CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Reduction in Sex-Based Mortality Difference with Implementation of New Cardiology Guidelines

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ABSTRACT

BACKGROUND: Mortality from acute coronary syndrome has historically been higher in women as compared with men. We hypothesized that adoption of a more sensitive definition for the diagnosis of acute myocardial infarction and managing patients according to the 2000 European Society of Cardiology and American College of Cardiology guidelines would reduce this difference.

METHODS: A retrospective cohort study was conducted of all acute coronary syndrome admissions to 7 regional tertiary hospitals in Israel during 1999-2004. The primary end point was all-cause 1-year mortality. Differences in risk between men and women were assessed using Cox proportional hazards regression.

RESULTS: The number of patients admitted with acute coronary syndrome was 20,206 and 15,583 before and after adoption of the guidelines, respectively. An invasive strategy during the index hospitalization was more frequent in men in both the pre- (47.6% vs 33.6, $P < .001$) and post- (55.7% vs 40.9%, $P < .001$) transition periods. Secondary prevention was intensified in the post-transition period in both sexes. Multivariate analysis adjusting for differences in baseline clinical characteristics between men and women and invasive strategy demonstrated that female sex was associated with increased 1-year mortality during the pretransition period (hazard ratio 1.34, 95% confidence interval, 1.24-1.45), but was not a significant factor in the post-transition period (hazard ratio 1.04, 95% confidence interval, 0.94-1.14).

CONCLUSIONS: The transition to the 2000 European Society of Cardiology and American College of Cardiology guidelines was associated with a reduction in the sex-based mortality difference in patients with acute coronary syndrome despite the fact that an early invasive strategy and secondary prevention continued to be underutilized in female patients in both periods.

 • *The American Journal of Medicine (2008) 121, 597-603*

KEYWORDS: Acute coronary syndrome; Cardiac enzymes; Sex; Survival

Whether there is a higher mortality for women following acute myocardial infarction has continued to be controversial, with several studies reporting excessive mortality,[1-4] while other more recent studies have suggested no sex-based difference.[5-8] The reasons for possible worse outcomes in women remain unclear. One potential explanation is that women with acute coronary syndrome are treated less aggressively then men.[4,9-11] However, there are fewer data about sex-specific outcomes of a mixed acute coronary syndrome population, including patients with or without biomarker elevation. The ability to discriminate groups with biomarker evidence of myonecrosis will clearly depend on the biomarker used and the threshold for elevation.

The 2000 European Society of Cardiology and American College of Cardiology (ESC/ACC) guidelines updated the diagnosis approach and management of patients with suspected acute coronary syndrome.[12] Hospitals in Israel adopted the new guidelines, including a switch in biomarkers from MB fraction or creatine kinase to troponin, as suggested by the guidelines.

We examined the hypothesis that the transition to the new guidelines, including the improved diagnosis and management, will narrow the difference in mortality between male and female patients with acute coronary syndrome.

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0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2008.01.041

METHODS

Acute coronary syndrome patients from all 7 major general hospitals (30% of general hospital beds in the country) of the Clalit Health Services, the largest integrated health maintenance organization in Israel (3.6 million ensurees, 55% of the population), were included in the study. Patients were included based on hospital discharge diagnosis ICD-9 (International Classification of Diseases, 9th revision) codes that represented either unstable angina or acute myocardial infarction.

In order to construct a synchronized database for the purpose of analysis, we used the index day of transition of each hospital to the new biomarker as a proxy for the guideline adoption. We refer to the period before the transition from creatine kinase MB to troponin as the "pretransition period" and to that following the transition as the "post-transition period." The 7 general hospitals switched assays over a period of 24 months—the earliest in April 2001 and the last in April 2003 (6 to troponin T and 1 to troponin I).

CLINICAL SIGNIFICANCE

- The transition to the 2000 European Society of Cardiology and American College of Cardiology guidelines on diagnosis of acute coronary syndrome patients was associated with a reduction in sex-based gap on 1-year mortality.
- After the adoption of the new guidelines, there was a significant increase in the rate of early catheterization and in the purchasing of secondary prevention drugs.
- Even after the adoption of the guidelines, female sex was associated with lower rates of in-hospital catheterization.

Data on diagnoses, co-morbid conditions, laboratory findings, in-hospital management, and outcome were taken from a central data warehouse of the Clalit Health Services. National data on survival were obtained from the Central Bureau of Statistics. The mortality status assessment was complete, with no patients lost to follow-up. For a sub-cohort of Clalit insured patients (approximately 80% of all patients), data on posthospitalization medications purchasing were obtained. Rate for the medications utilization was calculated for the cohort of 3-month posthospitalization survivors.

Type of acute coronary syndrome was defined by discharge diagnoses as unstable angina (ICD-9-CM codes 411, 411.1, 411.89), non-ST elevation myocardial infarction—unspecified infarction site or subendocardial infarction (ICD-9-CM codes 410.7- 410.9), or ST-elevation myocardial infarction (ICD-9-CM codes 410.0- 410.6).

We used the Charlson Index to compute the burden of comorbid conditions.[13] The Charlson Index contains 19 categories of comorbidity, which are primarily defined using ICD-9 diagnosis codes (a few procedure codes also are employed). The overall comorbidity score reflects the cumulative increased likelihood of 1-year mortality; the higher the score, the more severe the burden of comorbidity.

STATISTICAL ANALYSIS

For univariate analysis, we used Student's *t*-test for comparison of continuous variables and Pearson's chi-squared test for categorical variables. Normality of the data was tested with a one-sample Kolmogorov-Smirnov test to indicate the appropriateness of parametric testing. Mann-Whitney test and Kruskal-Wallis tests were used as nonparametric testing. Multivariable logistic regression analysis was used to assess differences in use of invasive strategy during the index hospitalization between men and women. All baseline variables distributed unevenly between men and women with $P < .10$ were included in the model. The final model included direct admission to the intensive care unit, age, Charlson Index, background comorbidities such as congestive heart failure, recurrent myocardial infarction, history of coronary artery bypass grafting, diabetes, dyslipidemia, hypertension, past or present smoking, type of acute coronary syndrome, and albumin and creatinine levels. The propensity score for selection of the invasive strategy was calculated based on the final model and was included as a continuous variable into the survival model.

For patients with multiple hospital admissions during the study period, the latest admission was used for calculation of survival time. Cox proportional hazard regression was used to assess the independent effect of sex on 1-year survival. Survival models were built for each period. Variables included in the model were selected based on a univariate association with survival, with $P < .10$. In the final model for each period, we included variables found to be significantly associated with the survival in at least one period. All reported *P* values are 2-sided and $P < .05$ was considered significant.

RESULTS

The average observation period among hospitals was 3.2 years before transition and 2.2 years afterward. The number of acute coronary syndrome admissions was 26,548 (20,206 patients, 287 hospital-months) during the pretransition period and 18,725 (15,583 patients, 185 hospital-months) during the post-transition period. Of the total 45,273 admissions, 22,502 (49.7%) were unstable angina and 22,772 (50.3%) were myocardial infarction. Most patients (81.1%) were admitted once during the study period, 13.7% were admitted twice, and 5.3% were admitted 3 or more times.

The global incidence of acute coronary syndrome remained unchanged following the transition to the new guideline; 686 ± 34 versus 689 ± 32 cases per month ($P = .83$), respectively. Unstable angina incidence decreased by 16.7%, from 383 ± 26 to 319 ± 17 cases per month, or 55.8% of total cases before and 46.4% after transition ($P =$

Table 1 Baseline Characteristics of the Acute Coronary Syndrome According to the Myocardial Damage Marker Period

	Pretransition Period			Post-transition Period		
	Women n = 7037	Men n = 13,169	*P*-Value	Women n = 5105	Men n = 10,478	*P*-Value
Type of acute coronary syndrome			<.001			<.001
Unstable angina, %	62.3	54.5		57.1	52.3	
Non-ST elevation MI, %	12.0	12.4		21.3	20.6	
ST elevation MI, %	25.7	33.1		21.6	27.1	
Age, years	71.5 ± 11.6	64.3 ± 13.3	<.001	72.4 ± 11.8	64.8 ± 13.3	<.001
Charlson Index, points	3.87 ± 1.71	3.26 ± 1.94	<.001	4.07 ± 1.74	3.38 ± 1.96	<.001
Previous ischemic heart disease, %	39.3	44.0	<.001	39.1	43.2	<.001
Recurrent MI, %	18.5	25.2	<.001	16.8	23.3	<.001
Previous PCI, %	8.4	12.8	<.001	17.3	23.8	<.001
Previous CABG, %	5.6	9.3	<.001	7.9	12.9	<.001
Previous congestive heart failure, %	16.5	16.3	0.74	16.4	15.6	0.22
Arterial hypertension, %	60.7	41.5	<.001	63.4	44.2	<.001
Dyslipidemia, %	39.5	41.7	<.001	46.6	48.5	.02
Diabetes mellitus, %	27.9	21.5	<.001	31.7	23.2	<.001
Smoking past or present, %	6.8	24.4	<.001	7.9	25.5	<.001
Chronic obstructive pulmonary disease, %	4.4	6.0	<.001	4.0	5.7	<.001
Creatinine, mg/dL	1.1 ± 0.6	1.3 ± 0.7	<.001	1.0 ± 0.6	1.2 ± 0.8	<.001
Albumin, g/dL	4.0 ± 0.5	3.8 ± 0.5	<.001	3.8 ± 0.5	3.9 ± 0.4	<.001

Abbreviations: MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting.

.001). Diagnosis of myocardial infarction increased by 20.8%, from 303 ± 19 cases per month before the transition to 370 ± 28, or 44.2 % of total acute coronary syndrome admissions before and 53.6% after the transition (P <.001).

Table 1 presents baseline patient characteristics by sex for each period. Overall, and in both periods, women represented approximately one third of the acute coronary syndrome population. They were older and had higher prevalence of diabetes and hypertension, and lower incidence of prior ischemic heart disease compared with men.

Diagnosis of myocardial infarction during the post-transition period compared with the pretransition period was more common for both men and women, but the odds of diagnosing myocardial infarction as opposed to unstable angina in the post-transition period relative to pretransition period was significantly higher for women (odds ratio [OR] 1.25, 95% confidence interval [CI], 1.16-1.34) than men (OR 1.09, 95% CI, 1.03-1.15). This resulted in a narrowing of the sex-based difference in proportion of acute coronary syndrome presenting as myocardial infarction from 7.8% in the pretransition period to 4.8% in the post-transition period.

There was a significant increase in the rate of early cardiac catheterization in both sexes and all types of acute coronary syndrome: women from 33.6% to 40.9%, men from 47.6% to 55.7% (see Table 2, online). There was an increase in women's odds of undergoing early cardiac catheterization as compared with men after the transition: relative risk of 0.64 (95% CI, 0.62-0.66) before and 0.73 (95% CI, 0.71-0.76) after the transition. Nevertheless, adjusted (logistic regression model) analyses revealed that female sex remained significantly associated with lower rates of cardiac catheterization during hospitalization irrespective of period: odds ratio for women versus men was 0.68 (95% CI, 0.63-0.73) before and 0.72 (95% CI, 0.67-0.78) after the transition.

Similarly, there was a significant increase in rate of purchasing secondary prevention drugs 3 months postdischarge in both sexes and all types of acute coronary syndrome cases (Table 3). This increase was more prominent for beta-blockers, angiotensin-converting enzyme inhibitors, and statins than for aspirin, probably due to an already high aspirin usage in the pretransition period. Although female sex remained significantly associated with lower rates of secondary prevention postdischarge, the pattern of usage between periods did change: women with non-ST elevation myocardial infarction got beta-blockers and statins in a more similar mode to women with ST elevation myocardial infarction in the post-transition period (drug purchasing relative ratio for beta-blockers 0.95 [95% CI, 0.91-1.00] post-transition vs 0.87 [95% CI, 0.82-0.92] pretransition; for statins 0.92 [95% CI, 0.86-0.98] post-transition vs 0.86 [95% CI, 0.78-0.98] pretransition).

Unadjusted 1-year mortality was higher for women overall in the pretransition (17.9% vs 11.9%, P <.001) and post-transition (17.1% vs 11.3%, P <.001) periods. Multivariable regression analysis revealed that female patients had higher risk of death within 1 year from hospitalization during the pretransition period but not during the post-transition period (Table 4, Figure). When stratified by type of acute coronary syndrome, the reduction in the sex-based difference in mortality during the post-transition period was

Table 3 Secondary Prevention in 3 Months Postdischarge Survivors According to Study Period and Sex

	Pretransition period n = 14,157			Post-transition period n = 10,897		
	Men Unstable Angina, n = 5333 Non-ST Elevation MI, n = 1033 ST elevation MI, n = 2873	Women Unstable Angina, n = 3363 Non-ST Elevation MI, n = 481 ST Elevation MI, n = 1074	Relative Risk (95% CI) for Women vs Men	Men Unstable Angina, n = 4044 Non-ST Elevation MI, n = 1415 ST Elevation MI, n = 1838	Women Unstable Angina, n = 2246 Non-ST Elevation MI, n = 679 ST Elevation MI, n = 675	Relative Risk (95% CI) for Women vs Men
Beta-blockers						
Unstable angina, %	79.5	79.6	1.00 (0.98-1.02)	82.9	83.0	1.00 (0.98-1.03)
Non-ST elevation MI, %	79.3	72.1	0.91 (0.85-0.97)	88.0	83.4	0.95 (0.91-0.99)
ST elevation MI, %	85.6	84.5	0.99 (0.96-1.02)	90.4	87.1	0.96 (0.93-1.00)
ACE inhibitors						
Unstable angina, %	57.3	63.5	1.11 (1.07-1.15)	68.8	71.9	1.05 (1.01-1.08)
Non-ST elevation MI, %	67.3	77.5	1.15 (1.08-1.23)	79.4	82.6	1.04 (1.00-1.09)
ST elevation MI, %	73.5	79.7	1.08 (1.05-1.13)	79.9	83.1	1.04 (1.00-1.08)
Aspirin						
Unstable angina, %	79.7	78.2	0.98 (0.96-1.00)	80.2	78.6	0.98 (0.95-1.01)
Non-ST elevation MI, %	82.3	86.5	0.99 (0.94-1.04)	84.2	80.9	0.96 (0.92-1.00)
ST elevation MI, %	88.0	86.5	0.98 (0.96-1.01)	89.9	85.2	0.95 (0.92-0.98)
Statins						
Unstable angina, %	61.6	60.0	0.98 (0.94-1.01)	78.2	73.6	0.94 (0.91-0.97)
Non-ST elevation MI, %	60.0	53.4	0.89 (0.81-0.98)	78.9	72.3	0.92 (0.87-0.97)
ST elevation MI, %	67.5	62.2	0.92 (0.87-0.97)	83.5	78.1	0.94 (0.89-0.98)

Abbreviations: MI = myocardial infarction; CI = confidence interval; ACE = angiotensin-converting enzyme.

Table 4 Cox Proportional Hazard Regression Models for 1-year Mortality after Hospitalization with Acute Coronary Syndrome with Incorporated Propensity Score for Undergoing Cardiac Catheterization during Hospitalization*

	Pretransition period n = 20,206			Post-transition period n = 15,584		
		95% CI For Hazard Ratio			95% CI For Hazard Ratio	
	Hazard Ratio	Lower	Upper	Hazard Ratio	Lower	Upper
Female sex	1.34	1.24	1.45	1.04	0.94	1.14
Age, per year	1.03	1.03	1.04	1.03	1.03	1.04
Charlson Index, per point	1.31	1.28	1.34	1.23	1.19	1.27
Creatinine, per mg/dL	1.07	1.03	1.12	1.15	1.11	1.18
Albumin, per g/dL	0.71	0.66	0.76	0.35	0.32	0.38
Cardiac catheterization during hospitalization	0.64	0.55	0.75	0.76	0.64	0.91
Unstable angina	1			1		
Non-ST elevation MI	2.25	2.00	2.52	2.33	2.05	2.65
ST elevation MI	2.27	2.04	2.52	2.39	2.07	2.77
Congestive heart failure	1.66	1.53	1.81	1.51	1.38	1.66
Diabetes mellitus	1.11	1.02	1.21	1.06	0.96	1.17
Interactions						
Non-ST elevation MI and cardiac catheterization during hospitalization	0.86	0.67	1.10	0.60	0.46	0.75
ST elevation MI and cardiac catheterization during hospitalization	0.70	0.57	0.85	0.72	0.57	0.90

Abbreviations: CI = confidence interval; MI = myocardial infarction.

*Propensity score based on logistic regression included direct admission to the intensive care unit, age, Charlson Index, background comorbidities such as congestive heart failure, recurrent myocardial infarction, history of coronary artery bypass grafting, diabetes, dyslipidemia, hypertension, past or present smoking, type of acute coronary syndrome, albumin and creatinine levels.

more evident in non-ST elevation types: unstable angina 1-year death hazard ratio for women versus men of 1.18 (95% CI, 1.03-1.34) before and 0.90 (95% CI, 0.76-1.06) after the transition; non-ST elevation myocardial infarction hazard ratio of 1.22 (95% CI, 1.04-1.43) before and 0.98 (95% CI, 0.85-1.14) after the adoption of new guidelines. In patients with ST elevation myocardial infarction, the sex gap was significant within both periods: hazard ratio of 1.52 (95% CI, 1.35-1.73) before and 1.25 (95% CI, 1.10-1.48) after the transition. Furthermore, selecting patients with non-ST elevation acute coronary syndrome elaborates the disappearance of the sex difference in 1-year mortality; hazard ratio for women of 1.21 (95% CI, 1.09-1.34) before and 0.96 (95% CI, 0.86-1.07) after the transition.

In order to adjust the effect of period transition for the possible influence of time trend on 1-year mortality, 2 additional analyses were performed. First, a narrow time frame of 6 months before and 6 months after the transition was constructed, and Cox proportional regression model was applied to the population admitted during this time frame. Again, the hazard ratio for women during the 6 months preceding the transition was 1.31 (95% CI, 1.09-1.34) and during 6 months following the transition, 1.00 (95% CI, 0.81-1.24). Second, we adjusted for the year of admission within both periods, which gained the hazard ratio of 1.33 (95% CI, 1.23-1.43) and 1.04 (95% CI, 0.95-1.14) before and after the transition, respectively.

DISCUSSION

We have demonstrated that after adoption of the 2000 European Society of Cardiology and American College of Cardiology guidelines for diagnosis and management of acute coronary syndrome, the proportion of patients diagnosed with myocardial infarction was higher in both men and women, and the difference was greater for women than for men. The main finding of the current study is the fact that the 1-year adjusted mortality risk, which was 31% higher for women as compared with men during the pretransition era, was almost similar for women and men during the post-transition period.

Poorer long-term survival in women with acute coronary syndrome compared with men has been reported in many studies, especially when outcomes have not been adjusted for baseline risk factors, such as age, diabetes, and hypertension, which are more frequent in women. However, multivariable adjustment for these confounders have generally suggested that female sex is not an independent risk factor.[9,14]

Because of its retrospective nature, we could only speculate on potential reasons for the reduction in differences in sex-related mortality in the 2 periods of our study.

- Better discriminatory properties of the biomarker were used in the post-transition period for the diagnosis of myonecrosis. Troponin, with its superior specificity and sensitivity compared with creatine kinase MB, better

identified myocardial infarction patients and therefore increased their chances of receiving guideline-based acute and post-discharge care. In this regard, among patients with non-ST elevation acute coronary syndrome, Wiviott et al[15] reported abnormal values of troponin in up to 54% of women, compared with only 29% with abnormal creatine kinase MB—an 86% increase. Whereas in men, this increase was only 50% (42% with abnormal creatine kinase MB and 63% with troponin). Therefore, transition to troponin could have led to a better outcome in women in particular. Our underlying assumption is that once a patient was labeled "myocardial infarction," he or she received improved in-hospital and postdischarge management. Data from the national surveys of myocardial infarction patients conducted every 2 years in Israel support the similarity of treatment of ST and non-ST elevation myocardial infarction.[16]

- The new guideline led to a more "appropriate" management of all types of acute coronary syndrome, in a manner that benefited women more. Several studies have now shown a mortality benefit of an early invasive strategy for acute coronary syndrome management, with benefit maximal among high-risk patients, including those with elevated biomarkers.[17-19] The updated 2002 American College of Cardiology/American Heart Association guidelines for treatment of acute coronary syndrome recommend equivalent treatment for both men and women.[20] Because more women with non-ST elevation acute coronary syndrome received the diagnosis of non-ST elevation myocardial infarction post-transition to the new guideline, women have been more favorably affected by the guideline. Although female sex continued to be associated with a lower rate early invasive strategy, the odds for a woman, as compared with a male counterpart, to undergo an early intervention increased after the transition. In patients with confirmed myocardial infarction in either biomarker period, women were 30% less likely than men to undergo an invasive strategy after adjusting for baseline risk factors. This finding, however, is similar to other studies that also have shown less aggressive management in terms of early catheterization and percutaneous coronary intervention.[9-11,21] In the most recent analysis from the 1999 French hospitals database of myocardial infarction, without adjustment for baseline risk factors, women were only half as likely to undergo an invasive strategy as men (OR 0.51, 95% CI, 0.49-0.53).[21] Of note, in our study, adjustment for the use of an invasive strategy did not correct for the significant sex-based mortality difference during the pretransition period. This might speak to the importance of appropriate use of an invasive strategy based on risk stratification rather than overall use. It also suggests that other risk-based treatments beyond an early invasive strategy may have been utilized based on a positive troponin. Of note, women with non-ST elevation myocardial infarction have narrowed the sex gap in early catheterization in the post-transition period in a manner similar to women with ST-elevation myocardial infarction. Women received less intensive postdischarge secondary prevention in both periods (Table 3), but female patients with non-ST elevation myocardial infarction received statins and beta-blockers in a manner similar to ST elevation female patients, narrowing the pretransition gap in secondary prevention.
- There is a limit to improvement beyond a certain rate of intervention in the initial setting of acute coronary syndrome. Apparently, this level has been reached in men with acute coronary syndrome before transition to the new guidelines, whereas female patients continued to improve in the post-transition period. The ICTUS trial suggested that beyond a certain level of intervention, there is no further improvement in outcomes in unstable acute coronary syndrome patients.[22] If so, before transition, interventions were underused in women but used appropriately in men, whereas in the post-transition period, women received better care and therefore increased their chance of survival. This also will mean that for men, post-transition improvements in care did not further improve the 1-year survival because they have reached their plateau. Indirect support for this hypothesis comes from the bi-annual surveys conducted in Israel that show a slow in decrease in mortality from acute coronary syndrome in the latter years.[16] As for the postdischarge management, secondary prevention has improved significantly in the post-transition period for all patients, reaching a level of 80% for statins, for example (Table 3). This may have contributed to the early (starting at 30 days) parallel survival curves between the sexes in the post-transition period (Figure).
- Our study has several potential limitations. We were not able to assess the severity of disease characteristics such as the size of the myocardial infarction or hemodynamic

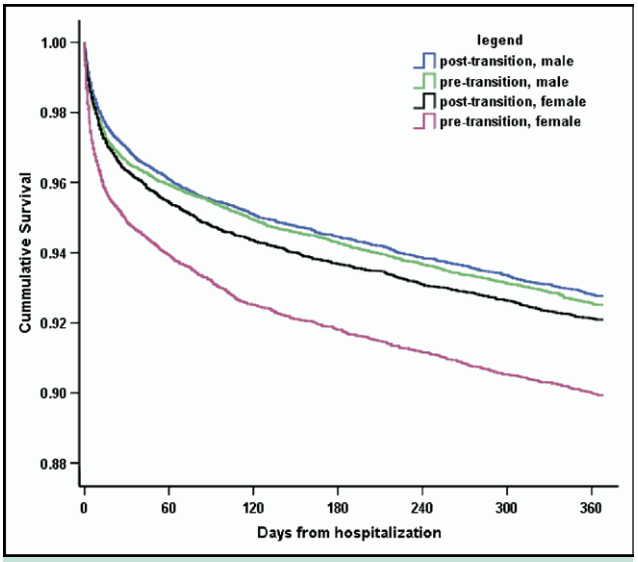

Figure Cox proportional hazard functions for 1-year survival at mean of covariates pre- and post-transition stratified by women vs men.

status of the study population. We used a computerized database encoded with ICD-9 as the method for defining the type of acute coronary syndrome, and thus, were not able to classify myocardial infarction as ST or non-ST elevation in a validated manner.

CONCLUSION

The transition to the 2000 ESC/ACC guideline on diagnosis of acute coronary syndrome patients was associated with almost elimination of an independent sex-based effect on 1-year mortality. This transition may have had a larger impact on accurate risk stratification in women and resulted in more appropriate use of an early invasive strategy, secondary prevention and, possibly, other risk-based treatments.

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Table 2 Coronary Catheterization Rate within Index Hospitalization According to Study Period and Sex

	Pretransition Period			Post-transition Period		
	Women n = 7037	Men n = 13,169	Relative Risk (95% CI)	Women n = 5105	Men n = 10,478	Relative Risk (95% CI)
All acute coronary syndromes	33.6	47.6	0.64 (0.62-0.66)	40.9	55.7	0.73 (0.71-0.76)
Unstable angina	31.4	41.4	0.76 (0.72-0.80)	35.0	45.4	0.77 (0.73-0.82)
Non-ST elevation MI	26.5	42.8	0.62 (0.54-0.70)	39.5	57.3	0.69 (0.64-0.75)
ST elevation MI	42.3	59.5	0.71 (0.67-0.76)	57.8	74.3	0.78 (0.74-0.82)

Abbreviations: CI = confidence interval; MI = myocardial infarction.