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Clinical Research

Clinical Outcomes in Younger Women Hospitalized With an Acute Myocardial Infarction: A Contemporary Population-Level Analysis

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See editorial by Humphries et al., pages 1661–1663 of this issue.

ABSTRACT

Background: For younger women with acute myocardial infarction (AMI), little is known regarding their contemporary care pathways and clinical outcomes.

Methods: We studied AMI patients aged 18-55 years, hospitalized from April 1, 2009, to March 31, 2019, in Ontario, Canada. We compared trends in comorbidities, angiographic findings, and revascularisation rates in men and women. The primary outcome was 1-year

RÉSUMÉ

Contexte : La trajectoire actuelle de soins et les résultats cliniques des jeunes patientes ayant subi un infarctus aigu du myocarde (IAM) sont mal connus.

Méthodologie : Nous avons mené une étude portant sur les patients de 18 à 55 ans ayant subi un IAM et hospitalisés entre le 1er avril 2009 et le 31 mars 2019 en Ontario (Canada). Nous avons comparé les tendances entre les hommes et les femmes pour les troubles con-

Despite improvements in the management and outcomes of patients with ischemic heart disease, large numbers of young women are hospitalized with an acute myocardial infarction (AMI).[1-4] Several studies have highlighted that women have worse clinical outcomes compared with men after AMI.[4-11] Some of those studies were limited to highly selected populations, such as patients enrolled in clinical trials[10,11] that included limited numbers of women, and others may not be representative of contemporary AMI care.[6-8] Moreover, only a few studies focused specifically on younger women with AMI (< 55 years old).[5,6,12-14] Those studies highlighted that younger women were a group at particularly high risk, who had more comorbidities, experienced more treatment delays in reperfusion therapy, had lower rates of referral or delayed referral for coronary angiography and revascularisation, and had much higher mortality rates than men or even worse outcomes compared with older women.[15,16] Vigourous efforts to address these treatment disparities with public education campaigns and calls to action have been aimed at the cardiology community.[4,5,13,14] Despite these efforts, there are concerns that the improvement in clinical outcomes experienced after AMI hospitalization is not being realized among younger women.[4,5,15,17]

To understand whether disparity continues to exist in processes of care and clinical outcomes, we studied the population of younger AMI patients hospitalized from 2009 to 2019 in Ontario, Canada.

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See page 1659 for disclosure information.

Methods

Data sources

Ontario is Canada's largest province, with a population of around 14 million, all of whom are provided universal health

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all-cause mortality or readmission for unstable angina, AMI, heart failure, or stroke. Inverse probability of treatment weighting was used to account for differences in baseline clinical characteristics between men and women.

Results: Among the 38,071 AMI patients included, 8,077 (21.2%) were women. Over the study period, women had increasing rates of diabetes (24.8% to 34.9%; $P_{trend} < 0.001$), and declining rates of smoking (53.2% to 41.7%; $P_{trend} < 0.005$). Although most patients received coronary angiography (96%), coronary revascularisation was less frequent among women than men (percutaneous coronary intervention: 61.9% vs 78.8% [$P < 0.001$]; surgery: 4.1% vs 6.0% [$P < 0.001$]). Women had more normal coronary anatomy (5.8% vs 1.7%; $P < 0.001$) and nonobstructive disease (22.8% vs 9.3%; $P < 0.001$) than men. Compared with men, the primary composite end point was significantly increased among women (10.0% vs 7.9%, adjusted HR 1.11; $P = 0.02$) and related to increased readmission rates for cardiovascular events. All-cause readmission was significantly increased among women (25.8% vs 21.1%, adjusted HR 1.34; $P < 0.0001$).

Conclusions: Coronary angiography is performed almost universally in younger women with AMI; however, coronary revascularisation is less frequent, perhaps reflecting less obstructive disease. Although mortality rates after AMI were similar between sexes, cardiovascular readmission rates and all-cause readmissions were significantly increased among women.

comitants, les observations à l'angiographie et les taux de revascularisation. Le paramètre d'évaluation principal était la mortalité toutes causes confondues ou la réadmission à hôpital en raison d'une angine instable, d'un IAM, d'une insuffisance cardiaque ou d'un accident vasculaire cérébral après un an. La pondération par probabilité inverse de traitement a été utilisée pour tenir compte des différences initiales dans les caractéristiques cliniques entre les hommes et les femmes.

Résultats : Parmi les 38 071 patients ayant subi un IAM admis à l'étude, 8 077 (21,2 %) étaient des femmes. Pendant la période visée, le taux de diabète chez les femmes a augmenté (de 24,8 % à 34,9 %; $P_{tendance} < 0{,}001$), et le taux de tabagisme a diminué (de 53,2 % à 41,7 %; $P_{tendance} < 0{,}005$). Bien qu'une angiographie coronarienne ait été effectuée dans presque tous les cas (96 %), la revascularisation coronarienne était moins fréquente chez les femmes que chez les hommes (intervention coronarienne percutanée : 61,9 % *vs* 78,8 % [$P < 0{,}001$]; intervention chirurgicale : 4,1 % *vs* 6,0 % [$P < 0{,}001$]). Les femmes avaient plus fréquemment que les hommes une anatomie normale des artères coronaires (5,8 % *vs* 1,7 %; $P < 0{,}001$) ou une coronaropathie non obstructive (22,8 % *vs* 9,3 %; $P < 0{,}001$). Par rapport aux hommes, la fréquence du critère d'évaluation principal regroupé était significativement plus élevée chez les femmes (10,0 % vs 7,9 %, RRI ajusté de 1,11; $P = 0{,}02$), accompagnée d'un taux de réadmission plus élevé pour des événements cardiovasculaires. La réadmission toutes causes confondues était significativement plus élevée chez les femmes que chez les hommes (25,8 % *vs* 21,1 %, RRI ajusté de 1,34; $P < 0{,}0001$).

Conclusions : L'angiographie coronarienne est pratiquement systématique chez les jeunes patientes ayant subi un IAM; toutefois, la revascularisation coronarienne est moins fréquente, ce qui pourrait s'expliquer par le plus faible taux de coronaropathies obstructives. Malgré des taux de mortalité similaires entre les sexes après un IAM, les taux de réadmission pour des événements cardiovasculaires et de réadmission toutes causes confondues étaient significativement plus élevés chez les femmes.

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We conducted an observational study using population-linked clinical and administrative data in Ontario, Canada. We used the CorHealth Ontario Cardiac Registry, which is a prospective clinical database that collects demographic, clinical, and procedural characteristics on all patients undergoing cardiac catheterisation and percutaneous coronary intervention (PCI) in Ontario, Canada. This clinical registry was then linked to several administrative databases with the use of unique encoded identifiers and analysed at ICES (formerly known as the Institute for Clinical Evaluative Sciences). The Canadian Institute for Health Information's Discharge Abstract Database (CIHI-DAD) was used to capture additional clinical comorbidities as well as ascertain admission status. The Ontario Health Insurance Plan physician claims database was used to determine physician follow-up. Statistics Canada census data were used to assess neighbourhood income information. The Registered Persons Database was used to determine the vital status of patients. The use of data in this study was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board.

Study population

The study cohort included patients aged 18-55 years, with a valid health card number and who were hospitalized with AMI in Ontario from April 1, 2009, to March 31, 2019. A diagnosis of AMI was identified by the International Classification of Diseases, 10th revision, Canada (ICD-10-CA) codes I21 and I22 in the CIHI-DAD. Patients who had a death date before the index date, left hospital against medical advice, were flagged as a nonurgent admission, or left hospital within 24 hours of admission were excluded. For patients with multiple AMI admissions to hospital in a given year, the first AMI was considered as the index event for study inclusion. An age threshold of 55 years or less to denote younger patients is consistent with previous studies.[12-14]

Angiographic data

Angiographic data obtained within 30 days of AMI hospitalization characterised the extent of coronary artery disease (CAD) as 0-3 vessels with $\geq$ 70% stenosis. Normal coronary arteries was defined as the absence of CAD on coronary angiography. Nonobstructive disease was defined as the presence of coronary artery disease with no significantly diseased vessels $\geq$ 70%. Significant left main CAD was

Table 1. Baseline characteristics, cardiac evaluations, revascularisation, and physician follow-up

	Total (n = 38,071)	Women (n = 8077)	Men (n = 29,994)	*P* value
Demographics				
Mean age, y	48.7 ± 5.6	48.9 ± 5.5	48.6 ± 5.6	0.002
Rural residency	5385 (14.1)	1300 (16.1)	4085 (13.6)	< 0.001
Mean length of stay, d	4.2 ± 4.6	4.5 ± 4.9	4.1 ± 4.5	< 0.001
Socioeconomic status				< 0.001
Lowest income quintile	8853 (23.3)	2203 (27.3)	6650 (22.2)	
Highest income quintile	5975 (15.7)	1081 (13.4)	4894 (16.3)	
Presentation				
STEMI	17,296 (45.4)	2898 (35.9)	14,398 (48.0)	< 0.001
Cardiac risk factors				
Diabetes	8605 (22.6)	2452 (30.4)	6153 (20.5)	< 0.001
Hypertension	15,748 (41.4)	3823 (47.3)	11,925 (39.8)	< 0.001
Dyslipidemia	18,877 (49.6)	3650 (45.2)	15,227 (50.8)	< 0.001
Current smoker	17,843 (46.9)	3673 (45.5)	14,170 (47.2)	0.005
Former smoker	5108 (13.4)	960 (11.9)	4148 (13.8)	< 0.001
Comorbidities				
Previous MI	3340 (8.8)	751 (9.3)	2589 (8.6)	0.06
Previous PCI	5020 (13.2)	882 (10.9)	4138 (13.8)	< 0.001
Previous CABG	888 (2.3)	193 (2.4)	695 (2.3)	0.702
Heart failure	1424 (3.7)	460 (5.7)	964 (3.2)	< 0.001
Renal disease	1567 (4.1)	537 (6.6)	1030 (3.4)	< 0.001
COPD	4661 (12.2)	1426 (17.7)	3235 (10.8)	< 0.001
Cancer	536 (1.4)	193 (2.4)	343 (1.1)	< 0.001
Peripheral vascular disease	1393 (3.7)	488 (6.0)	905 (3.0)	< 0.001
Cerebrovascular disease	384 (1.0)	145 (1.8)	239 (0.8)	< 0.001
Echocardiography during index hospitalization	25,857 (67.9)	5430 (67.2)	20,427 (68.1)	0.14
Left ventricular function*				< 0.001
< 20%	511 (1.4)	103 (1.4)	408 (1.4)	
20%-34%	2917 (8.0)	586 (7.8)	2331 (8.1)	
35%-49%	9715 (26.7)	1702 (22.6)	8013 (27.8)	
≥ 50%	17,035 (46.8)	3946 (52.5)	13,089 (45.4)	
Coronary angiography during index hospitalization	36,523 (95.9)	7549 (93.5)	28,974 (96.6)	< 0.001
Extent of disease				
≥ 50% lesion in left main artery	906 (2.5)	156 (2.1)	750 (2.6)	0.009
No. of diseased vessels ≥ 70%				< 0.001
0	4399 (12.1)	1711 (22.8)	2688 (9.3)	
1	19,270 (53.0)	3856 (51.3)	15,414 (53.4)	
2	8547 (23.5)	1315 (17.5)	7232 (25.1)	
3	4152 (11.4)	636 (8.5)	3516 (12.2)	
Normal coronary arteries	967 (2.5)	470 (5.8)	497 (1.7)	< 0.001
Revascularisation during index hospitalization				
PCI	28,622 (75.2)	4999 (61.9)	23,623 (78.8)	< 0.001
CABG	2133 (5.6)	329 (4.1)	1804 (6.0)	< 0.001
Outpatient follow-up within 90 days				
Cardiology follow-up	28,050 (74.5)	5668 (71.1)	22,382 (75.4)	< 0.001
Primary care follow-up	34,564 (91.8)	7450 (93.4)	27,114 (91.4)	< 0.001

Data are presented as mean ± SD or n (%).

CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

*Left ventricular function data was available for a subset of 36,368 patients: 7518 female, and 28,850 male.

defined as a stenosis of ≥ 50% involving the left main coronary artery.

Outcomes

The primary outcome of this study was a composite end point composed of 1-year all-cause mortality or hospitalization for unstable angina, AMI, heart failure, or stroke. Secondary outcomes included the individual components of the primary outcome and all-cause readmission at 30 days and 1 year. We also reported trends in the prevalence of cardiac risk factors over time, utilisation rates of invasive procedures (coronary angiography, PCI, or surgical revascularisation), and access to primary and speciality care after AMI.

Statistical analysis

We compared demographics and clinical characteristics of women and men by means of χ^2 test for categoric variables and analysis of variance for continuous variables as appropriate. To examine trends in risk factors, we stratified the patient cohort by fiscal year (April 1 to March 31) of the index hospitalization. Temporal changes in the prevalence of diabetes, hypertension, dyslipidemia, and current smoking were evaluated with linear regression.

Table 2. Weighted baseline characteristics, and cardiac evaluations

	Women	Men	Weighted standard difference
Demographics			
Mean age, y	48.7	48.7	0.003
Rural residency	14.8	14.2	0.017
Socioeconomic status			
Lowest income quintile	23.6	23.3	0.006
Highest income quintile	15.5	15.7	0.005
Presentation			
STEMI	46.4	46.2	0.005
Cardiac risk factors			
Diabetes	23.3	22.8	0.012
Hypertension	42.0	41.5	0.010
Dyslipidemia	49.9	49.6	0.005
Current smoker	48.0	47.0	0.021
Former smoker	13.4	13.4	0.0003
Comorbidities			
Previous MI	9.3	8.9	0.015
Previous PCI	13.5	13.2	0.009
Previous CABG	2.4	2.3	0.004
Heart failure	4.0	3.9	0.008
Renal disease	4.4	4.2	0.009
COPD	12.7	12.4	0.009
Cancer	1.0	1.0	0.001
Peripheral vascular disease	4.0	3.8	0.011
Cerebrovascular disease	1.0	1.0	0.001
Left ventricular function			
< 20%	1.5	1.4	0.008
20%-34%	7.7	7.7	0.001
35%-49%	25.2	25.5	0.007
≥ 50%	44.4	44.7	0.006
Extent of disease at angiography			
No. of diseased vessels ≥ 70%			
0	11.4	11.4	0.0001
1	50.2	49.9	0.006
2	21.4	21.7	0.007
3 or left main artery ≥ 50%	12.3	12.4	0.005

CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

The comparison of outcomes among men and women was performed using an inverse probability of treatment weighting (IPTW) approach to account for baseline differences between men and women.[18,19] Variables considered in the weighting are presented in Tables 1 and 2, including demographic variables (age, neighbourhood income quintile), cardiac risk factors, comorbidities, and admission characteristics (ST-segment elevation myocardial infarction, left ventricular ejection fraction, extent of coronary artery disease). Standardised differences were used to compare characteristics in the weighted sample, where differences of less than 0.1 indicated good balance.[20] In the weighted comparative samples, we used Cox proportional hazard models to estimate HRs and their 95% CIs for each outcome with the use of a robust variance estimator to account for the homogeneity in outcomes induced by weighting,[21] with men as the reference group. Adjusted Kaplan-Meier survival curves were estimated for men and women separately in the IPTW sample. A weighted log-rank test was used to compare group differences in survival functions.[22,23] All P values were 2 sided and < 0.05 was considered to be statistically significant. SAS version 9.3 (SAS Institute, Cary, NC) was used for all statistical analyses.

Results

Creation of the study cohort

There were 213,897 records for patients who were admitted to an acute care hospital in Ontario with a diagnosis of AMI from April 1, 2009, to March 31, 2019 (Fig. 1). After exclusions, the study cohort included 38,071 AMI hospitalizations involving 8,077 (21.2%) women. Notably, younger women accounted for approximately 11% of women of all ages admitted with AMI during the study period.

Baseline characteristics

The overall mean age at presentation with AMI was 48.7 ± 5.6 years, and the mean length of stay was 4.2 ± 4.6 days (Table 1). A greater proportion of younger women belonged to the lowest income quintile than did men (27.3% vs 22.2%). Overall, women had a significantly greater prevalence of cardiac and other comorbidities compared with men. Compared with men, women had a higher prevalence of diabetes (30.4% vs 20.5%), hypertension (47.3% vs 39.8%), chronic obstructive pulmonary disease (17.7% vs 10.8%), and renal failure (6.6% vs 3.4%). Rates of current smoking, dyslipidemia, and previous PCI were greater in men.

Risk factors that changed the most over time were the prevalence of diabetes and current smoking in women (Table 3 and Fig. 2). In 2009, nearly 25% of women had diabetes, and by 2018 the rate of diabetes increased to 34.9%. In contrast, the rates of diabetes increased by 3.9% from 18.2% to 22.1% in men over the same time period. Current smoking significantly decreased in both women and men during this time period (women: 53.2% in 2009 to 41.7% in 2018; men: 52.7% to 43.3%).

Cardiac evaluations and physician follow-up

About two-thirds of patients had echocardiography for left ventricular function assessment during AMI hospitalization (Table 1). Of those assessed, proportionally more women had left ventricular ejection fraction ≥ 50% than men (52.5% vs 45.4%; $P < 0.001$). Overall, 93.5% of women received coronary angiography during hospitalization compared with 96.6% of men. The use of coronary angiography increased significantly during the study period (women: 90.4% in 2009 to 95.9% in 2018 [$P_{trend} < 0.001$]; men: 94.0% in 2009 to 97.8% in 2018 [$P_{trend} < 0.001$]). Coronary angiography revealed a significantly greater prevalence of normal coronary arteries (5.8% vs 1.7%; $P < 0.001$), no significantly diseased vessels ≥ 70% (22.8% vs 9.3%; $P < 0.001$), and less multivessel disease in women compared with men. Women underwent significantly less coronary revascularisation during the index hospitalization than men (PCI: 61.9% vs 78.8% [$P < 0.001$]; coronary artery bypass graft surgery [CABG]: 4.1% vs 6.0% [$P < 0.001$]). Rates of 90-day follow-up with a cardiologist were slightly lower for women than men (71.1% vs.75.4%; $P < 0.001$) while more than 90% of patients had primary care follow-up within 90 days of AMI hospitalization.

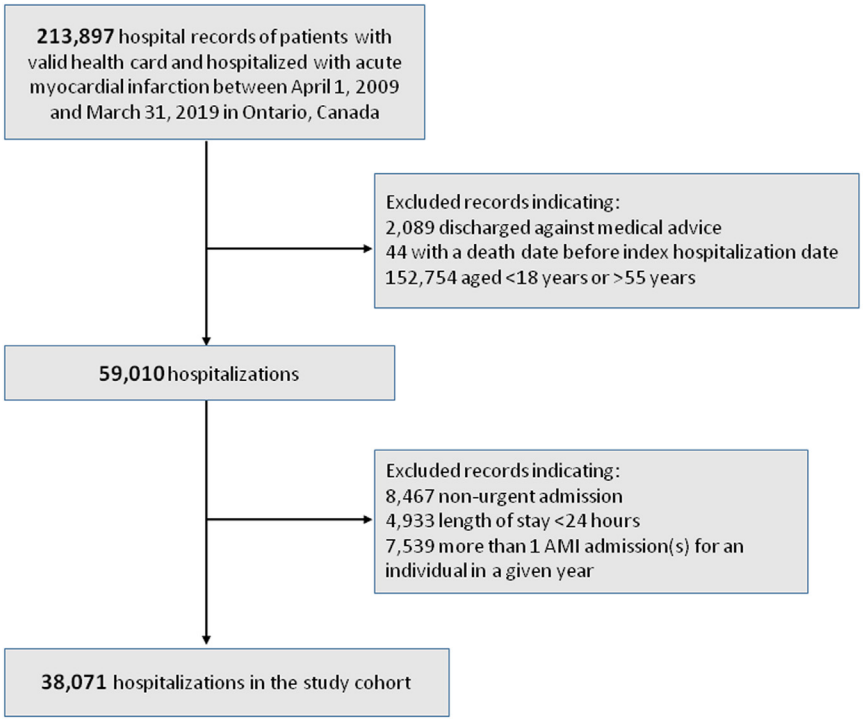

Figure 1. Construction of the hospitalized acute myocardial infarction (AMI) cohort.

Clinical outcomes

The incidence of the primary composite end point was significantly increased among women (10.0% vs 7.9%, adjusted HR [aHR] 1.11, 95% CI 1.02-1.21; $P = 0.02$) (Table 4; unadjusted clinical outcomes presented in Supplemental Table S1). This finding was driven by significantly higher rates of 1-year readmission for unstable angina or AMI, heart failure, and stroke experienced by women. Mortality rates were not significantly different between women and men at 1 year (2.9% vs 2.8%, aHR 1.03, 95% CI 0.88-1.20; $P = 0.70$). The incidence of 1-year all-cause readmission was significantly greater among women than men (25.8% vs 21.1%, aHR 1.34, 95% CI 1.27-1.42; $P < 0.0001$).

Discussion

This population-based study evaluated the characteristics, care patterns, and clinical outcomes in a cohort of younger women and men hospitalized with AMI in Ontario, Canada, and adds several insights. First, we found that younger women hospitalized with AMI had a significantly higher prevalence of cardiac risk factors and comorbidities compared with younger men with AMI. Second, we found a steady increase in the prevalence of diabetes in women over time, such that 24.8% had diabetes in 2009 compared with 34.9% in 2019. The prevalence of diabetes increased more among women than men during this period (10% vs 4%). Third, we noted a high prevalence of current smoking among younger patients of both sexes (40%-50%) and much higher than rates noted among the general population (10%).[24] A significant decline in current smoking rates occurred during the study period, somewhat more for women than for men. Fourth, we found that the use of coronary angiography was nearly universal for all younger patients; however, we observed much lower rates of PCI provided to women compared with men, suggesting sex differences in the pathophysiology of AMI. This assertion may be partially supported by the greater prevalence of normal coronary arteries and nonobstructive coronary artery disease observed at angiography among women compared with men. Finally, although 1-year mortality rates were similar among men and

Table 3. Temporal trends in the prevalence of cardiac risk factors

Risk factor	Sex	2009, %	2018, %	Annual % change (95% CI)	*P* value	$P_{interaction}$
Diabetes	Women	24.8	34.9	0.99 (0.80 to 1.19)	< 0.001	< 0.001
	Men	18.2	22.1	0.45 (0.25 to 0.65)	< 0.001	
Hypertension	Women	45.2	47.5	0.08 (−0.22 to 0.37)	0.62	0.80
	Men	38.7	40.8	0.13 (−0.17 to 0.42)	0.39	
Dyslipidemia	Women	44.9	46.7	0.04 (−0.29 to 0.38)	0.81	0.04
	Men	52.4	47.9	−0.46 (−0.79 to −0.12)	0.007	
Current smoking	Women	53.2	41.7	−0.93 (−1.45 to −0.40)	< 0.001	0.88
	Men	52.7	43.3	−0.87 (−1.40 to −0.34)	0.0013	

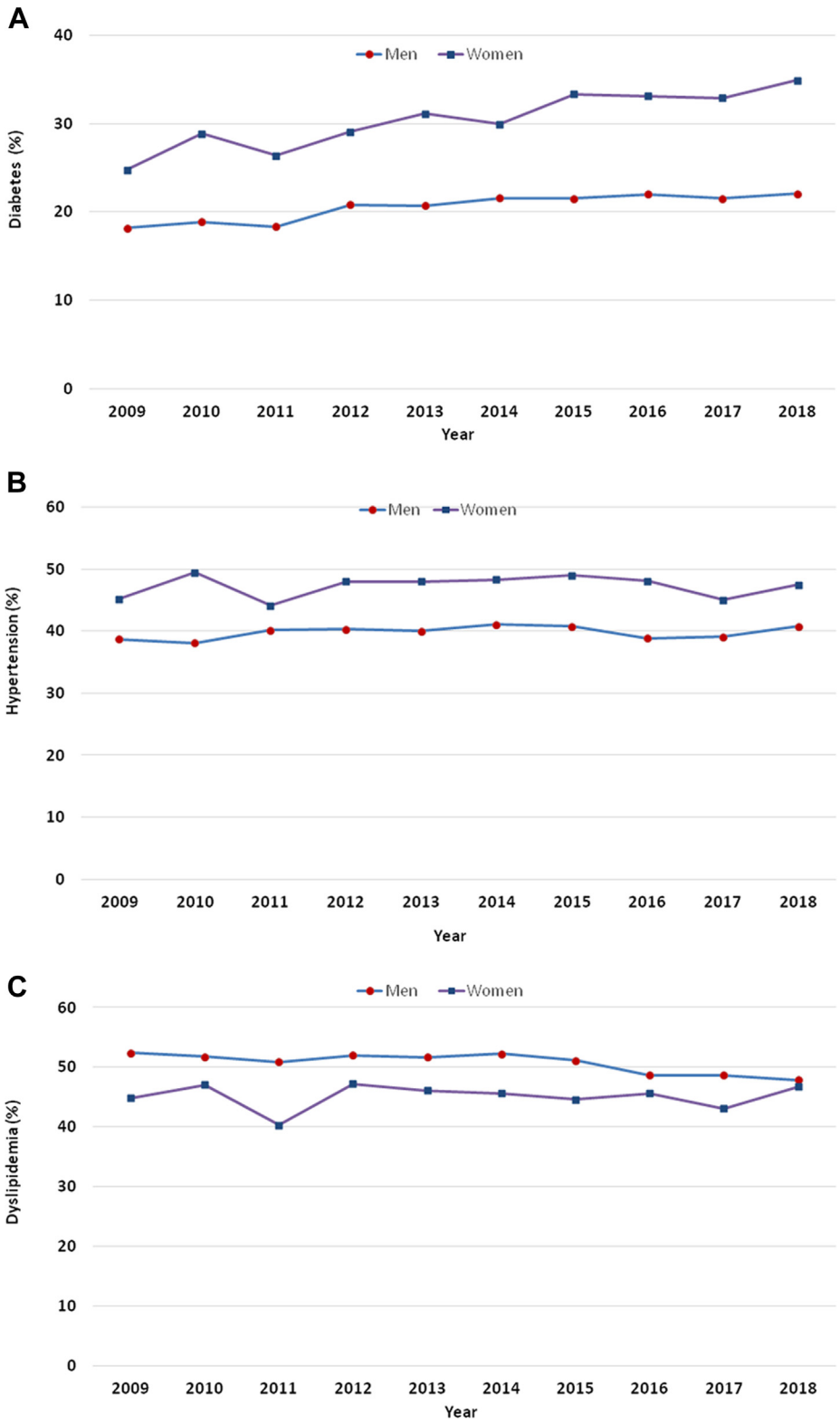

Figure 2. Trends in cardiac risk factors. (**A**) Diabetes; (**B**) hypertension; (**C**) dyslipidemia; (**D**) current smoking.

women, we observed significantly greater rates of 1-year rehospitalization for major adverse cardiovascular events and all-cause readmission among women.

Our contemporary study adds to the current understanding of potential sex differences in AMI treatment and outcomes among younger patients. Most of the published

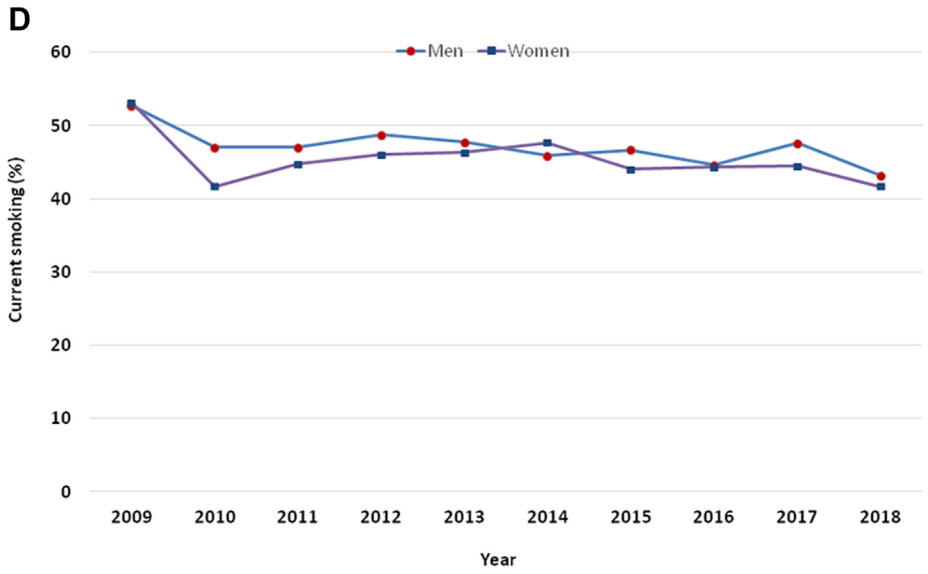

Figure 2. Continued.

literature on sex-based analyses of younger AMI patients used data collected before 2016.[5,6,8,12-14,25,26] For example, the landmark 1999 study by Vaccarino et al. found 3%-3.5% higher mortality rates among younger women with AMI compared with men and challenged cardiologists to take action for this high-risk group.[5] Some of the difference in outcomes between men and women in that early study may be explained by relatively low rates of prescribing evidence-based medications (aspirin, beta-blockers, and thrombolysis) and a 10% lower use of coronary angiography in women than men. The past decade has seen tremendous improvements in AMI care through both public and professional education campaigns (including the American Heart Association's Go Red for Women, Get With The Guidelines, and Mission Lifeline), reorganisation of health care systems around ST-segment elevation myocardial infarction care offering primary PCI or pharmaco-invasive approaches, and better pharmacotherapy for AMI (eg, potent antiplatelet therapy). In this context, it is encouraging to see that by 2019 in Ontario, certain care gaps identified in earlier studies appear to have closed such that the use of coronary angiography is largely universal for both sexes, the rates of primary and specialist care are high, and mortality rates over our study period were similar among men and women and relatively low overall.

Despite these aforementioned gains in the quality of AMI care, we observed that younger women continue to be readmitted for recurrent AMI, heart failure, and stroke to a significantly greater extent than younger men, and that all-cause readmissions rates are also significantly higher. Chest pain syndromes experienced after AMI hospitalization in women have a fairly broad differential diagnosis that includes stent thrombosis, loss of coronary side branches after PCI, extension of spontaneous coronary artery dissection (SCAD)—related dissection, coronary vasospasm, and microcirculatory dysfunction, in addition to noncardiac chest discomfort. The increased rate of all-cause readmission is an interesting finding given our angiographic data demonstrating higher rates of normal coronary arteries or nonobstructive disease among women. We expected that less angiographic disease may lead to fewer readmissions and less use of health care services in women, but this was not the case. A previous younger AMI cohort showed that women were more likely to be rehospitalized for all causes, but not cardiac causes.[27] Social determinants of health have been shown to play an important role after AMI in younger patients in both the US and Canada, with unemployment being associated with lower quality of care and increased cardiac readmissions.[28] Furthermore, greater symptom levels of depression,

Table 4. Clinical outcomes after inverse probability of treatment weighting adjustment

Adjusted outcome	Women, %	Men, %	HR (95% CI)	*P* value
Primary end point				
30 days	3.7	3.4	1.11 (0.97-1.28)	0.13
1 year	10.0	7.9	1.11 (1.02-1.21)	0.02
Mortality				
30 days	1.5	1.6	0.98 (0.79-1.21)	0.83
1 year	2.9	2.8	1.03 (0.88-1.20)	0.070
Unstable angina or AMI readmission				
30 days	1.6	1.4	1.16 (0.93-1.44)	0.19
1 year	5.4	4.2	1.34 (1.18-1.52)	< 0.0001
Heart failure hospitalization				
30 days	0.5	0.4	1.62 (1.13-2.32)	0.008
1 year	1.5	1.2	1.40 (1.13-1.75)	0.002
Stroke				
30 days	0.1	0.1	0.92 (0.42-2.03)	0.83
1 year	0.5	0.3	1.69 (1.15-2.47)	0.008
Revascularisation (PCI or CABG) after discharge				
30 days	1.5	2.3	0.77 (0.60-0.97)	0.03
1 year	5.8	6.7	1.03 (0.90-1.18)	0.66
All-cause readmission				
30 days	9.4	8.2	1.26 (1.15-1.38)	< 0.0001
1 year	25.8	21.1	1.34 (1.27-1.42)	< 0.0001

AMI, acute myocardial infarction; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention.

posttraumatic stress disorder, and perceived stress have been reported among younger women recovering from AMI compared with similarly aged men, as well as increased rates of mental stress—induced myocardial ischemia.[13,17,29,30] As previously observed among patients recovering from SCAD, an adverse psychosocial profile could result in increased emergency room visits or readmissions for chest pain or related symptoms.[31] Some readmissions could also be related to bleeding complications after AMI, given that more women than men are typically characterised as having high bleeding risk status,[32,33] or perhaps the presence of increased comorbidities at baseline among women may contribute to increased risk for rehospitalization after AMI. While we do not fully understand all the reasons for increased rates of all-cause readmissions among women compared with men, we suspect that differing pathophysiology for AMI (CAD, SCAD, coronary vasospasm, or microvascular dysfunction), new heart failure due to reduced ejection fraction, and varying comorbidities and psychosocial needs may be contributory factors. Possible strategies to avoid early readmissions among women could include increased referral rates to cardiac rehabilitation programs, including home-based programs, and those programs offering access to peer support groups. Furthermore, increasing the number of follow-ups and ensuring an early follow-up (2 weeks) after discharge for AMI may reduce the number of early readmissions or emergency room visits. Leveraging virtual care and physician extenders or other allied health professionals may make this a viable strategy to address unmet care needs among younger women recovering from AMI.

Consistent with other studies, we also found that younger women with AMI had a greater burden of cardiac risk factors and other comorbidities compared with younger men.[8,12,15,34] The Atherosclerosis Risk in Communities (ARIC) surveillance study reported 20-year trends (1995 to 2014) and sex differences in 8737 young AMI patients aged 34 to 54 years in 4 communities in the United States.[12] Over this period, among young women with AMI, the prevalence of hypertension increased by 9% (66% to 75%, vs 12% increase in younger men), diabetes increased by 2% (34% to 36%, vs 8% increase in younger men), and smoking declined by 10% (56% to 46% vs 6% decrease in younger men). In our study, the prevalence of diabetes in women increased by 10% in just 10 years, and that was greater than the increase of diabetes in men. By 2018, more than 1 in 3 young women with AMI had diabetes, almost one-half had hypertension, and dyslipidemia, and more than 2 in 5 were current smokers. Although it is encouraging to see a declining prevalence of current smoking in this cohort, we still observed that $> 40\%$ of patients were current smokers in 2018-2019. These estimates are consistent with other published reports in younger AMI populations.[35,36] Biery et al. reported lower socioeconomic status, increased rates of mental illness, alcohol use, and illicit drug use among current smokers with AMI at a younger age.[35] The increased burden of cardiovascular risk factors among younger women with AMI confirms the ongoing need for aggressive primary prevention measures that could potentially reduce the development of AMI in these vulnerable patients. In the postpandemic era, renewed attention to public education and primary prevention measures by national cardiovascular organisations would be worthwhile. Such initiatives would highlight the importance of healthy lifestyle choices, regular exercise, and the maintenance of normal body weight to prevent the development of hypertension, dyslipidemia, diabetes, and cardiovascular diseases.

Despite prior studies showing that women receive invasive angiography less often than men, we found that almost all young patients with AMI, regardless of sex, received coronary angiography. The increasing rates of angiography over time for both men and women is also consistent with increasing capacity for cardiac services within the Canadian health care system. Interestingly, we saw a large gap in the use of coronary revascularisation such that the PCI rate was lower by 16.9% and CABG rate by 1.9% for women compared with men. Previous studies have speculated that women with AMI had a lower rates of coronary revascularisation because of older age, comorbidities, smaller coronary arteries, or less obstructive plaques.[4,9] Although we were unable to distinguish all the reasons underlying these differences, we think, for several reasons, that the difference may not be a result of undertreatment of women. First, patients in our cohort were young and had fewer comorbidities overall compared with those studied in the prior literature, and therefore, concerns of risks associated with PCI are unlikely a reason to explain the observed sex difference. Second, selection bias would tend to occur at the time of selection of patients for coronary angiography and less likely to occur when obstructive lesions were identified. Third, there are increasingly recognised sex differences in the pathophysiology of AMI such that women are more likely to have AMI presentations due to coronary artery spasm, microvascular dysfunction, SCAD, or takotsubo stress—induced cardiomyopathy, for which conservative approaches with medical therapy are preferred over coronary revascularisation. The angiographic data available from our cohort support this assertion, with more women having normal coronary arteries (4.1% higher in women than men) and nonobstructive coronary artery disease (13.5% higher) among women.

Several potential limitations of our study merit discussion. First, we were unable to assess for potential sex differences in the use of evidence-based medications, because the Ontario drug benefit program only medication coverage provides for patients older than 65 years. Second, our study focused on harder outcomes such as mortality and repeated hospitalizations as the main clinical outcomes. We acknowledge that other measures, such as health-related quality of life, may be equally important in comparing outcomes between women and men but were unable to examine such outcomes owing to the lack of data. Third, although we observed a higher prevalence of preserved left ventricular function after AMI among women, suggesting smaller infarcts in women compared with men, we did not have access to cardiac enzyme data to further explore this finding.

In conclusion, we report that sex-based care gaps are gradually closing in Ontario on several fronts. Over the study period, we found similar adjusted mortality rates for young women and men after AMI hospitalization; however, rehospitalization rates for adverse cardiovascular events and all-cause readmission rates were significantly higher in women compared to men. By 2018, the use of coronary angiography was largely universal for both sexes, and high levels of primary and specialist care were taking place after hospitalization. The

lower rate of PCI among younger women may reflect increasing recognition of alternative pathophysiology for AMI among women in this age group. Our study also underscores the need for ongoing intensive primary prevention strategies directed at younger women.

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The authors have no conflicts of interest to disclose.

References

1. Tu JV, Khan AM, Ng K, Chu A. Recent temporal changes in atherosclerotic cardiovascular diseases in Ontario: clinical and health systems impact. Can J Cardiol 2017;33:378-84.
2. Report from the Canadian Chronic Disease Surveillance System: heart disease in Canada. Published, 2018, https://www.canada.ca/en/public-health/services/publications/diseases-conditions/report-heart-disease-Canada-2018.html#s1-1. Accessed February 15, 2021.
3. Virani SS, Alonso A, Benjamin EJ, et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. Circulation 2020;141:e139-596.
4. Mehta LS, Beckie TM, DeVon HA, et al. Acute myocardial infarction in women: a scientific statement from the American Heart Association. Circulation 2016;133:916-47.
5. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 participants. N Engl J Med 1999;341:217-25.
6. Vaccarino V, Parsons L, Peterson ED, Rogers WJ, Kiefe CI, Canto J. Sex differences in mortality after acute myocardial infarction: changes from 1994 to 2006. Arch Intern Med 2009;169:1767-74.
7. Jneid H, Fonarow GC, Cannon CP, et al. Sex differences in medical care and early death after acute myocardial infarction. Circulation 2008;118:2803-10.
8. Berg J, Bjorck L, Nielsen S, Lappas G, Rosengren A. Sex differences in survival after myocardial infarction in Sweden, 1987-2010. Heart 2017;103:1625-30.
9. Aggarwal NR, Patel HN, Mehta LS, et al. Sex differences in ischemic heart disease: advances, obstacles, and next steps. Circ Cardiovasc Qual Outcomes 2018;11:e004437.
10. Sarma AA, Braunwald E, Cannon CP, et al. Outcomes of women compared with men after non—ST-segment elevation acute coronary syndromes. J Am Coll Cardiol 2019;74:3013-22.
11. Kosmidou I, Leon MB, Zhang Y, et al. Long-term outcomes in women and men following percutaneous coronary intervention. J Am Coll Cardiol 2020;75:1631-40.
12. Arora S, Stouffer GA, Kucharska-Newton AM, et al. Twenty year trends and sex differences in young adults hospitalized with acute myocardial infarction. Circulation 2019;139:1047-56.
13. Bucholz EM, Strait KM, Dreyer RP, et al. Editor's choice—Sex differences in young patients with acute myocardial infarction: a VIRGO study analysis. Eur Heart J Acute Cardiovasc Care 2017;6:610-22.
14. Pelletier R, Humphries KH, Shimony A, et al. Sex-related differences in access to care among patients with premature acute coronary syndrome. CMAJ 2014;186:497-504.
15. Otten AM, Maas AH, Ottervanger JP, et al. Is the difference in outcome between men and women treated by primary percutaneous coronary intervention age dependent? Gender difference in STEMI stratified on age. Eur Heart J Acute Cardiovasc Care 2013;2:334-41.
16. Parvand M, Rayner-Hartley E, Sedlak T. Recent developments in sex-related differences in presentation, prognosis, and management of coronary artery disease. Can J Cardiol 2018;34:390-9.
17. Vaccarino V. Myocardial infarction in young women. Circulation 2019;139:1057-9.
18. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399-424.
19. Deb S, Austin PC, Tu JV, et al. A review of propensity-score methods and their use in cardiovascular research. Can J Cardiol 2016;32:259-65.
20. Austin PC, Stuart EA. Moving toward best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34:3661-79.
21. Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. Stat Med 2013;32:2837-49.
22. Austin PC, Schuster T. The performance of different propensity score methods for estimating absolute effects of treatments on survival outcomes: a simulation study. Stat Meth Med Res 2016;25:2214-37.

23. Xie J, Liu C. Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. Stat Med 2005;24:3089-110.

24. The 2020 Canadian Tobacco and Nicotine Survey. Available at: https://www150.statcan.gc.ca/n1/daily-quotidien/210317/dq210317b-eng.htm. 2021.

25. Khera S, Kolte D, Gupta T, et al. Temporal trends and sex differences in revascularisation and outcomes of ST-segment elevation myocardial infarction in younger adults in the United States. J Am Coll Cardiol 2015;66:1961-72.

26. Alkhouli M, Alqahtani F, Jneid H, Al Hajji M, Boubas W, Lerman A. Age-stratified sex-related differences in the incidence, management, and outcomes of acute myocardial infarction. Mayo Clin Proc 2021;96:332-41.

27. Pelletier R, Choi J, Winters N, et al. Sex differences in clinical outcomes after premature acute coronary syndrome. Can J Cardiol 2016;32:1447-53.

28. Raparelli V, Pilote L, Dang B, et al. Variations in quality of care by sex and social determinants of health among younger adults with acute myocardial infarction in the US and Canada. JAMA Netw Open 2021;4:e2128182.

29. Xu X, Bao H, Strait K, et al. Sex differences in perceived stress and early recovery in young and middle-aged patients with acute myocardial infarction. Circulation 2015;131:614-23.

30. Vaccarino V, Sullivan S, Hammadah M, et al. Mental stress—induced myocardial ischemia in young patients with recent myocardial infarction: sex differences and mechanisms. Circulation 2018;137:794-805.

31. Edwards KS, Vaca KC, Naderi S, Tremmel JA. Patient-reported psychological distress after spontaneous coronary artery dissection: evidence for post-traumatic stress. J Cardiopulm Rehabil Prev 2019;39:e20-3.

32. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. Circulation 2019;140:240-61.

33. Chandiramani R, Cao D, Claessen BE, et al. Sex-related differences in patients at high bleeding risk undergoing percutaneous coronary intervention: a patient-level pooled analysis from 4 postapproval studies. J Am Heart Assoc 2020;9:e014611.

34. Hao Y, Liu J, Liu J, et al. Sex differences in in-hospital management and outcomes of patients with acute coronary syndrome. Circulation 2019;139:1776-85.

35. Biery DW, Berman AN, Singh A, et al. Association of smoking cessation and survival among young adults with myocardial infarction in the Partners YOUNG-MI Registry. JAMA Netw Open 2020;3:e209649.

36. Yandrapalli S, Nabors C, Goyal A, Aronow WS, Frishman WH. Modifiable risk factors in young adults with first myocardial infarction. J Am Coll Cardiol 2019;73:573-84.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2022.06.023.