Does a similar procedure result in similar survival for women and men undergoing isolated coronary artery bypass grafting?

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ABSTRACT

Objectives: To (1) identify sex-related differences in risk factors and revascularization strategies for patients undergoing coronary artery bypass grafting (CABG), (2) assess whether these differences influenced early and late survival, and (3) determine whether clinical effectiveness of the same revascularization strategy was influenced by sex.

Methods: From January 1972 to January 2011, 57,943 adults—11,009 (19%) women—underwent primary isolated CABG. Separate models for long-term mortality were developed for men and women, followed by assessing sex-related differences in strength of risk factors (interaction terms).

Results: Incomplete revascularization was more common in men than women (26% vs 22%, $P < .0001$), but women received fewer bilateral internal thoracic artery (ITA) grafts (4.8% vs 12%; $P < .0001$) and fewer arterial grafts (68% vs 70%; $P < .0001$). Overall, women had lower survival than men after CABG (65% and 31% at 10 and 20 years, respectively, vs 74% and 41%; $P \leq .0001$), even after risk adjustment. Incomplete revascularization was associated equally ($P > .9$) with lower survival in both sexes. Single ITA grafting was associated with equally ($P = .3$) better survival in women and men. Although bilateral ITA grafting was associated with better survival than single ITA grafting, it was less effective in women—11% lower late mortality (hazard ratio, 0.89 [0.77-1.022]) versus 27% lower in men (hazard ratio, 0.73 [0.69-0.77]; $P = .01$).

Conclusions: Women on average have longer life expectancies than men but not after CABG. Every attempt should be made to use arterial grafting and complete revascularization, but for unexplained reasons, sex-related differences in effectiveness of bilateral arterial grafting were identified. (J Thorac Cardiovasc Surg 2017;153:571-9)

Unadjusted survival after coronary artery bypass grafting stratified by sex and single versus bilateral internal thoracic artery grafting.

Central Message

Although risk-adjusted survival after coronary artery bypass grafting is worse for women than men, every attempt should be made to fully revascularize all patients undergoing coronary artery bypass grafting and use bilateral internal thoracic artery grafting when possible.

Perspective

Long-term survival after coronary artery bypass grafting is worse for women than men even after adjustment for differences in strength of risk factors; however, in both men and women, complete coronary revascularization and use of bilateral internal thoracic artery grafting are associated with better long-term survival compared with incomplete revascularization and single internal thoracic artery or only saphenous vein grafting.

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If the same operation for coronary artery disease were performed in women and men with the same comorbidities and extent of coronary artery disease, would outcomes be the same? Women undergoing coronary artery bypass grafting (CABG) generally are older and sicker than men and have a disproportionate number of risk factors associated with poor outcomes¹⁻⁴; however, depending on the statistical approach, richness of the

Scanning this QR code will take you to supplemental figures, tables, and appendix for this article.

Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
ITA	= internal thoracic artery
LAD	= left anterior descending coronary artery
SVG	= saphenous vein graft

data set, and length of follow-up, studies differ on whether their outcomes after CABG are worse than those of men, all else being equal.^{1,2,5}

Although few sex-specific preoperative risk factors potentially are modifiable, surgeons can influence sex-specific variation in factors related to decisions about revascularization strategy, such as completeness of coronary revascularization and choice of bypass conduits.⁶ What is uncertain, however, is whether a similar revascularization approach for similar coronary artery disease in a woman and a man with similar comorbidities results in similar outcomes.

Therefore, our objectives were to (1) identify sex-associated differences in preoperative risk factors and revascularization strategies; (2) assess whether these differences, particularly in revascularization strategy, influence risk-adjusted early and late mortality; and (3) determine whether clinical effectiveness of the same revascularization strategy is influenced by sex.

PATIENTS AND METHODS

Patients

From January 1972 to January 2011, 57,943 adults, including 11,009 women (19%), underwent primary isolated CABG at Cleveland Clinic. Preoperative, operative, and postoperative variables were retrieved from the Cardiovascular Information Registry of the Heart and Vascular Institute. This registry is populated concurrently with patient care and has been approved for use in research by the institutional review board, with individual patient consent waived.

Revascularization Strategies

Completeness of revascularization was defined as a conduit placed to any coronary system (left anterior descending coronary artery [LAD], left circumflex coronary artery [LCx], or right coronary artery systems) with 50% or more stenosis, or grafting to both the LAD and LCx systems for left main disease $\geq 50\%$. Surgical revascularization strategies included the following main conduits: saphenous vein graft (SVG), single or bilateral internal thoracic artery graft, and radial artery graft.

Endpoints

In-hospital safety endpoints included those defined and assessed as quality benchmarks by the Society of Thoracic Surgeons National Database (see http://www.sts.org/sites/default/files/documents/STSAAdultCVDataSpecificationsV2_81.pdf). The effectiveness endpoint was all-cause time-related mortality and its instantaneous risk; all-cause mortality is a hard endpoint not subject to subjective interpretation. Systematic periodic follow-up data were obtained through the Cardiovascular Information Registry through year 2000, supplemented with information from the Social Security Death Master File, accessed on October 27,

2011, when it still contained all federal and state death records. To account for a reporting lag time of 6 months, a closing date of April 27, 2011, was used.

Median follow-up for women was 10 years; 25% of survivors were followed more than 19 years and 10% more than 27 years, with 126,462 patient-years of follow-up data available for analysis. Median follow-up for men was 12 years; 25% of survivors were followed more than 22 years and 10% more than 31 years, with 626,162 patient-years of follow-up data available for analysis.

Data Analysis

Analyses were performed with SAS version 9.2 statistical software (SAS Institute, Inc, Cary, NC).

Sex differences in preoperative characteristics, revascularization strategy, and in-hospital outcomes. Comparisons of preoperative characteristics, revascularization strategies, and in-hospital outcomes between women and men were made with the Wilcoxon rank-sum nonparametric test for continuous variables, and the χ^2 test (Fisher exact test when frequency was < 5) for categorical variables. $P \leq .05$ was considered a statistically significant difference. Logistic regression analysis was performed for hospital mortality by using variables in [Appendix E1](#) and bootstrap variable selection.⁷ Briefly, with a P -value criterion for retention of variables in the model of .05, variables from 500 resampled data sets with bootstrap reliability of 50% or more were included in the parsimonious model.

Sex differences in survival. Nonparametric survival estimates stratified by sex and revascularization strategy were obtained by using the Kaplan-Meier method and parametric estimates via a multiphase non-proportional hazards model.⁸ The parametric method was used to resolve the number of phases of instantaneous risk of death (hazard function) and to estimate shaping parameters (for details, see www.lerner.ccf.org/qhs/software/hazard/), because there was a short early period of elevated risk followed by a gradually rising late risk of death. These different phases of risk, labeled early and late ([Figure E1](#)), were data driven, resolved by temporal decomposition. Because of the orthogonal nature of such decompositions, separate streams of covariables were analyzed simultaneously in the same model.⁸ Because the shape of time-varying risk of death could differ for women and men, we constructed separate hazard models for each, as well as for the combined group. Survival estimates of matched US populations were generated for each patient from US life tables and according to age, sex, and race, then averaged.

Multivariable analysis was performed in the hazard function domain, incorporating variables simultaneously into all phases using those listed in [Appendix E1](#), with bootstrap variable selection as described in the previous text.

Women presenting for CABG were more symptomatic than men and more prone to have heart failure, hypertension, peripheral arterial and cerebrovascular disease, and pharmacologically treated diabetes ([Table 1](#)). By contrast, men had more diseased coronary arteries, previous myocardial infarctions, and a history of smoking. Therefore, the modeling strategy was as follows: Separate parsimonious models were developed for women and men, each in 3 steps: (1) preoperative factors only, (2) procedure-related and revascularization strategies only, and (3) preoperative and procedure/revascularization variables combined. Thereafter, a semisaturated model was created that included every variable identified either in the female or male model and an interaction term for each with female sex to determine female-male differences in risk-factor strength and statistical significance.

To test the global effect of female sex on survival, we created a nested model by excluding the variable "female" and all female-variable interactions from the semisaturated model. We then compared the log-likelihood of the nested models.

TABLE 1. Patient characteristics stratified by sex (n = 57,943)

Variable	Men (n = 46,934)		Women (n = 11,009)		P
	n*	No. (%) or Mean ± SD	n*	No. (%) or Mean ± SD	
Demographics					
Age, y	46,934	59 ± 10	11,009	64 ± 10	<.0001
Body mass index, kg·m ^{−2}	29,431	28 ± 4.7	8434	28 ± 6.0	.4
Race					
White	42,952	39,603 (92)	10,408	9477 (91)	.0001
Black	42,952	1032 (2.4)	10,408	631 (6.1)	<.0001
Other	42,952	2317 (5.4)	10,408	300 (2.9)	<.0001
Acuity					
NYHA functional class	46,534		10,944		<.0001
I		8172 (18)		1624 (15)	
II		18,045 (39)		3386 (31)	
III		4934 (11)		1487 (14)	
IV		15,383 (33)		4447 (41)	
Emergency operation	46,933	1125 (2.4)	11,008	448 (4.1)	<.0001
Coronary artery disease†					
LMT	43,524	6952 (16)	9905	1816 (18)	<.0001
LAD	44,859	41,414 (92)	10,340	9365 (91)	<.0001
LCx	44,606	32,630 (73)	10,230	6937 (68)	<.0001
RCA	44,651	36,607 (82)	10,250	8238 (80)	.0001
Cardiac comorbidity					
Preoperative AF or flutter	37,430	473 (1.3)	9407	123 (1.3)	.7
Heart failure	46,932	2750 (5.9)	11,009	1318 (12)	<.0001
Previous myocardial infarction	46,934	24,604 (52)	11,009	5426 (49)	<.0001
LV dysfunction	43,738		9938		<.0001
None		37,164 (85)		8112 (82)	
Mild		2835 (6.5)		751 (7.6)	
Moderate		2215 (5.1)		656 (6.6)	
Severe		1524 (3.5)		419 (4.3)	
Noncardiac comorbidity					
Peripheral arterial disease	46,934	4905 (10)	11,009	1725 (16)	<.0001
Hypertension	16,468	11,283 (69)	5328	4304 (81)	<.0001
Previous stroke	46,933	1788 (3.8)	11,009	686 (6.2)	<.0001
Pharmacologically treated diabetes	44,865	7246 (16)	10,619	3110 (29)	<.0001
History of smoking	45,114	25,315 (56)	10,731	4961 (46)	<.0001
Chronic obstructive pulmonary disease	16,468	1190 (7.2)	5328	446 (8.4)	.006
Bilirubin, mg·dL ^{−1}	14,359	0.66 ± 0.50	4563	0.52 ± 0.47	<.0001
Creatinine, mg·dL ^{−1}	15,977	1.2 ± 0.92	5181	1.1 ± 1.05	<.0001
Renal dialysis	8736	101 (1.2)	2916	57 (2.0)	.001
Cholesterol	35,480	228 ± 56	7658	240 ± 66	<.0001
Triglycerides, mg·dL ^{−1}	29,970	188 ± 128	6368	190 ± 131	.8
Hematocrit	14,791	41 ± 5.0	4799	36 ± 4.8	<.0001

SD, Standard deviation; NYHA, New York Heart Association; LMT, left main trunk; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; AF, atrial fibrillation; LV, left ventricular. *Patients with data available. †Stenosis $\geq$ 50%.

Missing values. To account for missing values for some covariables in the multivariable analysis, 5-fold multiple imputation was performed using the Markov chain Monte Carlo technique (SAS PROC MI and PROC MIANALYZE).⁹

Presentation. Categorical variables are summarized as frequencies and percentages, and continuous variables as mean $\pm$ standard deviation or 15th, 50th (median), and 85th percentiles when distributions are skewed. Transformation of scale of continuous variables was necessary to meet statistical model assumptions; therefore, results of the multiphase hazard models are presented with their coefficients, rather than hazard ratios.

Survival results are depicted with simple Kaplan-Meier stratifications according to sex; however, to illustrate risk-adjusted effects of revascularization strategy on survival, the semisaturated multivariable hazard model was solved for a typical female profile. Specifically, except for the variable being illustrated, model variables were fixed at the following values: age 65 years, body mass index 27 kg·m⁻², white race, New York Heart Association functional class III/IV, 3-system disease (maximum LAD stenosis 90%, maximum LCx stenosis 75%, maximum right coronary artery stenosis 90%), peripheral arterial disease, pharmacologically treated diabetes, preoperative creatinine 1.2 mg·dL⁻¹, preoperative cholesterol 236 mg·dL⁻¹, preoperative

triglycerides 159 mg·dL⁻¹, preoperative hematocrit 40%, complete revascularization with $\geq 50\%$ stenosis, and any intraoperative or preoperative blood products given.

RESULTS

Sex Differences in Revascularization Strategies

Incomplete revascularization was more common in men than women (Table 2); however, women received fewer arterial grafts, including less use of bilateral internal thoracic artery (ITA) grafts (Figure E2) and radial artery grafts than men, less use of total arterial revascularization, and greater use of SVGs to the LAD. They also were more likely to receive only SVGs for revascularization. The majority of operations for both women and men were performed with cardiopulmonary bypass, but more women had off-pump procedures.

Sex Differences in In-Hospital Outcomes

Although occurring infrequently, postoperative deep sternal wound infections and septicemia occurred more

often in women than men, and women experienced more postoperative strokes, renal failure, and renal failure requiring dialysis (Table 3). They also experienced new-onset atrial fibrillation more often and had more prolonged (>24 hours) postoperative mechanical ventilation. Women also had longer intensive care unit and postoperative lengths of stay. There was no significant difference in the occurrence of perioperative myocardial infarction. In-hospital mortality was greater for women than men even after risk adjustment (Table 3 and Table E1).

Sex Differences in Time-Related Survival

Overall, women had lower time-related survival than men after CABG (Figure 1), and this has persisted since the beginning of CABG at Cleveland Clinic (Figure E3). Consequently, the gap between survival of women in the general population and women after CABG was wider than that for men. After we adjusted for patient and revascularization strategy differences, female sex remained an independent risk factor for death overall ($P < .0001$) and

TABLE 2. Procedural details stratified by sex (n = 57,943)

Variable	Men (n = 46,934)		Women (n = 11,009)		P
	n*	No. (%) or mean ± SD	n*	No. (%) or mean ± SD	
CABG details					
Grafts					
ITA	46,934		11,009		<.0001
0		14,090 (30)		3590 (33)	
1		27,246 (58)		6890 (63)	
2		5598 (12)		529 (4.8)	
Radial artery	46,934	2852 (6.1)	11,009	495 (4.5)	<.0001
All arterial grafts	46,934	4356 (9.3)	11,009	927 (8.4)	.005
Saphenous vein	46,934	42,574 (91)	11,009	10,077 (92)	.007
Saphenous vein only	46,934	14,036 (30)	11,009	3568 (32)	<.0001
Grafting strategy to LAD	46,934	42,419 (90)	11,009	9966 (91)	.6
ITA	42,419	30,371 (72)	9966	6903 (69)	<.0001
SVG	42,419	12,289 (29)	9966	3122 (31)	<.0001
Grafting strategy to LCx	46,934	35,047 (75)	11,009	7837 (71)	<.0001
ITA	35,047	4927 (14)	7837	510 (6.5)	<.0001
SVG	35,047	30,046 (86)	7837	7161 (91)	<.0001
Grafting strategy to RCA	46,934	30,744 (66)	11,009	7473 (68)	<.0001
ITA	30,744	1325 (4.3)	7473	185 (2.5)	<.0001
SVG	30,744	28,703 (93)	7473	7168 (96)	<.0001
Completeness of revascularization†					
Incomplete revascularization	46,934	12,017 (26)	11,009	2388 (22)	<.0001
LMT	46,934	599 (1.3)	11,009	196 (1.8)	<.0001
LAD	46,934	1109 (2.4)	11,009	213 (1.9)	.007
LCx	46,934	3643 (7.8)	11,009	824 (7.5)	.3
RCA	46,934	8216 (18)	11,009	1446 (13)	<.0001
Support					
Off-pump revascularization	49,934	1375 (2.9)	11,009	601 (5.4)	<.0001
Cardiopulmonary bypass	46,934	45,559 (97)	11,009	10,408 (95)	<.0001
Cardiopulmonary bypass time, min	11,917	97 ± 32	3762	92 ± 32	<.0001
Myocardial ischemic time, min	13,332	64 ± 32	4345	57 ± 32	<.0001

SD, Standard deviation; CABG, coronary artery bypass grafting; ITA, internal thoracic artery; LAD, left anterior descending coronary artery; SVG, saphenous vein graft; LCx, left circumflex coronary artery; RCA, right coronary artery; LMT, left main trunk. *Patients with data available or applicable. † $\geq 50\%$ stenosis.

TABLE 3. In-hospital outcomes (n = 57,943)

Outcome	Men (n = 46,934)		Women (n = 11,009)		P
	n*	No. (%)	n*	No. (%)	
Hospital death	46,934	510 (1.1)	11,009	293 (2.7)	<.0001
Atrial fibrillation	46,934	6065 (13)	11,009	1628 (15)	<.0001
Prolonged ventilation (>24 h)	4272†	393 (9.2)	1407	189 (13)	<.0001
Reoperation for bleeding/tamponade	46,934	1858 (4.0)	11,009	386 (3.5)	.03
Septicemia	16,468†	265 (1.6)	5328	126 (2.4)	.0003
Deep sternal wound infection	44,862	573 (1.3)	10,619	191 (1.8)	<.0001
Permanent stroke	46,934	647 (1.4)	11,009	254 (2.3)	<.0001
Perioperative myocardial infarction	46,934	977 (2.1)	11,009	240 (2.2)	.5
Renal failure requiring dialysis	16,468†	118 (0.72)	5328	75 (1.4)	<.0001
Length of stay					
ICU, h	16,466†	24/24/72‡	5326	24/30/96‡	<.0001
Postoperative, d	45,811	6/8/10‡	10,843	6/8/12‡	<.0001

ICU, Intensive care unit. *Patients with data available. †Recently recorded outcomes. ‡15th/50th/85th percentiles. Median score test was used to compare medians and Wilcoxon rank-sum test to compare tails of distributions. P values are given for median score test.

both early ($P < .0001$) and late ($P = .01$) after CABG (Tables E2 and E3).

Effectiveness of Revascularization Strategies

Incomplete revascularization was associated with lower survival than complete revascularization in both men and women, with incompletely revascularized women having the worst survival—81% versus 87%, 58% versus 70%, and 25% versus 35% at 5, 10, and 20 years, respectively (Figure 2, A). Although risk-adjusted nomograms show considerable narrowing of these differences, the relationships to survival remained the same, without a differential effect attributable to sex ($P > .9$; Figures 2, B, and 3, Tables E2 and E3).

Use of ITA grafts was associated with better survival than use of SVGs alone and was best when bilateral ITA grafting was performed (Figure 3, Tables E2 and E3). Women receiving SVGs alone had the lowest survival, 80%, 58%, and 25% at 5, 10, and 20 years, respectively (Figure 4, A), compared with 86%, 68%, and 33% for men (Figure 4, B). Men with bilateral ITA grafts had the highest survival, 96%, 88%, and 63% at 5, 10, and 20 years, respectively, compared with 90%, 77%, and 48% for women (Figure 4, C and Figure 5). Women who received bilateral ITA grafting appeared to have survival similar to that of men after single ITA grafting ($P = .12$ after multivariable adjustment; Figure 4, D). Non-risk-adjusted actuarial estimates demonstrate that these relationships have been consistent across time (Figure E4).

DISCUSSION

Worse outcomes after CABG in women compared with men have been attributed to older age, delayed diagnosis and treatment, greater prevalence of comorbidities (respiratory disease, diabetes, hypertension, and heart failure), smaller size, more acute presentation, underuse of arterial grafts (specifically the ITA), and referral bias.^{3,5,10} These differences make it difficult to determine whether women's worse outcomes are related solely to a greater preoperative risk profile or to a less-than-ideal operation. Hence, in this study we used extensive risk adjustment to examine the association of these differences in revascularization strategies between male and female patients with survival after CABG.

Principal Findings

Women had less favorable preoperative characteristics than men, but received fewer bilateral ITA grafts and less all-arterial grafting as part of their revascularization strategy. Women also experienced greater morbidity and greater

FIGURE 1. Survival after cardiac surgery in men and women. Symbols represent Kaplan-Meier estimates at 5-year intervals and vertical bars confidence limits equivalent to ± 1 standard error. Solid curves are parametric survival estimates. Red lines and triangles represent women and blue lines and circles men. Dash-dot-dash lines are age-sex-race-matched survival estimates for the US population. Number of patients remaining at risk at 5-year intervals is shown beneath the horizontal axis.

FIGURE 2. Survival after coronary artery bypass grafting stratified by sex and completeness of revascularization. A, Unadjusted Kaplan-Meier estimates, with confidence limits equivalent to ± 1 standard error shown as vertical bars at 5-year intervals. Number of patients remaining at risk at 5-year intervals is shown beneath horizontal axis. B, Adjusted. Nomogram for survival of a patient with typical female characteristics based on the multivariable model (Tables E2 and E3), with variables held constant, as noted in the Methods. Single internal thoracic artery grafting is simulated for both men and women. CR, Complete revascularization; IR, incomplete revascularization.

in-hospital mortality after CABG than men. Unlike the general population, they had lower risk-adjusted long-term survival than men, with the worst survival noted in women who were incompletely revascularized and had no ITA grafting, and the best in men who were completely revascularized and had bilateral ITA grafting. The effectiveness of bilateral ITA grafting, however, was blunted in women compared with men.

Sex Differences in Revascularization Strategies

Our finding of less use of arterial conduits in women is consistent with results of other studies.^{11,12} In a study of 1758 patients undergoing primary isolated CABG between 2003 and 2005 that included 398 women (23%) and 1360 men (77%), Sharoni and colleagues¹³ found similar use of left ITA grafts (men, 99%; women, 98%;

FIGURE 3. Forest plot of early and late survival after coronary artery bypass grafting according to revascularization strategy, adjusted for differences in characteristics between women and men. Symbols represent the hazard ratio and horizontal bars 95% confidence limits. Note difference in horizontal scales. CR, Complete revascularization; SITA, single internal thoracic artery grafting; BITA, bilateral internal thoracic artery grafting.

$P = .2$) and radial artery grafts (men, 49%; women, 59%; $P = .12$) in both sexes. However, women received fewer right ITA grafts (women, 15%; men, 33%; $P < .01$). Among 374,918 Medicare beneficiaries aged 66 years or older who underwent isolated multivessel CABG between 1988 and 2008, Hlatky and colleagues¹⁴ found that ITA use increased from 31% in 1988 to 91% in 2008. However, ITA use remained lower in women (32%) than men (42%) in 2008 ($P = .04$).

Sex Differences in In-Hospital Outcomes

In this study, unadjusted analysis showed greater morbidity and higher in-hospital mortality for women, and this difference was not explained by their different comorbidity profile, in contrast to what has been reported previously.^{2,10,15} Our previous work showed similar in-hospital mortality among well-matched women and men²; however, in that study, only 26% of women could be matched with men, reflecting the marked dissimilarity between the sexes in baseline preoperative characteristics. Despite a higher overall morbidity, less complete revascularization, and more SVG use in women, occurrence of perioperative myocardial infarction was similar for both women and men.

Sex Differences in Long-Term Survival

We found lower unadjusted and risk-adjusted survival in women than men, and this has been consistent in our experience since the beginning of CABG. Other reports of long-term survival of women after CABG are inconsistent.¹⁵⁻¹⁸ It was in part the discrepancies in these findings that stimulated us to approach our study differently from those of the past. We did not focus on an overall result, as is the forte of a propensity-matching approach. Rather, we identified risk factors for death separately for women and men to establish a pool of factors. Then we looked for interactions—different strengths of association of these factors between women and men. This strategy highlights not only the

FIGURE 4. Survival after coronary artery bypass grafting stratified by sex and single versus bilateral internal thoracic artery grafting. *BITA*, Bilateral internal thoracic artery grafting; *SITA*, single internal thoracic artery grafting. A, Women. Format is as in Figure 2, A. B, Men. Format is as in Figure 2, A. C, Unadjusted. Format for Kaplan-Meier estimates is as in Figure 2, A. D, Adjusted. Variables as in Figure 2, B except that complete revascularization with $\geq 50\%$ stenosis was simulated for both men and women.

risk factors for death, but also how they may affect survival differently in women and men.

It is possible that the discrepancies arise because all-cause mortality is an incomplete metric of outcome. For

example, Vaccarino and colleagues¹⁹ found that after CABG, women showed less improvement in physical functioning than men. Less-favorable gains in functional status could be related to differences in revascularization strategies, such as less complete revascularization, or to more graft occlusions.^{18,20,21} Abramov and colleagues¹¹ attributed the higher prevalence of recurrent postoperative angina in women than in men after CABG to incomplete revascularization, graft occlusion, and progressive atherosclerosis, although they found no sex-related difference in performance of repeat revascularization. Kurlansky and colleagues²² reported greater risk of late myocardial infarction among women than propensity-matched men, all of whom received bilateral ITA grafts.

Effectiveness of Revascularization Strategies

We found that complete revascularization in both women and men was associated with better survival than incomplete revascularization. This finding is consistent with previous reports of decreased survival and increased adverse events with incomplete revascularization.^{23,24}

FIGURE 5. Unadjusted survival after coronary artery bypass grafting stratified by sex and single versus bilateral internal thoracic artery grafting.

The survival benefit associated with use of ITA grafting is well established.^{25,26} Similarly, use of more arterial conduits has been associated with decreased in-hospital and late mortality and lower recurrence of angina.^{27,28} However, although bilateral ITA use in women was associated with possibly better survival than single ITA grafting, it was only half as effective as in men. Why would women have different survival than men after bilateral ITA grafting? We hypothesize that this difference may be related to smaller coronary arteries, more diffuse coronary artery disease, and smaller arterial grafts in women. These factors could result in reduced effectiveness of arterial revascularization and possibly decreased graft patency.

In support of this hypothesis, Douglas and colleagues²⁹ reported that women had smaller coronary arteries and reduced graft patency compared with men. Roberts and Roberts³⁰ reported smaller cross-sectional area of the proximal coronary arteries in women that they attributed to differences in body weight and heart size, but others have found that these differences persisted after accounting for body size.^{31,32} Grafting small coronary arteries is associated with limitation of conduit flow, which correlates with increased operative mortality after CABG, even after adjusting for preoperative variables.^{31,33} Women also have higher rates of admission for recurrent angina and heart failure than men,^{20,34} but tend to have less extensive coronary artery disease and less collateral circulation.^{34,35}

Why did we find reduced effectiveness of bilateral, but not single, ITA grafting in women? The answer is unclear, although the left ITA is most commonly used to bypass LAD lesions, whereas the right ITA usually is used to bypass the second most important target, which is likely to be smaller than the left ITA target.

Clinical Implications

Although 2 ITA grafts are better than 1 for both women and men, bilateral grafting appears less effective in women in the long term. Hence, a patient's sex deserves special consideration in operative planning. Would a more meticulous harvesting of conduits and better coronary target selection narrow the outcome gap between men and women? How effective are the procedures currently in use? Is there a specific group of women who benefit more from bilateral ITA grafting and who are less susceptible to the risk of sternal wound infections? Identifying such a group of patients could increase appropriate use of bilateral ITA grafting.

Strengths and Limitations

This is a single-institution prospective cohort investigation in which unaccounted-for variables could have influenced outcomes. However, because of the inability to randomize sex, our study is a natural experiment. We considered variables known to be related to early and late

mortality in this patient population. Factors related to surgeons' decision-making about choice of conduit, and whether the predetermined revascularization strategy ultimately was performed, modified, or abandoned secondary to untoward intraoperative circumstances (eg, poor conduit after harvest), are unknown. In addition, our follow-up focused on all-cause long-term mortality. Although this is a hard endpoint, fatal and nonfatal myocardial infarction, stroke, need for repeat revascularization, compliance with rehabilitation, medications, and diet were not studied. Incomplete revascularization can be attributed to poor coronary targets versus surgeon choice; we were unable to distinguish between the 2 from our database.

A considerable strength of the study is that it spans 4 decades, permitting us to assess long-term mortality consequences of the initial revascularization strategy; indeed, this is the only way to obtain long-term information. At the same time, the 4-decade span introduces limitations. Thus, early outcomes (Tables E4 and E5) and late survival might have been influenced by changes in patient characteristics (Figure E5) and advances in both initial and longitudinal medical treatment, such as postoperative use of statins and antiplatelet medications, and intervention techniques, although these changes are likely to have influenced both sexes. We have demonstrated that sex differences in survival and differences with respect to revascularization strategy associated with long-term survival have been present in our experience since the beginning of CABG.

CONCLUSIONS

Every attempt should be made to achieve complete coronary revascularization and use arterial grafting in both women and men. The difference in effectiveness of bilateral ITA grafting needs to be considered in women at elevated risk for bilateral ITA harvesting complications.

Conflict of Interest Statement

Dr Sabik is the North American principal investigator for the Abbott Laboratories–sponsored left main coronary disease randomized trial (EXCEL), is on the Society of Thoracic Surgeons board of directors, and is on the scientific advisory board of Medtronic. All other authors have nothing to disclose with regard to commercial support.

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Key Words: coronary artery bypass grafting, sex, survival, cardiac surgery

APPENDIX E1. VARIABLES CONSIDERED IN ANALYSES

Demographics

Age (y), sex, race, weight (kg), height (cm), weight/height ratio, body surface area (m^2), body mass index ($\text{kg} \cdot \text{m}^{-2}$)

Acuity

New York Heart Association functional class (I-IV), emergency operation

Cardiac Comorbidity

Previous myocardial infarction, atrial fibrillation or flutter, complete heart block or pacemaker, heart failure

Noncardiac Comorbidity

Peripheral arterial disease, carotid disease, hypertension, chronic obstructive pulmonary disease, history of smoking, prior stroke, bilirubin ($\text{mg} \cdot \text{dL}^{-1}$), cholesterol ($\text{mg} \cdot \text{dL}^{-1}$), treated diabetes, triglycerides ($\text{mg} \cdot \text{dL}^{-1}$), creatinine ($\text{mg} \cdot \text{dL}^{-1}$), blood urea nitrogen ($\text{mg} \cdot \text{dL}^{-1}$), hematocrit (%), high-density lipoprotein cholesterol ($\text{mg} \cdot \text{dL}^{-1}$), low-density lipoprotein cholesterol ($\text{mg} \cdot \text{dL}^{-1}$)

Ventricular Function

Left ventricular dysfunction (none, mild, mild to moderate, moderate, moderate to severe, severe)

Coronary Artery Disease

Number of systems diseased ($\geq 50\%$ stenosis), maximum left main trunk (LMT) stenosis, LMT disease (0% , $\geq 70\%$, and $\geq 50\%$ stenosis), maximum left anterior descending coronary artery (LAD) stenosis, LAD system disease (0% , $\geq 70\%$, and $\geq 50\%$ stenosis), maximum left circumflex coronary artery (LCx) stenosis, LCx system disease (0% , $\geq 70\%$, and $\geq 50\%$ stenosis), maximum right coronary artery (RCA) stenosis, RCA system disease (0% , $\geq 70\%$, and $\geq 50\%$ stenosis)

Blood Product Use

Any intraoperative or preoperative blood products given.

Procedure

Number of internal thoracic artery (ITA) grafts (none, single, bilateral), incomplete revascularization (based on $\geq 50\%$ stenosis). Conduits used: arterial grafts, only arterial grafts, gastroepiploic or inferior epigastric artery, ITA, free ITA, in situ ITA, left ITA, right ITA, radial artery, saphenous vein, other conduit. Graft location: LAD diagonals, LAD (including LMT), LCx territory, RCA territory.

Support

Cardiopulmonary bypass (off-pump)

Experience

Date of operation (years since January 1, 1972)

FIGURE E1. Temporal decomposition of instantaneous risk (hazard) of death for women and men. A, Individual hazard phases, showing a rapidly declining early phase and a late rising phase. Concomitant information shrinks or expands the area under the early hazard phase and tilts the late hazard phase. B, As in A, but on expanded horizontal scale. C, Hazard phases added.

FIGURE E2. Use of ITA grafting by operative year. A, Use of any ITA graft accelerated in the early 1980s, and use of BITA grafting increased at that time, but on average has remained about 20% of cases. B, BITA grafting was more common in men than women throughout the study period. *ITA*, Internal thoracic artery; *BITA*, bilateral internal thoracic artery; *CABG*, coronary artery bypass grafting.

FIGURE E3. Persistence of risk-unadjusted survival for women and men after coronary artery bypass grafting. Kaplan-Meier estimates, with 68% confidence limits shown at 5-year intervals. A, 1970s. B, 1980s. C, 1990s. D, 2000s.

FIGURE E4. Survival in men and women according to revascularization strategy across the decades. Format is as in [Figure E3](#). A, 1970s. B, 1980s. C, 1990s. D, 2000s. *SITA*, Single internal thoracic artery graft; *ITA*, internal thoracic artery graft; *BITA*, Bilateral internal thoracic artery graft.

FIGURE E5. Temporal trend in patient demographics and comorbidities. Percentages by decade are depicted. *Left-hand blue bars* represent prevalences in men and *right-hand red bars* those in women. For age and BMI, box includes 25th and 75th percentiles, *horizontal bar* within box is the median, *whiskers* encompass values within 1.5 of IQR, and *individual dots* are extreme values. *BMI*, Body mass index.

TABLE E1. Risk factors for hospital mortality

Risk factor	Estimate $\pm$ SE	P
Demographics		
Female	0.59 $\pm$ 0.081	<.0001
Older age*	0.58 $\pm$ 0.059	<.0001
Lower BMI†	0.26 $\pm$ 0.107	.01
Acuity		
NYHA functional class II	−0.33 $\pm$ 0.089	.0002
Emergency operation	1.7 $\pm$ 0.103	<.0001
Coronary artery disease		
Left main trunk stenosis $\geq$ 70%	0.54 $\pm$ 0.108	<.0001
Number of systems diseased‡	0.32 $\pm$ 0.063	<.0001
Cardiac comorbidity		
Heart failure	0.57 $\pm$ 0.106	<.0001
Previous myocardial infarction	0.31 $\pm$ 0.078	<.0001
Greater left ventricular dysfunction	0.12 $\pm$ 0.031	<.0001
Noncardiac comorbidity		
Peripheral arterial disease	0.46 $\pm$ 0.089	<.0001
Stroke	0.44 $\pm$ 0.13	.0007
Pharmacologically treated diabetes	0.29 $\pm$ 0.091	.002
Higher creatinine§	0.73 $\pm$ 0.109	<.0001
Procedural		
Internal thoracic artery grafting	−0.86 $\pm$ 0.088	<.0001
Earlier date of operation¶	−0.030 $\pm$ 0.0058	<.0001
Intercept	−7.8 $\pm$ 0.26	<.0001

C-statistic = .81. SE, Standard error; BMI, body mass index; NYHA, New York Heart Association. *Exp(age/50), exponential transformation. †(25/BMI)², inverse squared transformation. ‡Stenosis $\geq$ 50%. §Logarithmic transformation. ¶Years from January 1, 1972.

TABLE E2. Incremental risk factors for time-related death, stratified by sex: early hazard phase

Risk factor	Men			Women			Difference from men	
	Coefficient $\pm$ SE	P	R (%) [*]	Coefficient $\pm$ SE	P	R (%) [*]	Coefficient $\pm$ SE	P
Demographics								
Older age [†]	0.55 $\pm$ 0.055	<.0001	100	0.35 $\pm$ 0.074	<.0001	100	-0.19 $\pm$ 0.089	.04
Lower BMI [‡]	0.26 $\pm$ 0.12	.03	98	0.20 $\pm$ 0.15	.19	23	-0.048 $\pm$ 0.19	.8
Acuity								
NYHA functional class								
II	-0.31 $\pm$ 0.096	.002	98	-0.58 $\pm$ 0.15	<.0001	99	-0.26 $\pm$ 0.17	.13
III/IV	-0.19 $\pm$ 0.088	.03	98	-0.26 $\pm$ 0.12	.03	99	-0.07 $\pm$ 0.15	.6
Emergency operation	1.24 $\pm$ 0.11	<.0001	100	1.13 $\pm$ 0.14	<.0001	100	-0.18 $\pm$ 0.17	.3
Coronary artery disease [§]								
LMT	0.46 $\pm$ 0.096	<.0001	98	0.21 $\pm$ 0.14	.14	15	-0.26 $\pm$ 0.17	.14
LAD	0.27 $\pm$ 0.10	.008	98	0.11 $\pm$ 0.14	.4	19	-0.18 $\pm$ 0.17	.3
LCx	0.32 $\pm$ 0.09	.0006	98	0.44 $\pm$ 0.11	<.0001	90	0.12 $\pm$ 0.14	.4
Cardiac comorbidity								
Atrial fibrillation or flutter	0.72 $\pm$ 0.17	<.0001	97	0.35 $\pm$ 0.32	.3	23	-0.26 $\pm$ 0.35	.5
Heart failure	0.41 $\pm$ 0.10	<.0001	97	0.49 $\pm$ 0.12	<.0001	96	0.11 $\pm$ 0.16	.4
Previous myocardial infarction	0.19 $\pm$ 0.073	.007	78	0.059 $\pm$ 0.099	.6	16	-0.13 $\pm$ 0.12	.3
Greater LV dysfunction	0.13 $\pm$ 0.030	<.0001	75	0.12 $\pm$ 0.037	.002	40	-0.012 $\pm$ 0.043	.8
Noncardiac comorbidity								
Peripheral arterial disease	0.48 $\pm$ 0.082	<.0001	100	0.38 $\pm$ 0.11	.0007	89	-0.087 $\pm$ 0.14	.5
Stroke	0.69 $\pm$ 0.11	<.0001	100	0.19 $\pm$ 0.16	.2	14	-0.49 $\pm$ 0.19	.009
History of smoking	0.27 $\pm$ 0.074	.0002	95	-0.061 $\pm$ 0.10	.5	9	-0.28 $\pm$ 0.12	.02
Higher creatinine [¶]	0.09 $\pm$ 0.058	.12	33	0.19 $\pm$ 0.081	.02	51	0.071 $\pm$ 0.097	.5
Lower cholesterol	0.32 $\pm$ 0.13	.01	39	0.49 $\pm$ 0.17	.008	80	0.22 $\pm$ 0.23	.3
Lower hematocrit [#]	-1.01 $\pm$ 0.16	<.0001	78	-0.64 $\pm$ 0.31	.04	12	0.37 $\pm$ 0.31	.2
Revascularization strategy								
Incomplete revascularization								
With $\geq$ 50% stenosis	0.25 $\pm$ 0.074	.0009	96	0.16 $\pm$ 0.11	.13	89	-0.097 $\pm$ 0.13	.4
ITA graft								
Single	-0.71 $\pm$ 0.078	<.0001	100	-0.57 $\pm$ 0.11	<.0001	100	0.15 $\pm$ 0.13	.2
Bilateral	-0.92 $\pm$ 0.18	<.0001	100	-0.63 $\pm$ 0.32	.05	100	0.25 $\pm$ 0.37	.5
Bilateral vs single	-0.21 $\pm$ 0.17	.2	100	-0.058 $\pm$ 0.31	.8	100	0.14 $\pm$ 0.36	.7
No graft vs single	0.70 $\pm$ 0.078	<.0001	100	0.57 $\pm$ 0.11	<.0001	100	-0.16 $\pm$ 0.13	.2
Support								
Cardiopulmonary bypass (off-pump)	-0.028 $\pm$ 0.19	.9	15	0.25 $\pm$ 0.20	.2	9	0.29 $\pm$ 0.28	.3
Blood product use								
Any intra- or postoperative blood product	0.69 $\pm$ 0.16	.0006	100	0.46 $\pm$ 0.28	.13	33	-0.27 $\pm$ 0.28	.3

Missing value flags for cholesterol and creatinine are used in the model to adjust for block missing data. SE, Standard error; R, reliability; BMI, body mass index; NYHA, New York Heart Association; LMT, left main trunk; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LV, left ventricular; ITA, internal thoracic artery.

^{*}Percent of times factor appeared in 500 bootstrap models. [†]Exp(age/50), exponential transformation. [‡](25/BMI)², inverse squared transformation. [§] $\geq$ 70% stenosis.

[¶]Log(creatinine), logarithmic transformation. ^{||}(230/cholesterol), inverse transformation. [#]Log(hematocrit), logarithmic transformation.

TABLE E3. Incremental risk factors for time-related death, stratified by sex: late hazard phase

Risk factor	Men			Women			Difference from men	
	Coefficient $\pm$ SE	P	R (%) [*]	Coefficient $\pm$ SE	P	R (%) [*]	Coefficient $\pm$ SE	P
Demographics								
Older age								
Age	0.025 $\pm$ 0.0052	<.0001	100	0.0046 $\pm$ 0.011	.7	100	−0.022 $\pm$ 0.012	.06
Age [†]	0.40 $\pm$ 0.078	<.0001	100	0.55 $\pm$ 0.15	.0002	100	0.21 $\pm$ 0.17	.2
Lower and higher BMI								
BMI	0.012 $\pm$ 0.0032	.0003	100	0.02 $\pm$ 0.0065	.007	94	0.0088 $\pm$ 0.0071	.2
BMI [‡]	0.083 $\pm$ 0.068	.2	100	0.19 $\pm$ 0.094	.04	94	0.11 $\pm$ 0.12	.4
Race								
White	0.074 $\pm$ 0.038	.05	100	0.059 $\pm$ 0.059	.3	33	−0.028 $\pm$ 0.071	.7
Acuity								
NYHA functional class III/IV	0.071 $\pm$ 0.013	<.0001	100	0.042 $\pm$ 0.026	.11	95	−0.035 $\pm$ 0.029	.2
Emergency surgery	−0.11 $\pm$ 0.044	.013	76	−0.15 $\pm$ 0.073	.04	59	−0.039 $\pm$ 0.086	.6
Coronary artery disease [§]								
LMT	0.12 $\pm$ 0.018	<.0001	100	0.046 $\pm$ 0.038	.2	41	−0.066 $\pm$ 0.042	.12
LAD	0.13 $\pm$ 0.024	<.0001	100	0.073 $\pm$ 0.045	.11	14	−0.058 $\pm$ 0.051	.3
LCx	0.13 $\pm$ 0.016	<.0001	100	0.15 $\pm$ 0.031	<.0001	99	0.019 $\pm$ 0.035	.6
RCA	0.09 $\pm$ 0.017	<.0001	100	0.094 $\pm$ 0.034	.006	99	0.0026 $\pm$ 0.038	>.9
Cardiac comorbidity								
Atrial fibrillation or flutter	0.43 $\pm$ 0.06	<.0001	100	0.50 $\pm$ 0.12	<.0001	99	0.076 $\pm$ 0.13	.6
Heart failure	0.37 $\pm$ 0.031	<.0001	100	0.32 $\pm$ 0.045	<.0001	100	−0.036 $\pm$ 0.055	.5
Previous myocardial infarction	0.15 $\pm$ 0.013	<.0001	100	0.11 $\pm$ 0.027	<.0001	99	−0.03 $\pm$ 0.03	.3
Greater LV dysfunction	0.11 $\pm$ 0.0079	<.0001	100	0.071 $\pm$ 0.014	<.0001	97	−0.027 $\pm$ 0.015	.08
Noncardiac comorbidity								
Peripheral arterial disease	0.38 $\pm$ 0.02	<.0001	100	0.37 $\pm$ 0.034	<.0001	100	−0.0046 $\pm$ 0.040	>.9
Stroke	0.26 $\pm$ 0.034	<.0001	100	0.30 $\pm$ 0.055	<.0001	100	0.058 $\pm$ 0.064	.4
Pharmacologically treated diabetes	0.42 $\pm$ 0.02	<.0001	100	0.51 $\pm$ 0.032	<.0001	100	0.12 $\pm$ 0.037	.003
History of smoking	0.24 $\pm$ 0.014	<.0001	100	0.23 $\pm$ 0.028	<.0001	100	0.0074 $\pm$ 0.03	.8
Higher creatinine [¶]	0.075 $\pm$ 0.010	<.0001	85	0.073 $\pm$ 0.025	.007	100	−0.018 $\pm$ 0.025	.5
Lower cholesterol	0.0038 $\pm$ 0.013	.8	16	0.034 $\pm$ 0.018	.06	100	0.039 $\pm$ 0.024	.10
Higher triglycerides	0.046 $\pm$ 0.013	.001	100	0.059 $\pm$ 0.025	.03	98	0.016 $\pm$ 0.027	.6
Revascularization strategy								
Incomplete revascularization								
With $\geq$ 50% stenosis	0.081 $\pm$ 0.015	<.0001	98	0.077 $\pm$ 0.032	.02	48	−0.0014 $\pm$ 0.035	>.9
ITA graft								
Single	−0.20 $\pm$ 0.015	<.0001	100	−0.17 $\pm$ 0.03	<.0001	100	0.032 $\pm$ 0.033	.3
Bilateral	−0.51 $\pm$ 0.031	<.0001	100	−0.29 $\pm$ 0.075	.0001	100	0.23 $\pm$ 0.081	.004
Bilateral vs single	−0.31 $\pm$ 0.029	<.0001	100	−0.12 $\pm$ 0.072	.10	100	0.20 $\pm$ 0.078	.011
No graft vs single	0.20 $\pm$ 0.015	<.0001	100	0.17 $\pm$ 0.030	<.0001	100	−0.032 $\pm$ 0.029	.3
Support								
Cardiopulmonary bypass (off-pump)	−0.083 $\pm$ 0.061	.17	9	−0.0072 $\pm$ 0.082	>.9	6	0.11 $\pm$ 0.10	.3
Blood product use								
Any intra- or postoperative blood product	0.069 $\pm$ 0.024	.006	89	0.051 $\pm$ 0.053	.3	7	−0.030 $\pm$ 0.059	.6

Missing value flags for cholesterol and creatinine are used in the model to adjust for block missing data. SE, Standard error; R, reliability; BMI, body mass index; NYHA, New York Heart Association; LMT, left main trunk; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; LV, left ventricular; ITA, internal thoracic artery. ^{*}Percent of times factor appeared in 500 bootstrap models. [†]Exp(age/50), exponential transformation. [‡](25/BMI)², inverse squared transformation. [§] $\geq$ 70% stenosis. [¶]Log(creatinine), logarithmic transformation. ^{||}(230/cholesterol)², inverse squared transformation.

TABLE E4. In-hospital outcomes stratified by era: 1972 to 2000

Outcome	Men (n = 41,090)		Women (n = 9083)		P
	n*	No. (%)	n*	No. (%)	
Hospital death	41,090	468 (1.1)	9083	261 (2.9)	<.0001
Atrial fibrillation	40,695	4462 (11)	8985	1182 (13)	<.0001
Reoperation for bleeding/tamponade	41,090	1724 (4.2)	9083	337 (3.7)	.03
Septicemia	10,624	167 (1.6)	3402	82 (2.4)	.001
Deep sternal wound infection	39,119	512 (1.3)	8723	148 (1.7)	.005
Permanent stroke	41,090	598 (1.5)	9083	224 (2.5)	<.0001
Perioperative myocardial infarction	41,090	966 (2.4)	9083	233 (2.6)	.2
Renal failure requiring dialysis	10,624	68 (0.64)	3402	38 (1.1)	.005
Length of stay†					
ICU, h	10,622	24/24/72	3400	24/24/96	<.0001
Postoperative, d	39,967	7.0/8.0/11	8917	6.8/8.0/12	.3

ICU, Intensive care unit. *Patients with data available. †15th/50th/85th percentiles. Median score test was used to compare medians and Wilcoxon rank-sum test to compare tails of distributions. P values are given for median score test.

TABLE E5. In-hospital outcomes stratified by era: 2000 to 2011

Outcome	Men (n = 5844)		Women (n = 1926)		P
	n*	No. (%)	n*	No. (%)	
Hospital death	5844	42 (0.72)	1926	32 (1.7)	.0002
Atrial fibrillation	5766	1603 (28)	1901	446 (23)	.0002
Reoperation for bleeding/tamponade	5844	134 (2.3)	1926	49 (2.5)	.5
Septicemia	5844	98 (1.7)	1926	44 (2.3)	.08
Deep sternal wound infection	5844	62 (1.1)	1926	43 (2.2)	.0001
Permanent stroke	5844	49 (0.84)	1926	30 (1.6)	.006
Perioperative myocardial infarction	5844	11 (0.19)	1926	7 (0.36)	.18
Renal failure requiring dialysis	5844	50 (0.86)	1926	37 (1.9)	.0001
Length of stay†					
ICU, h	5844	22/27/73	1926	23/31/96	<.0001
Postoperative, d	5844	4.9/6.1/9.1	1926	5.1/6.9/11	<.0001

ICU, Intensive care unit. *Patients with data available. †15th/50th/85th percentiles. Median score test was used to compare medians and Wilcoxon rank-sum test to compare tails of distributions. P values are given for median score test.