Gender profiling in coronary artery bypass grafting

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1704, 1707, and 2032.

Objective: Although women are reported to be at increased risk of poor outcome after coronary artery bypass grafting, female gender may simply be a marker of a high-risk profile. Therefore, the objective of this study was to characterize the difference between the female and male profiles of patients presenting for coronary artery bypass grafting.

Methods: From January 1993 to June 2002, 15,597 patients underwent isolated coronary artery bypass grafting at a single institution. Multivariable logistic regression was used to develop a model of female gender.

Results: Of 15,597 patients, 3596 (23%) were women. Eighteen variables were predictive of the female gender profile, including shorter stature, increased weight, more hypertension, insulin-treated diabetes mellitus, heart failure, and higher triglyceride and high-density lipoprotein cholesterol levels. Hematocrit, bilirubin, and creatinine values were lower in women compared with men.

Conclusions: The preoperative profiles of women and men undergoing coronary artery bypass grafting are dissimilar. Statistical modeling techniques provide a unique perspective on the preoperative profile of the female patient, who is known to be at a higher risk undergoing coronary artery bypass grafting.

When examining gender differences in outcome after cardiac surgical procedures, women have been typically profiled as high-risk primarily because of a disproportionate distribution of preoperative risk factors associated with adverse outcomes. There are numerous studies that tabulate differences in the gender distribution of preoperative baseline variables.¹⁻¹² This study characterizes the difference between the female and male profiles of patients presenting for coronary artery bypass grafting (CABG).

Methods

Patient Population and Data Collection

From January 1993 to June 2002, 15,597 patients underwent isolated CABG at the Cleveland Clinic Foundation; patients undergoing concomitant valvular procedures were excluded. Data were prospectively collected for 64 preoperative variables, including baseline demographics, clinical history, laboratory values, and cardiac catheterization findings, and entered into institutional computer databases by individuals trained in database collection methods. Institutional review board approval was obtained from the Cleveland Clinic Foundation to perform research analyses on these institutional databases.

Statistical Methods

The analysis identified a parsimonious set of characteristics that best differentiated men from women undergoing CABG, thus creating a gender profile.

Preliminary Analysis

Initial exploratory analyses were performed by calculating summary statistics for each variable. The only variables to have a considerable amount of missing data were triglyceride,

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TABLE 1. Baseline continuous variables according to gender

Characteristic	Female		Male		Student <i>t</i> test <i>P</i>
	N	Mean (SD)	N	Mean (SD)	
Demographics					
Age at surgery (yr)	3596	67 ± 10	12,001	64 ± 10	<.01
Height (cm)	3596	159 ± 7.6	12,001	174 ± 8.0	<.01
Weight (kg)	3596	73 ± 16	12,001	87 ± 16	<.01
Body mass index (kg/m ²)	3596	29 ± 6.3	12,001	29 ± 5.1	<.01
Body surface area (m ²)	3596	1.8 ± 0.2	12,001	2.0 ± 0.2	<.01
Preoperative laboratory values					
Hematocrit (%)	3596	37 ± 4.4	12,001	41 ± 4.4	<.01
Red cell mass estimate (L)	3596	1.5 ± 0.3	12,001	2.2 ± 0.4	<.01
Bilirubin (mg/dL)	3302	0.5 ± 0.3	11,220	0.7 ± 0.4	<.01
Albumin (g/dL)	3302	3.9 ± 0.5	11,182	4.1 ± 0.5	<.01
BUN (mg/dL)	3596	19 ± 11	12,001	19 ± 8.6	<.01
Serum creatinine (mg/dL)	3596	1.1 ± 0.8	12,001	1.2 ± 0.8	<.01
Triglycerides (mg/dL)	1751	203 ± 168	6988	183 ± 155	<.01
HDL cholesterol (mg/dL)	1746	45 ± 14	6978	38 ± 10	<.01
LDL cholesterol (mg/dL)	1718	132 ± 47	6884	128 ± 43	<.01

HDL, High-density lipoprotein; LDL, low-density lipoprotein; BUN, blood urea nitrogen.

high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol levels, with approximately 44% missing in each. These variables were examined further, but no obvious missing patterns were found. Thus, noninformative imputation was used, and missing value indicators were included in the final model. Univariable statistics were also initially computed to compare men and women using the Student *t* test for continuous variables and the chi-square test or Fisher’s exact test statistics for categorical variables.

Before modeling the data, continuous and ordinal variables were plotted against the logit of being female to identify possible transformations necessary to linearize the relationship.

Multivariable Analysis

Bootstrap aggregation (bagging) was used to identify variables and their candidate transformations.¹³ Coronary branches (mid, proximal, and distal) were excluded from the bagging analysis (discussed next). A total of 200 data sets of 15,597 were randomly selected with replacement and automatically analyzed by stepwise regression with an entry significance level of 0.10 and a significance level of 0.05 to stay in the model. Variables chosen in at least 50% of the models were considered for the final parsimonious model.

Aggregation Step

To account for correlation among covariates, a cluster analysis was performed by investigating variables that may instinctively cluster together, such as height, weight, body surface area, and body mass index. Exploratory analysis was performed within clusters by plots and intermediate modeling to identify any interactions and distinguish which parameters and transformations have the most distinct relationship with the probability of being female.

Finally, a parsimonious model was determined with the selected covariates and missing value indicators for the variables

where applicable. The model was further reduced by backward elimination of *P* values greater than .05. It is worth noting that although albumin appeared in 85% of the bootstrap models, it did not remain in the final model. Last, the coronary branches were successively added, yet none were found to significantly contribute to the quality of the model. All results were computed using SAS 8.2 software (SAS Institute Inc, Cary, NC).

Results
Baseline Characteristics

A summary of the distribution of baseline characteristics according to gender is presented in Tables 1 and 2. Of the 15,597 patients, 3596 (23%) were women and 12,001 (77%) were men. Women were older (Figure 1) and shorter (Figure 2), weighed less (Figure 3), and had a smaller body surface area and body mass index compared with men. The occurrence of many comorbid conditions was more frequent in women, such as more hypertension and insulin-treated diabetes, as well as a history of heart failure, prior stroke, renal disease, and peripheral vascular disease. Women also had lower preoperative hematocrit levels, lower calculated red blood cell mass (Figure 4), less favorable average LDL cholesterol and triglyceride profiles, and higher HDL cholesterol levels (Figure 5). Preoperative serum creatinine measurements were lower in women (Figure 6). Compared with men, women had a more unstable presentation reflected by a higher prevalence of unstable angina, preoperative intra-aortic balloon pump usage, and emergent surgery. Women more frequently received beta blockers and angiotensin-converting enzyme inhibitors. Men had a higher prevalence of smoking, alcohol use, and abnormal left ventricular ejection fractions, as well as more extensive

ACD

TABLE 2. Baseline categoric variables according to gender

Characteristic	Female		Male		Chi-square test <i>P</i>
	N	%	N	%	
Preoperative medication					
ACE inhibitors	1022	28	3042	25	<.01
Antiarrhythmics	462	13	1410	12	.08
Beta blockers	2091	58	6539	55	<.01
Calcium channel blockers	1218	34	4111	34	.67
Diabetic agent	378	11	1097	9.1	.01
Clinical history					
Myocardial infarction	1903	53	6681	56	<.01
Chronic obstructive pulmonary disease	298	8.3	742	6.2	<.01
Smoking	1581	44	8540	71	<.01
Heart failure	827	23	1657	14	<.01
Hypertension	2725	76	7612	63	<.01
Diabetes: insulin dependent	712	20	1194	10	<.01
Diabetes: non-insulin dependent	655	18	2083	17	.24
Stroke	280	7.8	664	5.5	<.01
Peripheral vascular disease	568	16	1516	13	<.01
Renal disease	42	1.2	94	0.8	.03
Alcohol use	97	2.7	1126	9.4	<.01
Atrial fibrillation	184	5.1	571	4.8	.38
Unstable angina	1490	41	4184	35	<.01
Preoperative valvular pathology					
Aortic valve regurgitation	215	6	543	4.5	<.01
Aortic valve stenosis	60	1.7	139	1.2	.02
Mitral valve regurgitation	715	20	1597	13	<.01
Coronary artery disease					
Any circumflex system disease	2957	83	10534	88	<.01
Any Left main disease	1374	38	4930	41	<.01
Any LAD system disease	3396	95	11546	97	<.01
Any RCA system disease	3144	88	10831	91	<.01
Symptoms					
NYHA class					<.01
1	452	13	1722	15	
2	1340	40	5439	48	
3	548	16	1417	13	
4	1035	31	2709	24	
Canadian angina class					<.01
0	79	2.3	258	2.3	
1	1069	32	3317	29	
2	1541	46	5916	52	
3	590	18	1492	13	
4	95	2.8	304	2.7	
Emergency surgery	143	4.0	324	2.7	<.01
Cardiogenic shock	20	0.6	36	0.3	.02
Intra-aortic balloon pump	128	3.6	270	2	<.01
Ventricular function					
Abnormal left ventricular function	1740	48	6505	54	<.01

ACE, Angiotensin-converting enzyme; LAD, left anterior descending; RCA, right coronary artery; NYHA, New York Heart Association.

coronary artery disease. Men also presented more frequently for coronary reoperations.

Parsimonious Model

The parsimonious analysis identified 18 variables that reflected the female profile (Table 3). This parsimonious model had high discriminatory ability to distinguish females from males, yielding a c statistic of 0.975. Shorter height, increased weight, more hypertension, insulin-treated diabe-

tes, and history of heart failure were significantly associated with the probability of female gender. The profile of women was further characterized by increased HDL levels, increased triglycerides, lower serum bilirubin, and a reduced red blood cell mass. In contrast, the male profile was characterized by more smoking, alcohol consumption, reduced left ventricular ejection fractions, and more extensive left main and circumflex coronary artery disease.

Figure 1. The gender distribution for age in patients undergoing CABG. Women are, on average, older than men. The numbers above the data points on the plot represent the sample size per bin.

Figure 2. The gender distribution for height. Women are of significantly shorter stature compared with men. The numbers above the data points on the plot represent the sample size per bin.

Discussion

Gaining insight into poor outcomes after coronary artery revascularization procedures requires close scrutiny of the preoperative risk profile in those patients considered highest risk for the procedures. Female gender has been associated with increased in-hospital morbidity and mortality after

CABG primarily because of the unfavorable preoperative risk profile in women. Women are reported to be older and of smaller stature¹⁻⁵ and have a higher prevalence of comorbidities.¹⁻⁶ Studies also show that women present with more advanced symptoms of congestive heart failure despite less extensive coronary artery disease and better pres-

Figure 3. The distribution of weight demonstrates that women characteristically weigh less than men. The numbers above the data points on the plot represent the sample size per bin.

Figure 4. A large percentage of women have lower estimated red blood cell mass. The numbers above the data points on the plot represent the sample size per bin.

ervation of left ventricular function when compared with men.^{2-4,7} The profile of women undergoing CABG surgery varies among the published investigations because of inconsistency in the data collected by the individual studies and the analysis of the variables.¹⁻¹²

Variables more commonly prevalent in women were not necessarily predictive of the female patient. Virtually all investigations report that, on average, female patients are significantly older than male patients undergoing CABG surgery. Although we found the prevalence of advanced age

Figure 5. In this study, women had significantly higher HDL levels compared with men. The numbers above the data points on the plot represent the sample size per bin.

Figure 6. Overall serum creatinine values were lower in women compared with men undergoing CABG. The numbers above the data points on the plot represent the sample size per bin.

to be greater in women, we did not find advanced age to be a significant predictor of female gender in the final parsimonious model.

The preoperative profile for women is distinct from that of the male patient population. Our parsimonious model has high discriminatory ability to distinguish females from

males among the demographic, angiographic, and laboratory values from the database. The 18 variables that were statistically predictive of female gender describe the female patient’s physiologic “milieu,” reflecting the patient’s cardiovascular status, organ function, laboratory profile, and physical stature.

TABLE 3. Factors associated with female gender (parsimonious model)

Direction in women	Parameter	Estimate (SE)	P	Bagging (%)
	Intercept	15 ± 0.98	<.001	—
Shorter	Height	−0.11 ± 0.0051	<.001	99
Higher	Weight	0.076 ± 0.0035	<.001	91
Lower	History of smoking	−0.93 ± 0.074	<.001	99
Higher	History of hypertension	0.54 ± 0.082	<.001	94
Higher	History of insulin-treated diabetes mellitus	0.52 ± 0.10	<.001	94
Lower	History of alcohol use	−1.33 ± 0.18	<.001	94
Higher	History of heart failure	0.18 ± 0.094	.052	78
Lower	Previous bypass graft disease	−0.60 ± 0.10	<.001	61
Lower	Preoperative aortic valve regurgitation	−0.36 ± 0.15	.017	71
Lower	Abnormal left ventricular function	−0.40 ± 0.075	<.001	66
Lower	Preoperative serum creatinine ^c (inverse)	3.5 ± 0.16	<.001	85
	Preoperative serum creatinine ^c (squared inverse)	−0.33 ± 0.028	<.001	—
Lower	Red blood cell mass	−7.4 ± 0.19	<.001	100
Lower	Preoperative bilirubin ^L	−0.71 ± 0.0.79	<.001	97
Higher	Preoperative triglycerides ^L	1.1 ± 0.093	<.001	95
Higher	Preoperative HDL cholesterol	0.056 ± 0.0047	<.001	96
Lower	Any left main disease	−0.24 ± 0.074	.001	78
Lower	Any circumflex system disease	−0.41 ± 0.10	<.001	78

^LLog transformation used.^cExploratory analysis of the effect of creatinine on the logit of being female indicated that including an inverse and squared inverse term improved the scale and linearity of the relationship.

Prior studies have described greater disabling symptoms in women despite less extensive coronary artery disease.^{3,7} We also found that women dominated the New York Heart Association functional classification 3 and 4 categories; however, they had better preserved ejection fractions and less extensive coronary artery disease compared with men. The final parsimonious model did not identify higher New York Heart Association classification categories as a significantly predictive variable for female gender.

In our study, the preoperative lipid profiles for women were distinctly different from men. Women had higher triglyceride, HDL, and LDL cholesterol values. Both the HDL and triglyceride variables were included in the final parsimonious model as significant predictors of female gender. Kannel and Wilson¹⁴ mentioned a metabolic link of clustered coronary risk factors among women: dyslipidemia, hypertension, and glucose intolerance. Data from the Framingham Heart Study support that 80% of women with elevated serum cholesterol levels had 1 or more other major risk factors. An incremental increase in the ratio of total and HDL cholesterol “steeply” increased the risk of coronary heart disease–related events.¹⁴ Additional laboratory values that distinguished women from men were lower preoperative serum creatinine and bilirubin measurements and lower preoperative red blood cell volume and hematocrit values. Reduced preoperative red blood cell volume measurements in women may have important implications with regard to hemodilution from the cardiopulmonary bypass machine and the subsequent use of red blood cells.

One of the primary limitations of this study is that we can only comment on predictors of female gender based on our measured covariates. Unmeasured variables could impact the final model. Second, our study collected clinical variables and does not explain the purported causes or mechanism for the progression of coronary artery disease. The addition of genetic information to further profile patients may contribute to mechanistic causes in the future. Furthermore, our study was from a single institution and characterizes only those patients with heart disease presenting for coronary artery revascularization.

Gender deserves specific consideration in the broad realm of coronary artery disease. Women may have less risk of developing coronary artery disease earlier in their lives. Data from the Framingham Heart Study indicate that high ratios of total and HDL cholesterol, diabetes, and electrocardiographic evidence of left ventricular hypertrophy eliminate the female advantage.¹⁴ The impact of aggressive risk factor modification programs on perioperative outcome is unknown. The key to implementing risk factor modification programs involves an understanding of the high-risk population that the programs are designed to target. A preoperative profile of women such as defined by our model can specifically target patients for intervention.

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