Ischemia with no obstructive coronary artery disease (INOCA): A patient self-report quality of life survey from INOCA international

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ABSTRACT

Background: There is limited information available regarding evidence of ischemia with no obstructive coronary arteries (INOCA) and quality of life.

Purpose: To determine associations between INOCA and self-reported physical, social, and mental health.

Methods: We conducted a survey of all members (n = 1579) of the INOCA International patient support group. Current self-reported diagnosis and health measures were collected. Functional capacity was retrospectively estimated using the Duke Activity Status Index (DASI), assessing levels of activities performed prior and after symptom onset.

Results: A total of 297 (20.8% response rate, 91% women) reported symptoms of chest pain, pressure, or discomfort in 92.9%. Overall, 34.4% were living with symptoms for ≥3 years before an INOCA diagnosis, and 77.8% were told their symptoms were not cardiac. Estimated functional capacity was higher prior to compared to after symptom onset (8.6 ± 1.8 METs vs 5.6 ± 1.8 METs; P < 0.0001). Most respondents reported an adverse impact of symptoms on their home life (80.5%), social life (80.1%), mental health (70.4%), outlook on life (69.7%), sex life (55.9%), and their partner/spouse relationship (53.9%), while approximately three-quarters reduced their work hours or stopped work completely, 47.5% retired early, and 38.4% applied for disability.

Conclusions: INOCA symptoms are associated with adverse physical, mental and social health quality of life. Increased patient awareness, physician recognition and diagnosis, and clinical trials are needed to develop evidence-based guidelines for this increasingly recognized cardiovascular disorder.

1. Introduction

The diagnosis of coronary artery disease (CAD) has traditionally focused on the presence of obstructive CAD. Nonetheless, it is estimated that at least 2 in every 5 patients with angina referred for elective angiography have nonobstructive coronary arteries, with rates even higher in women.[1,2] Ischemia does not require the presence of obstructive coronary arteries,[3] and this is recognized in the recent American Heart Association/American College of Cardiology chest pain guidelines expanding the definition of CAD to include both obstructive and nonobstructive CAD.[4] These same guidelines included a diagnostic pathway for evaluation of chest pain for those with evidence of myocardial ischemia but no obstructive coronary arteries (INOCA).[4]

Patients with INOCA pose both a diagnostic and therapeutic
challenge. Most patients with INOCA struggle for years to have an accurate diagnosis made, due to lack of physician awareness and limited availability of diagnostic testing and expertise in INOCA.[5] In addition, the optimal medical management for INOCA is not well-defined, given that medical therapy should be directed based on the diagnosis of the underlying cause of ischemia, which is best defined by invasive vasoreactive testing but this is not routinely performed.[6] As a result, patients with INOCA often live with protracted symptoms, undergo repeated diagnostic evaluations, and remain inadequately treated and inadequately diagnosed.[2]

To date, there is limited literature available on INOCA and quality of life. We sought to determine relations between INOCA symptoms and self-reported physical, social, and mental health. We hypothesized that all aspects of life could be adversely associated with INOCA symptoms.

2. Methods

The survey was provided to all members of the patient support group from the United Kingdom (UK)-Based INOCA International, which is an international organization for persons living with INOCA. Awareness of the survey was released by a newsletter, as well as on Twitter and Facebook but only members of the patient support group could access the platform to receive a link for the survey. Participants could fill the survey only once from a single IP address. The survey collection began on October 27, 2021 and was closed on December 27, 2021. The survey questions are included in Appendix 1. All data collected was anonymized and answered directly through SurveyMonkey®. Approval for this survey was received from the Cedars-Sinai institutional review board.

Assessment of functional capacity was measured using the Duke Activity Status Index (DASI), previously validated in women with suspected INOCA.[7] The survey assessed prior to and after the onset of symptoms. Functional capacity was calculated for each participant by converting the sum of DASI questionnaire scores to metabolic equivalents (METs) using the following formula: METs = 0.43 x DASI +9.6 / 3.5, as previously described.[8]

The statistical analysis included descriptive and frequency distributions, with chi-squared statistics for categorical variable comparisons, and t-tests for continuous variable comparisons. Simple linear regression was performed to determine the association of days lost due to poor health. All statistical analyses were conducted via STATA (College Station, TX) statistical software.

3. Results

Three hundred and twenty-eight respondents completed the survey. Given that the established membership of the patient support group of INOCA International is 1579, this represented a response rate of 20.8%. Thirty-one respondents reported not having INOCA, and by default could not answer any further questions in this survey and were excluded. Two hundred and ninety-seven respondents were finally included.

3.1. Characteristics of survey respondents

Most respondents were women (91.2%), which is slightly higher than the gender representation of the patient support group (83.3% women). The most common forms of diagnosis of INOCA in the respondents were coronary microvascular dysfunction (64.3%) and coronary artery spasm (50.5%). Almost two-thirds were diagnosed between the ages of 40 to 60 years. A history of myocardial infarction was reported in 22.6%. A medical history of migraines was common (46.5%), as was a history of any adverse pregnancy outcomes (47.1%), with 25.2% having at least one miscarriage. (Table 1).

| Table 1 |
|------------------|------------------|
| **Participant Characteristics** |
| **Respondents (N = 297)** |
| **Men** | 26 (8.8) |
| **Established Diagnoses** | **CMD** | 191 (64.3) |
| **Coronary Artery Spasm** | 150 (50.5) |
| **Nonobstructive atherosclerosis** | 18 (6.1) |
| **Heart Failure with Preserved Ejection Fraction** | 13 (4.4) |
| **Takotsubo Cardiomyopathy/Stress Cardiomyopathy** | 13 (4.4) |
| **Not given any diagnosis aside from INOCA** | 24 (8.1) |
| **Unknown** | 13 (4.4) |
| **INOCA** | 67 (22.6) |
| **Age at Diagnosis of INOCA** |
| <30 Years | 8 (2.7) |
| 30–40 | 29 (9.8) |
| 40–50 Years | 77 (25.9) |
| 50–60 Years | 115 (38.7) |
| >60 Years | 54 (18.2) |
| **Comorbidities** |
| Migraines/ frequent headaches | 138 (46.5) |
| Raynaud’s | 64 (21.5) |
| Thyroid disorder | 64 (21.5) |
| Rheumatoid Arthritis | 16 (5.5) |
| Lupus/ systemic lupus erythematosus | 4 (1.3) |
| Other autoimmune disorder | 64 (21.5) |
| History of stroke | 10 (3.3) |
| Kidney disease | 15 (5.1) |
| None | 76 (25.6) |
| Adverse Pregnancy Outcomes | 140 (47.1) |
| Hypertension During pregnancy | 55 (18.5) |
| Preeclampsia or Eclampsia | 38 (12.8) |
| Gestational Diabetes | 24 (8.1) |
| Preterm Delivery | 36 (12.1) |
| Miscarriage | 75 (25.2) |
| Does Not Apply To Me/I have Never Been Pregnant | 139 (46.8) |

Legend: INOCA -Ischemia with No Obstructive Coronary Arteries. MINOCA- Myocardial Infarction with No Obstructive Coronary Arteries.

3.2. Medical evaluation for INOCA symptoms

Most respondents (40.4%) had experienced INOCA symptoms for at least 1 to 5 years, with almost half of them experiencing symptoms for anywhere between 1 and 10 years before the diagnosis of INOCA was made, and 77.8% who had been told their symptoms were not cardiac. The symptoms the respondents experienced were numerous, but 92.9% reported symptoms of chest pain, chest pressure, or chest discomfort, and 80.6% reported shortness of breath. Only 8.4% felt the ambulance crew understood the diagnosis of INOCA and 15.3% would not call the ambulance for their INOCA symptoms because they felt their symptoms were not taken seriously. The most common triggers of INOCA reported were stress (79.8%), exercise/exertion (73.4%), and excitement/high emotional state (69%). For the women who had undergone menopause, 37.5% reported that their symptoms changed with menopause. The majority (50.2%) had seen 3 or more cardiologists for the treatment of INOCA. Additionally, 31.6% had been referred to a psychiatrist for their symptoms and 42.1% had been prescribed an anti-depressant. Most respondents (53.9%) had been told their symptoms were due to gastro-esophageal reflux disease, with 32% having undergone upper endoscopy for further evaluation. The majority of those surveyed reported that they were told that although their symptoms of INOCA may be unpleasant, they could not die from INOCA or have a heart attack (66.4%). Of the respondents who attended the emergency department for their symptoms, 69.4% were discharged without any treatment. (Table 2)

A minority (6.4%) were diagnosed with INOCA at the first consultation for the onset of symptoms. The majority (93.6%) reported multiple consultations before the diagnosis of INOCA was made. The majority (50.2%) also had consulted 3 or more cardiologists for the treatment of INOCA. All respondents underwent some diagnostic testing with non-invasive imaging performed in 93.3%, and 72.7% underwent

...
Table 2
INOCA Symptoms, Trigger, Referral Patterns & Evaluation

<table>
<thead>
<tr>
<th>Respondents (N= 297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years With INOCA Symptoms</td>
</tr>
<tr>
<td>&lt;1 Year</td>
</tr>
<tr>
<td>1-5 Years</td>
</tr>
<tr>
<td>5-10 Years</td>
</tr>
<tr>
<td>10-20 Years</td>
</tr>
<tr>
<td>&gt;20 Years</td>
</tr>
<tr>
<td>Time From Symptom Onset to Diagnosis of INOCA</td>
</tr>
<tr>
<td>&lt;1 Month</td>
</tr>
<tr>
<td>1 Month-1 Year</td>
</tr>
<tr>
<td>1-3 Years</td>
</tr>
<tr>
<td>3-10 Years</td>
</tr>
<tr>
<td>&gt;10 Years</td>
</tr>
<tr>
<td>Clinical Assessment of Symptoms</td>
</tr>
<tr>
<td>Told that symptoms were Not Cardiac</td>
</tr>
<tr>
<td>Seen in ED for Symptoms + Discharged without Treatment</td>
</tr>
<tr>
<td>Told that although symptoms of INOCA are unpleasant, you cannot die from it or have a heart attack</td>
</tr>
<tr>
<td>Had ever called an ambulance for symptoms</td>
</tr>
<tr>
<td>Knew when to call an ambulance or go to the hospital for INOCA symptoms</td>
</tr>
<tr>
<td>Ambulance Response to INOCA Symptoms</td>
</tr>
<tr>
<td>Taken to hospital + ECG + Monitor</td>
</tr>
<tr>
<td>No ambulance dispatched</td>
</tr>
<tr>
<td>Assessed by ambulance crew but not taken to hospital</td>
</tr>
<tr>
<td>Taken to hospital but no ECG or cardiac monitor performed</td>
</tr>
<tr>
<td>Ambulance crew understood the diagnosis of INOCA</td>
</tr>
<tr>
<td>Ambulance crew did not understand the diagnosis of INOCA</td>
</tr>
<tr>
<td>I never had to call an ambulance</td>
</tr>
<tr>
<td>I do not call the ambulance because they do not take my symptoms seriously</td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>General: Fatigue/exhaustion, Sweats</td>
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<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Chest pain/chest pressure/chest discomfort</td>
</tr>
<tr>
<td>Palpitations</td>
</tr>
<tr>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Back, shoulder, arm, neck, jaw pain</td>
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<tr>
<td>Neurologic: Confusion, brain fog, vision changes, light headedness, dizziness</td>
</tr>
<tr>
<td>Gastrointestinal: Nausea, reflux-like symptoms</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Triggers</td>
</tr>
<tr>
<td>Stress</td>
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<tr>
<td>Exercise/Exertion</td>
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<tr>
<td>Excitement or High Emotional State/Anger</td>
</tr>
<tr>
<td>Cold Weather</td>
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<tr>
<td>Change in Temperature or Weather Change</td>
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<tr>
<td>Triggered during Menstruation</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>No Known Triggers</td>
</tr>
<tr>
<td>Did Symptoms Change at Menopause?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Unsure</td>
</tr>
<tr>
<td>Have Not Undergone Menopause</td>
</tr>
<tr>
<td>Male- Does Not Apply</td>
</tr>
<tr>
<td>No Response</td>
</tr>
<tr>
<td>Prior to the Diagnosis of INOCA</td>
</tr>
<tr>
<td>Underwent Endoscopy to Assess for GERD</td>
</tr>
<tr>
<td>Underwent Endoscopy to Assess for GERD</td>
</tr>
<tr>
<td>Told Symptoms Were Not Cardiac</td>
</tr>
<tr>
<td>Referred to a Psychiatrist for Symptoms</td>
</tr>
<tr>
<td>Recommended to Start Antidepressant/Antianxiety Medication for Symptoms</td>
</tr>
<tr>
<td>Seen in the ED For Symptoms of INOCA &amp; Discharged Without Treatment</td>
</tr>
<tr>
<td>Total Consultants Seen Prior to INOCA Diagnosis</td>
</tr>
<tr>
<td>Diagnosed Right Away</td>
</tr>
<tr>
<td>1-2 Additional Consultants</td>
</tr>
<tr>
<td>3-5 Additional Consultants</td>
</tr>
<tr>
<td>&gt;5 Additional Consultants</td>
</tr>
<tr>
<td>Non-invasive Imaging</td>
</tr>
<tr>
<td>ECG</td>
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</tbody>
</table>

Table 2 (continued)

<table>
<thead>
<tr>
<th>Respondents (N= 297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiogram</td>
</tr>
<tr>
<td>Exercise Stress Test</td>
</tr>
<tr>
<td>Stress Echocardiogram</td>
</tr>
<tr>
<td>CT Angiogram</td>
</tr>
<tr>
<td>Cardiac MRI</td>
</tr>
<tr>
<td>PET Scan</td>
</tr>
<tr>
<td>Invasive Imaging</td>
</tr>
<tr>
<td>Cardiac Catheterization</td>
</tr>
<tr>
<td>Cardiac Catheterization with Acetylcholine Testing</td>
</tr>
<tr>
<td>Number of Cardiologists Consulted for Treatment of INOCA</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>≥3</td>
</tr>
<tr>
<td>Finding An INOCA Specialist</td>
</tr>
<tr>
<td>Self-Referred</td>
</tr>
<tr>
<td>Referred by Cardiologist</td>
</tr>
<tr>
<td>Referred by Family Doctor or Other Doctor</td>
</tr>
<tr>
<td>Never Under the Care of an INOCA Specialist</td>
</tr>
<tr>
<td>Currently Under the Care of an INOCA Specialist</td>
</tr>
</tbody>
</table>

Legend: CT computed tomography; ECG electrocardiogram; GERD Gastroesophageal Reflux Disease; INOCA Ischemia with No Obstructive Coronary Arteries, MRI magnetic resonance imaging; PET positron emission tomography, invasive imaging but only 32.7% underwent cardiac catheterization with acetylcholine testing. Self-referral to a cardiology specialist familiar with INOCA was reported by 35.7% of individuals, and 38.4% reported never being under the care of an INOCA specialist. Of the respondents, 49.2% were currently under the care of a cardiology specialist (Table 2).

3.3. Associations with health quality of life

**General Health:** At the time of the survey, most of the respondents living with INOCA reported their health as being fair (32.7%) or poor (19.2%) (Table 3).

**Physical Health:** Prior to the onset of INOCA symptoms, the mean functional capacity for those surveyed was 8.6 ± 1.8 METs, with 69.7% able to perform >8 METs. Following the onset of symptoms, the reported functional capacity was 5.6 ± 1.8 METs, with only 11.4% able to perform >8 METs. (Table 3, Table 4). Those who reported poorer health had a lower functional capacity (data not shown). Those with a prior myocardial infarction had lower post-diagnosis functional capacity compared to those without a myocardial infarction (5.5 ± 1.8 METs vs. 8.5 ± 1.9 METs, respectively; p < 0.0001). Those with self-reported kidney disease had lower symptom onset functional capacity compared to those without kidney disease (4.6 ± 1.0 METs vs. 5.7 ± 1.9 METs; p = 0.031), and those with any co-morbidities had a lower post-symptom onset functional capacity than those with no co-morbidities (5.1 ± 1.9 METs vs. 8.5 ± 1.8 METs; p = 0.0027).

**Social and Mental Health:** While living with INOCA, most of the respondents reported an adverse impact on their home life (80.5%), social life (80.1%), mental health (70.4%), outlook on life (69.7%), sex life (55.9%), and their partner/spouse relationship (53.9%). (Table 3) Those who reported an adverse impact of INOCA on specific aspects of their social and mental health had a significantly lower functional capacity compared to those who did not report any adverse impact of INOCA on those factors (Fig. 1). Those who reported that their sex life was adversely affected had lower mean functional capacity than those did not report any adverse impact (5.1 ± 1.5 METs vs. 6.9 ± 1.9 METs; p < 0.0001).

**Work and Disability:** Most respondents (69.0%) felt that there was an adverse impact on their work life while living with INOCA; and those who reported an adverse impact on their work life had a significantly lower mean functional capacity than those did not report any adverse impact on their work life (5.3 ± 1.5 METs vs. 7.6 ± 2.2 METs,
approximately 3 of every 4 respondents had either reduced their work hours or had stopped work completely, 47.5% retired early, and 38.4% applied for disability (Table 3). Of those who applied for disability, 47.5% retired early, and 38.4% were successful in receiving disability benefits, with those who were successful having a lower functional capacity than those who were not (4.8 ± 1.4 METs vs. 5.9 ± 2.1 METs, respectively; p < 0.0001). Those who applied for disability, retired early or reduced working hours had a significantly lower functional capacity than those who did not (Fig. 2).

Living with INOCA Symptoms and Days of Declining Health: After onset of symptoms, the respondents reported that for every 1 MET decrease in functional capacity, there was a loss of 3.0 ± 0.6 days of physical health per month, 1.8 ± 0.6 days of mental health per month, and 2.9 ± 0.7 days of inability to perform recreational activities per month (p < 0.0001) (Fig. 3).

4. Discussion

This study depicts adverse associations with many aspects of quality of life in INOCA patients. Patients reported that their physical, mental and social health were adversely impacted by INOCA symptoms indicative of reduced overall quality of life. Additionally, when compared to prior to the onset of INOCA symptoms, living with INOCA was associated with a significant reduction of approximately 3 METS of functional capacity, comparable to losing the ability to do light household activities of daily living (dressing, bathing, use the toilet independently), or being able to walk 1 block on level ground. Those who reported an adverse impact of INOCA on specific aspects of life had a relatively greater reduction in functional capacity, when compared with those who did not. These findings are unique, as there has been very limited data relating the patient experience of living with INOCA.

For the respondents of this survey, functional capacity was significantly reduced while living with INOCA when compared to prior to the onset of INOCA symptoms. Functional capacity is an established independent predictor of mortality,[9] particularly when functional capacity falls below 5 METS,[10] which in this surveyed population was the case for 5.1% prior to the onset of symptoms, but increased to 41.4% post-symptom onset. In the Women’s Ischemia Syndrome Evaluation (WISE) study, poor functional capacity in women with INOCA was associated with an adverse prognosis.[11] A prior evaluation of registry studies demonstrated that patients with INOCA have relatively greater physical limitations and anginal frequency than patients with stable obstructive coronary artery disease and acute myocardial infarction survivors.[12] This conflicts with findings from the WISE study, where functional capacity was demonstrated to be slightly greater in those women with nonobstructive CAD, when compared with obstructive CAD, using the DASI (5.0 METs ± 1.8 METS, respectively; p = 0.01).[13] In this current INOCA survey, following symptom onset functional capacity was similar to what was seen in WISE (5.6 ± 1.8 METS).[13] Further, the survey demonstrates for the first time a decline in functional capacity associated with worsened aspects of physical, mental, and social health. Specifically, for every 1 MET reduction in functional capacity once experiencing INOCA symptoms, there was a self-reported 3-day loss in physical health and ability to perform recreational physical activities per month, and 2 days per month with suboptimal mental health. The implication of poor functional capacity is important in understanding the impact of this disease and appreciating that the prognosis of INOCA is not benign.

Mental health was adversely impacted in 70.4% of those surveyed, with almost the same number reporting that INOCA had negatively affected their outlook on life. Psychological stress, which includes anxiety, depression, anger and personality disturbances, can be quite common in patients with CAD,[14] including those with INOCA.[15] It is estimated that the prevalence of depression is 15%–30% in those with coronary heart disease, and highest post MI and in women,[16] but it is unclear if these estimates included patients with nonobstructive CAD. The WISE study demonstrated that higher anxiety variables predicted more severe cardiac symptoms.[17] In a previously reported study of 66 patients with INOCA, cardiac anxiety levels as assessed using the
Fig. 1. Estimated Functional Capacity Based on Impact of INOCA on Specific Aspects of Life
Functional capacity based on impact of INOCA on specific aspects of life.
Legend: INOCA = Ischemia with No Obstructive Coronary Arteries; METs = metabolic equivalents.

Fig. 2. Estimated Functional Capacity Based on Impact of Living with INOCA on Work and Disability
Functional capacity in those living with INOCA based on specific aspects of work and application for disability.
Legend: INOCA = Ischemia with No Obstructive Coronary Arteries; METs = metabolic equivalents.
Cardiac Anxiety Questionnaire were significantly higher in INOCA patients when compared with prior assessments in patients with sudden cardiac death, and quite similar to those documented in patients with hypertrophic cardiomyopathy. [12] Psychological stress can induce endothelial dysfunction and be an underlying cause of INOCA, particularly coronary microvascular dysfunction and vasospasm. [18–20]

The social health of patients was adversely impacted in those living with INOCA symptoms, with at least 4 of every 5 respondents reporting that their symptoms adversely affected their home life and social life. Sexual activity may often decrease after a myocardial infarction due to fears of inducing another myocardial infarction or anginal symptoms, as was demonstrated in a study of myocardial infarction survivors, where 47% of patient abstained or reduced their sexual activity after their myocardial infarction. [21] This is comparable to the current survey results, where 1 in 2 patients reported that following onset of INOCA symptoms, their relationship with their partner/spouse and their sex life was adversely impacted. Providing counselling to patients regarding sexual activity after an acute myocardial infarction is far too infrequent, [22] but for those with INOCA or myocardial infarction with no obstructive coronary arteries (MINOCA), it remains unknown what counselling is provided, if any. Based on the 2021 AHA Scientific Statement on sexual activity and CVD, “sexual activity is reasonable for patients who can exercise ≥3–5 METs without any angina, without angina, excessive dyspnea, ischemic ST-segment changes, cyanosis, hypotension, or arrhythmia.” [23] In the current survey, 41.4% of the INOCA patients reported a functional capacity was <5 METs after onset of symptoms, and those who reported that their sex life was adversely impacted had a significantly lower functional capacity, compared with those whose sex life was not adversely affected.

We observed a significant association of living with INOCA symptoms on the ability to work, with almost 7 out of every 10 patients reporting that INOCA adversely affected their work life, resulting in more than half reducing their work hours or even retiring earlier than expected. Approximately one third of those surveyed changed their job or roles resulting in lower pay. Application for disability was also quite common in those living with INOCA. Our findings are consistent with a study of 66 patients where INOCA was assessed using cardiac magnetic resonance and demonstrated that patients with INOCA frequently missed work (1.1 ± 2.2 full workdays missed in last 2 weeks) and had work limitations, suggestive of a substantial economic impact by work productivity loss. [12] Nonetheless, this study did not address disability or changes in job or roles that also result in lower pay directly for the patient. A study from Denmark examined patients referred for coronary angiography for symptoms of stable angina, and demonstrated no difference in premature exit from the workforce or being on disability in those with obstructive and nonobstructive CAD. [24] The national register from Sweden demonstrated that persons of working ages with ischemic heart disease took 83.9 days per year of disability leave in the first post-event year after adjusting for age, sex and education (~6.9 days per month). [25] This was six-fold greater than the national average of disability days. Nonetheless, this prior study did not distinguish between those with obstructive versus nonobstructive CAD. Additionally, disability days leveled off within the second year similar to the pre-event year. [25]

The current results suggest that patients with INOCA often initially live with diagnostic uncertainty despite the presence of symptoms that adversely impact their lives. Most patients reported living with their symptoms for at least 1 year before a diagnosis was made, with almost half experiencing symptoms of INOCA for 1 to 10 years before diagnosis. More than half had seen three or more consultants before their diagnosis of INOCA was made, and three or more cardiologists for the treatment of INOCA. Many reported undergoing endoscopy or psychiatric evaluation of their symptoms. Even for these patients with a diagnosis of INOCA, less than a third had undergone cardiac catheterization with coronary
flow reserve testing to determine optimal medical therapies, given that there are many different forms of INOCA. This on top of a lack of understanding of INOCA even within the cardiology community, results in the signs and symptoms of INOCA often being downplayed, dismissed and often untreated and undiagnosed.[26]

5. Study limitations

There are several limitations in this study. Although most respondents were female, limiting implications somewhat to men, however INOCA is a condition that predominantly affects women. This survey was limited to the patient support group of INOCA International. Accordingly, the survey reflects: (1) participants had an established hypothesis is that the underlying pathophysiologic process may be due to underlying coronary microvascular ischemia.[29]

6. Conclusions

INOCA symptoms are associated with adverse physical, mental and social health quality of life, comparable to patients with symptoms of obstructive CAD. Additionally, functional capacity declines are evident following onset of INOCA symptoms. Increased patient awareness, physician recognition and diagnosis, and clinical trials are needed to develop evidence-based guidelines for this increasingly recognized cardiovascular disorder.

Disclosures

MG: None; NK: None; MG2: None; CB: Based on agreements held by the University of Glasgow, CB undertakes research and consultancy work with Abbott Vascular, AstraZeneca, Boehringer Ingelheim, GSK, HeartFlow, Novartis and Valo Health. He is supported by the British Heart Foundation (RE/18/6134217). PGC: nothing to disclose. JCK: Speaker honoraria from Menarini Farmaceutica srl and Servier. CNBM: Caladrius, Abbott Diagnostics, iRhythm.

Acknowledgment

The authors would like to thank the members of INOCA International for participating in this survey and contributing to our knowledge of living with INOCA.

Appendix 1 Survey

<table>
<thead>
<tr>
<th>INOCA Survey</th>
<th>We are interested in how living with INOCA (Ischemia with No Obstructive Coronary Arteries) has impacted your medical care, health and life. Your responses will remain anonymous. Thank you for your time in responding to our questions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question 1 Do you have Ischemia with No Obstructive Coronary Arteries (INOCA)? □ Yes □ No (if No, no further questions)</td>
<td></td>
</tr>
<tr>
<td>Question 2 Would you say that your general health is: □ Excellent □ Very Good □ Good □ Fair □ Poor</td>
<td></td>
</tr>
<tr>
<td>Question 3 Which of the following forms of INOCA were you diagnosed with? (Check all that apply) □ Coronary Microvascular Dysfunction □ Coronary Artery Spasm □ Nonobstructive Atherosclerosis □ Heart Failure with Preserved Ejection Fraction (HFpEF) □ Takotsubo’s Syndrome (also known as Stress Cardiomyopathy/“Broken Heart” Syndrome) □ I was not given a diagnosis aside from INOCA □ I don’t know</td>
<td></td>
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<tr>
<td>Question 4 How long did it take from the onset of your symptoms to getting a diagnosis of INOCA? □ Less than 1 months □ 1-12 months □ 1-3 years □ 3-5 years □ 5-10 years</td>
<td></td>
</tr>
</tbody>
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Question 5
Prior to your diagnosis of INOCA were you ever told your symptoms were due to Reflux or GERD (gastroesophageal reflux disease)?
☐ Yes
☐ No

Question 6
Prior to your diagnosis of INOCA did you undergo an endoscopy to assess for reflux/GERD based on your symptoms?
☐ Yes
☐ No

Question 7
Prior to your diagnosis of INOCA were you ever told your symptoms were not cardiac?
☐ Yes
☐ No

Question 8
Prior to your diagnosis of INOCA were you seen in the Emergency Room/A&E for your symptoms of INOCA and discharged without any treatment?
☐ Yes
☐ No

Question 9
Prior to your onset of symptoms of INOCA, which of the following could you previously do? (Check All That Apply)
☐ Take Care of Yourself (ie. dress, eat, bathe, use toilet)
☐ Walking Indoors
☐ Walk 200 yards (182 meters) on level ground
☐ Climb a flight of stairs or walk up a hill
☐ Run a Short Distance
☐ Do light work around the house (ie. dusting, washing dishes)
☐ Do moderate work around the house (ie. vacuuming, sweeping floors, carrying groceries)
☐ Do heavy work around the house (ie. scrubbing floors, lifting or moving heavy furniture)
☐ Do yardwork (ie. raking leaves, weeding, pushing a lawn mower)
☐ Have Sexual Relations
☐ Participate in Moderate Recreational Activities (ie. golf, bowling, doubles tennis, throwing baseball, kicking football)
☐ Participate in Strenuous Sports (ie. swimming, singles tennis, football, basketball, skiing)

Question 10
With your diagnosis of INOCA, which of the following can you currently do? (Check All That Apply)
☐ Take Care of Yourself (ie. dress, eat, bathe, use toilet)
☐ Walking Indoors
☐ Climb a flight of stairs or walk up a hill
☐ Run a Short Distance
☐ Do light work around the house (ie. dusting, washing dishes)
☐ Do moderate work around the house (ie. vacuuming, sweeping floors, carrying groceries)
☐ Do heavy work around the house (ie. scrubbing floors, lifting or moving heavy furniture)
☐ Do yardwork (ie. raking leaves, weeding, pushing a lawn mower)
☐ Have Sexual Relations
☐ Participate in Moderate Recreational Activities (ie. golf, bowling, doubles tennis, throwing baseball, kicking football)
☐ Participate in Strenuous Sports (ie. swimming, singles tennis, football, basketball, skiing)

Question 11
How many consultants/specialists/doctor did you see prior to your diagnosis of INOCA?
☐ 0 (meaning diagnosed right away)
☐ 1-2
☐ 3-5
☐ >5

Question 12
How many cardiologists have you consulted for treatment of your INOCA?
☐ 1
☐ 2
☐ 3-5
☐ >5

Question 13
Prior to your diagnosis of INOCA were you ever referred to a psychiatrist for your symptoms or was such a referral suggested to you by your doctor?
☐ Yes
☐ No

Question 14
Have you ever been started on, or been recommended to start, an antidepressant or antianxiety medication for your INOCA symptoms?
☐ Yes
☐ No

Question 15
Are you under the care of a specialist in INOCA?
☐ Yes
☐ No
☐ Awaiting Initial Appointment
☐ I Don’t Know

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If you under the care of a specialist in INOCA, how did you get to them?
□ Self-Referral (I found the specialist myself)
□ My Family Doctor/GP referred me to the INOCA specialist
□ Another cardiologist referred me to the INOCA Specialist
□ Another doctor referred me to the INOCA Specialist
□ I have never been under the care of an INOCA Specialist

Question 17
How many years have you had symptoms of INOCA for?
□ Less than 1 year
□ 1-5 years
□ 5-10 years
□ 10-20 years
□ >20 years

Question 17
At What Age were you Diagnosed with INOCA?
□ Less than 30
□ 30-40
□ 40-50
□ 50-60
□ 60-70
□ >70 years

Question 18
Have you ever had a Heart Attack?
□ Yes
□ No
□ Unsure

Question 19
Have you ever been told that although your symptoms of INOCA may be unpleasant, you cannot die from it and cannot have a heart attack?
□ Yes
□ No

Question 20
Have you ever had to call an Ambulance for your symptoms of INOCA?
□ Yes
□ No

Question 21
When you have called an Ambulance for your symptoms of INOCA, have you experienced any of the following? (choose all that apply)
□ Taken to the Hospital and Cardiac Monitor Attached and ECG performed
□ No Ambulance dispatched
□ Assessed by Ambulance Crew but not taken to the hospital
□ Taken to the Hospital but No Cardiac Monitor or ECG performed despite symptoms
□ Ambulance Crew Understood the Diagnosis of INOCA
□ Ambulance Crew DID NOT Understand the Diagnosis of INOCA
□ I have never had to call an Ambulance
□ I do not call the Ambulance because they do not take my symptoms seriously

Question 22
As a patient living with INOCA, do you know when to call for an ambulance or go to the hospital for your INOCA symptoms?
□ Yes
□ No

Question 23
Which diagnostic tests have you had related to your INOCA symptoms? (Check all that apply)
□ ECG
□ Echocardiogram (also called Echo)
□ Exercise Stress Test
□ Stress Echocardiogram (Also called Stress Echo)
□ CT Angiogram
□ Cardiac MRI
□ PET Scan
□ Cardiac Catheterization (Also called Angiogram)
□ Cardiac Catheterization (Also called Angiogram) with Acetylcholine Testing
□ None of the Above

Question 24
Which symptoms do you experience related to INOCA? (Check all that apply)
□ Chest Pain/Chest Pressure/Chest Discomfort
□ Shortness of Breath
□ Back Pain
□ Shoulder or Arm Pain or Pressure
□ Neck/Jaw Pain
□ Palpitations/Racing of the heart
□ Sweats
□ Lightheadedness, Dizziness
□ Nausea, reflux-like symptoms
□ Confusion, Brain Fog

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□ Vision Changes  
□ Other  
Question 25  
Have You Ever Left any Doctor’s Appointment and come away thinking they did not understand INOCA?  
□ All the Time  
□ Often  
□ Occasionally  
□ Never  
Question 26  
Have You Ever Had to Stop Working because of INOCA?  
□ Yes  
□ No  
Question 27  
Did You Had to Retire Early because of INOCA?  
□ Yes  
□ No  
Question 28  
Have You Ever Had to Reduce Working Hours because of INOCA?  
□ Yes  
□ No  
Question 29  
Have You Ever Had to Change Jobs or Roles for a Less Stressful Position because of your symptoms from INOCA?  
□ Yes  
□ No  
Question 30  
Have You Ever Had to Change Jobs or Roles that Resulted in Lower Pay Because of your Symptoms with INOCA?  
□ Yes  
□ No  
Question 31  
Have You Ever Had to Apply for Disability Benefits because of your symptoms with INOCA?  
□ Yes  
□ No  
□ I have never applied for disability benefits  
Question 32  
If You Had to Apply for Disability Benefits because of your symptoms with INOCA, was your application successful?  
□ Yes  
□ No  
Question 33  
Do You Ever Worry about being home alone?  
□ Yes  
□ No  
Question 34  
Do You Ever Worry about going out alone?  
□ Yes  
□ No  
Question 35  
Do You Drive?  
□ Yes,  
□ No, stopped due to INOCA symptoms  
□ Never Drove  
Question 36  
Did you have any of the following conditions during pregnancy? (check all that apply)  
□ Hypertension During pregnancy  
□ Preeclampsia or Eclampsia  
□ Gestational Diabetes  
□ Preterm Delivery  
□ Miscarriage  
□ Does Not Apply To Me, I have Never Been Pregnant  
Question 37  
Do you have any of the following conditions? (check all that apply)  
□ Migraines/ Frequent Headaches  
□ Raynaud’s  
□ Thyroid Disorder  
□ Rheumatoid Arthritis  
□ Lupus/ Systemic Lupus Erythematosus  
□ Other Autoimmune Disorder  
□ History of Stroke  
□ Kidney Disease  
□ None  
Question 38  
Do You Have Any of the Following Triggers for Your Symptoms of INOCA?  
□ Stress  
□ Exercise/Exertion  
□ Excitement or High Emotional State/Anger  
□ Cold Weather  
□ Change in Temperature or Weather Change  
□ Triggered during Menstruation

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.09.047.

References
