ORIGINAL RESEARCH

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

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***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.[3] 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

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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 noobstructive 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.

women with suspected INOCA enrolled in the National Heart, Lung, and Blood Institutes–sponsored WISE (Women Ischemia Syndrome Evaluation).

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 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,[7] followed by a death registry search.[8]

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.[7,9] The coronary angiographic findings were categorized accordingly: no CAD (<20% stenosis); or nonobstructive CAD (≥20 to <50% stenosis) in any major epicardial coronary artery.[7]

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.[8]

Traditional cardiovascular risk factors, including lipid panel, hypertension, and other risk factors were measured and defined as previously published.[8,10]

Angina hospitalizations were documented during telephone contact, and a scripted interview was completed by an experienced nurse or physician at the respective center.[7] 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.[7] Further stratification for hospitalizations including dates, frequency, length of stay, and reason for admission (angina, stroke, myocardial infarction, and heart failure) were obtained.[7]

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.[7] 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.[10] Among women with no CAD and nonobstructive CAD, age was 56±11 years, mean body mass index was 29.9±6.8 kg/m^2, 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

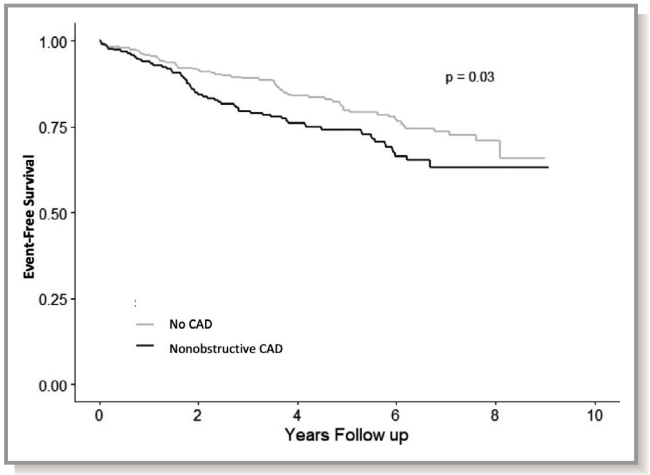

Figure. Angina hospitalization event-free survival in women with no and nonobstructive CAD. CAD indicates coronary artery disease.

follow-up visits compared with women withdrew were older (56.6±9.9 versus 54.1±12.3 mg/dL, *P*=0.02), had higher high-density lipoprotein levels (54.6±14.9 versus 50.3±15.2 mg/dL, *P*=0.01), and had a higher prevalence of aspirin use (54.4% versus 44.2%, *P*=0.02).

There was a statistically significant difference in angina hospitalization between women with no CAD and women with nonobstructive CAD (*P*=0.03) (Figure). Univariate predictors of angina hospitalization for these 2 combined groups using hazard ratios were hypertension 1.52 (1.06–2.18, *P*=0.024), dyslipidemia 1.54 (1.07–2.21, *P*=0.020), nonobstructive CAD 1.56 (1.10–2.21, *P*=0.012), use of nitrates 2.64 (1.84–3.76, *P*<0.0001), statins 1.81 (1.24–2.65, *P*=0.002), and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers 1.80 (1.23–2.65, *P*=0.003). Multivariate predictors of angina hospitalization using adjusted hazard ratios to baseline characteristics were significant for the 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 receptor blockers 1.81 (1.22–2.68, *P*=0.003).

When we added anginal characteristics into the multivariate model, including the chest pain descriptors of typical angina, number of symptoms checked, pain frequency, usual severity of pain (severity at its worst), "*chest pain severity at its worst*" had a statistically significant hazard ratio of 2.16 (1.29–3.64, *P*=0.004).

Discussion

Our observations indicate that women with no or nonobstructive CAD experienced relatively constant rates of angina hospitalizations over a longer-term follow-up period (Figure). Notably and consistent with our prior observations,[7] women with nonobstructive CAD had relatively higher rates of angina hospitalization than women with no CAD. These findings suggest that atherosclerosis-mediated coronary microvascular dysfunction may play a very important role in the severity of symptoms in the settings of nonobstructive CAD. Our findings are also consistent with a registry of all patients in Eastern Denmark[4] who were undergoing initial coronary angiography for stable angina and who had no obstructive CAD.[4] An almost 4-fold greater risk was observed for recurrent hospitalization because of angina (stable and unstable), heart failure, stroke, and myocardial infarction (hazard ratio 3.9, 95% 3.3–4.6, *P*<0.001) versus asymptomatic reference individuals.[4]

Traditional CAD risk factors including age, hypertension, diabetes mellitus, and smoking are also associated with increased morbidity and mortality in women with INOCA.[1] In our cohort, hypertension, dyslipidemia, nonobstructive CAD, use of nitrates, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and statins were significant predictors for angina hospitalization. These results may be because of the recognition of nonobstructive CAD risk by clinicians, higher symptom burden triggering medication use, both or other explanations. The impact of intensive medical therapy on outcomes, including recurrent angina hospitalization, has not been studied in controlled trials in the INOCA population. Further clinical trials are needed to inform future guidelines in the management of INOCA.

Over the past 2 decades, there has been a significant increase in the use of advanced cardiovascular imaging tools and improvement in the sensitivity and specificity of cardiovascular enzyme testing.[11,12] These changes are also accompanied by the increased use of preventive cardiovascular approaches by clinicians.[13] Despite all these advances in diagnosis and prevention, we continued to see constant rates of angina hospitalization among women with no CAD and women with nonobstructive CAD.

Study Limitations

One of the potential limitations of the study was the relatively high withdrawal/lost to longer-term follow-up (24%) in our cohort. However, our comparison between women who withdrew and women who completed the analysis demonstrated minimal clinically significant differences.

In conclusion, angina hospitalization rates continued at a relatively constant rate in all women with no obstructive CAD despite medical advances. Clinical trials have 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.

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