Sex differences in coronary catheterization and revascularization following acute myocardial infarction: Time trends from 1994 to 2003 in British Columbia

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BACKGROUND: Studies before the turn of the century reported sex differences in procedure rates. It is unknown whether these differences persist. **OBJECTIVES:** To examine time trends and sex differences in coronary catheterization and revascularization following acute myocardial infarction (AMI).

METHODS: A retrospective analysis was performed of all patients 20 years of age or older who were admitted to hospital in British Columbia with an AMI between April 1, 1994, and March 31, 2003. Segmented regression analysis was used to examine the inflection point of the time trend in 90-day catheterization rates post-AMI. Multivariable Cox regression modelling was used to evaluate sex differences in receiving catheterization and revascularization following AMI.

RESULTS: Ninety-day coronary catheterization rates increased significantly over the study period for both men and women ($P < 0.0001$ for trend), with a steeper increase beginning in September 2000. Women were less likely to undergo catheterization than men, even after adjustment for baseline differences; this sex effect was modified by age and care in the intensive care unit or cardiac care unit (ICU/CCU). Specifically, ICU/CCU admission eliminated the sex difference among patients who were younger than 65 years of age. Conditional on receiving cardiac catheterization post-AMI, female sex was not associated with a lower likelihood of receiving revascularization within one year (HR 0.96; 95% CI 0.91 to 1.02).

CONCLUSIONS: Despite recent increases in catheterization rates post-AMI, women were less likely to undergo catheterization than men. Interestingly, access to ICU/CCU care removed the sex difference in catheterization access in patients younger than 65 years of age.

Key Words: Acute myocardial infarction; Cardiac catheterization; Revascularization; Sex

Studies published before 1999 have reported sex differences in cardiovascular procedure rates following an acute myocardial infarction (AMI). Specifically, women underwent coronary catheterization and revascularization less frequently than men (1-6). Age-adjusted mortality rates were significantly higher in women (4-6). After 1999, several trials were published demonstrating improved outcomes in patients receiving an early invasive strategy (coronary catheterization with or without percutaneous coronary intervention [PCI]) compared with a conservative approach following non-ST elevation myocardial infarction (NSTEMI) (7-9). In

Les différences selon les sexes en cas de cathétérisme et de revascularisation après un infarctus aigu du myocarde : Les tendances dans le temps entre 1994 et 2003 en Colombie-Britannique

HISTORIQUE : Les études menées au tournant du siècle faisaient état de différences de taux d'interventions selon les sexes. On ne sait pas si ces différences persistent.

OBJECTIFS : Examiner les tendances dans le temps et les différences selon les sexes du cathétérisme coronarien et de la revascularisation après un infarctus aigu du myocarde (IAM).

MÉTHODOLOGIE : Les chercheurs ont procédé à une analyse rétrospective de tous les patients de 20 ans ou plus hospitalisés en Colombie-Britannique en raison d'un IAM entre le 1^{er} avril 1994 et le 31 mars 2003. L'analyse de régression segmentée a permis d'examiner le point d'inflexion de la tendance dans le temps des taux de cathétérisme 90 jours après un IAM. Le modèle de régression de Cox multivariable a permis d'évaluer les différences d'administration de cathétérisme et de revascularisation selon les sexes après un IAM.

RÉSULTATS : Les taux de cathétérismes coronaires au bout de 90 jours ont considérablement augmenté pendant la période de l'étude, tant chez les hommes que chez les femmes ($P < 0,0001$ en matière de tendance), l'augmentation étant plus marquée à compter de septembre 2000. Les femmes étaient moins susceptibles de subir un cathétérisme que les hommes, même après ajustement des différences de départ. Cet effet attribuable au sexe changeait selon l'âge et les soins à l'unité de soins intensifs ou de soins cardiaques (USI-USC). Notamment, l'hospitalisation à l'USI-USC éliminait la différence selon les sexes chez les patients de moins de 65 ans. Sous réserve d'avoir reçu un cathétérisme cardiaque après l'IAM, le sexe féminin ne s'associait pas à une diminution de la probabilité d'avoir reçu une revascularisation au bout d'un an (FC 0,96; 95 % IC 0,91 à 1,02).

CONCLUSIONS : Malgré l'augmentation récente du taux de cathétérisme après un IAM, les femmes étaient moins susceptibles de subir un cathétérisme que les hommes. Fait intéressant, l'accès à l'USI-USC faisait disparaître la différence d'accès au cathétérisme chez les patients de moins de 65 ans.

addition, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of patients with NSTEMI emphasized an early invasive approach in both men and women (10).

It is unknown whether sex differences in cardiac procedure rates post-AMI persist in the era emphasizing an early invasive strategy. We sought to examine trends in catheterization and revascularization rates following an AMI in British Columbia (BC) from 1994 to 2003. Specifically, we examined the effect of sex on receiving catheterization and revascularization adjusted for potential confounders.

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METHODS

Study populations

Two patient cohorts were studied. The first cohort (the AMI cohort) included 47,535 patients (20 years of age or older) who were admitted to hospital with a diagnosis of AMI between April 1, 1994, and March 31, 2003, in BC. Data were extracted from the BC Hospitalization Database, which includes data on all hospital admissions in BC and all cardiac catheterization procedures, both inpatient and outpatient. An AMI was defined according to the WHO's *International Statistical Classification of Diseases and Related Health Problems, Ninth Revision* coding system. All patients with a primary discharge diagnosis of AMI (410.x) with at least two days of stay in the hospital were eligible. A total of 5625 patients who had a previous AMI or previous catheterization, PCI or coronary artery bypass grafting (CABG) within one year of the index AMI were excluded because previous AMIs and cardiac procedures can affect the likelihood of receiving catheterization. Also, 1031 patients who died within the first two days of the index AMI admission date were excluded because of insufficient time to start treatments. After all exclusions, the final AMI cohort comprised 40,879 patients. The primary outcome was time to catheterization within one year of the index AMI.

The database used in the present analysis does not distinguish between ST elevation myocardial infarction (STEMI) and NSTEMI within the AMI diagnosis. Therefore, analyses were limited by the inability to distinguish between STEMI and NSTEMI patients in the present cohort. It is recognized that significantly fewer women than men present with ST elevation (27% versus 37%) (11). In addition, the recent literature supporting an early invasive strategy describes the NSTEMI population only. Despite these limitations, the results of the present study are important, particularly with regard to the interplay between sex, age and access to an intensive care unit or cardiac care unit (ICU/CCU). In addition, there is no evidence that there have been any changes in the proportion of patients with NSTEMI over time. Therefore, the data trend is still of importance.

In the second study cohort (the catheterization cohort), the aim was to evaluate the utilization of PCI or CABG by using the Cardiac Services BC Registry (CSBCR), a data set that includes substantive clinical detail, including coronary anatomy and ejection fraction. The CSBCR is a detailed prospective clinical registry of all cardiac procedures performed in BC. The present catheterization study cohort comprised 9531 patients with an AMI between May 1, 1999, and March 31, 2003, who underwent coronary catheterization within one year of their index AMI. A total of 298 patients with a normal angiogram were excluded, resulting in a final catheterization cohort of 9233 patients. The primary outcome of interest was sex differences in receiving revascularization (PCI or CABG) within one year of the index catheterization among patients with angiographic evidence of coronary artery disease (CAD).

Definitions

Index AMI admission was defined as the first AMI admission between April 1, 1994, and March 31, 2003, based on discharge diagnosis from hospital. Index coronary catheterization was defined as the first catheterization following the index AMI admission. Case complexity was defined according to the grouping methodology of the Canadian Institute for Health Information, which uses a four-level resource utilization index (1 = no complexity; 2 = complexity related to chronic conditions; 3 = complexity related to serious/important conditions; and 4 = complexity related to potentially life-threatening conditions).

Statistical analyses

Univariate comparisons of baseline characteristics between men and women were conducted using the χ^2 test. Time trend analysis for 90-day catheterization rates was conducted using the Mantel-Haenszel χ^2 test. The inflection point of the time trend in 90-day catheterization rates was also examined using the segmented regression model. Ninety days was chosen as the cut-off for catheterization rate analysis

because the majority of catheterizations post-AMI were expected to be performed within 90 days.

Kaplan-Meier estimates and the log-rank test were used to evaluate the univariate association between sex and receiving catheterization within one year after index AMI admission. In the AMI cohort, a Cox regression model was used to evaluate the sex effect on receiving catheterization, adjusted for potential confounders including age, renal disease, congestive heart failure (CHF), cerebrovascular disease (CVD), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), hypertension, hyperlipidemia, liver disease, cancer, presentation with shock or ventricular fibrillation arrest, ICU/CCU use, admission year, hospital category (with or without catheterization facilities), physician specialty, case complexity level and neighbourhood income. Physician specialty was classified into three categories – cardiologist, internist, and general practitioner or other physician type – based on the specialty of the most responsible physician at the index AMI admission. The set of potential confounders was selected based on clinical relevance among all available risk factors in the BC Hospitalization Database. The interactions between sex and age, sex and ICU/CCU use, and sex and year of AMI admission were also examined.

In the catheterization cohort (ie, patients who underwent catheterization within one year of their index AMI), a Cox regression model was used to examine the association between sex and receiving revascularization within one year of index catheterization. This was adjusted for age, extent of CAD, ejection fraction, DM, CHF, renal disease, hyperlipidemia, hypertension, PVD, CVD, COPD, liver disease, cancer, neighbourhood income group and catheterization year. The set of potential confounders was selected based on clinical relevance of all available risk factors in the CSBCR. The interactions between sex and age, and between sex and catheterization year were also examined.

All statistical analyses were performed using SAS version 9 (SAS Institute Inc, USA) and R version 2.2.1 (an open-source statistical language).

RESULTS

Sex differences in coronary catheterization rates post-AMI

Women comprised 34.3% of the AMI cohort. Women were older and had significantly more hypertension, DM, CHF, CVD, COPD and shock, and a higher case complexity level than men. In contrast, men tended to have more hyperlipidemia. Women 75 years of age or older were significantly less likely to access ICU/CCU care compared with men 75 years of age or older (56.6% versus 62.7%). Women were more likely to live in low-income neighborhoods than men (47.4% versus 41.0%) (Table 1).

In both women and men, 90-day coronary catheterization rates increased over the study period (April 1, 1994, through December 31, 2002) ($P < 0.0001$ for trend). In women, the 90-day coronary catheterization rates increased from 31.0% in 1994 to 49.4% in 2002; in men, this rate increased from 41.6% to 66.1% (Figure 1). Similar increasing trends in 90-day catheterization rates post-AMI were observed for both women and men over the study period. A segmented regression model with a common slope and one common inflection point for men and women was developed. The common inflection point was estimated to be September 2000 (95% CI April 2000 to February 2001). The common slope surrounding the inflection point indicated that the 90-day catheterization rates increased by 0.26% pre- and 2.19% postinflection point for every three-month period. The sex difference in 90-day coronary catheterization rates persisted throughout the nine-year study period (Figure 1).

The probability of undergoing catheterization within one year of AMI was 42.5% for women and 57.9% for men (Figure 2). After adjustment for baseline characteristics, women were still less likely to undergo catheterization, but this sex effect was modified by age and ICU/CCU use ($P < 0.0001$ for interaction of sex and age; $P < 0.0001$ for interaction of sex and ICU/CCU use). For patients who did not receive ICU/CCU care, women were consistently less likely to receive catheterization in all age groups; in contrast, in patients who received ICU/CCU care, sex differences only appeared in older

TABLE 1
Baseline characteristics of acute myocardial infarction patients by sex (n=40,879)

Characteristics	Women (n=14,038)	Men (n=26,841)	P
Age, years			<0.01
<55	8.1	19.8	
55–64	12.5	22.0	
65–74	25.3	27.1	
≥75	54.2	31.4	
Diabetes	20.8	17.1	<0.01
Heart failure	27.0	17.6	<0.01
Renal disease	2.8	2.7	0.58
Hyperlipidemia	5.5	7.0	<0.01
Hypertension	27.9	21.1	<0.01
Peripheral vascular disease	1.4	1.5	0.28
Cerebrovascular disease	3.8	2.9	<0.01
Pulmonary disease	8.9	8.0	<0.01
Liver disease	0.1	0.2	0.28
Cancer	0.1	0.0	0.04
Shock	2.5	1.5	<0.01
Arrest/ventricular fibrillation	3.7	3.7	0.95
Case complexity level			<0.01
Level 1	75.2	79.6	
Level 2	12.0	10.6	
Level 3	7.6	6.3	
Level 4	5.2	3.6	
Intensive/cardiac care unit use	65.7	73.8	<0.01
Admitted to hospital	25.1	24.8	0.49
Admitting physician			<0.01
Cardiologist	27.2	31.3	
Internist	33.6	37.3	
General practitioner/other	39.2	31.4	
Neighbourhood income			<0.01
Low	47.4	41.0	
Middle	17.4	17.8	
High	30.2	35.3	
Data missing	5.1	6.0	

Data presented as %

patients (65 years of age or older) (Figure 3). There was no interaction between sex and AMI admission year.

Sex differences in coronary revascularization after cardiac catheterization following AMI

In the cardiac catheterization cohort, comprising 9233 patients, 2525 (27.3%) were women. Women were older and had significantly more DM, hypertension, PVD, CHF, CVD, COPD and liver disease than men. In contrast, women had fewer diseased coronary vessels and less hyperlipidemia (Table 2). Similar to the AMI cohort, more women than men came from a low-income neighbourhood (47.6% versus 40.7%).

The probability of receiving revascularization within one year of the index catheterization following an AMI was 72.8% for women and 79.6% for men (log-rank $P < 0.0001$). After adjusting for baseline characteristics, women were as likely to undergo revascularization as men (HR 0.96; 95% CI 0.91 to 1.02). While younger age was significantly associated with receiving revascularization, there was no interaction between sex and age. Also, there was no interaction between sex and catheterization year.

DISCUSSION

Coronary catheterization rates post-AMI increased significantly over the nine-year study period for both men and women. A steeper increase in 90-day catheterization rates post-AMI began in September 2000. Women were significantly less likely than men to receive coronary catheterization post-AMI and, after adjustment for baseline differences, this

Figure 1) Three-month time trend of 90-day catheterization rates. The proportion of patients undergoing catheterization within 90 days of index admission in three-month intervals are represented by open circles and triangles for women and men, respectively. The line of best fit for each sex (thick solid line) was determined by segmented regression analysis. The inflection point is represented by the vertical solid line and the associated 95% CIs by the vertical dashed lines. AMI Acute myocardial infarction

Figure 2) Cumulative probability of receiving catheterization after acute myocardial infarction within one year

finding persisted in all age groups for patients who were not receiving ICU/CCU care. For patients who received ICU/CCU care, the sex difference appeared only in the older patients (65 years of age or older). Among patients who received coronary catheterization following AMI, women were as likely as men to undergo revascularization procedures (PCI or CABG).

Time trends in coronary catheterization rates post-AMI

Several studies have documented marked increases in the rates of coronary catheterization (3-6) and revascularization (3-6,11-13) following an AMI between 1975 and 2004. The first study (7) to report on the benefit of an early invasive approach following NSTEMI was published in August 1999 (Fragmin and Fast Revascularisation during Instability in Coronary artery disease [FRISC-II]). This was followed by two more publications in 2001 (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction [TACTICS-TIMI]-18) (8) and 2002 (Randomized Intervention Trial of unstable Angina [RITA]-3) (9) that further supported this strategy. Importantly, in September 2000, the ACC/AHA guidelines for the management of patients with NSTEMI emphasized an early invasive approach (10). In Ontario, the inflection point for post-AMI angiography use predated publication of the FRISC-II trial by 11 months (14). In contrast, based on our BC data, the inflection point for post-AMI catheterization use was September 2000, which was

Figure 3 Adjusted sex 'risk' in receiving catheterization presented as HR (95% CI). CCU Cardiac care unit; ICU Intensive care unit. Age presented in years

13 months following publication of the FRISC-II trial and coincident with the release of the 2000 ACC/AHA guidelines. It is possible that the acute rise in catheterizations in BC was, in part, a result of these publications; however, other potential factors, such as advances in technology, may also have had an important role. Of note, during the time-frame of the present study, the number of interventional cardiologists and cardiac catheterization laboratories remained stable.

Sex differences in coronary catheterization rates post-AMI

Earlier studies (1,3,15-18) from the United States and Europe support our findings of a significant sex difference in catheterization rates post-AMI. In Canada, studies from Quebec (1988 to 1995) (4), Ontario (1992 to 1996) (5) and Alberta (1994 to 1999) (6) all confirm lower catheterization rates in women than in men.

The studies mentioned above were conducted before the year 2000. Our study provides updated trends, confirming the continued finding of a sex difference in patients of all ages, although, only in the absence of ICU/CCU care. Interestingly, among patients who did receive ICU/CCU care, the sex difference remained only in patients 65 years of age or older. Perhaps the decision regarding whether to proceed to angiography is made earlier on, specifically in the process of deciding on referral to an acute care centre with an ICU/CCU.

Sex differences in coronary revascularization rates post-AMI

Earlier studies (1,3-6,16,17,19-23) found differing results regarding sex differences in revascularization rates, and some studies (1,4,6,19-22) have reported lower rates of revascularization in women than in men post-AMI. In our study, sex was significantly associated with receiving revascularization univariately, but this effect disappeared after the adjustment for age and extent of CAD. Our results are consistent with the results of the study by Ghali et al (23), in which the sex differences in rates of revascularization were fully explained after adjusting for baseline characteristics, mainly extent of CAD. This underlines the importance of proper and complete correction for baseline differences.

Possible explanations for the sex difference in procedure access

Several theories attempt to explain the sex differences observed in cardiac care. One observation is that women tend to present with more atypical AMI symptoms than men (24). Second, it remains controversial whether women derive the same benefit from an early invasive approach following AMI compared with men (25-27). Third, physician bias may also contribute to the sex differences observed. Schulman et al (28) demonstrated that sex independently affected whether a physician referred a patient with chest pain for coronary catheterization even after adjusting for baseline characteristics, symptoms and the physician's estimation of the likelihood of CAD. Interestingly, the sex of the treating physician does not appear to contribute to the sex difference (29). Fourth, patient willingness to undergo invasive cardiac procedures may contribute to the sex difference. Women tend to rate their cardiac disease as less severe than men, even after controlling for other measures of

TABLE 2

Baseline characteristics of patients undergoing coronary revascularization by sex (n=9233)

Characteristic	Women (n=2525)	Men (n=6708)	P
Age, years			<0.01
<55	13.3	26.1	
55-64	20.9	27.4	
65-74	31.0	28.1	
≥75	34.8	18.4	
Pulmonary disease	12.7	9.8	<0.01
Renal disease	4.4	3.9	0.26
Hyperlipidemia	53.1	56.2	<0.01
Hypertension	61.9	48.5	<0.01
Heart failure	22.0	14.2	<0.01
Cerebrovascular disease	9.6	7.0	<0.01
Diabetes	28.8	23.4	<0.01
Peripheral vascular disease	10.1	7.1	<0.01
Liver disease	5.5	4.1	<0.01
Cancer	6.4	5.2	0.03
Extent of diseased vessel			<0.01
Less than 50%	5.1	2.0	
1-vessel disease	28.6	24.6	
2-vessel disease	25.1	26.7	
3-vessel disease	33.9	37.8	
Left main disease	7.4	9.0	
Ejection fraction, %			0.02
<30	4.1	5.0	
30-50	28.2	30.2	
>50	51.4	50.6	
Data missing	16.2	14.3	
Neighbourhood income			<0.01
Low	47.6	40.7	
Middle	19.0	18.3	
High	29.9	35.9	
Data missing	3.5	5.1	

Data presented as %

disease severity (30). Finally, our results demonstrate that ICU/CCU care modified the sex effect on catheterization rates. Perhaps sex differences in catheterization are driven more by the decision to refer for ICU/CCU care in a tertiary centre than the decision to proceed with an invasive approach.

Limitations

Our study has several limitations inherent to administrative data. First, the *International Statistical Classification of Diseases and Related Health Problems, Ninth Revision* coding system cannot differentiate between STEMI and NSTEMI patients. Many of our conclusions regarding trends in catheterization rates with respect to the publication of major trials were in the NSTEMI population. While NSTEMI patients represent the bulk of acute coronary syndrome cases, we were unable to determine whether the trends we reported applied to STEMI or NSTEMI patients, or both. Second, while we did correct for factors such as age, comorbidities, physician and hospital characteristics, neighbourhood income level, admission year and case complexity, we were unable to correct for procedure appropriateness. Third, our reported rates of comorbidities tended to be lower than those quoted in clinical trials. While this under-reporting of comorbidities is a limitation in the study, it is unlikely that this phenomenon varied by sex.

CONCLUSIONS

Catheterization rates post-AMI increased significantly from 1994 through 2003. Women were significantly less likely to undergo

catheterization even after adjustment for baseline characteristics; however, this sex effect was modified by age and ICU/CCU care. Specifically, among patients who did not receive ICU/CCU care, women were less likely than men to undergo catheterization in all age groups. For patients with ICU/CCU care, only older women (65 years of age or older) were less likely than men to receive coronary catheterization. Among patients who underwent coronary catheterization following their index AMI, women were as likely as men to undergo coronary revascularization within one year of catheterization.

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