Outcomes of coronary artery bypass grafting in patients with inflammatory rheumatic diseases: An 11-year nationwide cohort study

Chao-Han Lai, MD, PhD,^a Wu-Wei Lai, MD,^a Meng-Jiun Chiou, BS,^c Liang-Miin Tsai, MD,^b Jih-Sheng Wen, MD,^a and Chung-Yi Li, PhD^{c,d}

Objective: Patients with inflammatory rheumatic diseases have an increased risk of developing coronary atherosclerosis. However, outcomes of surgical revascularization in these patients have been rarely studied. We aimed to determine whether, or which, inflammatory rheumatic diseases may pose effects on mortality and adverse cardiac outcomes after coronary artery bypass grafting.

Methods: By using the National Health Insurance Research Database of Taiwan, we identified 40,639 adult patients who underwent first-time coronary artery bypass grafting between 2000 and 2010. Among these patients, 101 had rheumatoid arthritis, 56 had systemic lupus erythematosus, and 73 had ankylosing spondylitis. The odds ratios (ORs) of operative mortality and hazard ratios (HRs) of overall mortality and adverse cardiac outcomes after coronary artery bypass grafting (ie, myocardial infarction and repeat revascularization) in relation to rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis were estimated.

Results: With adjustment for potential confounders including patient characteristics, hospital levels, and combined surgery, systemic lupus erythematosus was an independent predictor for operative mortality (adjusted OR, 2.63; 95% confidence interval [CI], 1.04-6.65; $P = .04$) and ankylosing spondylitis was marginally associated with operative mortality (adjusted OR, 2.41; 95% CI, 0.99-5.88; $P = .054$). Systemic lupus erythematosus was a significantly independent predictor for overall mortality during the follow-up period (adjusted HR, 2.23; 95% CI, 1.51-3.31; $P < .0001$) and might increase the risk of repeat revascularization (adjusted HR, 1.89; 95% CI, 0.97-3.68; $P = .06$). Neither rheumatoid arthritis nor ankylosing spondylitis was significantly associated with overall mortality and adverse cardiac outcomes.

Conclusions: Our study may help surgeons and physicians recognize the potential risks inherent to systemic lupus erythematosus and ankylosing spondylitis when conducting coronary artery bypass grafting and providing follow-up care. (*J Thorac Cardiovasc Surg* 2015;149:859-66)

See related commentary on pages 866-8.

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Despite recent advances in diagnostic procedures and therapeutic modalities, coronary artery disease (CAD) remains

the leading cause of death globally.¹ It is well established that several conventional risk factors (eg, age, male gender, diabetes, and hypertension) account for the development of CAD. Other novel risk factors have been implicated recently. Evidence suggests the essential role of chronic inflammation in the pathogenesis of coronary atherosclerosis.²⁻⁵ Inflammatory rheumatic diseases, a group of disorders that primarily affect joints, may involve different organ systems with a wide spectrum of clinical manifestations. These inflammatory rheumatic disorders may result in chronic, relapsing, and systemic inflammatory responses and increase cardiovascular risks in affected patients.²⁻⁷ Patients with inflammatory rheumatic diseases have a high burden of cardiovascular diseases that may cause increased morbidity and mortality.

Although patients with inflammatory rheumatic diseases seem to be more susceptible to coronary atherosclerosis, outcomes of patients who underwent surgery for coronary revascularization have not been well documented. Although several studies demonstrated single-hospital experiences of coronary artery bypass grafting (CABG) in patients with inflammatory rheumatic diseases, all except 1 were case

From the Departments of Surgery^a and Internal Medicine,^b National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; Department of Public Health,^c College of Medicine, National Cheng Kung University, Tainan, Taiwan; and Department of Public Health,^d College of Public Health, China Medical University, Taichung, Taiwan.

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Address for reprints: Chung-Yi Li, PhD, Department of Public Health, College of Medicine, National Cheng Kung University, No. 1, University Rd, Tainan 70101, Taiwan (E-mail: cyl99@mail.ncku.edu.tw).

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Abbreviations and Acronyms

ASp	= ankylosing spondylitis
CABG	= coronary artery bypass grafting
CAD	= coronary artery disease
CI	= confidence interval
CKD	= chronic kidney disease
DM	= diabetes mellitus
ESRD	= end-stage renal disease
HR	= hazard ratio
IBD	= inflammatory bowel disease
ICD-9-CM	= <i>International Classification of Diseases, Ninth Revision, Clinical Modification</i>
NHIRD	= National Health Insurance Research Database
OR	= odds ratio
PCI	= percutaneous coronary intervention
PM-DM	= polymyositis-dermatomyositis
RA	= rheumatoid arthritis
SLE	= systemic lupus erythematosus
SSc	= systemic sclerosis

series/reports collecting 7 patients or less.⁸⁻¹² The largest among these series included 44 patients with inflammatory rheumatic diseases, composed mainly of patients with rheumatoid arthritis (RA).¹³ Limited surgical experiences in any single center were probably due to the rarity of this special patient population. Thus, conducting investigations using a large database would be a reasonable and practical approach.¹³⁻¹⁵

The National Health Insurance Research Database (NHIRD) of Taiwan contains a large sample size and high validity of diagnosis for catastrophic illnesses (eg, inflammatory rheumatic diseases, cancers, and end-stage renal disease [ESRD]) in the claims data. This database may provide a valuable and real-world platform to review the outcomes of various surgical procedures in patients with certain rare diseases. Literature reviews indicate that a number of inflammatory rheumatic diseases, including RA, systemic lupus erythematosus (SLE), ankylosing spondylitis (ASp), systemic sclerosis (SSc), polymyositis-dermatomyositis (PM-DM), and inflammatory bowel diseases (IBDs), are risk factors for the development of CAD, myocardial infarction, and cardiovascular death.²⁻⁷ Through the NHIRD of Taiwan, we attempted to describe the characteristics and outcomes of patients with inflammatory rheumatic diseases undergoing CABG and to conduct risk analysis to recognize whether, or which, inflammatory rheumatic diseases might be associated with increased risks of mortality and adverse cardiac outcomes during the perioperative period and long-term follow-up.

PATIENTS AND METHODS**The Coronary Artery Bypass Grafting Cohort**

This retrospective cohort study was performed using the NHIRD of Taiwan. Our access to the NHIRD was approved by the Review Committee of the National Health Research Institutes. The whole study was approved by the Institutional Review Board of National Cheng Kung University Hospital (approval number A-EX-102-010). The details of the NHIRD of Taiwan are shown in [Appendix E1](#).

The procedures that established the study cohort are summarized in [Figure 1](#). We selected hospitalizations with the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) procedure codes for CABG from January 1, 2000, to December 31, 2010. Overall, there were 41,113 hospitalizations for CABG during the study period. Among these hospitalizations, we identified a total of 40,639 adult patients aged at least 18 years who underwent first-time CABG as the CABG cohort. By using the ICD-9-CM diagnosis codes, we extracted patients with RA, SLE, ASp, SSc, PM-DM, and IBD from the database. In the CABG cohort, the diagnosis of RA was preoperatively established in 101 patients (0.25%), SLE was preoperatively established in 56 patients (0.14%), and ASp was preoperatively established in 73 patients (0.18%). Patients with SSc (7 patients), PM-DM (7 patients), and IBD (2 patients) were few in number and thus were not included for further analysis.

Comorbidities and Outcome Measurements

On the basis of the hospital care data and prior hospitalizations of each patient, we recognized baseline medical comorbidities using ICD-9-CM codes, including hypertension, diabetes mellitus (DM), dyslipidemia, congestive heart failure, chronic kidney disease (CKD), peripheral artery disease, prior stroke, and chronic obstructive pulmonary disease. Patients with ESRD were further identified from the patients with CKD if they were registered with a dialysis catastrophic illness certificate. We also identified whether the patients were hospitalized with the diagnosis of acute coronary syndrome. In addition, we recorded the levels of hospitals (medical centers, regional hospitals, or district hospitals) where the CABG procedures were conducted. Concomitant procedures, such as valve procedures and thoracic aortic surgery, were also recorded.

Outcomes measured and analyzed in this study included operative mortality, overall mortality, and adverse cardiac outcomes, including myocardial infarction and repeat revascularization, after CABG surgery. All patients of this cohort were evaluated for any occurrence of myocardial infarction and hospitalization for repeat revascularization (defined as percutaneous coronary intervention [PCI] or re-CABG) until mortality, withdrawal from the insurance program, or December 31, 2010. For myocardial infarction and repeat revascularization, the date of the first episode would be counted if patients experienced it more than 1 time. The ICD-9-CM codes of procedures, diseases, and adverse outcomes described in this study are listed in [Table E1](#).

Statistical Analysis

The patients who did not have these inflammatory rheumatic diseases associated with CAD constituted the control group of this study. Patients with different inflammatory rheumatic diseases were compared separately with the control group to describe the differences in baseline characteristics and outcomes. Categorical variables, expressed as numbers and percentages, were compared by the chi-square test or Fisher exact test as necessary. Continuous variables, expressed as mean $\pm$ standard deviation, were compared by the Student *t* test. Kaplan-Meier estimates of overall survival, freedom from myocardial infarction, and freedom from repeat revascularization were plotted. Logistic regression analysis was performed to estimate the odds ratios

FIGURE 1. Study flow chart: cohort assembly of 40,639 adult patients undergoing first-time surgical revascularization for CAD between 2000 and 2010 in the NHIRD of Taiwan. *ASp*, Ankylosing spondylitis; *CABG*, coronary artery bypass grafting; *IBD*, inflammatory bowel disease; *PM-DM*, polymyositis-dermatomyositis; *RA*, rheumatoid arthritis; *SLE*, systemic lupus erythematosus; *SSc*, systemic sclerosis.

(ORs) of operative mortality associated with RA, SLE, and ASp with adjustment for potential confounding variables that have been taken into account in relevant studies,¹⁶⁻¹⁹ including patient characteristics (age, sex, hypertension, DM, dyslipidemia, congestive heart failure, CKD, peripheral artery disease, prior stroke, chronic obstructive pulmonary disease, and acute coronary syndrome), hospital levels, and combined surgery. To estimate the hazard ratios (HRs) of overall mortality after CABG associated with RA, SLE, and ASp, Cox proportional hazard regression model was performed with adjustment for potential confounding variables. The model performance was assessed by using the C-statistic (for logistic) or Harrell's C (for Cox). To assess the HRs of myocardial infarction and repeat revascularization associated with RA, SLE, and ASp, we conducted competing risk regression models in which mortalities over the follow-up period were treated as competing risk events. The competing risk of mortality is an important consideration in studies involving geriatric patients with considerable comorbidities.²⁰ The difference between traditional survival analysis and competing risk approach may not be substantial when the follow-up time is short or if the competing risk is low. Nevertheless, under the circumstances that the proportion of patients experiencing a competing risk is equal or greater to the proportion of patients experiencing the primary outcome, or when the follow-up period is more than 5 years, competing risk analyses should be performed to demonstrate unbiased results.²⁰ The HRs of competing risk regression were computed using the "sterreg" command in STATA (StataCorp LP, College Station, TX), which is based on Fine and Gray's²¹ proportional hazard regression model. Statistical analyses

were performed using SAS software (SAS Institute Inc, Cary, NC) and STATA for Windows (StataCorp LP, College Station, Tex).

RESULTS

Baseline Characteristics and Operative Data

Comparisons of baseline characteristics and operative data between patients without inflammatory rheumatic diseases (control group) and patients with RA, SLE, and ASp in the CABG cohort are summarized in Table 1. Of the 40,397 patients without inflammatory rheumatic diseases, the mean age was 65.5 years with a male-to-female ratio of approximately 3:1. Patients undergoing CABG in Taiwan had a high prevalence of CKD (7.2%), ESRD (4.4%), and prior stroke (17.2%).

Of the 101 patients with RA, the mean age was similar to that of the control group, but the distribution was more centralized to the 60- to 69-year age group. Despite a male predominance, patients with RA were still less male predominant than those without inflammatory rheumatic diseases. In addition, patients with RA had significantly lower proportions of DM and history of stroke than the control group. The 56 patients with SLE in the cohort were significantly younger and

TABLE 1. Comparisons of baseline characteristics and operative data between patients without coronary artery disease–associated inflammatory rheumatic diseases (control group) and patients with rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis in the coronary artery bypass grafting cohort of Taiwan, 2000-2010

Characteristics*	Control group (n = 40,397)	Patients with inflammatory rheumatic diseases					
		Patients with RA† (n = 101)	P value‡	Patients with SLE† (n = 56)	P value‡	Patients with ASp† (n = 73)	P value‡
Age group			.009		<.0001		.002
<50 y	3549 (8.8)	3 (3.0)		15 (26.8)		15 (20.6)	
50-59 y	8521 (21.1)	21 (20.8)		21 (37.5)		20 (27.4)	
60-69 y	12,581 (31.1)	43 (42.6)		12 (21.4)		19 (26.0)	
70-79 y	12,830 (31.8)	33 (32.7%)		8 (14.3%)		16 (21.9%)	
≥80 y	2916 (7.2)	1 (1.0%)		0 (0)		3 (4.1%)	
Age (y, mean ± SD)	65.5 ± 10.9	65.9 ± 8.2	.71	56.8 ± 11.6	<.0001	61.1 ± 11.7	.0005
Sex§			.0001		<.0001		.01
Male	30,459 (75.4)	58 (57.4%)		19 (33.9%)		66 (90.4%)	
Female	9913 (24.5)	43 (42.6%)		37 (66.1%)		7 (9.6%)	
Medical comorbidities							
Hypertension	28,357 (70.2)	64 (63.4)	.13	39 (69.6)	.93	56 (76.7)	.22
DM	19,330 (47.9)	33 (32.7)	.002	12 (21.4)	<.0001	32 (43.8)	.49
Dyslipidemia	15,232 (37.7)	31 (30.7)	.15	15 (26.8)	.09	33 (45.2)	.19
CHF	11,179 (27.7)	31 (30.7)	.50	15 (26.8)	.88	19 (26.0)	.75
CKD	2914 (7.2)	4 (4.0)	.21	20 (35.7)	<.0001	3 (4.1)	.31
ESRD	1782 (4.4)	2 (2.0)	.11	19 (33.9)	<.0001	2 (2.7)	.21
PAD	2006 (5.0)	3 (3.0)	.36	4 (7.1)	.16	3 (4.1)	.22
Prior stroke	6947 (17.2)	9 (8.9)	.03	7 (12.5)	.35	15 (20.6)	.45
COPD	4989 (12.4)	15 (14.9)	.45	4 (7.1)	.24	13 (17.8)	.16
ACS	9084 (22.5)	29 (28.7)	.13	11 (19.6)	.61	12 (16.4)	.22
Hospital level			.29		.0002		.16
Medical center	22,047 (54.6)	48 (47.5)		46 (82.1)		44 (60.3)	
Regional hospital	16,408 (40.6)	46 (45.5)		8 (14.3)		23 (31.5)	
District hospital	1942 (4.8)	7 (6.9)		2 (3.6)		6 (8.2)	
Combined surgery	4523 (11.2)	7 (6.9)	.17	9 (16.1)	.25	13 (17.8)	.07
Valve procedures	4225 (10.5)	7 (6.9)	.25	8 (14.3)	.35	13 (17.8)	.04
Aortic surgery	720 (1.8)	0 (0)	.16	2 (3.6)	.19	2 (2.7)	.24
Total hospital cost (NTD, mean ± SD)	414,181 ± 209,580	423,677 ± 190,038	.65	436,540 ± 222,220	.43	454,484 ± 360,830	.10

ACS, Acute coronary syndrome; ASp, ankylosing spondylitis; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ESRD, end-stage renal disease; NTD, New Taiwan Dollar; PAD, peripheral artery disease; RA, rheumatoid arthritis; SD, standard deviation; SLE, systemic lupus erythematosus. *Data are expressed as patient number (%) unless otherwise indicated. †Two patients with a combination of RA and SLE were counted in both RA and SLE patient groups. One patient with a combination of RA and ASp was counted in both RA and ASp patient groups. ‡P values were calculated by comparison with the control group. §Sex data were missing or undetermined in 25 patients (0.06%).

more female predominant compared with the control group. Patients with SLE had a significantly lower proportion of DM but were more likely to have CKD and ESRD. Of note, the CABG procedures conducted for patients with SLE were highly concentrated in medical centers. The 73 patients with ASp were significantly younger and more male predominant than patients without inflammatory rheumatic diseases. The frequencies of medical comorbidities, the distribution of hospital levels, and the proportions of overall combined procedures in patients with ASp were not significantly different from those of the control group. Finally, the average total hospital costs per hospitalization of patients with RA, SLE, and ASp were generally equal to that of patients without inflammatory rheumatic diseases.

Operative Mortality and Overall Mortality

Figure 2, A, depicts the Kaplan–Meier estimates of overall survival of the CABG cohort. Among the 3 inflammatory rheumatic diseases, SLE was associated with significantly increased odds of operative mortality (crude OR, 2.55; 95% confidence interval [CI], 1.05-6.20; $P = .04$), whereas RA and ASp were not (Table 2). To further assess whether RA, SLE, or ASp might be independently associated with operative mortality, multiple logistic regression analysis was performed. After adjustment for potential confounding variables, SLE was an independent predictor for operative mortality (adjusted OR, 2.63; 95% CI, 1.04-6.65; $P = .04$) and ASp was associated with increased risk of operative mortality at the margin of significance (adjusted

FIGURE 2. Kaplan–Meier estimates of overall survival (A), freedom from myocardial infarction (B), and freedom from repeat revascularization (C) in patients without CAD-associated inflammatory rheumatic diseases (control group) and patients with RA, SLE, and ASp in the CABG cohort of Taiwan, 2000–2010. The proportions and 95% CIs of overall survival, freedom from myocardial infarction, and freedom from repeat revascularization at 2, 4, 6, 8, and 10 years are summarized in Table E2. ASp, Ankylosing spondylitis; CABG, coronary artery bypass grafting; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

OR, 2.41; 95% CI, 0.99–5.88; $P = .054$). The HRs of overall mortality associated with RA, SLE, and ASp are shown in Table 2. Among the 3 inflammatory rheumatic diseases, SLE was significantly associated with overall mortality (crude HR, 1.60; 95% CI, 1.08–2.36; $P = .02$), whereas RA and ASp were not (Table 2). After controlling for potential confounding variables, SLE remained an independent predictor for overall mortality after CABG (adjusted HR, 2.23; 95% CI, 1.51–3.31; $P < .0001$).

Adverse Cardiac Outcomes

The Kaplan–Meier estimates of freedom from myocardial infarction and freedom from repeat revascularization

after CABG are shown in Figure 2, B and C. It should be noted that freedom from these 2 adverse cardiac events is not event-free survival; mortalities are considered to be competing risk events rather than noninformative censoring events in these analyses. The occurrences of myocardial infarction and repeat revascularization of the CABG cohort and HRs of myocardial infarction and repeat revascularization associated with RA, SLE, and ASp are shown in Table 3. Among the 3 inflammatory rheumatic diseases, SLE was significantly associated with repeat revascularization after CABG (crude HR, 2.08; 95% CI, 1.07–4.07; $P = .03$), whereas neither RA nor ASp was significantly associated with myocardial

TABLE 2. Odds ratios of operative mortality and hazard ratios of overall mortality after coronary artery bypass grafting associated with rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis

Variables	Operative mortality			Overall mortality	
	Mortality rate (95% CI)	Crude OR (95% CI)	Adjusted OR* (95% CI)	Crude HR (95% CI)	Adjusted HR† (95% CI)
Control group (n = 40,397)	4.0 (3.8–4.2)	1.00	1.00	1.00	1.00
RA (n = 101)	3.0 (0.6–8.4)	0.85 (0.29–2.47)	0.81 (0.27–2.39)	1.14 (0.82–1.59)	1.20 (0.87–1.67)
SLE (n = 56)	8.9 (3.0–19.2)	2.55 (1.05–6.20)	2.63 (1.04–6.65)	1.60 (1.08–2.36)	2.23 (1.51–3.31)
ASp (n = 73)	6.9 (0.8–12.9)	1.91 (0.80–4.59)	2.41 (0.99–5.88)	1.06 (0.72–1.57)	1.40 (0.94–2.07)

ASp, Ankylosing spondylitis; CI, confidence interval; HR, hazard ratio; OR, odds ratio; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus. *Based on the multiple logistic regression analysis (C-statistic = 0.71) with adjustment for age, sex, hypertension, DM, dyslipidemia, congestive heart failure, CKD, peripheral arterial disease, prior stroke, chronic obstructive pulmonary disease, acute coronary syndrome, hospital levels, and combined valve and aortic surgery. †Based on Cox proportional hazard regression model (Harrell's C = 0.72) with adjustment for age, sex, hypertension, DM, dyslipidemia, congestive heart failure, CKD, peripheral arterial disease, prior stroke, chronic obstructive pulmonary disease, acute coronary syndrome, hospital levels, and combined valve and aortic surgery.

TABLE 3. Hazard ratios of myocardial infarction and repeat revascularization after coronary artery bypass grafting associated with rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis

Variables	Myocardial infarction		Repeat revascularization	
	Crude HR (95% CI)	Adjusted HR* (95% CI)	Crude HR (95% CI)	Adjusted HR* (95% CI)
Control group (n = 40,397)	1.00	1.00	1.00	1.00
RA (n = 101)	0.78 (0.32-1.86)	0.78 (0.32-1.87)	1.14 (0.58-2.24)	1.09 (0.56-2.13)
SLE (n = 56)	1.41 (0.58-3.40)	1.32 (0.54-3.25)	2.08 (1.07-4.07)	1.89 (0.97-3.68)
ASp (n = 73)	0.63 (0.20-1.94)	0.68 (0.22-2.09)	0.64 (0.24-1.70)	0.62 (0.23-1.63)

ASp, Ankylosing spondylitis; CI, confidence interval; HR, hazard ratio; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus. *Based on Fine and Gray's²¹ proportional hazard regression model with adjustment for age, sex, hypertension, DM, dyslipidemia, congestive heart failure, CKD, peripheral arterial disease, prior stroke, chronic obstructive pulmonary disease, acute coronary syndrome, hospital levels, and combined valve and aortic surgery.

infarction or repeat revascularization after CABG. After controlling for possible confounding variables, repeat revascularization occurred more frequently in patients with SLE with a marginal level of significance (adjusted HR, 1.89; 95% CI, 0.97-3.68; $P = .06$).

DISCUSSION

Decades of studies have gradually established the link between inflammatory rheumatic diseases (eg, RA) and accelerated atherosclerosis, as evidenced by higher frequencies of CAD and cardiovascular deaths in patients with these disease entities.²⁻⁵ Because CABG is currently 1 of the 2 main revascularization strategies for patients with CAD, we aimed to elucidate the impact of different CAD-associated inflammatory rheumatic diseases on patients who needed CABG as their revascularization therapy. Even in this nationwide database, the patients with SSc, PM-DM, and IBD were still too rare to provide sufficient numbers for analyses. Therefore, we focused on patients with preoperatively diagnosed RA, SLE, or ASp, and compared baseline characteristics and surgical results of these patients versus those who did not have inflammatory rheumatic diseases. Probably because of the significant differences in disease characteristics among RA, SLE, and ASp, the outcomes of patients with these inflammatory rheumatic diseases undergoing CABG were considerably diverse.

The largest single-hospital series among relevant literature reported by Birdas and colleagues¹³ consisted of 44 patients with inflammatory rheumatic diseases (0.8%) that were identified from a total of 5496 patients undergoing CABG during a study period of 7 years. Of the 44 patients, 35 (79.6%) had RA, 8 had SLE, and 1 had scleroderma. The authors found that the early mortality of CABG in patients with inflammatory rheumatic diseases was acceptable (2/44, 4.5%) compared with that reported by the Society of Thoracic Surgeons database (2.7%; $P > .05$). More recently, Varghese and colleagues¹⁴ investigated the in-hospital outcomes of patients with RA after coronary revascularization using the Nationwide Inpatient Sample in the United States. In this large database study that collected 5485 patients (0.8%) with RA identified from 674,994 patients undergoing coronary revascularization, patients with RA were less

likely than patients without RA to undergo CABG rather than PCI. In addition, although RA is a widely accepted risk factor for CAD and patients with RA have a higher risk for cardiovascular death, patients with RA in this cohort had an improvement of inpatient mortality and a reduced length of hospitalization after coronary revascularization, regardless of CABG or PCI, compared with the control group. In agreement with previous results reported by Varghese and colleagues,¹⁴ patients with RA in our study were less likely to die during the perioperative period in contrast to those without inflammatory rheumatic diseases, although statistical significance was not achieved. In addition, we found that the risks of overall mortality, myocardial infarction, and repeat revascularization in patients with RA were substantially similar to those of patients without inflammatory rheumatic diseases (Tables 2 and 3). Taken together, these observations suggested that patients with RA should go ahead with the CABG procedures if indicated because these patients had at least equal outcomes in comparison with those without inflammatory rheumatic diseases.

Although previous studies focused mainly on RA, we broadened the scope of our study to explore the impact of SLE and ASp on patients undergoing CABG. By using a nationwide database approach, we found that CABG procedures for patients with SLE in this cohort were more likely to be conducted in medical centers. Despite younger age and a lower prevalence of traditional risk factors for CAD (eg, DM), patients with SLE had accelerated atherosclerosis^{4,22} and a higher prevalence of CKD and ESRD. It is plausible to speculate that patients with SLE had poorer medical conditions than usual, leading to a higher risk of surgical mortality. CABG in patients with SLE has been considered to be a surgical challenge because these patients usually have unique characteristics of multiple organ involvement and long-term use of immunosuppressants, such as steroids.⁸ Graft thrombosis is a major concern in these patients, and thus postoperative administration of heparin has been recommended.^{8,9,12} Even after adjustment of potential confounding factors, SLE was still an independent predictor of operative mortality and overall mortality (Table 2). In addition, SLE might increase the risk of repeat revascularization after CABG (Table 3).

Although details of graft choices were unavailable in the NHIRD of Taiwan, accelerated vein graft stenosis could be the cause and extensive arterial grafting has been advised in these patients.¹⁰ In a PCI cohort reported by Maksimowicz-McKinnon and colleagues,²³ patients with SLE were more likely to experience myocardial infarction and more often required repeat PCI than patients without SLE within 1 year. Therefore, patients with SLE may be more likely to experience adverse cardiac outcomes after coronary revascularization by CABG or PCI, and thus post-revascularization risk reduction should be more aggressive.

Study Limitations

First, we conducted a nationwide study involving only small numbers of patients with inflammatory rheumatic diseases and adverse outcomes, fully understanding that these results can only be considered as suggestions for future studies in large clinical databases (eg, the Society of Thoracic Surgeons Adult Cardiac Database or the Nationwide Inpatient Sample in the United States¹⁴ used by Varghese and colleagues¹⁴). Second, large reimbursement cuts in Taiwan, as attested to by the low total hospital costs in the CABG cohort, may reduce the quality of cardiac care.²⁴ Whether this economic factor brought more negative impacts on patients with inflammatory rheumatic diseases undergoing CABG was uncertain because these patients inevitably need multidisciplinary care. Thus, our findings require further validation in other healthcare systems. Third, some variables of interest were unavailable in this secondary data analysis, such as the extent of CAD, intraoperative choice of bypass grafts, details of immunosuppressants during the follow-up period, and causes of death; therefore, these variables cannot be considered in the analyses. Finally, although studies have demonstrated the high accuracy of ICD-9 diagnosis in the NHIRD of Taiwan,^{25,26} the validity issue related to the medical claim data is always a concern. In addition, a relatively small percentage of data missing or miscoding of diagnoses is inherent in studies using large databases. Nevertheless, such coding errors are random and should not be a valid argument for the observed findings of our study because such nondifferential disease misclassification tends to bias the results toward the null.

CONCLUSIONS

We studied the impact of RA, SLE, and ASp on patients undergoing CABG. Among patients undergoing CABG, those with RA had outcomes similar to those of patients without inflammatory rheumatic diseases. SLE was an independent prognostic predictor of both operative mortality and overall mortality and was probably associated with repeat revascularization, whereas ASp appeared to be associated with operative mortality. Because CAD is highly prevalent in patients with inflammatory rheumatic diseases, our findings may help surgeons and physicians recognize

the inherent risks associated with SLE and ASp in patients undergoing CABG.

The study was based on data from the NHIRD provided by the National Health Insurance administration, Ministry of Health and Welfare of Taiwan, and managed by the National Health Research Institutes of Taiwan. However, the interpretation and conclusions contained do not represent those of the National Health Insurance administration, Ministry of Health and Welfare of Taiwan, or the National Health Research Institutes of Taiwan.

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EDITORIAL COMMENTARY

Inflammation: The classic double-edged sword

Paul Kurlansky, MD

See related article on pages 859-66.

Inflammation (from the Latin *inflammare*—*in-*, meaning *into*, plus *flamma*, meaning *flame*) is a complex protective response that is designed to respond to invading pathogens, to eliminate the initial cause of cellular injury, to remove necrotic tissues, and to initiate a process of repair. The role of the inflammatory response in the pathogenesis of coronary artery disease has become increasingly well recognized and defined (Figure 1).¹ Inflammation has not only been implicated in the potential pleomorphic benefits of statins but has been offered as an explanation for the association of cardiovascular disease with periodontal disease,² as well as for the reduced incidence of cardiac events after the receipt of influenza vaccine.³ The inflammatory process can be both pathogenic and protective. It is therefore highly appropriate to examine the potential interaction between inflammatory disease and cardiovascular disease. Such analyses may shed new light on pathogenesis while illuminating risks, alternatives, and novel therapeutic targets in treatment. It is in this arena that Lai and colleagues⁴ report their findings of coronary artery bypass grafting (CABG) in patients with inflammatory rheumatic diseases in this issue of the *Journal*. The source of data had several notable advantages: the National Health

Insurance Research Database of Taiwan essentially includes all the medical interactions in an entire population across time. Although the database is administrative in nature, the specific diagnoses of interest actually undergo particular scrutiny and validation because they are tied to governmental benefits. It would seem that a decade of data from such a compelling source, which includes more than 40,000 patients undergoing CABG, should certainly yield robust information regarding the diagnoses in question. Unfortunately, the actual numbers were quite small—101 patients with rheumatoid arthritis (RA), 56 with systemic lupus erythematosus (SLE), and 73 with ankylosing spondylitis. Because of the distinct natures of these syndromes, Lai and colleagues⁴ were wise to avoid the potential additional confusion of lumping them together to increase their numbers.

The prevalence of RA is estimated to be 0.5% to 1.0% of the general population, affecting women approximately twice as often as men.⁵ Given that 40% of deaths among patients with RA are from cardiovascular disease and that their risk of mortality is approximately double that of an age-matched population, it is somewhat surprising that there were not more patients with this syndrome in this sample who were submitted to CABG.⁶ Although mortality is more closely related to congestive heart failure, RA patients carry a 2-fold independent risk of myocardial infarction and stroke, a risk that rises to 3-fold with a disease duration exceeding 10 years.⁷ This apparent discrepancy may well reflect not only differing patterns of disease prevalence but also selection criteria among various therapeutic options. Obviously, without information regarding the patients with RA and coronary artery disease who did not undergo CABG, no inference can be drawn regarding the relative benefits of CABG in this population.

SLE, on the other hand, is a disease known to have wide variation depending on sex, ethnic, and cultural factors.

From the Department of Surgery, Columbia University, New York, NY.

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Address for reprints: Paul Kurlansky, MD, Department of Surgery, Columbia University, Black Building 210, 650 W 168th St, New York, NY 10032 (E-mail: pk2245@cumc.columbia.edu).

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APPENDIX E1. NATIONAL HEALTH INSURANCE RESEARCH DATABASE OF TAIWAN

The Taiwan National Health Insurance (NHI) program, a mandatory single-payer health insurance system in which all Taiwanese citizens are obliged to participate, has been implemented since 1995. According to the website of the NHI administration (<http://www.nhi.gov.tw>), the NHI program covered 99% of the population of Taiwan (~23 million people) at the end of 2012. In 2013, 93.7% of the clinics and hospitals in Taiwan, including more than 100 regional hospitals and tertiary referral medical centers, had contracts with the NHI program and provided medical services reimbursed by the NHI administration. The data associated with medical care are routinely collected by the National Health Research Institutes to generate the

NHIRD. To protect the privacy of patients and physicians, the NHIRD is released to clinical researchers in an electronically encrypted form. The NHIRD consists of comprehensive information, including encrypted patient identification numbers, sex, date of birth, dates of admission and discharge, hospitals providing the services, surgical or interventional procedures, examinations and diagnosis codes, outcomes at hospital discharge (recovered, died, or transferred), and fees for medical cares. The *International Classification of Diseases, Ninth Revision, Clinical Modification* is used to define diseases and procedures. The NHIRD is one of the largest among administrative medical care databases currently available in the world and has been used to publish hundreds of medical research articles in diverse fields.

TABLE E1. International Classification of Diseases, Ninth Revision, Clinical Modification codes of procedures, diseases, and adverse outcomes

Procedures, diseases, and adverse outcomes	ICD-9-CM codes
Procedures	
CABG	36.1
Valve procedures	35.1, 35.2
Thoracic aortic surgery	38.45
Diseases	
RA	714.0
SLE	710.0
ASp	720.0
SSc	710.1
PM-DM	710.4, 710.3
IBD	555, 556
Hypertension	401-405, 437.2
DM	250, 357.2, 362.0, 366.41
Dyslipidemia	272
CHF	428
CKD	585
PAD	443, 444
Prior stroke	430-438
COPD	490-496
ACS	410, 411, 413
Adverse outcomes	
Myocardial infarction	410
PCI	00.66, 36.01, 36.02, 36.05, 36.06, 36.07, 36.09

ACS, Acute coronary syndrome; ASp, ankylosing spondylitis; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; IBD, inflammatory bowel diseases; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PM-DM, polymyositis-dermatomyositis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

TABLE E2. Proportions and 95% confidence intervals of overall survival, freedom from myocardial infarction, and freedom from repeat revascularization at 2, 4, 6, 8, and 10 years in patients without coronary artery disease-associated inflammatory rheumatic diseases (control group) and patients with rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis in the coronary artery bypass grafting cohort of Taiwan, 2000-2010

Time (y)	2	4	6	8	10
Overall survival					
Controls	79.3% (78.9-79.8)	70.8% (70.3-71.2)	62.0% (61.5-62.6)	52.6% (52.0-53.3)	42.7% (41.9-43.6)
RA	79.6% (69.8-86.5)	63.6% (51.4-73.6)	54.0% (40.4-65.8)	48.0% (33.6-61.0)	42.0% (25.6-57.5)
SLE	70.0% (55.6-80.5)	64.2% (48.6-76.1)	56.1% (38.9-70.3)	28.5% (10.4-49.8)	19.0% (4.1-42.3)
ASp	76.7% (64.7-85.1)	72.8% (60.2-82.1)	61.1% (45.6-73.5)	57.1% (40.6-70.5)	35.7% (12.6-59.9)
Freedom from MI					
Controls	96.6% (96.4-96.7)	94.7% (94.4-94.9)	92.7% (92.4-93.0)	90.5% (90.1-90.8)	87.8% (87.2-88.3)
RA	97.6% (90.5-99.4)	96.1% (88.4-98.7)	91.6% (80.1-96.6)	91.6% (80.1-96.6)	91.6% (80.1-96.6)
SLE	95.9% (84.5-99.0)	89.8% (74.3-96.2)	89.8% (74.3-96.2)	83.4% (61.0-93.5)	83.4% (61.0-93.5)
ASp	98.5% (90.0-99.8)	96.5% (86.4-99.1)	96.5% (86.4-99.1)	92.6% (76.9-97.8)	92.6% (76.9-97.8)
Freedom from repeat revascularization					
Controls	96.1% (95.9-96.3)	93.1% (92.8-93.4)	90.3% (89.9-90.6)	87.1% (86.7-87.6)	83.6% (83.0-84.3)
RA	92.7% (84.5-96.7)	87.6% (77.2-93.5)	87.6% (77.2-93.5)	87.6% (77.2-93.5)	87.6% (77.2-93.5)
SLE	89.8% (77.1-95.7)	86.7% (72.3-93.9)	73.1% (52.4-85.9)	73.1% (52.4-85.9)	73.1% (52.4-85.9)
ASp	98.5% (89.7-99.8)	96.4% (86.3-99.1)	93.8% (81.6-98.0)	90.1% (74.3-96.4)	90.1% (74.3-96.4)

Data are expressed as proportion (95% CI). ASp, Ankylosing spondylitis; MI, myocardial infarction; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.