

Supplemental Appendix

Supplemental Appendix S1: Supplemental Methods

Definitions of Baseline Characteristics

All variables are per diagnosis at baseline, unless indicated otherwise (e.g. “history of...”).

Variable	Definition
<i>Demographics</i>	
Age	Patient’s age at first clinic visit, calculated by subtracting the year of their first WHC visits by their year of birth.
Race	Self-reported with options: African-Canadian, Caucasian, East Asian, First Nation, South Asian, Other. “Other” includes mixed ancestry. As the large majority of this cohort identified as solely Caucasian, this variable was made into a binary.
Partnered status	Self-reported marital status, categorized into a binary wherein “partnered” refers to common law or married, and not partnered refers to single, widowed or divorced.
Education	Self-reported with options: High school or less, some post-secondary (any amount of college or university up to and including a Bachelor’s degree), and post-secondary above a

	Bachelor's (e.g., law degree, Master's, doctorate, PharmD, MD, etc.).
Working status	Self-reported and categorized as employed, not employed" (including if retired), or on medical leave/disability.
<i>Clinical</i>	
Family history of premature cardiovascular disease	Self-reported as any first-degree relative (parent, sibling, child) having had a cardiovascular diagnosis under 65 years old for women or under 55 years old for men.
Dyslipidemia	Defined in consults as total cholesterol \geq 240 mg/dL [6.2 mmol/L], low density lipoprotein cholesterol \geq 160 mg/dL [4.1 mmol/L], high-density lipoprotein cholesterol \leq 40 mg/dL [1.0 mmol/L] and triglycerides \geq 200 mg/dL [2.3 mmol/L] ¹ .
Diabetes	Defined in consults as fasting plasma glucose \geq 126 mg/dL (7 mmol/L) in at least 2 baseline measurements and a hemoglobinA1c \geq 6.5% ² .
Hypertension	Defined in consults as systolic/diastolic blood pressure \geq 140/90mmHg per the Canadian hypertension guidelines ³ .
Obesity	Body mass index (BMI) of \geq 30 kg/m ² , calculated from the most recent height and weight measurements in the patient's health records ⁴ .
Smoking history	Self-reported as current, former, or never smoker.

<p>Chronic kidney dysfunction</p>	<p>Indicated in consults as defined by abnormalities in either kidney structure or function for >3 months including an estimated glomerular filtration rate (eGFR) of under 60 mL/min/1.73 m², albuminuria >3 mg/mmol by albumin to creatinine ratio, urine sediment abnormalities, kidney transplant history, or structural abnormalities detected by imaging⁵.</p>
<p>History of arrhythmia</p>	<p>Indicated in past or current physician consults such as atrial fibrillation, sick sinus syndrome, ventricular tachycardia or ventricular fibrillation.</p>
<p>History of prior transient ischemic attack (TIA)</p>	<p>As diagnosed by a neurologist or other attending specialist and is defined as a temporary episode of neurological dysfunction caused by a brief disruption cerebral perfusion⁶.</p>
<p>Thyroid dysfunction</p>	<p>A thyroid disorder of hypothyroidism or hyperthyroidism indicated in consults as defined by triiodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone (TSH) levels under or over clinical thresholds^{7,8}. Thyroid dysfunction due to an autoimmune cause (e.g., Grave's, Hashimoto's), infectious (e.g., thyroiditis) or surgical causes requiring supplemental thyroid medications (e.g., thyroidectomy) are included.</p>
<p>History of migraines</p>	<p>Indicated in past or current physician consults, and/or self-report, defined as a type of headache characterized by</p>

	recurrent attacks of moderate to severe unilateral pulsating pain ⁹ .
History of Raynaud’s syndrome	Indicated in past or current physician consults, and/or self-report, defined as episodic vasospasm to the distal extremities, usually triggered by exposure to cold temperatures ¹⁰ .
History of chronic obstructive pulmonary disease (COPD)	Indicated in past or current physician consults, defined as a pulmonary disease characterized by chronic respiratory symptoms due to abnormalities in the airways and/or alveoli, leading to chronic progressive airflow obstruction ¹¹ .
History of any autoimmune disease	Indicated in past or current physician consults.
History of clinical anxiety	Indicated in past or current physician consults, and encompasses anxiety-related diagnoses of post-traumatic stress disorder, panic disorder, and phobias ¹² .
<i>Female-specific</i>	
Menopause status	Indicated in physician consults and confirmed by self-report as pre-, peri-, post-, or surgical due to a hysterectomy. Surgical and post-menopausal status was defined as not having had a menstrual period for over 6 months ¹³ . Perimenopausal status is defined as the transitional phase preceding menopause, characterized by hormonal fluctuations, irregular menstrual cycles, and the onset of

	vasomotor symptoms, marking the end of reproductive capacity ¹³ .
Number of children born	Self-reported as number of births in the patient's lifetime. The number of children in multiparous pregnancies are included in this count.
Preeclampsia or hypertension in pregnancy	Indicated in past or current physician consults, and/or self-report, and is defined as gestational systolic/diastolic blood pressure $\geq 140/90$ mmHg (with proteinuria, for preeclampsia) ¹⁴ .
Polycystic ovarian syndrome (PCOS)	Indicated in past or current physician consults, and/or self-report as defined by two of: oligo- and/or anovulation; clinical and/or biochemical signs of hyperandrogenism; imaging evidence of polycystic ovaries ¹⁵ .

Definitions of Vasomotor Diagnoses

Regarding specific etiologies, for both CMD and coronary vasospasm, we used the Coronary Vasomotion Disorder International Study Group (COVADIS) definition of probable and definite¹⁶. In brief, definitive CMD is diagnosed when all 4 the following criteria were met: (1) symptoms of myocardial ischemia, (2) Absence of CAD (<50% stenosis in any epicardial artery), (3) objective evidence of ischemia (on exercise stress testing or stress imaging), and (4) evidence of impaired coronary microvascular function on coronary flow reserve invasive testing by coronary flow reserve (CFR) or index of microcirculatory resistance (IMR)¹⁶. Probable CMD includes the first three criteria but

not the fourth¹⁶. Regarding coronary vasospasm, the COVADIS group developed three criteria for diagnosis including (1) nitrate responsive angina (2) transient ischemic ECG changes including >1mm of ST depression or elevation at the time of symptoms and (3) transient >90% constriction of an epicardial artery during coronary angiography either spontaneously or in response to a provocative stimulus such as acetylcholine or ergonovine. Definite vasospasm is defined as the first criteria plus either the second or the third criteria. Probable angina is defined as the first criteria without the second or third¹⁷.

Supplemental Methods References

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³ Rabi DM, McBrien KA, Sapir-Pichhadze R, et al. Hypertension Canada's 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children. *Can J Cardiol*. 2020;36(5):596-624.

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¹¹ Global Initiative for Chronic Obstructive Lung Disease. 2024 GOLD Report. Available at: <https://goldcopd.org/2024-gold-report/>. 2024. [Accessed on February 4, 2024]

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¹⁴ Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. *Obstet Gynecol*. 2020;135(6):e237-e260.

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¹⁷ Beltrame JF, Crea F, Kaski JC, et al. Coronary Vasomotion Disorders International Study Group (COVADIS). International standardization of diagnostic criteria for vasospastic angina. *Eur Heart J.* 2017;38(33):2565-2568.

Supplemental Tables

Supplemental Table S1. Counts and proportions of medications and therapies in patients with MINOCA and INOCA by timepoint.

Category	Class	Medication	MINOCA (n=47)		INOCA (n=109)	
			Baseline	3yr	Baseline	3yr
Antiplatelets/ Anticoagulants	Antiplatelet	ASA	30 (64)	31 (66)	38 (35)	39 (36)
		Any non-ASA	6 (13)	3 (3)	3 (3)	3 (3)
	Anticoagulant	Any	0 (0)	1 (2)	3 (3)	4 (4)
Anti-Anginal	BB	Any	16 (34)	18 (38)	29 (27)	38 (35)
	CCBs	DHPs (amlodipine, nifedipine)	20 (43)	22 (47)	32 (29)	55 (50)
		Non-DHPs (diltiazem, verapamil)	6 (13)	8 (17)	17 (16)	27 (25)
	Nitrates	Short-acting nitrates (spray)	8 (17)	16 (34)	19 (17)	38 (35)
		Long-acting nitrates (patch, IMN or IDN)	9 (19)	19 (40)	24 (22)	58 (53)
	Other	Ivabradine	0 (0)	2 (4)	1 (1)	3 (3)
		Ranolazine	0 (0)	2 (4)	0 (0)	24 (22)
	Cholesterol- Lowering	Statin	Any	21 (45)	25 (53)	34 (31)
Other		Ezetimibe	1 (2)	1 (2)	0 (0)	6 (6)
		PCSK9 Inhibitor	0 (0)	0 (0)	0 (0)	4 (4)

Other Therapies	ACE/ARB	Any	12 (26)	14 (30)	21 (19)	28 (26)
	Diuretic	Any	1 (2)	3 (6)	14 (13)	16 (15)
	Antiglycemic	Insulin	0 (0)	0 (0)	3 (3)	4 (4)
		GLP-1 agonists (eg. semaglutide)	0 (0)	0 (0)	1 (1)	1 (1)
		SGLT-2 inhibitors (eg. empagliflozin)	0 (0)	0 (0)	0 (0)	1 (1)
		Other (incl. metformin)	2 (4)	2 (4)	6 (6)	9 (8)
	Antidepressant	Any	10 (21)	9 (19)	26 (24)	26 (24)
	HRT	Any	2 (4)	3 (6)	12 (11)	13 (12)
	Spinal cord stimulator	0 (0)	1 (2)	0 (0)	1 (1)	

All values presented as n (%).

P-values denoted by hyphen (-) reflect too few n in at least one cell (n<5) in the group (MINOCA or INOCA) to interpret statistical significance.

ACE = Angiotensin-converting enzyme inhibitor, **ARB** = Angiotensin II receptor antagonist, **ASA** = Acetylsalicylic acid, **BB** = Beta blocker, **CCB** = Calcium channel blocker, **DHP** = 1,4-Dihydropyridine, **GLP-1** = Glucagon-like peptide-1, **HRT** = Hormone replacement therapy, **IDN** = Isosorbide dinitrate, **IMN** = Isosorbide mononitrate, **PCSK9** = Proprotein convertase subtilisin/kexin type 9, **SGLT-2** = Sodium-glucose cotransporter-2

Supplemental Table S2. Changes in therapies between WHC baseline and 3 years post-baseline.

Category	Class	Medication	MINOCA (n=47)				INOCA (n=109)			
			On pre-WHC and stayed on	Prescribed in WHC	Take n off in WHC	Never on	On pre-WHC and stayed on	Prescribed in WHC	Take n off in WHC	Never on
Antiplatelets/ Anticoagulants	Antiplatelet	ASA	24 (51)	7 (15)	6 (13)	10 (21)	25 (23)	14 (13)	13 (12)	57 (52)
		Any non-ASA	0 (0)	1 (2)	6 (13)	40 (85)	1 (1)	2 (2)	2 (2)	104 (95)
	Anticoagulant	Any	0 (0)	1 (2)	0 (0)	46 (98)	2 (2)	2 (2)	1 (1)	104 (95)
Anti-Anginal	BB	Any	10 (21)	8 (17)	6 (13)	23 (49)	23 (21)	15 (14)	6 (6)	65 (60)
	CCBs	DHPs (amlodipine, nifedipine)	16 (34)	6 (13)	4 (9)	21 (45)	26 (24)	29 (27)	6 (6)	48 (44)
		Non-DHPs (diltiazem, verapamil)	4 (9)	4 (9)	2 (4)	37 (79)	15 (14)	12 (11)	2 (2)	80 (73)
	Nitrates	Short-acting nitrates (spray)	7 (15)	9 (19)	1 (2)	30 (64)	11 (10)	27 (25)	8 (7)	63 (58)
		Long-acting nitrates (patch, IMN or IDN)	6 (13)	13 (28)	3 (6)	25 (53)	17 (16)	41 (38)	7 (6)	44 (40)
	Other	Ivabradine	0 (0)	2 (4)	0 (0)	45 (96)	1 (1)	2 (2)	0 (0)	106 (97)

		Ranolazine	0 (0)	2 (4)	0 (0)	45 (96)	0 (0)	24 (22)	0 (0)	85 (78)
Cholesterol-Lowering	Statin	Any	19 (40)	6 (13)	2 (4)	20 (43)	32 (29)	15 (14)	2 (2)	60 (55)
	Other	Ezetimibe	1 (2)	0 (0)	0 (0)	46 (98)	0 (0)	6 (6)	0 (0)	103 (94)
		PCSK9 Inhibitor	0 (0)	0 (0)	0 (0)	47 (100)	0 (0)	4 (4)	0 (0)	105 (96)
Other	ACE/ARB	Any	11 (23)	3 (6)	1 (2)	32 (68)	19 (17)	9 (8)	2 (2)	79 (72)
	Diuretic	Any	0 (0)	3 (6)	1 (2)	43 (91)	9 (8)	7 (6)	5 (5)	88 (81)
	Antiglycemic	Insulin	0 (0)	0 (0)	0 (0)	47 (100)	3 (3)	1 (1)	0 (0)	105 (96)
		GLP-1 agonists (eg. semaglutide)	0 (0)	0 (0)	0 (0)	47 (100)	1 (1)	0 (0)	0 (0)	108 (99)
		SGLT-2 inhibitors (eg. empagliflozin)	0 (0)	0 (0)	0 (0)	47 (100)	0 (0)	1 (1)	0 (0)	108 (99)
		Other (incl. metformin)	2 (4)	0 (0)	0 (0)	45 (96)	6 (6)	3 (3)	0 (0)	100 (92)
	Antidepressant	Any	7 (15)	2 (4)	3 (6)	35 (74)	22 (20)	4 (4)	4 (4)	79 (72)
	HRT	Any	2 (4)	1 (2)	0 (0)	44 (94)	11 (10)	2 (2)	1 (1)	95 (87)
	Spinal cord stimulator		0 (0)	1 (2)	0 (0)	46 (98)	0 (0)	1 (1)	0 (0)	108 (99)

All values presented as n (%).

ACE = Angiotensin-converting enzyme inhibitor, **ARB** = Angiotensin II receptor antagonist, **ASA** = Acetylsalicylic acid, **BB** = Beta blocker, **CCB** = Calcium channel blocker, **DHP** = 1,4-Dihydropyridine, **GLP-1** = Glucagon-like peptide-1, **HRT** = Hormone replacement therapy, **IDN** = Isosorbide dinitrate, **IMN** = Isosorbide mononitrate, **PCSK9** = Proprotein convertase subtilisin/kexin type 9, **SGLT-2** = Sodium-glucose cotransporter-2

Supplemental Table S3. Comparing counts of participants that had changes in SAQ subdomain questionnaire scores from baseline to 3 years later that were above the questionnaire-specific minimal clinically important difference (MCID) range (“improved”), within the MCID range (“no change”) or below the MCID range (“worsened”).

Group	MCID category	Physical Limitations	Angina Frequency	Quality of Life	Treatment Satisfaction
MINOCA (n=51)	Improved	9 (18)	18 (35)	25 (49)	20 (39)
	No change	29 (57)	19 (37)	15 (29)	18 (35)
	Worsened	7 (14)	9 (18)	6 (12)	7 (14)
	<i>Missing</i>	6 (12)	5 (10)	5 (10)	6 (12)
INOCA (n=112)	Improved	40 (36)	57 (51)	66 (59)	45 (40)
	No change	45 (40)	35 (31)	29 (26)	32 (29)
	Worsened	18 (16)	13 (12)	7 (6)	24 (21)
	<i>Missing</i>	9 (8)	7 (6)	10 (9)	11 (10)

All values represented as n (%).

Supplemental Table S4. Mean questionnaire scores for SAQ subdomains within timepoints (baseline, year 3) between group status (depression at baseline or not). p describes if there are significant differences between means of each group (depression at baseline or not) within each timepoint. Δp describes if there are significant differences between the slopes between each group across timepoints.

SAQ Subdomain	Baseline mean (SD)			Year 3 mean (SD)			Δ scores (Y3-Baseline)		
	Depression at baseline (n=71)	No depression at baseline (n=92)	p	Depression at baseline (n=71)	No depression at baseline (n=92)	p	Depression at baseline (n=71)	No depression at baseline (n=92)	Δp
Physical limitations	50 (22)	61 (18)	< 0.001	56 (23)	66 (16)	0.006	7 (18)	5 (17)	0.42
Angina frequency	47 (27)	59 (26)	0.006	62 (28)	72 (24)	0.03	16 (24)	13 (25)	0.39
Quality of Life	38 (24)	48 (22)	0.006	60 (22)	67 (20)	0.06	22 (21)	17 (26)	0.25
Treatment Satisfaction	66 (22)	73 (18)	0.02	76 (20)	78 (18)	0.43	11 (26)	5 (23)	0.19

Supplemental Table S5. Mean questionnaire scores and standard deviation (SD) for SAQ subdomains and summary scores within timepoints (baseline, year 3) between group status (ranolazine at year 3 or not). p describes if there are significant differences between means of each group (ranolazine at year 3 or not) within each timepoint. Δp describes if there are significant differences between the slopes between each group across timepoints.

SAQ Subdomain	Baseline mean (SD)			Year 3 mean (SD)			Δ scores (Y3-Baseline)		Δp
	Ranolazine at year 3 (n=26)	No ranolazine at year 3 (n=137)	p	Ranolazine at year 3 (n=26)	No ranolazine at year 3 (n=137)	p	Ranolazine at year 3 (n=26)	No ranolazine at year 3 (n=137)	
Physical limitations	44 (17)	58 (21)	< 0.001	48 (19)	64 (19)	< 0.001	4 (16)	6 (18)	0.56
Angina frequency	36 (22)	57 (27)	< 0.001	56 (22)	70 (27)	0.01	19 (23)	12 (25)	0.18
Quality of Life	30 (16)	46 (24)	< 0.001	58 (18)	65 (22)	0.08	27 (23)	18 (25)	0.09
Treatment Satisfaction	61 (20)	72 (20)	0.01	79 (15)	77 (19)	0.54	18 (24)	5 (25)	0.02