Gender Differences in Hospital Mortality and Use of Percutaneous Coronary Intervention in Acute Myocardial Infarction. Microsimulation Analysis of the 1999 Nationwide French Hospitals Database

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ABSTRACT

Background—Women with acute myocardial infarction (AMI) have higher hospital mortality than men. This difference has been ascribed to their older age, more frequent comorbidities, and lower use of revascularization. The aim of this study is to assess these factors in relation to excess mortality in women.

Methods and Results—All hospital admissions in France with a discharge diagnosis of AMI were extracted from the national payment database. Logistic regression on mortality was performed for age, comorbidities, and coronary interventions. Nonparametric microsimulation models estimated percutaneous coronary intervention (PCI) and mortality rates women would experience if they were "treated like men". Data were analyzed from 74 389 patients hospitalized with AMI, 30.0% of whom were women. Women were older (75 vs 63 years, $P<0.001$) and had higher hospital mortality than men (14.8 vs 6.1%, $P<0.0001$). PCIs were more frequent in men (7.4 vs 4.8%; 24.4 vs 14.2 with stent; $P<0.001$). Mortality adjusted for age and comorbidities was higher in women ($P<0.001$), with an excess adjusted absolute mortality of 1.95%. Simulation models related 0.46% of this excess to reduced use of procedures. Survival benefit related to PCI was lower amongst women.

Conclusions—*T*he difference in mortality between men and women with AMI is due largely to the different age structure of these populations. However, age-adjusted hospital mortality was higher for women, and was associated with a lower rate of PCI. Simulations suggest that women would derive benefit from more frequent use of PCI, although these procedures appear less protective than in men.

Key Words: acute myocardial infarction gender; mortality; revascularization

Previous studies have shown higher crude hospital mortality rates for acute myocardial infarction in women compared with men. Part of the difference is accounted for by the older age and higher prevalence of comorbidities in women.[1] Lower use of revascularization procedures in women may also account for some of the excess mortality. Indeed, findings from large database studies[2-11] have indicated that women with acute myocardial infarction tend to undergo less aggressive hospital management than men. However, the relation of lower rates of revascularization is debated: some studies have found that the excess mortality in women was explained by older age and higher baseline risk,[12-17] or that it was restricted to a subgroup of female patients, while others have suggested that under-treatment in women had no effect on early mortality from acute myocardial infarction.[18,19]

Thus, while it is agreed that age-adjusted mortality after acute myocardial infarction is higher in women than in men, uncertainty remains about whether this finding is related to differences in baseline risk or in management (particularly the use of revascularization), and whether the latter is related to gender bias (the Yentl syndrome[20]) or to differences in eligibility for aggressive therapies or patient preferences.[21]

The aim of the present study was to compare age-adjusted, gender-specific hospital mortality for patients hospitalized for acute myocardial infarction, and to determine whether mortality variations could be explained by gender differences in epidemiology, in patterns of use of percutaneous coronary intervention (PCI), or in the benefit of PCI.

Methods

Patients

All hospital admissions in France during 1999 with an ICD-9 discharge diagnosis of acute myocardial infarction were extracted from a national database. This database is used for hospital payment and provides medical records for all patients discharged from both private and public hospitals. The database is inclusive of all admissions nationwide because French hospitals are financed by a single payer. Each admission is characterized by discharge diagnoses and procedure codes that determine the diagnosis-related group and reimbursement. In France, a patient classification system has been implemented since 1983 and is based on the apDRG model that was developed in the United States.

Records for acute myocardial infarction were analyzed to exclude coding errors.[22] Ensuring an inclusive and clean data set, and obtaining administrative clearance for access to individual patient data, requires approximately 5 years, explaining the lag between the time the data set was obtained and the analysis. Demographic data, primary and secondary diagnoses, and procedural and immediate outcome data were extracted. Information on outcomes post-discharge was not available.

Study Variables and Outcome

Demographic variables included sex and age. Comorbid conditions were captured by secondary diagnoses: heart failure, valvular disease, conduction disease, diabetes mellitus, severe hypertension, renal insufficiency, stroke, and peripheral arterial disease. Procedural data included those related to cardiac catheterization, percutaneous coronary angioplasty, and stenting. The outcome variable was mortality during the index admission. For the sake of simplicity, and because it has become rare to perform PCI without stenting, PCI with stenting was considered to be representative of coronary interventions.

Statistical Methods

Categorical data are presented as percentages, with absolute numbers. Logistic regressions were performed to test for gender differences in mortality and use of coronary interventions in each age group. Odds ratios are reported, and Wald tests and confidence intervals (CIs) are provided to check for the

significance of differences between proportions. Multivariable logistic regressions were performed to adjust for differences in age, comorbidities, and intervention rates.

A series of microsimulation models were developed in the spirit of the Oaxaca decomposition, creating a hypothetical set of events (procedures and outcomes) for the population.[23-26]

The first simulation predicted the probability of PCI and mortality, depending on gender, comorbidities and use of PCI, and the death rate of women if they were "treated like men". This simulation assessed gender differences due to variation in treatment while controlling for gender differences in age and comorbidities (Appendix). We hypothesized that the only difference between men and women was the decision to use invasive procedures, and computed the probability of death of women if treated like men of the same age and with similar comorbidities. Each woman was attributed the age- and comorbidity-specific probability of PCI plus stent obtained from the male population. We then computed whether this "men-like" procedure rate resulted in reduced mortality in women. The second simulation tested the hypothesis that the outcome of PCI would differ according to gender, resulting in a higher death rate.[27] The model was built for PCI plus stent.

All tests were two-sided and $P<0.05$ was considered statistically significant. All analyses were performed using the StataSE 8 software and SAS® statistical package (SAS V8.2, SAS Inc. Cary, NC).

Statement of Responsibility

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

The database included 74 389 admissions for acute myocardial infarction, of which women represented 30.0%. The mean age of women was 75 years versus 63 years for men (P<0.001). The age structure of the population by gender is illustrated in Table 1. Given the older age of women, comorbidities were more frequent in women than in men (P<0.001) (Table 1).

Use of Interventional Procedures

During the index admission, men were more likely to undergo coronary angiography and intervention than women, and this observation was consistent across all age groups (P<0.001) (Table 2A). Overall, the ratio of interventions to total coronary angiography was higher in men than in women, although this difference was heterogeneous with respect to age: below 75 years, angiography more frequently led to PCI in men than in women, whereas the converse was true in patients aged over 75 years (Table 2A).

Hospital Mortality

The crude hospital mortality rate was higher for women than for men (14.8 vs 6.1%, P<0.0001). The odds ratio for crude mortality rates was 2.65 (95% CI, 2.52–2.79). This 8.64% difference was due mainly to gender differences in the age distribution. After adjustment for age (using the age distribution of women as reference), the absolute gender difference in mortality was 1.95% (Table 3). Across age categories, crude mortality and mortality adjusted for comorbidities were consistently higher among women (Table 2B).

The use of coronary interventions was associated with lower mortality after adjustment for age and comorbidities (P<0.01) (Figure 1). After adjustment for comorbidities and the use of interventions, mortality remained consistently and significantly higher for women compared with men for each age category with the exception of patients aged over 85 years (P=0.08) (Figure 2). The type of hospital to which patients were admitted, as well as the volume of acute myocardial infarctions treated per hospital, had no impact on gender differences in mortality (data not shown).

Simulations

The 1.95% age-adjusted gender difference in mortality was explored further by simulations to determine its relation to gender differences in the use of coronary interventions, in the outcome of procedures, and in the impact of comorbidities.

Simulated Rates of PCI Plus Stent

In the first simulation, an expected rate of PCI plus stenting for women was computed using the probability of men with the same age and comorbidities (Table 2C). The expected simulated rate of PCI plus stenting in women was 17.5% compared to observed rates of 14.2% in women and 24.4% in men. Therefore, approximately one-third of the observed difference in the use of PCI plus stenting appeared to be related to gender disparity, and two-thirds to age and comorbidities.

Simulated Rates of Mortality

The relationship of reduced provision of PCI to the 1.95% gender gap in mortality (14.78% in women versus 12.83% age-adjusted in men, Table 3) was explored in the second simulation, which computed "expected" mortality rates in women using two models (Table 2C):

- Model 1 computed the expected probability of death of women if they had experienced the hospital rates of PCI plus stent of men of a similar age. Overall, this expected mortality would be 14.32%, thus accounting for 0.46% (relative percentage 23.6%) of the age-adjusted 1.95% gender gap.
- Model 2 allowed for possible gender differences in the impact of comorbidities and PCI plus stent on mortality by computing the expected probability of death of women if they had similar rates of coronary interventions but also a similar response to PCI and comorbidities as men. The expected mortality in women calculated by this method would be 12.55%, instead of 14.78%, accounting for 1.77% (relative percentage 90.8%) of the 1.95% gender gap.

Thus, of the 8.64 point crude excess mortality in women with acute myocardial infarction, 6.69 is explained by the age structure of the population, 0.46 by the difference in procedure rates, and 1.77 by gender differences in the outcome of procedures and the impact of comorbidities (Table 3). The residual (–0.28) is related to differences in other characteristics (including unobservable characteristics). Thus,

one-quarter of the gender gap appears to be related to differential use of PCI plus stent between men and women.

The potential impact of increasing intervention rates in women (by following the same decision rules as for men) is illustrated in Figure 3, which displays the distributions of the observed age-adjusted mortality and the expected mortality in women. Age-adjusted mortality would be reduced (shifted to the left) across the entire risk distribution if rates of interventions were the same in women as in men.

Discussion

The present analysis confirms the higher age-adjusted mortality rate from acute myocardial infarction in women relative to men, the so-called "gender gap", reported in previous studies.[1-19] This gender gap was associated with strong gender differences in the provision of PCI during the index admission. We explored the possibility of gender disparities in the provision of healthcare for acute myocardial infarction patients, but could not ascertain from the database whether such differences in revascularization could be explained by variation in eligibility, exclusion criteria, or patients' preferences. The results of our study show that, after adjustment for age and comorbid conditions, there was a persistent mortality difference between men and women. Simulations of the expected mortality in women, if they had been referred for PCI as frequently as men with similar characteristics, suggest that gender disparities in the provision of reperfusion accounted for approximately one-quarter of the modifiable excess mortality. We explored the possibility that this gender difference could result from a predominance of treatments for acute myocardial infarction provided to women in potentially "lower-quality" institutions (e.g. community hospitals or low-volume facilities) and found no difference between men and women (data not shown). The French healthcare system provides identical coverage and access to healthcare for men and women, regardless of employment or social status. We therefore conclude that our results strongly support the hypothesis of gender disparity.

This finding provides a rationale for implementing measures to ensure optimal provision of coronary interventions in women experiencing a myocardial infarction. In addition, the simulations indicate that more liberal use of PCIs in women would likely result in consistent benefit across all risk strata. An additional finding from the simulations was that the use of PCI in women may be associated with a reduced benefit compared with that in men, possibly because of anatomical or biological differences.

Underuse of invasive procedures in women with acute myocardial infarction has been reported previously, although the independent relationship between sex and worse outcomes is still debated.[28] There is recent evidence from the United States that, despite widespread debate regarding the gender gap, sex differences in the provision of therapies in acute myocardial infarction have remained unchanged.[29] However, in that analysis, gender differences in the provision of therapeutic interventions

and in outcomes were less marked than in the present study and were largely influenced by appropriateness of procedures.[30]

The issue of less-aggressive treatment resulting in higher mortality in women was raised as early as 1991 by Healy.[20] The present simulations indicate that, even if women were treated "just like men", some excess mortality would remain. The explanation for the reduced protective effect against mortality afforded by PCI in women is unclear. It may be related to generally poorer outcomes of PCI in women (less benefit and greater complication rates), possibly because of smaller target vessel size, increased vessel tortuosity, and other biological differences. Indeed, previous analyses have found that women had an excess risk of death or myocardial infarction in the early post-PCI period compared with men,[31] particularly when interventions are attempted in an unstable setting[32] (although these differences pertained mostly to women undergoing coronary artery bypass grafting), but that these differences appear to abate over time.[31]

The impact of lower revascularization rates in women on mortality strengthens the case for better dissemination and implementation of guidelines regarding acute myocardial infarction treatment in women.[33]

Limitations

This analysis is subject to several limitations. The database included all forms of acute myocardial infarction regardless of delay to presentation, presence of ST-segment elevation, and eligibility for reperfusion therapy, as myocardial infarction was defined by ICD-9 coding. No data were collected regarding ethnicity, because French law explicitly prohibits the collection of such variables, or detailed medication use including the use of fibrinolysis. In addition, our analysis pertains to all indications for PCI during the index admission but does not allow to explore which procedures were done as primary PCI rather than elective PCI or to assess the appropriateness of the indications, a factor that has been linked to gender differences in use of procedures.[30] In that respect, it is important to acknowledge that no information is available in our dataset regarding the angiographic features in men and women. Yet, there may be important gender differences in vessel size, tortuosity, and in general eligibility for PCI, which may

translate into differences in the use of PCI (such as women having smaller diseased vessels size, which could account for the lower ratio of PCI to angiography in women compared with men (54% vs 58%).

This analysis pertains to a data set that is 7 years' old, and some changes in practice have taken place over this period, related mainly to more frequent use of primary PCI. However, it is uncertain whether these changes have been unbalanced across gender. This analysis relied upon a discharge database to document comorbidities, therefore only a limited amount of information was available and potential confounder variables may have been missed. While the prospective payment system creates an incentive to record exhaustively secondary diagnoses and procedures, its use to finance French hospitals has so far been limited, resulting in potential under-reporting. Because comorbid conditions affect women more frequently than men (particularly with regard to peripheral arterial disease, which tends to be under-diagnosed in women), under-reporting of comorbidities may result in an artificial underestimation of the gender gap. The simulations used to estimate expected rates of reperfusion or hospital mortality in women if they were "treated like men" are subject to caution because medical organizational factors such as delayed diagnosis are not accounted for. Finally, outcomes were assessed at discharge, and previous analyses[31] have suggested that gender differences in early outcomes may become attenuated over a longer follow-up. Overall, this type of simulation may simplify a series of complex variables involved in patient care and thus the estimates of the effect of each therapy may be imprecise.

The strength of our findings lies in the size of the population and the use of microsimulation analyses. The latter have been introduced in econometric models comparing salaries in men and women and were recently extended to other economic fields such as health-econometric studies. To our knowledge, they have not been used yet in the analysis of healthcare delivery.

Author contributions

Study concept and design: Milcent, Dormont, Durand-Zaleski, Steg

Acquisition of data: Milcent, Dormont

Analysis and interpretation of the data: Milcent, Dormont, Durand-Zaleski, Steg

Drafting of the manuscript: Durand-Zaleski, Steg

Critical revision of the manuscript for important intellectual content: Milcent, Dormont, Durand-Zaleski, Steg

Statistical analysis: Milcent, Dormont

Administrative, technical or material support: Dormont, Steg

Study supervision: Dormont

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Figure legends

Figure 1. Impact of coronary interventions (after adjustment for age and comorbidities) on hospital mortality.

Figure 2. Impact of gender on hospital mortality across age categories, after adjustment for comorbidites and use of coronary interventions.

Figure 3. Probability density of age-adjusted mortality and simulated mortality (based on simulation 2) using revascularization decision rules used for men.

TABLE 1. Distribution of Hospital Admissions for Acute Myocardial Infarction by Age and Gender, and Comorbidities of Patients with Acute Myocardial Infarction

	N	Men (n=52 041) (70.0%)	Women (n=22 348) (30.0%)
Age, y			
≤55	18 332	31.4	9.0
56–65	13 671	21.8	10.3
66–75	19 909	26.7	26.9
76–85	15 331	15.7	32.1
>85	7146	4.4	21.6
Total	74 389	100	100
Comorbidity, %			
History of coronary artery disease	24.2	24.8	23.0
Valvular disease	7.5	6.4	10.1
Conduction disease	19.4	17.6	23.4
Hypertension	27.7	24.5	35.0
Heart failure	14.3	11.3	21.2
Stroke	3.0	2.7	3.5
Peripheral arterial disease	6.4	6.8	5.3
Other vascular disease	0.7	0.5	1.1
Diabetes	14.6	13.1	18.0
Renal failure	3.9	3.7	4.6

P<0.001 for all comparisons between men and women

TABLE 2. Use of Coronary Intervention, Hospital Mortality, and Simulated Rates of Percutaneous Coronary Intervention Plus Stenting and Simulated Mortality Rates According to Age Group

A. Use of Coronary Intervention (*P*<0.001 for all Comparisons)

Age Group, y	Angiography Only, Men	Angiography Only, Women	PCI*, Men	PCI*, Women	PCI*+Stent, Men	PCI*+Stent, Women	Observed Gender Difference	PCI*+Stent, Women Relative To Men OR (95% CI‡)	PCI*/Angio,† Men	PC W
≤55, %	24.6	28.4	9.1	8.3	31.3	25.2	6.1	0.74 (0.66–0.82)	62.1	
56–65, %	24.9	26.6	7.9	6.7	28.1	23.4	4.7	0.78 (0.70–0.86)	59.1	
66–75, %	24.9	24.3	7.3	6.6	22.1	19.9	2.2	0.88 (0.81–094)	54.1	
76–85, %	16.7	12.2	5.0	4.2	15.1	11.2	3.9	0.71 (0.64–0.77)	54.6	
>85, %	4.3	1.9	1.6	1.0	5.0	2.5	2.5	0.49 (0.38–0.64)	60.6	
Overall, %	22.6	16.2	7.4	4.8	24.4	14.2	10.3	0.51 (0.49–0.53)	58.5	

B. Hospital Mortality in Patients with Acute Myocardial Infarction

Age Group, y	N	Mortality In Men — N (%)	Mortality In Women — N (%)	Odds Ratio (95% CI‡) In Women Vs Men	*P* Value	Odds Ratio (95% CI‡) In Women Vs Men Adjusted for Comorbidities	A
≤55	18 332	218 (1.3)	39 (1.9)	1.46 (1.04–2.06)	0.03	1.53 (1.08–2.16)	
56–65	13 671	312 (2.8)	87 (3.8)	1.38 (1.09–1.76)	<0.01	1.49 (1.17–1.91)	

66–75	19 909	849 (6.1)	484 (8.1)	1.34 (1.20–1.51)	<0.000	1.51 (1.34-1.70)
76–85	15 331	1148 (14.1)	1246 (17.4)	1.28 (1.18–1.40)	<0.000	1.43 (1.30-1.56)
>85	7146	668 (28.9)	1448 (29.9)	1.05 (0.94–1.12)	0.38	1.15 (1.03-1.29)
Total	74 389	3195 (6.1)	3304 (14.8)	1.37 (1.30–1.46)	<0.001	2.65 (2.52-2.79)

C. Simulated Rates of PCI* Plus Stenting and Simulated Mortality Rates in Women

Age Group, y	PCI*+Stent, Men, %	PCI*+Stent, Women, %	Expected PCI*+Stenting Rate, Women, %	Expected Vs Observed Difference In Women, %	Simulation 1: Expected Mortality In Women (Procedure Rates Of Men), %	Simulation 2: Expected I Women (Procedure R Response To Proced Comorbidities Of M
≤55	31.3	25.2	31.6	6.4	1.8	1.4
56–65	28.1	23.4	27.7	4.3	3.5	2.8
66–75	22.1	19.9	22.1	2.2	7.5	5.7
76–85	15.0	11.2	15.0	3.8	17.1	14.1
>85	5.0	2.5	4.5	2.0	29.5	28.0
Overall	24.4	14.2	17.5	3.4	14.3	12.6

*PCI denotes percutaneous coronary intervention

† denotes coronary angioplasty

‡CI denotes confidence interval

TABLE 3 Decomposition of Gender Differences in Average Death Rates

Average death rate for men	6.1
Average death rate for men, adjusted for age distribution*	12.83
Average death rate for women	14.78
Average death rate for women adjusted for differences in procedure rates	14.32
Difference (women vs men)	8.64
Difference due to variations in age distribution	6.69
Age-adjusted difference	1.95
of which:	
Difference due to gender variation in procedure rates	0.46
Difference due to gender variation in reactions to secondary diagnoses and procedures	1.77
Residual: difference due to gender variation in other characteristics (e.g., secondary diagnoses and unobservable characteristics)	–0.28

*Women's age distribution was the reference.