Sex Differences in Outcomes After Cardiac Catheterization

Effect Modification by Treatment Strategy and Time

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Context Studies comparing outcomes of cardiac care in women vs men yield various results, with some suggesting worse outcomes for women and others suggesting equivalent outcomes.

Objective To determine whether extent of coronary disease, treatment strategy, and follow-up time influence the risk of death in women vs men among patients who have had cardiac catheterization.

Design, Setting, and Patients We studied a large inception cohort by using detailed clinical data from a registry of 37401 patients undergoing cardiac catheterization in Alberta, Canada, from 1995-2000, with follow-up through December 31, 2001.

Main Outcome Measures The risk of death for women vs men was assessed for all patients combined and then in analyses stratified by degree of coronary anatomic risk and by treatment strategy (no revascularization, percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG] surgery). The latter analysis included a graphic assessment of the changing relative risk over time for women vs men.

Results Women had higher 1-year mortality than men did (5.6% vs 4.6%; $P<.001$). However, stratified analyses demonstrated that sex differences in risk occurred only early after catheterization and were most apparent among patients undergoing revascularization. The early risk-adjusted relative risks for women vs men were elevated at 3.49 (95% confidence interval [CI], 1.95-6.24) for CABG surgery and 2.38 (95% CI, 1.48-3.83) for PCI on day 1 after catheterization, with a subsequent decrease in relative risk over time to equivalence in risk between sexes before 1 year.

Conclusions Sex-based differences in death rates after cardiac catheterization are time- and treatment-specific. This finding may at least partially explain the discrepancies in results from earlier studies on sex differences in outcomes of cardiac care.

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SEX DIFFERENCES IN CARDIAC CARE and outcomes have been widely investigated since Steingart et al[1] stimulated clinicians to consider sex-based biases in care practices. Investigators have examined sex differences in access to cardiac procedures and outcomes after myocardial infarction (MI) or the diagnosis of coronary artery disease (CAD).[2-18] Many studies have suggested that women have less access to care or poorer outcomes,[2-9] whereas others have concluded that there are few or no differences[10-17] or, under particular circumstances, that women fare better than men.[16] After more than a decade of investigation, however, consistent findings are wanting, perhaps because of unavailability of detailed clinical data, variability of patient samples, and variability of follow-up times.

The Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) is a database containing detailed clinical data for all residents of Alberta, Canada, who undergo cardiac catheterization in the province.[19] This database represents a resource for cardiovascular outcomes research and has recently been used to study sex differences in access to coronary revascularization.[11]

In this study, we extend that recent work to study sex differences in survival after cardiac catheterization. We assessed survival outcomes for all women vs men and then made outcome comparisons stratified for degree of coronary anatomic risk and mode of treatment after catheterization (no revascularization, percutaneous coronary intervention [PCI], or coronary artery bypass graft [CABG] surgery). We also conducted a detailed analysis of time as a potential

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modifier of the risk of death for women vs men.

METHODS

Data Source and Variables

Patients in APPROACH were followed up longitudinally for assessment of long-term outcomes after cardiac catheterization. Clinical risk variables recorded at cardiac catheterization included sex, age, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, cerebrovascular disease, elevated creatinine level (≥2.26 mg/dL [≥200 µmol/L), dialysis status, diabetes, hypertension, hyperlipidemia, liver or gastrointestinal disease, malignancy or metastatic disease, previous MI, previous PCI, previous CABG surgery, previous thrombolytic therapy for MI, and smoking status (categorized as "never," "former," or "current"). The indication for catheterization was recorded in 1 of 4 categories: MI within 8 weeks of catheterization, stable angina, unstable angina, or other (eg, arrhythmias). Extent of coronary disease was recorded and used to derive the weighted Duke Index and Duke Myocardial Jeopardy Score.[20-23] Left ventricular ejection fraction was graded into 5 categories: less than 30%, 30% to 50%, more than 50%, ventriculogram not done (usually because of renal insufficiency or severely depressed cardiac function), and information missing. The occurrence of revascularization procedures after catheterization was also systematically recorded.

The outcome of interest for this study, all-cause mortality, was ascertained through semiannual linkage to records from the Alberta Bureau of Vital Statistics. We analyzed data from patients undergoing cardiac catheterization in 1995 through 2000, with follow-up of patients through December 31, 2001. The APPROACH study protocol was approved by the ethics review boards of the Universities of Calgary and Alberta. The requirement for informed consent was waived.

Analysis

We used χ^2 and 2-sample *t* tests to compare the clinical characteristics of men and women. The distributions for age of women and men met assumptions of normality and equal variances. We used Kaplan-Meier plots and log-rank tests to compare unadjusted survival of women vs men for 1 year after catheterization. We also compared unadjusted survival of women vs men, stratified by coronary anatomic risk, with patients categorized into high risk (left main coronary artery stenosis, 3-vessel disease, or 2-vessel disease with proximal left anterior descending involvement) and low risk (other 2-vessel disease, 1-vessel disease, lesions with <50% stenosis, and normal) anatomy groups.

For our analysis stratified by initial treatment strategy, we grouped patients according to first revascularization treatment received within a year of catheterization: PCI, CABG, or no revascularization. We focused only on the first revascularization procedure after catheterization because that is the procedure most likely linked to the results of coronary angiography.

We used Cox proportional hazards models to model survival but found that, regardless of treatment modality, the effect of sex violated the proportional hazards assumption because the risk of events in women vs men changed over time (traditional proportional hazards models assume that this relative risk is fixed). This finding led us to confine our analysis of outcomes by sex over time to the graphic examination of relative risks estimated by plotting splines through residuals from Cox models that excluded the sex variable. For these graphic methods, we relied on restricted cubic splines plotted through rescaled Schoenfeld residuals.[24,25]

We also used logistic regression to examine the association between sex and outcomes at 30 days and 1 year while controlling for severity of illness. All potential risk variables were retained in the models regardless of statistical significance because our objective was to focus primarily on the odds ratios (ORs) for patient sex while controlling for all other potential confounders. Analyses were stratified by treatment group (no revascularization, PCI, CABG surgery) and coronary anatomy (low risk, high risk). We also performed a modified propensity analysis for which we modeled propensity (ie, likelihood) to be selected to CABG surgery or PCI (2 propensity models) and then assessed the OR for death in women vs men across tertiles of propensity. All analyses were performed with S-Plus (version 6.1 for Windows; Insightful Corp, Seattle, Wash). The level of significance used for tests was .05.

RESULTS

Of 37 401 patients studied, 11 199 were women. Women were significantly older than men and had more comorbid conditions, including congestive heart failure, chronic lung disease, cerebrovascular disease, diabetes, hypertension, liver disease, and malignancy (TABLE 1). Women were less likely to have had an MI or to have had cardiac interventions. Women tended to have a higher left ventricular ejection fraction, and their coronary anatomy was generally of lower risk than was that of men. Correspondingly, women had lower median weighted Duke Index values[23] and were less likely than men to have revascularization procedures after catheterization.

Women had higher 1-year mortality than men (626/11 199 [5.6%] vs 1203/26 202 [4.6%]; $P<.001$). The unadjusted survival curves (FIGURE 1) for all patients revealed a higher mortality in women vs men during 1 year after cardiac catheterization ($\chi^2_1=17.3$, $P<.001$). Particularly in the early post-cardiac catheterization period, there was a significant decline in survival among women compared with men.

Analysis Stratified by Anatomic Risk

The unadjusted survival curves for patients with low-risk coronary anatomy suggested little difference between low-risk women and men in survival rates after cardiac catheterization ($\chi^2_1=3.4$; $P=.06$; Figure 1). In contrast, the curves for patients with high-risk coronary anatomy revealed that women had poorer survival early after cardiac cath-

eterization, followed by similar death rates beyond approximately 40 days once the period of early risk had ended (χ^2_1=83.2; P<.001).

Analysis Stratified by Revascularization Treatment Group

To further investigate the early mortality risk in women with high-risk anatomy, we stratified patients by treatment group (no revascularization, PCI, CABG surgery). For PCI and CABG surgery treatment groups, there was a markedly increased early risk for mortality for women vs men (FIGURE 2). For the CABG surgery group, the adjusted relative risk for mortality for women vs men was 3.49 (95% confidence interval [CI], 1.95-6.24) on day 1 after catheterization. The risk for women subsequently decreased to a level equivalent to that for men (ie, relative risk of 1.0) at 157 days. A similar pattern was seen in patients who underwent PCI: the relative risk was 2.38 (95% CI, 1.48-3.83) on day 1 after catheterization and dropped to 1.0 at 342 days. The risk profiles of women and men in the "no revascularization" group did not follow this pattern; the relative risk of mortality in women vs men remained similar and near 1.0 throughout follow-up.

These findings of changing relative risks over time were confirmed by logistic regression analyses of mortality at 2 points (TABLE 2). For patients who did not undergo revascularization, there were more modest, statistically insignificant sex differences in odds of mortality.

For the analyses shown in Figure 2 and Table 2, we intentionally used time of catheterization as a common "time zero" across treatment groups. For the PCI group, this analysis accurately reflects time of actual treatment, given the short median waiting time of 1 day for PCI. For CABG surgery, the median wait was 22 days. As a result, the early hazard seen immediately after catheterization was based on data from some patients who had their CABG immediately after catheterization but also on data for others who had not yet undergone CABG. Therefore, we performed sensitivity analyses for which plots were replicated by using the time of revascularization (PCI or CABG surgery) as time zero. These sensitivity analyses revealed an almost identical picture of elevated early hazard in women vs men. The only difference with the main analyses presented in Figure 2 is that the hazard ratio for the CABG surgery

Table 1. Baseline Characteristics for Women and Men

Variable	No. (%) Women (n = 11 199)	No. (%) Men (n = 26 202)	Difference, %	*P* Value
Age, mean (SD), y	64.9 (3.4)	61.6 (3.4)	3.2	<.001
Comorbidities*				
Congestive heart failure	1902 (17.0)	3594 (13.7)	3.3	<.001
Peripheral vascular disease	876 (7.8)	1998 (7.6)	0.2	.45
Chronic pulmonary disease	1404 (12.5)	2441 (9.3)	3.2	<.001
Cerebrovascular disease	838 (7.5)	1538 (5.9)	1.6	<.001
Creatinine >2.26 mg/dL	264 (2.4)	677 (2.6)	−0.2	.21
Dialysis	149 (1.3)	380 (1.5)	−0.1	.39
Diabetes	2317 (20.7)	4658 (17.8)	2.9	<.001
Hypertension	6647 (59.4)	12 748 (48.7)	10.7	<.001
Hyperlipidemia	4997 (44.6)	12 365 (47.2)	−2.6	<.001
Liver/GI†	479 (4.3)	905 (3.5)	0.8	.001
Malignancy	448 (4.0)	888 (3.4)	0.6	.004
Previous MI	4495 (40.1)	13 736 (52.4)	−12.3	<.001
Previous PCI	748 (6.7)	2737 (10.4)	−3.7	<.001
Previous CABG surgery	473 (4.2)	2298 (8.8)	−4.6	<.001
Previous lytic therapy	782 (7.0)	2322 (8.9)	−1.9	<.001
Smoking status				
Never	5988 (53.5)	8985 (34.3)	19.2	<.001
Former	2592 (23.1)	10 012 (38.2)	−15.1	
Current	2619 (23.4)	7205 (27.5)	−4.1	
Clinical indication for catheterization				
Myocardial infarction	2646 (23.6)	7725 (29.5)	−5.9	<.001
Stable angina	3197 (28.5)	8007 (30.6)	−2.0	
Unstable angina	3565 (31.8)	7123 (27.2)	4.6	
Other	1791 (16.0)	3347 (12.8)	3.2	
Coronary anatomic risk‡				
High	3152 (28.1)	11 498 (43.9)	−15.8	<.001
Low	8047 (71.9)	14 704 (56.1)	15.8	
Weighted Duke Index, median (IQR)	32 (0-56)	48 (32-63)	16	<.001§
Ejection fraction, %				
<30	398 (3.6)	1391 (5.3)	−1.8	<.001
30-50	1657 (14.8)	5523 (21.1)	−6.3	
>50	7347 (65.6)	14 782 (56.4)	9.2	
Not done because of instability	689 (6.2)	1676 (6.4)	−0.2	
Missing information	1108 (9.9)	2830 (10.8)	−0.9	
Treatment within 1 year of catheterization				
No revascularization	6696 (59.8)	11 390 (43.5)	16.3	<.001
PCI	2996 (26.8)	8908 (34.0)	−7.2	
CABG surgery	1507 (13.5)	5904 (22.5)	−9.1	

Abbreviations: CABG, coronary artery bypass graft; GI, gastrointestinal; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention.
SI conversion factor: To convert creatinine to μmol/L, multiply by 88.4.
*Comorbidities were recorded at catheterization by catheter laboratory staff, as documented in the medical record and supplemented by patient report.
†Any cormorbid disease involving the liver or GI tract.
‡High risk includes left main coronary artery stenosis, 3-vessel disease, or 2-vessel disease with proximal left anterior descending artery disease; low risk includes other 2-vessel disease, 1-vessel disease, lesions with <50% stenosis, and normal anatomy.
§Wilcoxon rank sum test.

group decreased to 1.0 at approximately 125 days rather than 157 days.

Disentangling Procedural Risk From Anatomic Risk

To distinguish whether the revascularization procedures themselves imparted higher early risk to women as opposed to high-risk coronary anatomy, which revascularized patients tend to have, we performed an additional stratified logistic regression analysis with separate analyses for high-risk and low-risk anatomy patients in each of the treatment groups (Table 2). The early risk among nonrevascularized high-risk women is less pronounced than the early risks in the PCI and CABG surgery analyses. For nonrevascularized women with low-risk anatomy, the odds for mortality were similar to that for men at 30 days and 1 year (Table 2).

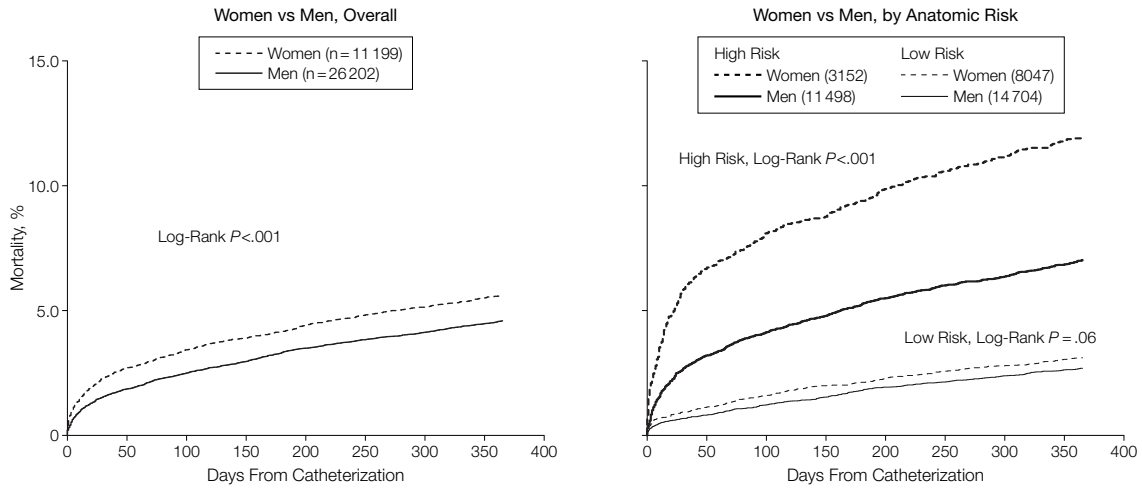
The results of the analyses stratified by propensity to undergo PCI or CABG surgery essentially replicate the results in Table 2. The propensity analysis revealed that the risk for women vs men is highest when propensity (ie, likelihood) to be revascularized is high. This finding is most notable for those who actually were revascularized but is also present to some extent in the "no revascularization" group. The similarity between the analyses stratified by propensity and by anatomic risk (Table 2) is expected, given that the strongest driver of propensity to undergo a revascularization procedure is having high-risk anatomy.

We explored potential interaction effects between sex and other variables such as age and comorbidities but did not find any other clinically or statistically notable interactions.

COMMENT

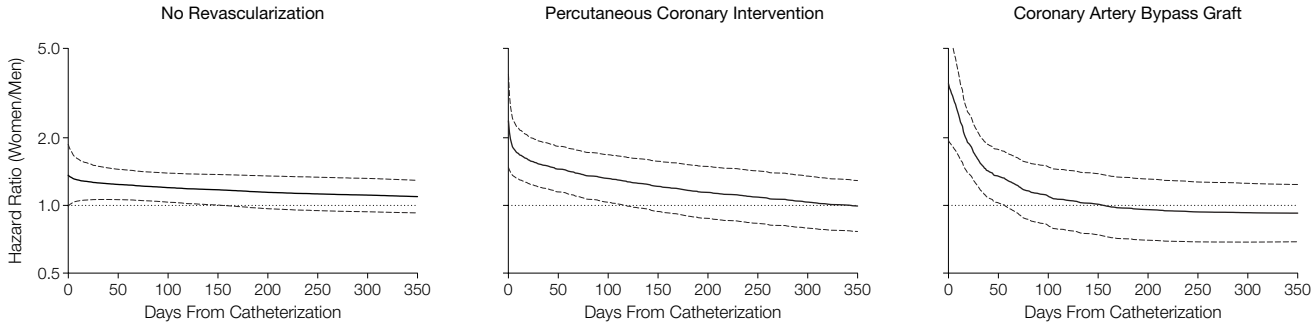
Our study extends current understanding of sex differences in outcomes after cardiac catheterization by identifying a close link between anatomic risk, treatment modality, and time in mortality outcomes. We prospectively investigated sex differences in survival after cardiac catheterization in a large (n=37 401) unselected cohort of patients. Many previ-

Figure 1. Unadjusted Survival Curves of Women vs Men After Cardiac Catheterization and Stratified by Anatomic Risk



High risk includes left main coronary artery stenosis, 3-vessel disease, or 2-vessel disease with proximal left anterior descending involvement and low risk includes other 2-vessel disease, 1-vessel disease, lesions with <50% stenosis, and normal anatomy groups.

Figure 2. Risk-Adjusted Hazard Ratios for Women vs Men, Plotted Against Time and Stratified by Treatment After Cardiac Catheterization



The hazard ratios are adjusted for all of the clinical risk factors listed in Table 1. The dashed lines indicate 95% confidence intervals.

Table 2. Risk-Adjusted Odds Ratios for Mortality at 30 Days and 1 Year for Women Relative to Men, Categorized by Treatment Received and Anatomic Risk*

	OR (95% CI)	
	At 30 Days	At 1 Year
No revascularization		
All	1.40 (1.09-1.81)	1.10 (0.94-1.28)
Low risk	1.07 (0.71-1.63)	0.92 (0.75-1.13)
High risk	1.62 (1.19-2.20)	1.34 (1.08-1.66)
PCI		
All	1.70 (1.21-2.38)	1.36 (1.08-1.71)
Low risk	1.71 (1.01-2.89)	1.25 (0.89-1.75)
High risk	1.70 (1.11-2.59)	1.45 (1.07-1.96)
CABG surgery		
All	2.22 (1.52-3.24)	1.42 (1.10-1.83)
Low risk	1.58 (0.52-4.81)	0.86 (0.44-1.68)
High risk	2.31 (1.56-3.43)	1.54 (1.18-2.02)

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; OR, odds ratio; PCI, percutaneous coronary intervention.
*High risk includes left main coronary artery stenosis, 3-vessel disease, or 2-vessel disease with proximal left anterior descending artery disease. Low risk includes other 2-vessel disease, 1-vessel disease, lesions with >50% stenosis, and normal anatomy.

ous studies on sex differences in outcomes used data from single centers or hospital discharge data, relied on short follow-up times, focused only on specific patient groups, or used relatively small samples.[2,14,16,18] Many of these earlier studies thus provide a limited and inconsistent view, with some reporting that women are at similar or even lower risk than men after treatment for unstable angina[2] or after PCI[12] or CABG surgery.[14,16]

Malenka et al[7] argued that a reason for the lack of consistency in the findings across studies is that many were single-center studies that were too small to find differences. Using a larger regional sample of patients undergoing PCI (n=13 061 procedures), they found that women treated with PCI had higher in-hospital mortality than men, even after adjustment for relevant clinical factors.[7] Vaccarino et al,[6] also studying a large sample of patients (n=384 878) after MI, reported an increase in risk for women vs men, most notably in an unadjusted analysis (in-hospital mortality 16.7% for women vs 11.5% for men) but also after adjustment for clinical severity. Subsequent work by this same group[8,9] revealed a similarly higher risk of in-hospital mortality for women vs men after PCI and CABG surgery. Interestingly, each of these studies focusing on short-term outcomes[6,8,9] also revealed that it is particularly younger women who are at high risk relative to men and that the risk difference between sexes decreases with increasing age. We did not find any such evidence of an interaction effect between age and sex, perhaps because we were studying longer-term outcomes for a broad spectrum of patients.

Our findings provide a potential explanation for the variability in findings across studies. Outcomes for women vs men appear to be time-sensitive and procedure-specific, so studies investigating only short-term outcomes in specific clinical or treatment subgroups will tend to have different findings than studies investigating longer-term outcomes in other patient subgroups. Our results suggest that studies focusing on short-term outcomes after CABG surgery will tend to find large differences in outcomes by sex, whereas a study focusing on longer-term outcomes in medically treated patients will perhaps find more modest sex differences.

We need to learn more about what places women at early risk when they undergo revascularization after cardiac catheterization. Our data allow us to describe these epidemiologic phenomena, but the APPROACH registry does not permit us to identify underlying mechanisms. Although existing data demonstrate potentially important sex differences in cardiac anatomy,[26] women may also have some as-yet unidentified physiologic risk factor or combinations (interactions) of anatomic and physiologic risk factors.

Our findings of notable sex differences in outcomes early after PCI and CABG surgery suggest that it is particularly in these areas that sex-based technologic differences need to be investigated. We propose that special attention be paid to early physiologic factors (eg, mediators of thrombosis for women), technologic factors (eg, investigational technologies, PCI and CABG surgery techniques/equipment tailored for women), and recovery variables that may clarify women's risk profiles. Moreover, we need to continue to investigate caregiver decision making for women vs men.

Our study has some limitations. First, it was limited to patients who have had cardiac catheterization and thus does not account for the outcomes of women who are not referred for this procedure. We cannot determine whether the worse outcomes noted early after revascularization for women were due to the procedures themselves or to the greater incidence of comorbidities in women brought to the catheterization laboratory. Second, there could have been different medication use between sexes in the year after catheterization that could explain some of our findings. However, this explanation is relatively unlikely because a recent study of pharmacotherapy after MI in Calgary, Alberta,[27] revealed that medication therapy early after MI did not differ between sexes. Third, we focused only on all-cause mortality as the outcome because it is most readily and reliably captured in APPROACH and has been widely studied by others and because our mortality analyses reveal intriguing findings on early risk differences by sex. Fourth, our method for ascertaining mortality (using data from the Bureau of Vital Statistics) leaves the possibility of missing patients who had a catheterization procedure but then moved out of the province. We antici-

pate, however, that such unmeasured loss to follow-up is negligible because only Alberta residents' data were used in these analyses and because Alberta is in a trend of remarkable inward (rather than outward) migration. Furthermore, it would generally be atypical for someone to decide to leave Alberta soon after catheterization while in the midst of a CAD evaluation. A final caveat is that we focused on outcomes within the first year after catheterization because we had complete ascertainment of survival to 1 year and because we believed that the most notable finding was the markedly elevated hazard early after catheterization. In sensitivity analyses extending to 7 years, the risk for women vs men remained generally stable and in fact drifted downward to a level slightly below that for men but with wide confidence intervals that included equivalence of risk by sex.

Despite these limitations, our study extends current understanding of sex-based differences in cardiac outcomes by demonstrating their time- and treatment-sensitive nature, a finding that may at least partially explain the discrepancy in results from earlier studies. Given that the mechanisms underlying our findings are not explained, we propose a research agenda in search of explanations for the sex-based outcome differences that we have demonstrated. Such work will represent a crucial first step toward therapeutic solutions.

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Study concept and design: King, Ghali, Curtis, Graham.
Acquisition of data: Curtis, Galbraith, Graham.
Analysis and interpretation of data: King, Ghali, Faris, Curtis, Galbraith, Knudtson.
Drafting of the manuscript: King, Faris, Ghali.
Critical revision of the manuscript for important intellectual content: King, Ghali, Faris, Curtis, Galbraith, Graham, Knudtson.
Statistical expertise: Ghali, Faris.
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