Receipt of Cardiac Medications Upon Discharge Among Men and Women With Acute Coronary Syndrome and Nonobstructive Coronary Artery Disease

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ABSTRACT

Background: Management of acute coronary syndrome (ACS) patients with nonobstructive epicardial coronary artery disease (CAD) remains poorly understood.

Hypothesis: Acute coronary syndrome patients with nonobstructive CAD are less likely to receive effective cardiac medications upon discharge from the hospital.

Methods: We identified patients hospitalized with ACS that underwent coronary angiography and had a 6-month follow-up. Patients were grouped by CAD severity: nonobstructive CAD (<50% blockage in all vessels) or obstructive CAD (⩾50% blockage in ⩾1 vessels). Data were collected on demographics, medications at discharge, and adverse outcomes at 6 months, for all patients.

Results: Of the 2264 ACS patients included in the study: 123 patients had nonobstructive CAD and 2141 had obstructive CAD. Cardiac risk factors including hypertension and diabetes were common among patients with nonobstructive CAD. Men and women with nonobstructive CAD were less likely to receive cardiac medications compared to patients with obstructive CAD including aspirin (87.8% vs 95.0%, $P = 0.001$), β-blockers (74.0% vs 89.2%, $P < 0.001$), or statins (69.1% vs 81.2%, $P = 0.001$). No gender-related differences in discharge medications were observed for patients with nonobstructive CAD. However, women with nonobstructive CAD had similar rates of cardiac-related rehospitalization as men with obstructive CAD (23.3% and 25.9%, respectively).

Conclusions: Patients with nonobstructive CAD are less likely to receive evidence-based medications compared to patients with obstructive CAD, despite the presence of CAD risk factors and occurrence of an ACS event. Further research is warranted to determine if receipt of effective cardiac medications among patients with nonobstructive CAD would reduce cardiac-related events.

Introduction

Approximately 10% to 25% of women and 6% to 10% of men with acute coronary syndrome (ACS) have "normal" or nonobstructive atherosclerotic coronary artery disease (CAD) defined as <50% stenosis.[1] Although the risk for adverse events post-ACS is lower in nonobstructive CAD patients, this group is not event-free.[2] Data from the Thrombolysis in Myocardial Infarction trials (TIMI 11B, TIMI 16, TIMI 22) suggest that 10% of such patients may suffer either myocardial infarction (MI), unstable angina (UA) requiring hospitalization, revascularization, stroke, or death.[1]

Currently, data on ACS patients with nonobstructive CAD is limited. Prior studies have observed that women admitted for cardiac-related diagnoses, are more likely to have nonobstructive CAD on coronary angiogram,[3–6] however the management of nonobstructive CAD is not well studied. Understanding the risk factor profile, ACS type, and the receipt of use of cardiac medications among women and men with nonobstructive CAD may add insight to current practice patterns and clinical outcomes. Therefore, we evaluated the clinical factors and rate of receipt at discharge for aspirin, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, and clopidogrel or ticlopidine, among men and women ACS patients with nonobstructive epicardial CAD compared to men and women ACS patients with obstructive epicardial CAD.

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Methods

All patients admitted to the University of Michigan Health System's ACS registry (n = 3514) between January 1999 and August 2004 with a diagnosis of ACS were eligible for study inclusion. Patients who did not receive coronary angiography during the index hospitalization or did not have 6-month follow-up data were excluded (n = 1250). Acute coronary syndrome was defined as UA, ST-segment elevation myocardial infarction (STEMI), or non-ST-segment elevation myocardial infarction (NSTEMI). The diagnosis of ACS was documented by standardized definitions which included the presence of symptoms consistent with acute coronary insufficiency, increases in cardiac enzymes (CK-MB >2 times upper limit of the hospital's normal range and/or positive troponin I), and/or positive acute electrocardiographic changes including: (1) transient ST-segment elevations of $\geqslant$1 mm in 2 or more contiguous leads, (2) ST-segment depressions of $\geqslant$1 mm, (3) new T-wave inversions of $\geqslant$1 mm, and (4) new left bundle branch block.[7,8] Patients under the age of 18 were excluded from the study. Full details of the University of Michigan Health System's ACS registry have been published previously.[9]

Independent variables included demographics (age, sex, race) and medical history as documented in the patients' medical records (smoking status, history of angina, MI, hyperlipidemia, peripheral vascular disease, diabetes mellitus, hypertension, prior stroke), and CAD family history (defined as having any blood relative [parents, siblings, children] with a history of angina, MI, and/or sudden cardiac death before the age of 55). Information regarding ACS type and in-hospital events was collected via chart review as described above. Discharge medications that were assessed included the following: aspirin, β-blockers, ACE inhibitors, statins, and clopidogrel or ticlopidine. Patients with contraindications to these medications were excluded from the study. Measured outcomes of patients included in-hospital recurrent ischemia (defined as further symptoms of angina with or without ischemic electrocardiographic changes while in the hospital), and 6-month outcomes such as rehospitalization for cardiac reasons (defined as any unscheduled rehospitalization/s for heart disease), nonfatal MI, nonfatal stroke, all-cause death, and major adverse cardiovascular events (MACE; defined as death from cardiac causes, nonfatal MI, nonfatal stroke, rehospitalization for cardiac causes, and/or unscheduled coronary revascularization).

Study site coordinators, physicians, and cardiology research nurses were trained and given a manual of operations to correctly identify patients eligible for study inclusion and accurately abstract the data from medical charts. Data not within the set limit ranges, inconsistencies, and/or unrecorded fields were flagged and then returned for clarification and correction. The 6-month follow-up data were obtained via telephone calls. At least 3 phone call attempts were made to contact patients to query their health status before any medical record data collection occurred. All aspects of this study were approved by the institutional review board at the University of Michigan and informed consent was obtained from all patients.

Acute coronary syndrome patients who underwent cardiac catheterization were divided into 2 groups: (1) nonobstructive CAD (<50% stenosis in all vessels) and (2) obstructive CAD ($\geqslant$50% stenosis in $\geqslant$1 vessels), based on the angiographers' interpretations. A cutoff of 50% was used based on previous studies.[5,10] Within each CAD stratum, differences in characteristics were determined by sex. Differences in characteristics between those with and without nonobstructive CAD were also compared. A P value of $\leqslant$0.05 was considered statistically significant. For testing differences between 2 groups, either the t test or the Wilcoxon rank sum test for continuous variables was used as indicated by the data. For categorical data, the χ^2 statistic was used with a Yates' correction factor as indicated by the data. A Fisher exact test was used if the expected number of observations in any cell was <5.

Bivariate analyses among patients in both groups of CAD severity were performed to determine if a relationship existed between prescribing at least 3 of 4 cardiac medications (aspirin, β-blocker, ACE inhibitor, statin) at the time of discharge and rehospitalization rates for cardiac causes. We opted to evaluate 3 out of 4 of these medications (excluding clopidogrel and ticlopidine) as the evidence to support the prescription of clopidogrel post-ACS had not been published until 2001—2 years after the present study patients were enrolled.[11] Statistical analysis software 8.2 (SAS Institute, Cary, NC) was used for all analyses.

Results

A total of 2264 ACS patients were included in the study and were followed for 6 months post-hospital discharge. Of these, 67.6% (n = 1530) were men and 93.6% (n = 2119) were white (Table 1). The majority of patients were classified as having obstructive CAD (94.6%) of which 1473 were men and 668 were women. Nonobstructive CAD was observed in 123 patients (5.4%), of which 57 were men and 66 were women. Women were significantly more likely to have nonobstructive CAD upon angiography compared to men (9.0% vs 3.7%, $P < 0.001$). Nonobstructive CAD patients averaged 4 years younger, were less likely to be white, and less likely to have a prior history of angina or hyperlipidemia, compared to obstructive CAD patients. Rates of traditional cardiovascular risk factors were similar among the 2 groups including current smoking, family history of CAD, diabetes, hypertension, peripheral vascular disease, and stroke. Prevalence of diabetes ranged from 21.2% among women with nonobstructive CAD to 32.2% for women with obstructive CAD. High rates of hypertension were also observed among the women (70.8% for women with

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Table 1. Demographic, Medical History, ACS Characteristics, and In-hospital Events of Coronary Artery Disease Patients Stratified by Severity of Coronary Artery Disease Status (n = 2264)[a]

	Nonobstructive CAD				Obstructive CAD				
Demographics	All Patients (n = 123) n (%)	Men (n = 57) n (%)	Women (n = 66) n (%)	P_1	All Patients (n = 2141) n (%)	Men (n = 1473) n (%)	Women (n = 668) n (%)	P_1	P_2
Age, mean (SD), y	58.7 ± 15.4	54.4 ± 15.0	62.3 ± 14.9	0.004	62.7 ± 12.8	61.4 ± 12.4	65.4 ± 13.2	<0.001	<0.01
Nonwhite race	12 (16.4)	5 (13.5)	7 (19.4)	0.49	133 (8.7)	79 (7.6)	54 (11.3)	0.02	0.03
Past medical history									
Current smoking	27 (22.0)	188 (31.6)	9 (13.6)	0.02	558 (26.3)	397 (27.2)	161 (24.2)	0.15	0.29
Angina	33 (26.8)	14 (24.6)	19 (28.8)	0.60	928 (43.4)	624 (42.4)	304 (45.6)	0.17	<0.001
Myocardial infarction	42 (34.1)	23 (40.4)	19 (28.8)	0.18	786 (36.7)	537 (36.5)	249 (37.3)	0.72	0.57
Hyperlipidemia	59 (48.4)	32 (56.1)	27 (41.5)	0.11	1374 (64.3)	941 (64.0)	433 (64.9)	0.69	<0.001
CAD family history	39 (45.3)	15 (37.5)	24 (52.2)	0.17	528 (49.8)	367 (50.5)	161 (48.3)	0.52	0.43
PVD	8 (6.6)	5 (8.8)	3 (4.6)	0.36	253 (11.9)	160 (10.9)	93 (14.0)	0.04	0.07
Diabetes mellitus	29 (23.6)	15 (26.3)	14 (21.2)	0.51	601 (28.1)	385 (26.2)	216 (32.3)	0.003	0.28
Hypertension	75 (61.5)	29 (50.9)	46 (70.8)	0.02	1461 (68.4)	946 (64.4)	515 (77.2)	<0.001	0.11
Prior stroke	9 (7.3)	2 (3.5)	7 (10.6)	0.13	186 (8.7)	106 (7.2)	80 (12.0)	<0.001	0.60
ACS type									
STEMI	18 (14.6)	10 (17.5)	8 (12.1)	0.40	539 (25.2)	392 (26.6)	147 (22.0)	0.023	0.008
NSTEMI	81 (65.9)	32 (56.1)	49 (74.2)	0.04	1192 (55.7)	808 (54.9)	384 (57.5)	0.26	0.03
UA	24 (19.5)	15 (26.3)	9 (13.6)	0.08	410 (19.1)	273 (18.5)	137 (20.5)	0.28	0.92

Abbreviations: CAD, coronary artery disease; LV, left ventricular; NSTEMI, non-ST-elevation myocardial infarction; PVD, peripheral vascular disease; SD, standard deviation; STEMI, ST-elevation myocardial infarction; UA, unstable angina; VF, ventricular fibrillation.
[a] Data are presented as number (percentage) unless otherwise indicated. Percentages are based on available data.
P_1 represents the difference between men and women within each CAD category; P_2 represents the difference between CAD categories among all patients.

nonobstructive CAD and 77.2% for women with obstructive CAD).

Among ACS patients with nonobstructive CAD, women were on average older than men (Table 1). Women were more likely to have a prior history of hypertension, but less likely to smoke. Other cardiovascular risk factors were similar between the men and women with nonobstructive CAD.

Among patients with obstructive CAD, women were older than men and were more likely to be nonwhite (11.3% vs 7.6%, $P = 0.02$; Table 1). Women reported similar rates of current smoking compared to men, but were more likely to have a history of peripheral vascular disease, diabetes mellitus, hypertension, or prior stroke, compared to men with obstructive CAD. No sex-related differences were observed for a history of angina, prior MI, hyperlipidemia, or family history of CAD, among obstructive CAD patients.

In regards to ACS type, patients with obstructive CAD were more likely to present with a STEMI compared to those with nonobstructive CAD, while rates of NSTEMI were higher among those with nonobstructive CAD. Among nonobstructive CAD patients, 57 of the 66 women had positive biomarkers and 42 of the 55 men had positive biomarkers. Rates of UA were similar between the 2 groups. Among men and women with nonobstructive CAD, women were more likely to present with NSTEMI compared to men, while no statistically significant differences were observed for men and women with obstructive CAD and NSTEMI. Rates of STEMI were higher among men with obstructive CAD compared to women with obstructive CAD.

Receipt of cardiac medications at time of discharge was similar for men and women with nonobstructive CAD, but less frequently prescribed, as compared to those with obstructive CAD (Table 2). Compared to patients

Table 2. Discharge Medications Administered to Coronary Artery Disease Patients Stratified by Severity of Coronary Artery Disease

	Nonobstructive CAD				Obstructive CAD				
Medications	All Patients (n = 123) n (%)	Men (n = 57) n (%)	Women (n = 66) n (%)	P_1	All Patients (n = 2141) n (%)	Men (n = 1473) n (%)	Women (n = 668) n (%)	P_1	P_2
Aspirin	108 (87.8)	51 (89.5)	57 (86.4)	0.60	2034 (95.0)	1414 (96.0)	620 (92.8)	0.002	0.001
β-Blockers	91 (74.0)	40 (70.2)	51 (77.3)	0.37	1910 (89.2)	1328 (90.2)	582 (87.1)	0.04	<0.001
ACE inhibitors	77 (62.6)	36 (63.2)	41 (62.1)	0.91	1404 (65.6)	992 (67.3)	412 (61.7)	0.01	0.50
Statins	85 (69.1)	39 (68.4)	46 (69.7)	0.88	1739 (81.2)	1217 (82.6)	522 (78.1)	0.01	0.001
Clopidogrel or ticlopidine	44 (35.8)	23 (40.4)	21 (31.8)	0.33	1567 (73.2)	1088 (73.9)	479 (71.7)	0.30	<0.001
⩾3 of 4 medications[a]	44 (69.0)	37 (64.5)	48 (72.7)	0.35	1839 (85.9)	1292 (87.7)	547 (81.9)	<0.001	<0.001

Abbreviations: ACE, angiotensin-converting enzyme; CAD, coronary artery disease.
[a] The 4 medications considered were aspirin, β-blockers, ACE inhibitors, and statins.
P_1 represents the difference between men and women within each CAD category; P_2 represents the difference between CAD categories among all patients.

Table 3. Six-month Follow-up Events Among Coronary Artery Disease Patients Stratified by Severity of Coronary Artery Disease Status

	Nonobstructive CAD				Obstructive CAD				
6-month outcomes	All Patients (n = 123) n (%)	Men (n = 57) n (%)	Women (n = 66) n (%)	P_1	All Patients (n = 2141) n (%)	Men (n = 1473) n (%)	Women (n = 668) n (%)	P_1	P_2
Rehospitalization	17 (15.6)	4 (7.5)	13 (23.2)	0.02	547 (29.1)	335 (25.9)	212 (36.0)	<0.001	0.002
Myocardial infarction	1 (1.0)	1 (2.0)	0 (0.0)	0.31	106 (7.0)	65 (6.3)	41 (8.5)	0.12	0.02
Stroke	0 (0.0)	0 (0.0)	0 (0.0)	. . .	20 (1.1)	14 (1.1)	6 (1.0)	0.91	0.27
Revascularization (unscheduled)	1 (1.0)	1 (2.2)	0 (0.0)	. . .	145 (8.3)	83 (6.9)	62 (11.4)	0.002	0.009
Death	5 (4.1)	2 (3.5)	3 (4.5)	0.77	80 (3.7)	44 (3.0)	36 (5.4)	<0.01	0.85
MACE	21 (17.1)	7 (12.3)	14 (21.2)	0.19	634 (29.6)	388 (26.3)	246 (36.8)	<0.001	0.003

Abbreviations: CAD, coronary artery disease; MACE, major adverse cardiovascular events including death from cardiac causes, nonfatal myocardial infarction, and nonfatal stroke.
P_1 represents the difference between men and women within each CAD category; P_2 represents the difference between CAD categories among all patients.

with obstructive CAD, patients with nonobstructive CAD were less likely to be discharged on aspirin, β-blockers, statins, and clopidogrel or ticlopidine, with a similar trend observed for receipt of ACE inhibitors. Overall, patients with nonobstructive CAD were significantly less likely to receive 3 of 4 of these evidence-based medications (EBMs). Of note, women with nonobstructive CAD were less likely to receive aspirin, β-blockers, ACE inhibitors, and statins upon discharge as compared to the men.

As expected, 6-month cardiac outcomes were lower among those with nonobstructive CAD (Table 3). No statistical difference was noted for 6-month mortality when comparing ACS patients with nonobstructive CAD and obstructive CAD, however the event rate was low for both groups. The rates of rehospitalization among women with nonobstructive CAD (23.2%) were similar to that observed for men with obstructive CAD (25.9%), and significantly higher than that of men with nonobstructive CAD. In terms of discharge medications and rates of cardiac-related rehospitalization, no significant differences were observed among men and women who received >3 of 4 EBMs (aspirin, β-blockers, ACE inhibitors, and statins) compared to those who did not. Of the 17 patients with nonobstructive CAD, who were rehospitalized within 6 months, approximately one-third did not receive 3 of 4 EBMs (64.7% vs 35.3%); however, the number of subjects rehospitalized was extremely small which limited our power to detect meaningful differences.

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Discussion

In this large cohort from a single academic center, we observed approximately 6% of men and women admitted with ACS had nonobstructive CAD by coronary angiography, with a higher proportion among women compared to men. Both men and women with nonobstructive CAD had significant rates of cardiovascular risk factors, and were less likely to receive cardiac medications including aspirin, β-blockers, statins, and clopidogrel or ticlopidine, at the time of discharge compared to patients with obstructive CAD. Furthermore, women with nonobstructive CAD had similar rates of cardiac-related rehospitalization as men with obstructive CAD within the first 6 months of discharge from the index hospitalization.

The incidence of ACS patients with nonobstructive CAD in our study is similar to what has been observed in previous reports of ACS.[1,3,10] The higher rates of nonobstructive CAD among female patients has been observed in several other studies as well.[10,12] Data from 3 TIMI trials noted rates of nonobstructive CAD between 9% to 25%,[1] while the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) Quality Improvement Initiative observed 8.6% of the study population had nonobstructive CAD.[13] The Women's Ischemia Syndrome Evaluation Study (WISE) and Global Utilization for Streptokinase and TPA for Occluded Coronary Arteries (GUSTO) IIb studies also reported significant rates of nonobstructive CAD among women referred for angiography.[5,6] In our investigation, women with nonobstructive CAD were more likely to be older and were more likely to have chronic hypertension compared to the men, while both men and women had similar rates of diabetes. However, our observations are consistent with prior studies which have examined gender differences in ACS patients, where women were older and have a higher prevalence of hypertension compared to men.[6,14–18]

We observed a significantly lower rate of receipt for cardiac medication among patients who were found to have nonobstructive CAD, despite the high prevalence of cardiovascular risk factors. In a similar study, 180 ACS patients with nonobstructive CAD were observed to have lower rates of receipt for aspirin, ACE-inhibitors, β-blockers, and clopidogrel.[12] In our cohort, almost 40% of patients with nonobstructive CAD did not receive ACE-inhibitors at the time of discharge, despite the diagnosis of ACS and high rates of hypertension and diabetes in this group.

We found no significant differences in all-cause mortality between men and women with nonobstructive CAD. We noted 4% of patients with nonobstructive CAD died during the 6-month follow-up, in contrast to a similar study by Dwyer et al which observed no deaths or recurrent MI among ACS patients with nonobstructive CAD.[12] However, rates of readmissions were similar between the 2 studies.

Women with nonobstructive CAD were more than 3 times more likely to be rehospitalized for cardiac causes than men. Furthermore, women with nonobstructive CAD had comparable rehospitalization rates to that of men with obstructive CAD. While the presented data do not provide definitive reasons for these observations, it is plausible that rehospitalization was due to recurrent episodes of chest pain from microvascular disease, particularly given the CAD risk factor burden observed in the group with nonobstructive CAD. Unfortunately, given the small numbers of patients with nonobstructive CAD in this cohort, it is not possible to examine multiple factors via multivariate analysis. Prior studies suggest a significant benefit to the receipt of medications in ACS patients in terms of recurrent cardiac events and progression of coronary atherosclerosis.[19–21] It remains to be seen whether risk factor modification among men and women with nonobstructive CAD would result in decreased rehospitalization.

Several limitations of this study exist. This study included patients with documented ACS who were part of a large ongoing registry in 1 academic medical center; however, the numbers of men and women with nonobstructive CAD is small. This cohort includes a spectrum of ACS patients and as such offers a "real-life" perspective of ACS treatment by including a heterogeneous study population as compared with randomized control trial study populations. However, as this study has an observational design, inherent limitations and potential biases (including selection bias) may exist. For the present analysis, only patients who underwent coronary angiography were included and therefore this information may not be generalizable to patients who do not receive cardiac angiography. Angiographic data were based on clinical reports and was not adjudicated by a core lab, and thus may be subject to some degree of between-person variability. Second, while we do follow patients for up to 6 months, we do not have information regarding adherence to medications which can certainly play a factor in clinical outcomes. Finally, categorizing of CAD severity as obstructive CAD based on our criteria meant grouping ACS patients with less severe disease together with patients with multiple and/or more severely stenotic lesions; however, the primary aim of this study was to examine management among ACS patients with nonobstructive CAD. In addition, this type of categorization of CAD severity has been done in prior studies.[4,10,21]

Conclusion

Significant improvements in the management of patients presenting with ACS have occurred over the past several decades. However, we observed lower rates of receipt of cardiac medications at the time of discharge among men and women ACS patients with nonobstructive disease. Increased use of cardiac medications and modification of risk factors among patients with nonobstructive CAD

may reduce their rehospitalization rates and decrease their progression of coronary atherosclerosis, though larger, long-term studies are needed to further examine this hypothesis.

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