RESEARCH PAPER

Age Difference Explains Gender Difference in Cardiac Intervention Rates After Acute Myocardial Infarction

La différence d'âge explique la différence entre hommes et femmes dans les taux d'intervention cardiaque après un infarctus aigu du myocarde

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Abstract

Many investigators have reported higher rates of cardiac procedures for males than females after acute myocardial infarction (AMI), suggesting that men are treated more aggressively than women. However, others have reported no significant differences after controlling for age, resulting in uncertainty about the existence of a true gender bias in cardiac care. In this study, a population-based cohort approach was used to calculate age-specific procedure rates by sex from administrative data. Chi-square tests and generalized linear modelling were used to assess gender differences and interactions. For all four procedures studied, rates were significantly higher for males than females ($p<0.01$). However, age-specific rates revealed few significant differences by gender and a sharp decrease in intervention rates with age for both males and females. Generalized linear modelling confirmed that patient age was a significant predictor of intervention rates, whereas sex was not. The significant gender difference in overall rates was completely confounded by the older age profile of female AMI patients compared to their male counterparts.

Résumé

Plusieurs chercheurs ont observé de plus haut taux d'interventions cardiaques pour les hommes que pour les femmes après un infarctus aigu du myocarde (IAM), laissant croire que les hommes sont traités de façon plus agressive que les femmes. Toutefois, d'autres chercheurs indiquent qu'il n'y a pas de différence significative si on contrôle le facteur âge, ce qui mène à une incertitude quant à l'existence réelle d'un biais lié au sexe dans les soins cardiaques. Dans la présente étude, nous avons utilisé une démarche populationnelle fondée sur des cohortes afin de calculer, à partir de données administratives, les taux d'intervention selon le sexe et pour des âges précis. Nous avons utilisé des tests du khi carré et la modélisation linéaire généralisée pour évaluer les interactions et les différences entre les sexes. Pour les quatre interventions étudiées, les taux étaient significativement plus élevés pour les hommes que pour les femmes (p<0,01). Toutefois, les taux associés à des âges précis indiquent peu de différence significative entre les sexes ainsi qu'une nette diminution des taux d'intervention selon l'âge tant pour les hommes que pour les femmes. La modélisation linéaire généralisée a permis de confirmer que l'âge des patients est un indicateur significatif des taux d'intervention, alors que le sexe ne l'est pas. Pour l'ensemble des taux dans les cas d'IAM, la différence significative entre les sexes s'estompe complètement quand on compare le profil des femmes plus âgées avec celui de leurs homologues masculins.

Heart disease is a leading cause of morbidity and mortality for both men and women in Canada and the United States (Manuel et al. 2003; Statistics Canada 2007; National Centre for Health Statistics 2008). Although the combined number of deaths from heart disease and stroke is now equal between males and females in Canada (Heart and Stroke Foundation of Canada 2007; Statistics Canada 2007), there are still more acute myocardial infarctions (AMIs) among males, and males experience AMIs at younger ages than females (Chandra et al. 1998; Alter et al. 2002; Bertoni et al. 2004; Tu et al. 2003; Shaw et al. 2004; Williams et al. 2004; Vaccarino et al. 2005; Anand et al. 2005; Fang and Alderman 2006). However, these differences have not always been adequately controlled for in studies of treatment rates, resulting in conflicting evidence about the existence of a gender bias in clinical care after AMI. In 2006, the Canadian Cardiovascular Outcomes Research Team (CCORT) published a comprehensive atlas that included cross-provincial comparisons of heart disease burden, cardiac care patterns and outcomes (ICES 2006). Subsequently, the GENESIS team published a report focusing on gender-based differences in heart disease and cardiac care (Pilote et al. 2007). Both these influential Canadian teams, as well as the Heart and Stroke Foundation of Canada (2007), have called for further exploration of male and female patterns of heart disease and cardiac care.

Investigators from many countries have reported that intervention rates after AMI are higher for males than females, suggesting that men are treated more aggressively than women (Ayanian and Epstein 1991; Steingart et al. 1991; Udvarhelyi et al. 1992; Maynard et al. 1992; Krumholz et al. 1992; Every et al. 1993; Chiriboga et al. 1993; Jaglal et al. 1994; Kostis et al. 1994; Funk and Griffey 1994; Kudenchuk et al. 1996; Woods et al. 1998; Chandra et al. 1998; Shin et al. 1999; Hanratty et al. 2000; Gottlieb et al. 2000; de Gevigney et al. 2001; Alter et al. 2002; Heer et al. 2002; Bertoni et al. 2004; Shaw et al. 2004; Bakler et al. 2004; Williams et al. 2004; Anand et al. 2005; Martinez-Selles et al. 2005; Vaccarino et al. 2005; Fang and Alderman 2006). However, the results from a number of those studies (Steingart et al. 1991; Maynard et al. 1992; Krumholz et al. 1992; Funk and Griffey 1994; Shin et al. 1999; Hanratty et al. 2000; Gottlieb et al. 2000; Alter et al. 2002; Heer et al. 2002; Bertoni et al. 2004; Shaw et al. 2004; Bakler et al. 2004; Williams et al. 2004; Vaccarino et al. 2005), along with others (Vacek et al. 1995; Khaykin et al. 2002; Rathore et al. 2003; Pilote et al. 2004; Moriel et al. 2005), show that when patient age is adequately controlled for, the apparent gender difference is often diminished or becomes statistically non-significant. The current uncertainty is most pronounced for bypass surgery rates, for which some investigators report no gender difference after controlling for age, clinical characteristics or both (Steingart et al. 1991; Maynard et al. 1992; Funk and Griffey 1994; Kostis et al. 1994; Gottlieb et al. 2000; Ghali et al. 2002), while others report that rates among males remain higher than those for females even after adjustment (Ayanian and Epstein 1991; Udvarhelyi et al. 1992; Krumholz et al. 1992; Jaglal et al. 1994; Woods et al. 1998; de Gevigney et al. 2001; Rathore et al. 2003; Bertoni et al. 2004; Shaw et al. 2004; Vaccarino et al. 2005; Blomkalns et al. 2005; Pilote et al. 2004; Fang and Alderman 2006). Proposed explanations for gender differences include possible sex-related differences in anatomy (e.g., blood vessel size), operative risk and suitability for percutaneous coronary intervention (PCI) versus bypass surgery (Rathore et al. 2003; Bertoni et al. 2004; Jacobs and Eckel 2005; Barrett-Connor 2007).

However, many of these studies were not population-based, did not adequately control for age or did not restrict analyses to AMI patients only, in whom the indication for these procedures is strongest. Therefore, the purpose of this study was to examine cardiac intervention rates after AMI in males and females, using a population-based cohort approach with careful control for age.

Materials and Methods

The rates of four diagnostic and therapeutic cardiac interventions were compared for all male and female AMI patients in the province of Manitoba, Canada. The analysis used a population-based cohort approach, including all residents age 40 or older identified in the anonymized administrative data housed at the Manitoba Centre for Health Policy. This data system contains complete and validated health service records for virtually every resident of the province (Roos et al. 2005). The Health Research Ethics Board of the University of Manitoba approved this study as part of a larger project on gender differences in health and healthcare use (Fransoo et al. 2005).

The AMI cohort included all residents hospitalized for AMI (most responsible diagnosis ICD-9-CM code 410) in the three-year period April 1, 1999, through March 31, 2002. Patients hospitalized for AMI in the previous two years were excluded, as were patients discharged alive but who had stayed less than three days in hospital ("rule-out" cases), based on the validation work of Tu and colleagues (1999). Sex was coded as either male or female for all residents.

Rates of each of the following procedures were calculated separately for males and females: diagnostic cardiac catheterization (ICD-9-CM codes 37.21–37.23 or 88.52–88.57); percutaneous transluminary coronary angioplasty (PTCA) (codes 36.01, 36.02 or 36.05); coronary stent insertion (code 36.06); and coronary artery bypass surgery (codes 36.10–36.14 or 36.19). The latter three procedures all depend on previous or concurrent cardiac catheterization, which was confirmed for over 95% of male and 96% of female patients receiving those procedures.

Procedure rates for males and females were compared using chi-square tests during initial ("index") AMI hospitalization and at 30, 90 and 365 days thereafter, to determine whether gender differences exist and any change over that period. Age-specific rates of each procedure at each time point were also calculated for both sexes, using five-year age groups, starting at age 40. In keeping with confidentiality requirements, results based on fewer than five events were suppressed.

A series of generalized linear models (one for each procedure at each time period) was created to determine the influence of age and sex on intervention rates after AMI. Each model also included a quadratic term for age (age^2) to model potential non-linear trends, and an interaction term between age and sex, to model potential differences in age trends by gender.

To control for the inflation of type I error due to multiple testing, the "false discovery rate" method of Benjamini and Hochberg (1995) was used to calculate p values. All analyses were performed on a Unix server with SAS version 9.1 (SAS Institute, Cary, NC).

Results

The AMI cohort included more males (4,199) than females (2,645), and males were younger than females: the mean (SD) age was 67.4 years (12.9) for males versus 74.3 years (11.9) for females. Figure 1 shows the age distribution of male and female AMI patients.

FIGURE 1. Number of AMIs by age and sex

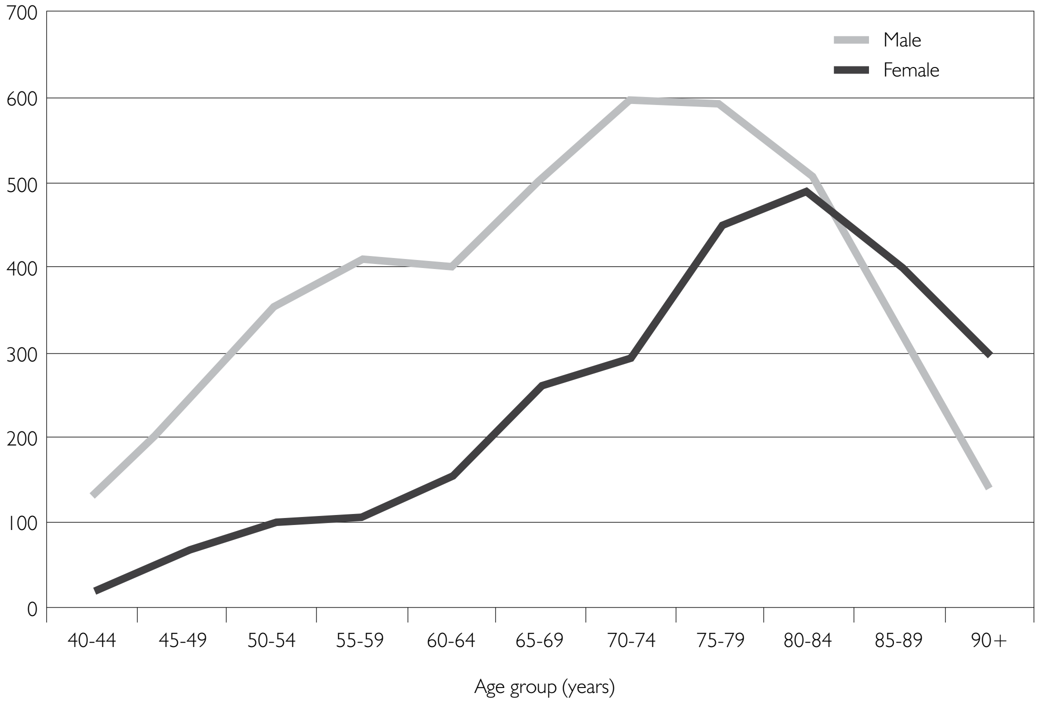

Table 1 contains the number and the proportion of male and female AMI patients receiving each procedure during index hospitalization and by 30, 90 and 365 days thereafter. For each procedure at each time period, the number of procedures performed among males was double that for females. The differences in the proportion of males versus females receiving each procedure were smaller, but still highly significant in almost all cases. However, these results do not take patient age into account.

Figure 2 shows the crude rates of cardiac catheterization during index hospitalization for males and females in each five-year age group. The overlapping confidence intervals indicate that within every age group, male and female catheterization rates were not statistically different. In both sexes, the proportion of patients receiving catheterization was much lower among older patients than younger patients. Similar trends were found for all four procedures at all four time points.

Table 2 shows the results from the generalized linear models. In all models, the age–sex interaction term was not significant, so results were taken from models without that term.

The results in Table 2 show that sex was not significantly related to rates of any of the procedures at any of the time periods, whereas patient age and the quadratic age term (age^2) were highly significant in all models. The coefficient associated with the quadratic age term was less than one, indicating that the slope decreased with age.

TABLE 1. Number and proportion of AMI patients receiving procedures

	Number of AMI patients: 3,280 males, 1,963 females				
	Number of AMI patients receiving procedure		Proportion of AMI patients receiving procedure		Sex difference in proportions
	Male	Female	Male	Female	(*p* value)
During index hospitalization					
Cardiac catheterization	1,144	527	34.9%	26.8%	<0.0001
Angioplasty	518	212	15.8%	10.8%	<0.0001
Stent nsertion	456	197	13.9%	10.0%	<0.0001
Bypass surgery	76	26	2.3%	1.3%	0.012
By 30 days after AMI					
Cardiac catheterization	1,348	620	41.1%	31.6%	<0.0001
Angioplasty	598	244	18.2%	12.4%	<0.0001
Stent insertion	533	226	16.3%	11.5%	<0.0001
Bypass surgery	209	90	6.4%	4.6%	0.007
By 90 days after AMI					
Cardiac catheterization	1,501	675	45.8%	34.4%	<0.0001
Angioplasty	656	265	20.0%	13.5%	<0.0001
Stent insertion	584	245	17.8%	12.5%	<0.0001
Bypass surgery	267	106	8.1%	5.4%	0.0002
By 365 days after AMI					
Cardiac catheterization	1,675	754	51.1%	38.4%	<0.0001
Angioplasty	719	288	21.9%	14.7%	<0.0001
Stent insertion	649	266	19.8%	13.6%	<0.0001
Bypass surgery	364	138	11.1%	7.0%	<0.0001

Discussion

There were many more AMIs among males than females, a finding that partly explains why the number of procedures performed among males was higher than that for females for each procedure at each time point. Gender differences in the proportion of patients receiving procedures were much smaller than differences in the number of procedures performed, but remained highly significant, demonstrating that the difference in the number of AMIs explains some but not all of the gender difference in the number of procedures performed.

FIGURE 2. Percentage of AMI patients receiving cardiac catheterization during AMI hospitalization

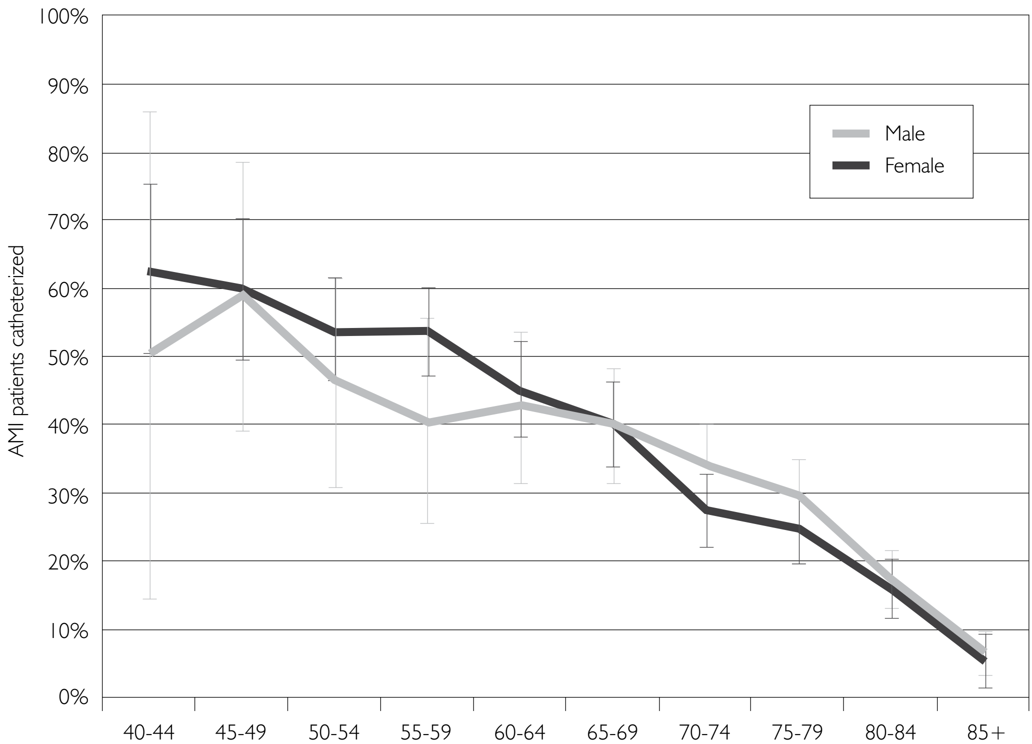

TABLE 2. Results of generalized linear models of intervention rates

	Sex (male=1)		Age (linear)		Age^2 (quadratic)	
	Coefficient	*p* value	Coefficient	*p* value	Coefficient	*p* value
During index hospitalization						
Cardiac catheterization	0.008	0.930	0.147	<0.0001	-0.001	<0.0001
Angioplasty	0.074	0.637	0.150	0.0004	-0.002	<0.0001
Stent insertion	0.011	0.930	0.151	0.001	-0.002	<0.0001
Bypass surgery	0.433	0.342	0.389	0.0003	-0.003	0.0001
By 30 days after AMI						
Cardiac catheterization	0.047	0.637	0.145	<0.0001	-0.001	<0.0001
Angioplasty	0.088	0.603	0.146	0.0002	-0.002	<0.0001
Stent insertion	0.048	0.784	0.155	0.001	-0.002	<0.0001
Bypass surgery	0.126	0.603	0.346	<0.0001	-0.003	<0.0001

TABLE 2. Continued

By 90 days after AMI						
Cardiac catheterization	0.076	0.603	0.152	<0.0001	-0.001	<0.0001
Angioplasty	0.116	0.603	0.146	0.0002	-0.002	<0.0001
Stent insertion	0.073	0.637	0.155	0.0004	-0.002	<0.0001
Bypass surgery	0.250	0.342	0.370	<0.0001	-0.003	<0.0001
By 365 days after AMI						
Cardiac catheterization	0.077	0.603	0.162	<0.0001	-0.002	<0.0001
Angioplasty	0.122	0.603	0.133	0.001	-0.001	<0.0001
Stent insertion	0.094	0.603	0.140	0.001	-0.001	<0.0001
Bypass surgery	0.261	0.286	0.361	<0.0001	-0.003	<0.0001

However, these overall rates mask the fact that as age increases, the rates of all interventions decrease sharply for both males and females (Figure 2). This decrease in procedure rates with age is consistent with previous research (Ayanian and Epstein 1991; Udvarhelyi et al. 1992; Maynard et al. 1992; Krumholz et al. 1992; Kostis et al. 1994; Shin et al. 1999; Alter et al. 2002; Khaykin et al. 2002; Rathore et al. 2003; Pilote et al. 2004; Shaw et al. 2004; Williams et al. 2004), and is likely related to the increased co-morbidity, frailty and higher operative risk among older patients (Mark 2000; Tecce et al. 2003; Jacobs and Eckel 2005; Ayanian 2006; Barrett-Connor 2007).

Results from the generalized linear models for all four procedures at all four time points confirmed that age was a strong predictor of procedure rates, and that sex was not significant. The coefficient associated with the age^2 term is less than one, indicating that the decline in procedure rates decelerated with age in a non-linear fashion (i.e., the slope became less steep with age).

Therefore, the significant gender differences seen in the overall rates of procedures were completely confounded by the older age profile of female versus male AMI patients. Males were not treated more aggressively than females; rather, older patients were less likely to receive interventions, and female AMI patients were older than their male counterparts.

Comparisons with CCORT Atlas data

The composition of the AMI cohort is the same as that reported in the CCORT Atlas, with almost two-thirds of all AMI patients being male, and female AMI patients having an older age distribution than their male counterparts (Tu et al. 2003). Both studies revealed a sharp decline in procedure rates with age for males and females (Pilote et al. 2004), a finding that is critical for the interpretation of results. In both the CCORT analysis and this study, the large difference in overall rates is driven by the older age profile of female versus male AMI patients. Examining age-specific results dramatically reduces the apparent gender difference in the CCORT data and closes the gap completely in our results. This finding may be partly attributable to the smaller (five-year) age groups used in this study, as others have shown that even within the age groups used in the CCORT analysis, women were significantly older than men (Alter et al. 2002). Data from other jurisdictions might also reveal small or no gender differences if analyzed using narrower age groups.

Comparisons with other studies

In studies of gender differences in cardiac care using data up to 1995, many investigators reported significantly higher intervention rates for males than females (Ayanian and Epstein 1991; Udvarhelyi et al. 1992; Every et al. 1993; Chiriboga et al. 1993; Jaglal et al. 1994; Kostis et al. 1994; Vacek et al. 1995; Kudenchuk et al. 1996; Woods et al. 1998; de Gevigney et al. 2001), although some reported no difference after controlling for age (Steingart et al. 1991; Krumholz et al. 1992; Maynard et al. 1992; Funk and Griffey 1994; Vacek et al. 1995; Wong et al. 1998). Almost all newer studies show that gender differences are non-significant or marginal after controlling for age (Hanratty et al. 2000; Gottlieb et al. 2000; Rathore et al. 2002, 2003; Khaykin et al. 2002; Bertoni et al. 2004; Pilote et al. 2004; Bakler et al. 2004; Williams et al. 2004; Moriel et al. 2005; Vaccarino et al. 2005). In the two exceptions (Fang and Alderman 2006; Kaul et al. 2007), the outcome measure was "any revascularization," which includes both CABG and PCI, leaving the possibility that CABG rates had a gender difference while PCI rates did not. In some studies, PCI rates for females were higher than those for males (Steingart et al. 1991; Krumholz et al. 1992; Rathore et al. 2003; Vaccarino et al. 2005; Wong et al. 1998; Kilaru et al. 2000), although not all differences reached statistical significance.

Some reports showing significant gender differences in treatment rates did not adjust for age of AMI patients, including the US National Registry of Myocardial Infarction–I trial (Chandra et al. 1998), a large retrospective study from the United Kingdom (Shaw et al. 2004), and a recent international study (Anand et al. 2005). Studies incorporating clinical measures have shown that differences in clinical characteristics also help explain gender differences in intervention rates, sometimes in addition to the difference explained by age (Ghali et al. 2002), sometimes in conjunction with simultaneous age control (Wong et al. 1998; Rathore et al. 2002; Blomkalns et al. 2005) and sometimes without including age (Kilaru et al. 2000).

The finding of equal bypass surgery rates in this study is consistent with findings reported by some investigators (Steingart et al. 1991; Maynard et al. 1992; Funk and Griffey 1994; Kostis et al. 1994; Gottlieb et al. 2000; Ghali et al. 2002), but contrary to others reporting higher bypass surgery rates for males than females even after age adjustment (Ayanian and Epstein 1991; Udvarhelyi et al. 1992; Krumholz et al. 1992; Jaglal et al. 1994; Woods et al. 1998; de Gevigney et al. 2001; Rathore et al. 2003; Bertoni et al. 2004; Shaw et al. 2004; Vaccarino et al. 2005; Blomkalns et al. 2005; Pilote et al. 2004; Fang and Alderman 2006), suggesting the need for further study.

The key limitation of this study is the lack of detailed clinical data, which limits the ability to assess appropriateness. As a result, it is impossible to know the "right" rate of each of the procedures. There is also the issue of undiagnosed or "silent" AMIs. An early paper from the Framingham investigators reported that undiagnosed AMIs were more common among females and older males (Kannel and Abbott 1984), though more recent work shows that this difference disappears after controlling for age (Boland et al. 2002; de Torbal et al. 2006). Our findings cannot rule out the possibility of gender bias in diagnosis of AMI. However, our results show that once diagnosed, female AMI patients were as likely as males of the same age to get each of these interventions.

The findings of this study show that there is currently no gender bias in key cardiac interventions after AMI in Manitoba, and suggest that similar analyses in other jurisdictions may reveal similar findings. Lower procedure rates for females were completely explained by their older age profile compared to male AMI patients, because intervention rates drop sharply with age for both males and females.

These results are important for clinicians and policy makers, as they show that while the age of the patient plays a role in post-AMI intervention decisions, the sex of the patient does not. The equal treatment of male and female AMI patients shown in our study may reflect a changing reality in clinical practice, as almost all other recent studies that adequately controlled for age also revealed non-significant or marginal sex differences. Bypass surgery may be the exception and requires additional research. Furthermore, demonstrating equality in rates of treatment after AMI does not address other issues regarding gender differences in heart disease, including possible differences in risk factors, presentation, diagnosis, patient preferences and effectiveness of various treatments.

Future research in this area should employ careful age control and could include a more thorough examination of how gender differences in treatment rates have changed over time. Several investigators in the United States and Canada have documented a narrowing of gender differences over time (Khaykin et al. 2002; Harrold et al. 2003; Bertoni et al. 2004; Alter et al. 2006), though others found no change (Lucas et al. 2006). Further study could also broaden the follow-up to include other types of treatments and outcomes of care.

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