ORIGINAL RESEARCH

Outcomes of Women and Men With Acute Coronary Syndrome Treated With and Without Percutaneous Coronary Revascularization

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***Background*—**Women hospitalized with a non-ST segment elevation acute coronary syndrome (ACS) have worse clinical outcomes compared with men. An early invasive strategy with prompt coronary revascularization may mitigate sex differences in outcomes. However, few contemporary studies have evaluated whether clinical outcomes differ between women and men presenting with ACS treated with an early invasive strategy.

***Methods and Results*—**A population-based cohort of hospitalized ACS patients who received prompt cardiac catheterization from 2008 to 2011 in Ontario, Canada and followed for up to 2 years was studied. Clinical outcomes were compared between men and women, stratified by the use of coronary revascularization. Inverse probability weighting using the propensity score accounted for measured differences in baseline characteristics between men and women. Among the 23 473 ACS patients who received cardiac catheterization during an index hospitalization, 66.1% of men and 51.8% of women received coronary revascularization during the same hospitalization. In the propensity-weighted cohort of patients who received coronary revascularization, the 1-year rate of death or recurrent ACS was 10.6% for men (referent) compared with 13.1% for women (hazard ratio 1.24; 95% CI 1.16–1.33). In contrast, outcomes for patients who did not receive coronary revascularization did not differ significantly between women and men at 1 year (17.8% versus 16.9%; hazard ratio 1.06; 95% CI 0.99–1.14) or at longer follow-up.

***Conclusions*—**An increased risk of adverse clinical outcomes was observed for women with ACS undergoing an early invasive strategy and coronary revascularization compared with men. **(*J Am Heart Assoc*. 2017;6:e004319. DOI: 10.1161/JAHA.116.004319.)**

Key Words: acute coronary syndrome • percutaneous coronary intervention • secondary prevention • sex-specific • women

Women hospitalized with an acute coronary syndrome (ACS) are at a higher risk for adverse outcomes as compared to men.[1–4] Extensive evaluations have suggested that these discrepancies are multifactorial.[5] They are partly explained by clinical differences where women with ACS are older at presentation, have a higher burden of comorbidities, and tend to present later and with more atypical symptoms compared with men.[3,6–10] In addition, there are sex-based differences in the primary and secondary treatment of coronary disease.[11–13] For instance, the use of an early invasive strategy of prompt coronary angiography with revascularization as appropriate is substantially lower in women once non-ST elevation ACS is recognized,[14–19] even though high-risk women may derive similar benefit from an invasive strategy as men.[19–21] Some have therefore advocated that increased use of early revascularization, and sex-specific thresholds for high-sensitivity troponin, may mitigate existing sex differences in outcomes following presentation with ACS.[17,22,23] However, few population-based studies have evaluated whether clinical outcomes of ACS patients differed between women and men who received early revascularization.

To address this gap in knowledge, we identified a cohort of patients who were hospitalized with ACS and managed with an early invasive strategy of cardiac catheterization. We hypothesized that outcome differences between men and women may be related to whether coronary revascularization was performed after cardiac catheterization. Accordingly, we first compared outcomes of men and women who received coronary revascularization during hospitalization for ACS.

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Second, we also compared clinical outcomes between women and men not treated with revascularization after cardiac catheterization during this time.

Methods

Data Sources

Each of the 18 hospitals that provide invasive cardiac care in Ontario, Canada is mandated to provide clinical information of all cardiac catheterizations, percutaneous interventions (PCI), and coronary artery bypass grafting surgeries (CABG) to the Cardiac Registry of the Cardiac Care Network (CCN) of Ontario. Abstractors at each cardiac invasive center gather data on demographics, clinical characteristics, procedure data, and relevant comorbid conditions. The Canadian Institute for Health Information (CIHI) Discharge Abstract Database was used to capture additional comorbidities and subsequent hospitalizations. The Ontario Registered Persons Database was used to determine mortality of patients during follow-up. The Ontario Drug Benefit prescription database was used to determine outpatient prescription drug use for patients aged 65 years or older. These datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences. The need for written informed consent was waived under Ontario's legislation regarding the privacy of health information because all data were stripped of any identifying information. This study was approved by the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Canada.

Study Cohort

Adult patients over the age of 20 years and less than 105 years, who were hospitalized with an ACS from October 1, 2008 to September 30, 2011 in Ontario, Canada were included. Identification of patients with acute myocardial infarction and unstable angina (UA) were based on the CIHI Discharge Abstract Database using previously validated International Classification of Disease 10th revision codes I20, I21, I22, I23.82, I24. We further identified an ACS episode as a hospitalization with a non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina and excluded patients who experienced ACS as an in-hospital complication, who were admitted to noncardiac surgical services, had an ST-segment elevation myocardial infarction (STEMI), or cardiogenic shock using information from the CCN cardiac registry. We also excluded patients who had a previous hospital admission for ACS, a prior PCI or CABG surgery in the prior 3 years. Patients with missing or invalid data were also excluded from analysis. For patients who had multiple ACS hospitalizations during the study period, the first hospitalization was considered for entry into the cohort.

Definition of an Early Invasive Strategy and Subsequent Treatment

Our cohort was restricted to patients who underwent an early invasive strategy, defined as those who had a cardiac catheterization during their hospital admission. We further stratified patients into coronary revascularization group or medical therapy group based on whether PCI or CABG was subsequently performed within the index ACS hospitalization.

Outcomes

The primary outcome of our study was defined as a composite of all-cause mortality or recurrent hospitalization for ACS (myocardial infarction or unstable angina) within 1 year. For patients who did not undergo coronary revascularization, the follow-up time began at the time of cardiac catheterization. For patients who received PCI or CABG, the follow-up time began at the time of the revascularization. Secondary outcomes were the incidence of the individual components of the composite outcome events. Events were captured at the time of ACS hospitalization to the end of 2 years of follow-up. ACS rehospitalization was identified from the CIHI Discharge Abstract Database as described earlier. Complete follow-up for each outcome was available for all patients included in the cohort.

Statistical Analysis

We compared demographics and clinical characteristics of women and men, stratified by whether coronary revascularization or medical therapy was performed after the initial invasive evaluation. We used χ^2 tests for comparing categorical variables and the Wilcoxon rank sum test for continuous variables between men and women with each of the 2 treatment strategies.

Subsequent analyses were conducted separately in strata defined by revascularization strategy (yes versus no). An inverse probability of treatment weighting approach was used to account for the effects of confounding on outcomes between men and women. Inverse probability of treatment weighting is a propensity score method that uses weights based on the propensity score to create a synthetic sample in which the distribution of measured baseline covariates is independent of sex.[24,25] In our study, the propensity score was constructed using a logistic regression model that estimated the probability of being female conditional on the following covariates: age, non-ST-segment elevation myocardial infarction/unstable angina risk based on the Thrombolysis in Myocardial Infarction score (which incorporates age ≥65 years, ≥3 risk factors for coronary artery disease, known coronary artery disease [stenosis ≥50%], severe anginal symptoms [≥2 anginal events in the 24 hours

preceding ACS presentation], use of aspirin in the past 7 days, ST-segment deviation ≥0.05 mV, and elevated serum cardiac markers of necrosis), past medical history (hypertension, hyperlipidemia, diabetes mellitus, smoking, cerebrovascular disease, peripheral arterial disease, heart failure, atrial fibrillation, chronic obstructive pulmonary disease, or chronic kidney disease requiring dialysis), extent of coronary artery disease, left ventricular ejection fraction, serum creatinine, and level of hospital services (availability of cardiac catheterization only, PCI, and/or cardiac surgery capacity).

Subjects were then weighted by the inverse probability of treatment received (ie, women were weighted by the reciprocal of their conditional probability of being a woman, while men were weighted by the reciprocal of their conditional probability of being a man). Standardized differences were used to compare characteristics in the weighted sample, where differences of less than 0.1 were taken to indicate good balance.[26] In the weighted comparative samples, we used Cox proportional hazard models to estimate hazard ratios (HR) and their 95% CI for each outcome using a robust variance estimator,[27] with men considered as the referent group. Adjusted Kaplan–Meier survival curves were estimated for men and women separately in the inverse probability of treatment weighting sample. A weighted log-rank test was used to compare group differences in survival functions.[28,29] All *P* values were 2-sided and <0.05 was considered statistically significant. SAS version 9.3 (SAS Institute, Cary, NC) was used for all statistical analyses.

Results

Patient Characteristics Before Propensity Weighing

During the study period, 23 473 patients were hospitalized with ACS in Ontario, Canada and treated with an early invasive strategy with a cardiac catheterization during the index hospitalization (Table 1). Among these patients, there were 15 381 men and 8092 women, of whom a significantly lower proportion of women (51.8%) received coronary revascularization during the index hospitalization as compared to men (66.1%). Their baseline and clinical characteristics are presented in Table 1. Among revascularized patients, the mean time from hospital admission to diagnostic angiography was slightly longer for women (2.4 [SD 1.8] days) compared with men (2.2 [SD 1.7] days) (*P*<0.001). The mean time from the diagnostic catheterization to revascularization was similar for women (1.5 [SD 3.23] days) and men (1.5 [SD 3.19] days) (*P*=0.19). Women were older and presented more frequently with a history of cardiac risk factors, heart failure, atrial fibrillation, and medical comorbidities as compared to men. Despite having greater comorbidities, women had less prognostically important coronary artery disease. Women also underwent revascularization with PCI more frequently than men.

Among the 9111 patients who did not receive coronary revascularization during the index hospitalization despite early cardiac catheterization, the mean time from hospital admission to diagnostic angiography was 2.8 days (SD 1.8) for women and 2.6 days (SD 1.8) for men (*P*<0.001). Similar sex differences were observed in which women were older, had more comorbidities but less likely significant coronary artery disease on cardiac catheterization.

Patient Characteristics After Propensity Weighting

Table 2 shows the characteristics of these ACS patients by sex and coronary revascularization status after propensity-score weighting. For patients who received coronary revascularization, the mean age was 63 years and 31% had a history of diabetes mellitus. The majority of patients received PCI (83%). Within strata defined by use of coronary revascularization, the distribution of baseline covariates was well balanced between men and women.

Outcomes

Rates of cardiovascular outcomes by sex and revascularization status in the inverse probability of treatment weighting cohort are shown in Table 3. Kaplan–Meier curves for death, death or ACS, and ACS alone are shown in Figures 1 and 2. In the coronary revascularization stratum, the composite rate of death or recurrent ACS in the weighted sample was 5.5% for women and 4.4% for men at 30 days (*P*<0.001). After propensity score weighting, women treated with revascularization were at higher risk of death or recurrent ACS compared with men within 30 days (HR, 1.24, 95% CI, 1.12–1.38), which remained throughout 1 year (13.1% versus 10.6%; HR 1.24; 95% CI 1.16–1.33) and 2 years (17.4% versus 14.8%; HR 1.20; 95% CI 1.13–1.27). Among events contributing to the primary outcome, results were consistent for a sex difference in recurrent ACS but not overall mortality (Table 3).

In contrast, sex-based differences in clinical outcomes were not observed among the early invasive strategy patients who did not undergo coronary revascularization. At 30 days, among medically managed patients, the rate of death or ACS was 7.7% in women and 7.6% in men (HR 1.02; 95% CI 0.92–1.13). At 1 year, the rate of death or ACS was 17.8% in women and 16.9% in men treated with medical therapy alone (HR 1.06; 95% CI 0.99–1.14). Results remained consistent at 2 years (23.0% versus 21.9%; HR 1.05; 95% CI 0.99–1.12).

Table 1. Baseline Characteristics Stratified by Sex and Treatment Before Inverse Probability of Treatment Weights

	Catheterization With Coronary Revascularization			Catheterization Without Coronary Revascularization		
Characteristic	Women (n=4195)	Men (n=10 167)	*P* Value	Women (n=3897)	Men (n=5214)	*P* Value
Age, mean±SD, y	67.34±12.14	61.65±11.88	<0.001	66.84±12.71	62.96±13.07	<0.001
Median (IQR)	68 (58–77)	61 (53–70)	<0.001	68 (58–77)	63 (53–73)	<0.001
ACS risk category*						
High risk	898 (21.4%)	2256 (22.2%)	0.199	617 (15.8%)	792 (15.2%)	0.075
Intermediate risk	1499 (35.7%)	3477 (34.2%)		1355 (34.8%)	1721 (33.0%)	
Low risk	1798 (42.9%)	4434 (43.6%)		1925 (49.4%)	2701 (51.8%)	
PCI during hospitalization	3606 (86.0%)	8282 (81.5%)	<0.001	—	—	—
Cardiac risk factors						
Diabetes mellitus	1495 (35.6%)	2970 (29.2%)	<0.001	1348 (34.6%)	1855 (35.6%)	0.329
Hyperlipidemia	2534 (60.4%)	5870 (57.7%)	0.003	2308 (59.2%)	3065 (58.8%)	0.672
Hypertension	3338 (79.6%)	7047 (69.3%)	<0.001	3139 (80.5%)	3820 (73.3%)	<0.001
History of smoking	1926 (45.9%)	6233 (61.3%)	<0.001	1600 (41.1%)	3088 (59.2%)	<0.001
Cerebrovascular disease	298 (7.1%)	552 (5.4%)	<0.001	347 (8.9%)	415 (8.0%)	0.107
Peripheral vascular disease	257 (6.1%)	514 (5.1%)	0.01	236 (6.1%)	391 (7.5%)	0.007
Serum creatinine, μmol/L						
≤120	3517 (83.8%)	8359 (82.2%)	0.001	3279 (84.1%)	4228 (81.1%)	<0.001
121 to 180	184 (4.4%)	613 (6.0%)		202 (5.2%)	453 (8.7%)	
>180	68 (1.6%)	177 (1.7%)		75 (1.9%)	149 (2.9%)	
Unknown	426 (10.2%)	1018 (10.0%)		341 (8.8%)	384 (7.4%)	
Dialysis	53 (1.3%)	103 (1.0%)	0.188	58 (1.5%)	86 (1.6%)	0.542
Heart failure	435 (10.4%)	706 (6.9%)	<0.001	608 (15.6%)	627 (12.0%)	<0.001
Chronic obstructive pulmonary disease	381 (9.1%)	705 (6.9%)	<0.001	466 (12.0%)	479 (9.2%)	<0.001
Atrial fibrillation	262 (6.2%)	492 (4.8%)	<0.001	373 (9.6%)	466 (8.9%)	0.3
Any significant CAD	4042 (96.4%)	9846 (96.8%)	0.135	1575 (40.4%)	3354 (64.3%)	<0.001
1 vessel with significant stenosis	2261 (53.9%)	5010 (49.3%)	<0.001	736 (18.9%)	1334 (25.6%)	<0.001
2 vessel with significant stenosis	1166 (27.8%)	3025 (29.8%)	0.019	435 (11.2%)	982 (18.8%)	<0.001
3 vessel with significant stenosis	587 (14.0%)	1760 (17.3%)	<0.001	382 (9.8%)	1008 (19.3%)	<0.001
Left main or 3 vessel CAD	762 (18.2%)	2252 (22.2%)	<0.001	506 (13.0%)	1250 (24.0%)	<0.001
Hospital availability of invasive services						
Cardiac catheterization only	282 (6.7%)	616 (6.1%)	0.289	374 (9.6%)	447 (8.6%)	0.155
Cardiac catheterization and PCI	536 (12.8%)	1277 (12.6%)		551 (14.1%)	782 (15.0%)	
PCI and CABG capable	3377 (80.5%)	8274 (81.4%)		2972 (76.3%)	3985 (76.4%)	

ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; IQR, interquartile range; PCI, percutaneous coronary intervention.
*ACS risk category is defined as high (Thrombolysis in Myocardial Infarction [TIMI] risk score 5–7), intermediate (TIMI risk score 3–4), and low (TIMI risk score 1–2).

In-Hospital Events, Processes of Care After Hospital Discharge

To explore potential reasons associated with worse outcome in women who received coronary revascularization, we examined in-hospital events, use of evidenced-based medical therapy and follow-up in the propensity-weighted cohort (Table 4). We found higher rates of blood transfusion in women than men (12.8% versus 7.3%), and slightly higher rates of in-hospital stroke (0.7% versus 0.4%) and in-hospital spontaneous myocardial infarction (1% versus 0.8%) in the coronary revascularization group. In contrast, these events rates were not substantially different among patients who did not undergo revascularization.

Table 2. Baseline Characteristics Stratified by Sex and Treatment After Inverse Probability of Treatment Weights

	Catheterization With Coronary Revascularization			Catheterization Without Coronary Revascularization		
Characteristic	Women (n=4195)	Men (n=10 167)	Std Diff	Women (n=3897)	Men (n=5214)	Std Diff
Age, mean±SD, y	62.8±23.3	63.2±14.4	0.0197	64.2±20.8	64.5±17.2	0.0182
Median (IQR)	62 (53–73)	63 (54–72)	0.0197	64 (54–75)	64 (55–75)	0.0182
ACS risk category*						
High risk	910 (21.7%)	2229 (21.9%)	0.0057	597 (15.3%)	802 (15.4%)	0.0013
Intermediate risk	1455 (34.7%)	3520 (34.6%)	0.001	1291 (33.1%)	1747 (33.5%)	0.008
Low risk	1831 (43.6%)	4417 (43.4%)	0.0038	2008 (51.5%)	2665 (51.1%)	0.0085
PCI during hospitalization	3461 (82.5%)	8408 (82.7%)	0.005	—	—	—
Cardiac risk factors						
Diabetes mellitus	1342 (32%)	3172 (31.2%)	0.0169	1424 (36.5%)	1857 (35.6%)	0.0193
Hyperlipidemia	2395 (57.1%)	5930 (58.3%)	0.0252	2287 (58.7%)	3055 (58.6%)	0.0018
Hypertension	2983 (71.1%)	7333 (72.1%)	0.0229	2959 (75.9%)	3969 (76.1%)	0.0045
History of smoking	2479 (59.1%)	5829 (57.3%)	0.0355	2057 (52.8%)	2720 (52.2%)	0.0128
Cerebrovascular disease	250 (5.9%)	599 (5.9%)	0.0022	316 (8.1%)	431 (8.3%)	0.0055
Peripheral vascular disease	232 (5.5%)	553 (5.4%)	0.0037	279 (7.2%)	364 (7%)	0.0072
Serum creatinine, μmol/L						
≤120	3455 (82.4%)	8401 (82.6%)	0.007	3196 (82%)	4281 (82.1%)	0.0021
121 to 180	227 (5.4%)	563 (5.5%)	0.0056	291 (7.5%)	381 (7.3%)	0.0064
>180	77 (1.8%)	175 (1.7%)	0.0086	107 (2.7%)	133 (2.6%)	0.0115
Unknown	436 (10.4%)	1028 (10.1%)	0.0092	302 (7.8%)	419 (8%)	0.0101
Dialysis	48 (1.1%)	111 (1.1%)	0.0044	71 (1.8%)	90 (1.7%)	0.0077
Heart failure	332 (7.9%)	803 (7.9%)	0.0003	539 (13.8%)	711 (13.6%)	0.0057
Chronic obstructive pulmonary disease	331 (7.9%)	783 (7.7%)	0.0068	413 (10.6%)	569 (10.9%)	0.0096
Atrial fibrillation	213 (5.1%)	531 (5.2%)	0.0067	333 (8.5%)	467 (9%)	0.0149
Any significant CAD	4044 (96.4%)	9837 (96.8%)	0.0195	2108 (54.1%)	2890 (55.4%)	0.0271
1 vessel with significant stenosis	2135 (50.9%)	5147 (50.6%)	0.0051	916 (23.5%)	1199 (23%)	0.012
2 vessel with significant stenosis	1205 (28.7%)	2967 (29.2%)	0.0099	635 (16.3%)	817 (15.7%)	0.0173
3 vessel with significant stenosis	664 (15.8%)	1677 (16.5%)	0.0184	518 (13.3%)	851 (16.3%)	0.0853
Left main or 3 vessel CAD	885 (21.1%)	2133 (21%)	0.0027	826 (21.2%)	1019 (19.5%)	0.041
Hospital availability of invasive services						
Cardiac catheterization only	257 (6.1%)	632 (6.2%)	0.0039	350 (9%)	480 (9.2%)	0.0074
Cardiac catheterization and PCI	523 (12.5%)	1286 (12.7%)	0.0057	571 (14.6%)	759 (14.6%)	0.0025
PCI and CABG capable	3415 (81.4%)	8249 (81.1%)	0.0072	2976 (76.4%)	3975 (76.2%)	0.0029

ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; IQR, interquartile range; PCI, percutaneous coronary intervention; Std Diff, standardized difference.

*ACS risk category is defined as high (Thrombolysis in Myocardial Infarction [TIMI] risk score 5–7), intermediate (TIMI risk score 3–4), and low (TIMI risk score 1–2).

For patients over 65 years of age who received revascularization, the 30-day unadjusted postdischarge rate of use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was 66.9% in women and 62.4% in men, adenosine diphosphate receptor antagonist use was 82.2% versus 74.5%, and statins was 85.7% versus 83.8% (all $P<0.001$). No significant difference was observed in the prescribed rates of β-blockers. Within 30 days of discharge, 86.3% of women and 84.6% of men were seen by a primary care physician, while 39.1% of women and 40.6% of men were evaluated by a cardiologist. An echocardiogram was performed within 30 days of hospital discharge among 13.8% of women and 13.2% of men.

Table 3. Incidence of Short-Term and Long-Term Clinical Outcomes by Sex and Treatment Category in the Weighted Sample

	Catheterization With Coronary Revascularization			Catheterization Without Coronary Revascularization		
Outcome	Women (n=4195)	Men (n=10 167)	HR (95% CI)	Women (n=3897)	Men (n=5214)	HR (95% CI)
30 days						
Death or ACS	230 (5.5%)	451 (4.4%)	1.24 (1.12–1.38)	300 (7.7%)	395 (7.6%)	1.02 (0.92–1.13)
Death	51 (1.2%)	126 (1.2%)	0.99 (0.80–1.21)	86 (2.2%)	110 (2.1%)	1.05 (0.86–1.28)
ACS	185 (4.4%)	334 (3.3%)	1.35 (1.20–1.52)	230 (5.9%)	308 (5.9%)	1.01 (0.89–1.13)
1 year						
Death or ACS	548 (13.1%)	1080 (10.6%)	1.24 (1.16–1.33)	694 (17.8%)	879 (16.9%)	1.06 (0.99–1.14)
Death	145 (3.5%)	318 (3.1%)	1.10 (0.97–1.25)	259 (6.6%)	354 (6.8%)	0.98 (0.87–1.09)
ACS	451 (10.7%)	831 (8.2%)	1.33 (1.24–1.44)	535 (13.7%)	641 (12.3%)	1.12 (1.03–1.21)
2 year						
Death or ACS	732 (17.4%)	1500 (14.8%)	1.20 (1.13–1.27)	896 (23.0%)	1143 (21.9%)	1.05 (0.99–1.12)
Death	210 (5.0%)	516 (5.1%)	0.99 (0.89–1.10)	376 (9.6%)	505 (9.7%)	0.99 (0.91–1.09)
ACS	597 (14.2%)	1127 (11.1%)	1.31 (1.22–1.40)	666 (17.1%)	826 (15.8%)	1.08 (1.01–1.16)

ACS consists of unstable angina and myocardial infarction. ACS indicates acute coronary syndrome; HR, hazard ratio.

Discussion

In this population-based cohort of Ontario patients presenting with ACS who underwent an early diagnostic angiography, several sex-based differences in management and outcomes were observed. Women with ACS, despite undergoing a coronary angiogram, continue to be treated with coronary revascularization only about half of the time and considerably less frequently than men. Among those revascularized, women had consistently higher risk for major adverse cardiovascular events compared with men. In contrast, men and women managed with medical therapy after early invasive evaluation with cardiac catheterization had overall higher, but relatively similar, outcomes after ACS at longer term. Among patients treated with early revascularization, our results were predominantly driven by sex differences in recurrent ACS as opposed to mortality. Based on our findings, it is unclear whether greater use of early coronary revascularization alone may mitigate sex-based risk differences in outcomes following ACS.

The current findings add to the literature of previously reported sex-based differences in outcomes following myocardial infarction,[1–4] and suggest that sex differences in outcomes remain among patients who undergo early revascularization.[30] While we cannot identify the exact reason underlying these differences, several potential hypotheses could be discounted. First, several clinical differences between men and women were minimized with the use of rigorous propensity weighting. We incorporated several prognostic factors including those within the Thrombolysis in Myocardial Infarction risk score, which has been shown to function equally well in women and men compared with other risk scores.[31] We also found that use of evidence-based medical therapy was actually higher among at least older women than men after hospital discharge. In addition, there was little sex difference in follow-up patterns as men and women promptly visited their primary care physicians and cardiologists in similar frequencies after discharge.

Accordingly, sex-based differences in coronary revascularization outcomes may be in part related to differences in selection of treatment strategies and/or response to invasive treatment in women compared with men.[32] For instance, we observed that women were more frequently revascularized with PCI as opposed to CABG compared with men. Other studies have suggested that women with ACS are more likely to have nonobstructive epicardial coronary disease,[33] smaller epicardial coronary arteries,[34] less traditional focal plaque rupture on angiography,[35,36] and have more microvascular dysfunction, diffuse disease, or plaque erosion.[36] The resultant higher burden of functional coronary disease, and incomplete revascularization among women with anatomical disease, predispose to a higher burden of symptoms, including angina and dyspnea, which may have driven the subsequent observed sex-difference in risk of recurrent ACS as opposed to all-cause mortality.

We also found higher rates of bleeding and blood transfusion in women than men (12.8% versus 7.3%) in the coronary revascularization group, both known to be associated with negative consequences.[37,38] Women presenting with ACS are at higher risk for major bleeding, at least in part related to inappropriate overdosing of antithrombotic therapy independent of other clinical risk factors.[39,40]

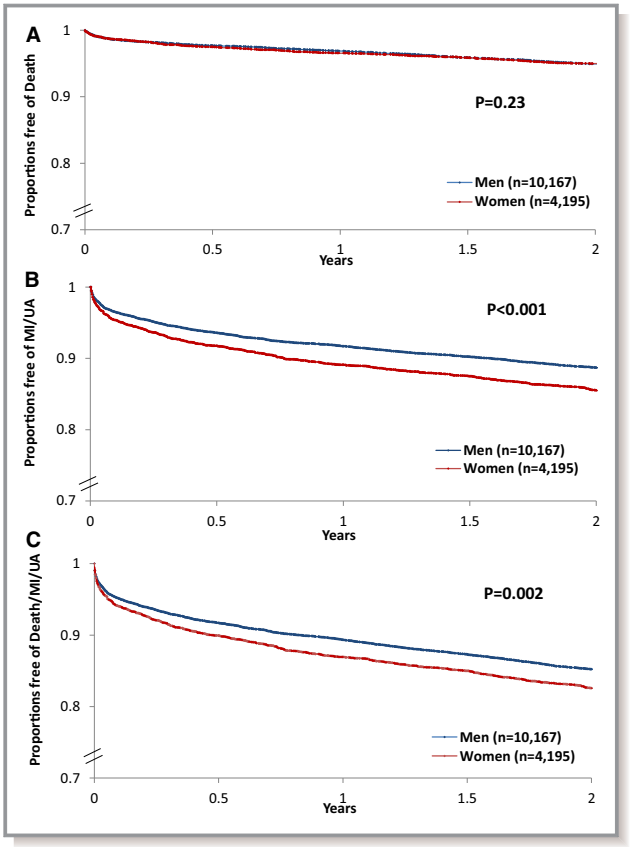

Figure 1. Adjusted Kaplan–Meier curves for patients who underwent diagnostic catheterization and coronary revascularization by sex. A, Death. B, MI/UA. C, Death/MI/UA. Blue line: Men (n=10 167); Pink line: Women (n=4195). Kaplan–Meier curves were derived from the inverse probability of treatment-weighted propensity score, which estimated the probability of being female or male conditional on the following covariates: age, NSTEMI/UA risk based on the Thrombolysis in Myocardial Infarction (TIMI) score (which incorporates age ≥65 years, ≥3 risk factors for CAD, known CAD [stenosis ≥50%], severe anginal symptoms [≥2 anginal events in the 24 hours preceding ACS presentation], use of aspirin in the past 7 days, ST-segment deviation ≥0.05 mV, and elevated serum cardiac markers of necrosis), past medical history (hypertension, hyperlipidemia, diabetes mellitus, smoking, cerebrovascular disease, peripheral arterial disease, heart failure, atrial fibrillation, chronic obstructive pulmonary disease, or chronic kidney disease requiring dialysis), extent of coronary artery disease, left ventricular ejection fraction, serum creatinine, and level of hospital services (availability of cardiac catheterization only, PCI, and/or cardiac surgery capacity). ACS indicates acute coronary syndrome; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; NSTEMI, non-ST segment elevation myocardial infarction; UA, unstable angina.

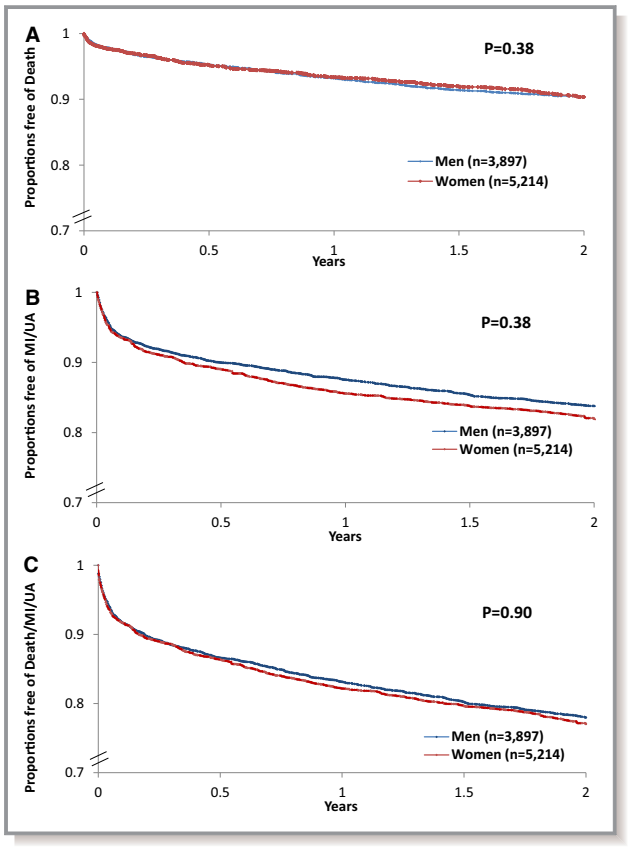

Figure 2. Adjusted Kaplan–Meier curves for patients who underwent diagnostic catheterization only without revascularization by sex. A, Death. B, MI/UA. C, Death/MI/UA. Blue line: Men (n=3897); Pink line: Women (n=5214). Kaplan–Meier curves were derived from the inverse probability of treatment-weighted propensity score, which estimated the probability of being female or male conditional on the following covariates: age, NSTEMI/UA risk based on the Thrombolysis in Myocardial Infarction (TIMI) score (which incorporates age ≥65 years, ≥3 risk factors for CAD, known CAD [stenosis ≥50%], severe anginal symptoms [≥2 anginal events in the 24 hours preceding ACS presentation], use of aspirin in the past 7 days, ST-segment deviation ≥0.05 mV, and elevated serum cardiac markers of necrosis), past medical history (hypertension, hyperlipidemia, diabetes mellitus, smoking, cerebrovascular disease, peripheral arterial disease, heart failure, atrial fibrillation, chronic obstructive pulmonary disease, or chronic kidney disease requiring dialysis), extent of coronary artery disease, left ventricular ejection fraction, serum creatinine, and level of hospital services (availability of cardiac catheterization only, PCI, and/or cardiac surgery capacity). ACS indicates acute coronary syndrome; CAD, coronary artery disease; MI, myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; UA, unstable angina.

However, women are at higher risk for vascular complications and blood transfusions even when antithrombotic therapies are weight adjusted.[41,42] Other bleeding avoidance strategies, including vascular closure devices and radial access, may further reduce these risks.[43] Together, these findings emphasize that careful monitoring of weight and renal function be continuously factored when selecting antithrombotic dosing to reduce bleeding, particularly in women, and that further research into sex-based bleeding avoidance strategies remains prudent.[44]

Table 4. Use of Health Services and Medications 30 Days From Discharge After Inverse Probability of Treatment Weights

	Catheterization With Coronary Revascularization			Catheterization Without Coronary Revascularization		
Characteristic	Women (n=4195)	Men (n=10 167)	Std Diff	Women (n=3897)	Men (n=5214)	Std Diff
In-hospital events						
Red blood cell transfusion	538 (12.8%)	745 (7.3%)	0.18	275 (7.1%)	263 (5%)	0.08
Bleeding	122 (2.9%)	234 (2.3%)	0.04	76 (1.9%)	81 (1.5%)	0.03
Myocardial infarction	42 (1%)	85 (0.8%)	0.02	20 (0.5%)	25 (0.5%)	0.01
Stroke	28 (0.7%)	40 (0.4%)	0.04	15 (0.4%)	22 (0.4%)	0.01
Healthcare utilization within 30 days of discharge						
Visited cardiology physician	1642 (39.1%)	4127 (40.6%)	0.03	1688 (43.3%)	2688 (51.6%)	0.17
Visited family physician	3620 (86.3%)	8599 (84.6%)	0.05	3225 (82.8%)	4150 (79.6%)	0.08
Echocardiogram	581 (13.8%)	1344 (13.2%)	0.02	1233 (23.6%)	724 (18.6%)	0.12
Medication use within 30 days of discharge*	n=2323	n=3592		n=2092	n=2117	
ADP receptor antagonist	1910 (82.2%)	2677 (74.5%)	0.19	1013 (48.4%)	1113 (52.6%)	0.08
Anticoagulant (warfarin or DOACs)	187 (8.1%)	345 (9.6%)	0.05	208 (9.9%)	244 (11.5%)	0.05
ACE/ARB	1554 (66.9%)	2242 (62.4%)	0.09	1265 (60.5%)	1256 (59.3%)	0.02
β-Blocker	1677 (72.2%)	2565 (71.4%)	0.02	1311 (62.7%)	1417 (66.9%)	0.09
Statin	1991 (85.7%)	3009 (83.8%)	0.05	1518 (72.6%)	1649 (77.9%)	0.12

ACE/ARB indicates angiotensin-converting enzyme/angiotensin II receptor blockers; ADP, adenosine diphosphate; DOACs, direct oral anticoagulants; Std Diff, standardized difference.
*Among patients 65 years old and older.

As well, we found lower rates of coronary revascularization in women even among patients selected to undergo an early invasive evaluation. This observation is consistent with other studies, particularly evident among younger women, who less frequently are referred for invasive management despite having higher rates of in-hospital mortality and long-term secondary cardiovascular events.[10] We found a higher risk of adverse outcomes among women compared with men treated with coronary revascularization; however, our observation should not be interpreted as a reason to withhold revascularization in appropriately selected women presenting with ACS. In fact, data from randomized trials have shown that an early invasive strategy reduces adverse cardiovascular events to a similar extent in higher risk ACS men and women, particularly when presenting with positive biomarkers.[20]

Our study has several limitations that merit consideration. First, observational studies are subject to the potential influence of confounding. Accordingly, we used a propensity method and successfully balanced all the observed patient and systematic factors between men and women. Nevertheless, these methods are still subject to the potential influence of unmeasured confounding. For example, we did not have detailed clinical data on the presentation of ACS such as extent of biomarker elevation, electrocardiographic changes, or extensive laboratory testing. Second, we defined obstructive coronary artery disease on the basis of a >50% stenosis in the left main coronary artery or >70% stenosis in the epicardial vessels. We were unable to use alternative definitions of obstructive coronary artery disease, but prior research has shown this definition to be robust.[45] Third, outpatient prescription drug data were only available for patients 65 years or older, limiting our ability to fully explore whether sex differences in therapeutic trajectories and compliance were present. Nevertheless, among older women who underwent revascularization, there were similar or higher rates of cardioprotective drugs observed compared with men. Finally, the main objective of this study was to evaluate potential sex differences stratified by the use of coronary revascularization. The nonrandomized design of our analysis precluded a comparison of whether coronary revascularization was more or less beneficial in men or women.

In conclusion, we observed sex-specific differences in outcomes of patients with ACS treated with coronary revascularization in Ontario. Compared with men, women treated with coronary revascularization had a higher risk for recurrent cardiovascular events. Differences in risk were not seen between women and men treated with medical therapy alone. Thus, sex-based disparities in outcomes following cardiac catheterization for ACS persisted despite revascularization. Further research is needed to better understand whether inherent differences in underlying comorbidities or response to invasive therapy and its associated treatment impact outcomes and to develop strategies to reduce the higher rates of adverse outcomes in women treated with coronary revascularization following ACS.

Author Contributions

Udell, Tu, and Ko conceived and designed the study; Udell, Qiu, Koh, and Ko wrote the statistical analysis plan, analyzed and interpreted the data; Udell wrote the first draft of the paper; Udell, Qiu, Koh, Austin, Wijeysundera, Bagai, Yan, Goodman, Tu, and Ko critically revised the draft paper for important intellectual content. Qiu was responsible for data acquisition. Udell, Tu, and Ko obtained funding. Ko provided administrative, technical, and material support. Udell and Ko are the guarantors. Qiu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Udell all outside the submitted work: Consulting: Amgen, Janssen, Merck, Novartis, Sanofi Pasteur; honoraria: Janssen (symposia), Novartis (steering committee); grant support: Novartis (site investigator). Dr Yan outside the submitted work: Grant support: AstraZeneca. All other authors have reported they have no relationships to disclose.

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