Angina Hospitalization Rates in Women With Signs and Symptoms of Ischemia But no Obstructive Coronary Artery Disease: A Report from the WISE (Women's Ischemia Syndrome Evaluation) Study

Haider Aldiwani, Cedars-Sinai Heart Smidt Institute
Melody Zaya, Cedars-Sinai Heart Smidt Institute
Nissi Suppogu, Cedars-Sinai Heart Smidt Institute
Odayme Quesada, Cedars-Sinai Heart Smidt Institute
B. Delia Johnson, University of Pittsburgh
Puja Mehta, Emory University
Chrisandra Shufelt, Cedars-Sinai Heart Smidt Institute
John Petersen, University of Florida
Babak Azarbal, Cedars-Sinai Heart Smidt Institute
Bruce Samuels, Cedars-Sinai Heart Smidt Institute

Only first 10 authors above; see publication for full author list.

Journal Title: JOURNAL OF THE AMERICAN HEART ASSOCIATION
Volume: Volume 9, Number 4
Publisher: WILEY | 2020-02-18, Pages e013168-e013168
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1161/JAHA.119.013168
Permanent URL: https://pid.emory.edu/ark:/25593/vk2p0

Final published version: http://dx.doi.org/10.1161/JAHA.119.013168

Copyright information:
© 2020 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an Open Access work distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Accessed April 8, 2022 10:36 AM EDT
Angina Hospitalization Rates in Women With Signs and Symptoms of Ischemia But no Obstructive Coronary Artery Disease: A Report from the WISE (Women’s Ischemia Syndrome Evaluation) Study

Haider Aldiwni, MD;* Melody Zaya, MD, MS;* Nissi Suppogu, MD; Odayme Quesada, MD; B. Delia Johnson, PhD; Puja K. Mehta, MD; Chrisandra Shufelt, MD, MS; John Petersen, MD; Babak Azarbal, MD; Bruce Samuels, MD; R. David Anderson, MD; Leslee J. Shaw, PhD; Saibal Kar, MD; Eileen Handberg, PhD; Sheryl F. Kelsey, PhD; Carl J. Pepine, MD; C. Noel Bairey Merz, MD

Background—Recurrent hospitalization is prevalent in women with signs and symptoms of ischemia and no obstructive coronary artery disease. We hypothesized that rates of angina hospitalization might have changed over time, given advances in diagnostic and therapeutic approaches.

Methods and Results—We evaluated 551 women enrolled in the WISE (Women’s Ischemia Syndrome Evaluation) study with no obstructive coronary artery disease (CAD) for a follow-up period of 9.1 years. We analyzed angina hospitalization rates using the Kaplan-Meier method. Univariate analysis and multivariable Cox proportional hazard models were developed for prediction of angina hospitalization in women with signs and symptoms of angina and no CAD. A total of 223 women had nonobstructive CAD (>20–50% <stenosis) and 328 had no CAD (<20% stenosis). Among women with either no or nonobstructive CAD, the mean age was 56±11 years, 56% had hypertension, 46% dyslipidemia, 51% were smokers, and 10% had prior myocardial infarction. The rates of angina hospitalization for a maximum of 9.1 years showed near-linear increases in both groups (P=0.03). Hypertension, dyslipidemia, nonobstructive CAD, use of nitrates, statins, and angiotensin-converting enzyme inhibitors were univariate predictors of angina hospitalization. Adjusted multivariate hazard ratios for angina hospitalization were significant for use of nitrates 2.58 (1.80–3.69, P<0.0001), statins 1.80 (1.20–2.70, P=0.004), and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers 1.81 (1.22–2.68, P=0.003).

Conclusions—Angina hospitalization rates continued at a relatively constant rate in all women with no obstructive CAD despite medical advances. Clinical trials aimed at reducing angina hospitalization rates and identifying the pathophysiological mechanisms contributing to angina symptoms in women with no CAD and women with no obstructive CAD. (J Am Heart Assoc. 2020;9: e013168. DOI: 10.1161/JAHA.119.013168.)

Key Words: angina • coronary artery disease • hospitalization • women

Cardiovascular disease is the leading cause of death in women in the United States.1 More women than men experience signs and symptoms of ischemia with no obstructive coronary arteries (INOCA).1 In a study of almost 400,000 patients undergoing diagnostic coronary angiography for suspected obstructive coronary artery disease (CAD), 59% had either normal angiograms or nonobstructive (<50% stenosis) CAD.2 Women with INOCA are at risk for major adverse cardiovascular events versus women with normal angiography and/or no symptoms.3,4 The American College of Cardiology-National Cardiovascular Data Registry and National Heart, Lung and Blood Institute-sponsored WISE (Women’s Ischemic Syndrome Evaluation) databases suggest there may be at least 3 to 4 million women and men with INOCA, and that this condition is more prevalent in women than in men.1,3,5,6 The increasingly recognized prevalence of INOCA may be attributed, in part, to the increasing use of highly sensitive cardiac enzyme tests, improved advanced imaging, and/or use of primary prevention therapies that may alter the presentation of the atherosclerotic disease process. Current data are limited regarding temporal trends of advances in ischemic heart disease diagnostics and treatment. We investigated rates of angina hospitalization over time in...
Clinical Perspective

What Is New?
- Evaluate angina hospitalization among women with signs and symptoms of ischemia but no obstructive coronary artery disease.
- Discuss the difference in angina hospitalization between women with no coronary artery disease and women with no obstructive coronary artery disease.
- Identify the predictors in angina hospitalization among women with signs and symptoms of ischemia but no obstructive coronary artery disease.

What Are the Clinical Implications?
- Women with ischemia with no obstructive coronary arteries are often undiagnosed, inadequately treated by clinicians, and often labeled as normal.
- This report highlights the importance of this cardiovascular disease and its contribution to burden of angina hospitalization.
- Women with no obstructive coronary artery disease experience more angina hospitalization than women with no coronary artery disease, reflective of the high symptom burden and possibly undertreatment.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. Our study cohort consisted of 551 women with signs and symptoms of INOCA enrolled in the National Heart, Lung, and Blood Institute–sponsored WISE (Women Ischemia Syndrome Evaluation) study cohort consisted of 551 women with signs and symptoms of INOCA enrolled in the National Heart, Lung, and Blood Institutes–sponsored WISE study (NCT00000554) between September 1996 and March 2000 and followed for a maximum of 9.1 years. The study was approved by institutional review boards at University of Florida and Cedars-Sinai, and all subjects provided written informed consent. Outcome data used in this report were collected in 2 consecutive collection phases. During the first phase, patients were contacted at 6 weeks and at 1-year intervals after enrollment for a maximum of 9 years, followed by a death registry search.

All women underwent clinically indicated coronary angiography for suspected obstructive CAD at enrollment. The majority had angina and either an abnormal stress test or history of myocardial infarction. The coronary angiographic findings were categorized accordingly: no CAD (<20% stenosis); or nonobstructive CAD (≥20 to <50% stenosis) in any major epicardial coronary artery.

Angina was assessed at baseline through a series of detailed questions that addressed the location of pain, whether it was provoked by stress or exertion, whether it was relieved by rest or nitroglycerin, whether it wakes the patient from sleep or not, and frequency of the pain 6 weeks before their evaluation.

Traditional cardiovascular risk factors, including lipid panel, hypertension, and other risk factors were measured and defined as previously published.

Angina hospitalizations were documented during telephone contact, and a scripted interview was completed by an experienced nurse or physician at the respective center. Each subject or family member was queried for occurrence of major adverse cardiac events, hospitalizations for angina, repeated baseline detailed questions, medications, and invasive/noninvasive imaging testing. Further stratification for hospitalizations including dates, frequency, length of stay, and reason for admission (angina, stroke, myocardial infarction, and heart failure) were obtained.

Kaplan-Meier–estimated rates of angina hospitalization over 9.1 years were developed for women with no CAD and nonobstructive CAD to compare the difference in angina hospitalization based on anatomical classification, although we reported in our prior publication the rates of angina hospitalization based on angiographic severity score. Univariate analysis and multivariable Cox proportional hazard models were developed for prediction of angina hospitalization using baseline cardiovascular risk factors and medications.

Results

Overall, the women with no CAD (n=328), and nonobstructive CAD (n=223) had relatively similar risk profiles, as previously detailed. Among women with no CAD and nonobstructive CAD, age was 56±11 years, mean body mass index was 29.9±6.8 kg/m², 54% had hypertension, 46% dyslipidemia, 19% were smokers, 51% had a history of smoking, 16% had diabetes mellitus, and 10% had a history of prior myocardial infarction. Overall medication use included aspirin in 51%, statin 19%, nitrates 25%, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers 21%, and β-blockers 33%.

The median follow-up periods for no or nonobstructive CAD were 5.3 and 4.9 years, respectively. Among women with no/ nonobstructive CAD, there were 58 deaths, 33 of which were related to cardiac causes, while 131 (24%) women withdrew or were lost to long-term follow-up. Given the number of women who withdrew or were lost to long-term follow-up, we compared women with and without longer-term follow-up visits including age, baseline characteristic, cardiovascular risk factors, and medications. Women who completed the
Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA

Angina Hospitalization in Women With INOCA
numbers N01HV68161, N01HV68162, N01HV68163, N01HV68164, U01HL64829, U01HL64914, U01HL64924, K23HL105787, T32HL69751, R01HL090957, R01HL36310, R01HL56921, and UM1HL087366; the National Institute on Aging (NIA) under grant number R03AG032631; the National Center for Research Resources (NCRR) under grant number MO1RR000425; the National Center for Advancing Translational Sciences (NCATS) under grant numbers UL1TR000124, UL1TR000064, and UL1TR001427. This work was also supported by grants from the Gustavus and Louis Pfeiffer Research Foundation, Danville, NJ; The Ladies Hospital Aid Society of Western Pennsylvania, Pittsburgh, PA; The Society for Women’s Health Research (SWHR), Washington, DC; QMED, Inc., Laurence Harbor, NJ; The Women’s Guild of Cedars-Sinai, the Edythe L. Broad, the Constance Austin Foundation, Cedars-Sinai Medical Center, Los Angeles, CA; the Gatorade Trust and the PCORnet-One Florida Clinical Research Consortium CDRN-1501-26692, University of Florida, Gainesville, FL.

Disclosures

Dr. Quesada has received a research grant from NIH (T32HL116273). Dr. Mehta has received research grants from Gilead and General Electric. Dr. Kar receives consulting fees from Abbott Vascular, Boston Scientific and Lifetech, as well as contracted research support from Abbott Vascular and Boston Scientific. Dr. Bairey Merz has received an honorarium from Abbott Diagnostics and serves as a Board Director for iRhythm. Dr. Pepine: Research Grant; Modest; Gilead Sciences, Inc, Pfizer, Park-Davis, Sanofi-Aventis, Fujisawa HealthCare Inc, Baxter, Brigham & Women’s Hospital, AstraZeneca, NIH/NHLBI, Amorcyte/Neostem, Cytori, InfraReDx, NHLBI/NCCR CTSA grant 1UL1RR029890, AHA. Consultant/Advisory Board; Modest; NIH Study Section of Cardiovascular Sciences Small Business Activities 2RG1 CVS-K-10, Lilly/Cleveland Clinic DSMB Member for a Phase 2 Efficacy and Safety Study of Ly2484595, Medtelligence, NHLBI Study Section for Progenitor Cell Biology Consortium, NHLBI DSMB Chair for Freedom Trial. Dr. Handberg receives research grants (significant, ≥$5000) from Aastrom Biosciences, Amorcyte, Biocardia, Brigham and Women’s Hospital, Capricor, Cytori Therapeutics, Department of Defense, Direct Flow Medical, Duke Clinical Research Institute, East Carolina University, Everyfit Inc., Medtronic, Merck & Co., Mesoblast, National Institutes of Health (NIH), NIH through University of Rochester, NIH through Brigham and Women’s Health, NIH through University of Texas, PCORI, and Sanofi Aventis; Research grant and educational grant (modest, < $5000) from Gilead Sciences; Unrestricted educational grants (modest) for the Vascular Biology Working Group from Amgen, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Ionis, and Relypsa; and Consultant fees (modest) from Bristol-Myers Squibb Company; The remaining authors have no disclosures to report.

References