent themes characterizing the experiences of the women with INOCA as they sought diagnoses for their symptoms: (1) distress from symptoms of uncertain cause; (2) a long journey to reach a definitive diagnosis; (3) diagnosis enabled a path forward; and (4) Commitment to promoting awareness and supporting other women. These themes highlight aspects of the disease experience that can be addressed in the care of patients. For example, our findings suggest that women with INOCA struggle with a high symptom burden and make sense of these symptoms when test results return to normal. We also learned that symptoms pose a threat to women’s personal and professional identity and negative health care interactions can incur further uncertainty and trauma. Still, in the process of navigating symptoms that were not easily defined, women drew upon self-advocacy and fortitude, building therapeutic alliances with clinicians who were willing to listen. They also consulted varied sources of information, including notes from their medical record. Women who received a diagnosis through angiography combined with CFT reported feeling relief and validation. Participants described that a definitive diagnosis was empowering and gave them greater agency over their bodies. Some participants also expressed concern that a patient’s sex, gender, race, or ethnicity may impact clinicians’ perception of symptoms and referral patterns. Many participants reported being motivated to address bias by sharing their stories and supporting women experiencing similar health issues.

These findings are corroborated by other studies in the literature. Women with INOCA commonly go undiagnosed as they are more likely to experience missed opportunities and delays along the entire diagnostic pathway. When recognized, having a
definitive diagnosis of INOCA can lead to improved outcomes. The CorMicA trial provided evidence that management guided by an interventional diagnostic procedure with CFT and subsequent stratified therapy improves anginal symptoms and quality of life in patients with INOCA.\textsuperscript{14} Although it is hard to distinguish the benefits derived from receiving a diagnosis with the benefits of more tailored medical therapy focused on the identified endotype, it is possible that receiving a definitive diagnosis promoted greater patient understanding of the disease mechanism and greater control and agency, as illustrated in our study. A qualitative study from the Netherlands used visual illustrations to map the healthcare experiences of patients with INOCA: the journey to diagnosis is long and complex and many barriers persist for patients across the globe.\textsuperscript{28} Another recently published survey from an INOCA patient support group echoed our findings: patients reported an adverse impact of symptoms on their home life, mental health, outlook on life, relationships, and workforce participation.\textsuperscript{10}

The findings of this study are critically important to the care of women with or suspected of having INOCA. Women with new chest pain that is unexplained by traditional first-line testing should be referred for more advanced testing, either noninvasive or invasive. The 2021 American Heart Association/American College of Cardiology chest pain guidelines\textsuperscript{29} recommend specific diagnostic algorithms that should be more broadly adopted. Second, although many clinicians are not comfortable with uncertainty, participants in this study reported feeling more trusting of their clinicians when they were transparent about that uncertainty. Third, patients desire sensemaking; they want to be partners in their care to determine what is causing their symptoms and develop solutions or therapies. Fourth, many patients with INOCA relate to bias and
disparities in women’s heart health that relate to sex, gender, race, and ethnicity, and want to share their stories with the hope that this will impact care patterns for other women.

Results from this qualitative study provide novel insights into how women experience the symptoms of INOCA and their interactions with clinicians and the healthcare system. For healthcare providers and researchers seeking to improve health care experiences and quality of life for women with INOCA, these findings, from the voices of women with INOCA, hold powerful lessons and tips for more patient-centered care.
DISSEMINATION

Abstracts derived from the research were presented as a virtual oral presentation during
the 2021 American Heart Association (AHA) Scientific Session and a poster presentation
during the 2022 American College of Cardiology (ACC) Scientific Session.

Tseng, L., Shah, S., Curry, L., and Spatz, E. S. 2021. Illness Perception and the Impact of
a Definitive Diagnosis on Women with Ischemia Without Obstructive Coronary
Artery Disease: A Qualitative Study. Circulation, 144(Suppl_1), A11244-A11244.

Tseng, L. Y., Göç, N., Kunnirickal, S., Odanovic, N., Schwann, A., Cherlin, E. J., ... and
Shah, S. 2022. Perception of Illness Stratified by Invasive Phenotype in Women
with Ischemia and No Obstructive Coronary Artery. Journal of the American
College of Cardiology, 79(9_Supplement), 1152-1152.

The results of the study were published as an original research manuscript in
Circulation: Cardiovascular Quality and Outcomes in July 2023.

on women with ischemia and no obstructive coronary artery disease: a qualitative
study. Circulation: Cardiovascular Quality and Outcomes, 16(8), 521-529.

The original research article was published with an editorial by Shea E. Hogan,
MD, MSCS, and Prateeti Khazanie, MD, MPH at the University of Colorado.

Hogan, S. E. and Khazanie, P. 2023. Path Less Traveled: Providing Optimal Patient Care
on the Road of Diagnostic Uncertainty. Circulation: Cardiovascular Quality and
Outcomes, 16(8), 530-532.

The early results of this study were reported by the Yale Daily News. The
publication of the final manuscript was reported by Healio and featured in ACC
Cardiovascular News Digest.

Zhang, B. 2021 “University researchers to study gender disparities in heart disease
diagnosis.” Yale Daily News.
The results of this study informed a subsequent project led by Samit Shah, MD, PHD, that received funding from the U.S. Food and Drug Administration (FDA) Centers of Excellence in Regulatory Science and Innovation (CERSIs) to improve care for women with ischemia and no obstructive coronary artery disease.

Attention from researchers at other institutions indicated the significance and relevance of the study to the broader scientific community. Efforts were made to form formal collaborations with researchers at the Tilburg University in the Netherlands.

The published results of this study were shared with all study participants. Furthermore, the publication of results garnered attention from multiple international patient advocacy groups including the International Heart Spasms Alliance, INOCA International, and MINOCA International.
Participants were selected from a local registry of women with known or suspected ischemic heart disease who underwent clinically indicated invasive coronary angiography. All consecutive women who underwent coronary physiology testing (CFT) at the time of angiography to establish INOCA endotypes were eligible for inclusion. From the same registry, we used a purposeful sampling approach to select a comparison group who did not undergo CFT. Among 26 women with INOCA (ischemia and no obstructive coronary artery disease) and who underwent angiography+CFT, 22 women consented to enroll in the study. Another 26 women with INOCA who did not undergo CFT (and therefore did not have a definitive diagnoses) were selected as a purposeful sample for the angiography alone group, among whom 16 agreed to participate. In total, 16 patients declined to participate, citing reasons such as time constraints and having limited insights to share; 7 participants were unable to be reached by phone after 3 attempts on different days. The final sample included 20 patients who underwent coronary angiography and CFT and 9 underwent coronary angiography alone, which was sufficient to achieve thematic saturation.
# Table 1. Interview Guide

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Can you tell me about your heart condition diagnosis?</td>
<td>Open-ended question that provides a comfortable way into the interview. Gain first-person perspective on interviewee’s symptom trajectory, name of their condition, understanding of their disease, as well as their source of information.</td>
</tr>
<tr>
<td>2</td>
<td>Can you tell me more about the heart catheterization you received on xx date?</td>
<td>Elicit respondents’ descriptions of the treatment process itself, (not) receiving a diagnosis immediately following the treatment, as well as their reactions towards the (lack of) diagnosis. Encourage the respondents to narrate their journey in seeking a diagnosis and the challenges they have faced in negotiating the healthcare system.</td>
</tr>
<tr>
<td>3</td>
<td>How did your heart condition affect your life prior to seeking medical help/receiving the diagnosis? What about after you received your diagnosis?</td>
<td>Encourage respondents to talk about all aspects of which they perceive their heart condition to affect their quality of life, things that occur during the care-seeking process and in day-to-day life.</td>
</tr>
<tr>
<td>4</td>
<td>Following the heart catheterization procedure, did you make any changes in your lifestyle, and/or did your doctor make any medication changes?</td>
<td>Give the interviewer the opportunity to explore a broad range of factors that the interviewee considers relevant to their health and prognosis, including but not limited to the use of nonpharmacological therapies, cardiac rehabilitation, changes in diet and exercise, stress management, and social support.</td>
</tr>
<tr>
<td>5</td>
<td>Is there anything else that you would like to address before we wrap up the interview? Do you have any questions for me?</td>
<td>Capture additional themes of interest</td>
</tr>
<tr>
<td>Participant Characteristics</td>
<td>Total</td>
<td>Angiograph y+CFT*</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------</td>
<td>-------------------</td>
</tr>
<tr>
<td>n (%)</td>
<td>29</td>
<td>20</td>
</tr>
</tbody>
</table>

### Sociodemographic Characteristics

<table>
<thead>
<tr>
<th>Age, y, mean (range)</th>
<th>59.7 (41-79)</th>
<th>58.0 (41-79)</th>
<th>63.6 (59-77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race and ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>23 (79)</td>
<td>16 (80)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>1 (3)</td>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (7)</td>
<td>1 (5)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (10)</td>
<td>2 (10)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/Partnered</td>
<td>19 (66)</td>
<td>13 (65)</td>
<td>6 (67)</td>
</tr>
<tr>
<td>Divorced/separated/widowed/single</td>
<td>10 (34)</td>
<td>7 (35)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Health Insurance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>21 (72)</td>
<td>16 (80)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Medicare</td>
<td>5 (17)</td>
<td>2 (10)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Medicaid</td>
<td>3 (10)</td>
<td>2 (10)</td>
<td>1 (11)</td>
</tr>
</tbody>
</table>

### Clinical Characteristics

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>9 (31)</td>
<td>3 (15)</td>
<td>6 (67)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (48)</td>
<td>11 (55)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>19 (65)</td>
<td>11 (55)</td>
<td>8 (89)</td>
</tr>
<tr>
<td>Abnormal baseline EKG</td>
<td>15 (51)</td>
<td>10 (50)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Abnormal baseline stress test</td>
<td>14 (48)</td>
<td>7 (35)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Number of stress tests prior to angiography, median (range)</td>
<td>1 (0-4)</td>
<td>1 (0-4)</td>
<td>1 (1-3)</td>
</tr>
<tr>
<td>Number of emergency visits /hospitalizations prior, median (range)</td>
<td>1 (0-5)</td>
<td>1 (0-7)</td>
<td>1 (0-5)</td>
</tr>
<tr>
<td>Post CFT* Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary microvascular dysfunction</td>
<td>7 (35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasospastic angina</td>
<td></td>
<td>8 (40)</td>
<td></td>
</tr>
<tr>
<td>Coronary microvascular dysfunction &amp; vasospastic angina</td>
<td>3 (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others†</td>
<td></td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>Time from symptom onset to diagnosis, months, median (range)</td>
<td></td>
<td>17.7 (1-193)</td>
<td></td>
</tr>
<tr>
<td>Change in medical therapy post procedure</td>
<td></td>
<td>19 (95)</td>
<td></td>
</tr>
</tbody>
</table>

* CFT: coronary functional testing.
† Others include elevated resting flow and non-cardiac chest pain.
Table 3. Themes and subthemes

<table>
<thead>
<tr>
<th>Themes</th>
<th>Subthemes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distress from symptoms of uncertain etiology</td>
<td><strong>Symptom constellation</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Struggle for sense-making</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Emotional toll</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Threat to personal and professional identity</strong></td>
</tr>
<tr>
<td>A long journey to reach a definitive diagnosis</td>
<td><strong>Self-advocacy and fortitude</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Healthcare interactions brought about further uncertainty and trauma</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Therapeutic alliance</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Sources of information</strong></td>
</tr>
<tr>
<td>Diagnosis enabled a path forward</td>
<td><strong>Relief and validation</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Empowerment</strong></td>
</tr>
<tr>
<td>Commitment to promoting awareness and supporting other women</td>
<td><strong>Recognition of sex and racial/ethnic disparities</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Support for other women</strong></td>
</tr>
</tbody>
</table>
Table 4. Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

<table>
<thead>
<tr>
<th>No</th>
<th>Item</th>
<th>Guide questions/description</th>
<th>Answers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Domain 1: Research team and reflexivity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Personal Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Interviewer/facilitator</td>
<td>Which author/s conducted the interview or focus group?</td>
<td>L.Y.T conducted the interview.</td>
</tr>
<tr>
<td>2</td>
<td>Credentials</td>
<td>What were the researcher's credentials? E.g. PhD, MD</td>
<td>The researchers’ credentials are: L.Y.T., MS; N.G., MS, A.N.S, MD; E.J.C, PhD; S.J.K, MD; N.O., MD; L.A.C, PhD; S.M.S, MD, PhD; E.S.S., MD, MHS.</td>
</tr>
<tr>
<td>3</td>
<td>Occupation</td>
<td>What was their occupation at the time of the study?</td>
<td>The researchers’ occupation at the time of the study were: L.Y.T., medical student; N.G., program administrator, global health institute; A.N.S., resident physician, internal medicine; E.J.C., research associate, global health institute; S.J.K., clinical fellow, cardiology; N.O., clinical fellow, interventional cardiology; L.A.C, faculty, global health institute; S.M.S, associate professor, interventional cardiology; E.S.S, associate professor of cardiology and epidemiology.</td>
</tr>
<tr>
<td>4</td>
<td>Gender</td>
<td>Was the researcher male or female?</td>
<td>The following researcher identify as female: L.Y.T., N.G., A.N.S., E.J.C., S.J.K., N.O., L.A.C, E.S.S.; the following researcher identify as male: S.M.S..</td>
</tr>
<tr>
<td>5</td>
<td>Experience and training</td>
<td>What experience or training did the researcher have?</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Relationship established</td>
<td>Was a relationship established prior to study commencement?</td>
<td>No relationship was established prior to study commencement.</td>
</tr>
</tbody>
</table>
### Participant knowledge of the interviewer

What did the participants know about the researcher? e.g. personal goals, reasons for doing the research.

The participants knew that the researcher conducting the interview was a medical student interested in women's health research, and that the rest of the research team included cardiologists and qualitative research expert.

### Interviewer characteristics

What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic.

The interviewer (L.Y.T.) reports no bias or assumptions prior to conducting the interviews.

---

### Domain 2: study design

#### Theoretical framework

<table>
<thead>
<tr>
<th>Methodological orientation and Theory</th>
<th>What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>We adopted the constant comparison method to guide our data analysis.</td>
</tr>
</tbody>
</table>

#### Participant selection

<table>
<thead>
<tr>
<th>Sampling</th>
<th>How were participants selected? e.g. purposive, convenience, consecutive, snowball</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The angiography+coronary physiology testing (angiography+CFT) group of participants were selected as a consecutive sample, and the angiography alone group were selected as a convenience sample. The selection process was detailed under the Study Design and Sample section.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Method of approach</th>
<th>How were participants approached? e.g. face-to-face, telephone, mail, email</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participants were approached via telephone.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample size</th>
<th>How many participants were in the study?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>There were 29 participants in the study.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-participation</th>
<th>How many people refused to participate or dropped out? Reasons?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16 potentially eligible patients declined to participate, citing time constraints and limited insights to share. 7 enrolled participants were lost to follow up, defined as unable to reach by phone after 3 attempts on different days.</td>
</tr>
</tbody>
</table>

### Setting
<table>
<thead>
<tr>
<th>Setting of data collection</th>
<th>Where was the data collected? e.g. home, clinic, workplace</th>
<th>Data was collected over Zoom (version 5.13.11), a videotelephony software program, under HIPAA compliance.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of non-participants</td>
<td>Was anyone else present besides the participants and researchers?</td>
<td>No additional person was present besides the participants and researchers.</td>
</tr>
<tr>
<td>Description of sample</td>
<td>What are the important characteristics of the sample? e.g. demographic data, date</td>
<td>Important characteristics of the sample was presented in Table 1.</td>
</tr>
<tr>
<td>Data collection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interview guide</td>
<td>Were questions, prompts, guides provided by the authors? Was it pilot tested?</td>
<td>An interview guide with questions, prompts, and guides is provided in the supplemental files (Table S1). It was pilot tested.</td>
</tr>
<tr>
<td>Repeat interviews</td>
<td>Were repeat interviews carried out? If yes, how many?</td>
<td>No repeat interview was carried out.</td>
</tr>
<tr>
<td>Audio/visual recording</td>
<td>Did the research use audio or visual recording to collect the data?</td>
<td>We used audio recording to collect the data.</td>
</tr>
<tr>
<td>Field notes</td>
<td>Were field notes made during and/or after the interview or focus group?</td>
<td>No filed notes were made during or after the interviews.</td>
</tr>
<tr>
<td>Duration</td>
<td>What was the duration of the interviews or focus group?</td>
<td>The average duration of the interviews was 31min.</td>
</tr>
<tr>
<td>Data saturation</td>
<td>Was data saturation discussed?</td>
<td>Data saturation was discussed routinely during the data analysis phase.</td>
</tr>
<tr>
<td>Transcripts returned</td>
<td>Were transcripts returned to participants for comment and/or correction?</td>
<td>The transcripts were not returned to participants for comment or correction.</td>
</tr>
</tbody>
</table>

**Domain 3: analysis and findings**

Data analysis
<table>
<thead>
<tr>
<th>2</th>
<th>Number of data coders</th>
<th>How many data coders coded the data?</th>
<th>Two data coders, L.Y.T and N.G, coded the data.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Description of the coding tree</td>
<td>Did authors provide a description of the coding tree?</td>
<td>A description of the coding tree was provided in Table 2.</td>
</tr>
<tr>
<td>2</td>
<td>Derivation of themes</td>
<td>Were themes identified in advance or derived from the data?</td>
<td>The themes were derived from the data.</td>
</tr>
<tr>
<td>2</td>
<td>Software</td>
<td>What software, if applicable, was used to manage the data?</td>
<td>The data was managed using ATLAS.ti Scientific Software, version 8 (ATLAS.ti, Berlin, Germany).</td>
</tr>
<tr>
<td>2</td>
<td>Participant checking</td>
<td>Did participants provide feedback on the findings?</td>
<td>Participants did not provide feedback on the findings.</td>
</tr>
</tbody>
</table>

### Reporting

<table>
<thead>
<tr>
<th>2</th>
<th>Quotations presented</th>
<th>Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number</th>
<th>Participant quotations were presented to illustrate each minor theme. Quotations were identified.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Data and findings consistent</td>
<td>Was there consistency between the data presented and the findings?</td>
<td>There was consistency between the data presented and the findings.</td>
</tr>
<tr>
<td>3</td>
<td>Clarity of major themes</td>
<td>Were major themes clearly presented in the findings?</td>
<td>Major themes were clearly presented in the findings.</td>
</tr>
<tr>
<td>3</td>
<td>Clarity of minor themes</td>
<td>Is there a description of diverse cases or discussion of minor themes?</td>
<td>Descriptions of diverse cases and minor themes were included.</td>
</tr>
</tbody>
</table>
REFERENCES


guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, 78(22), e187-e285.