Original Research

Burden of Carcinoid Heart Disease in Patients With Carcinoid Syndrome Initiating Somatostatin Analogues

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ABSTRACT

Purpose: As a result of overproduction of serotonin, patients with uncontrolled carcinoid syndrome (CS) may develop carcinoid heart disease (CaHD). However, the prevalence and health care resources to manage CaHD are not well understood. This study investigated the prevalence and economic burden of CaHD among adults with CS in the United States.

Methods: This retrospective study analyzed insurance claims of patients with CS initiating somatostatin analogue (SSA) therapy. Eligible patients had ≥1 medical claim for CS with continuous insurance coverage for 1 year before and at least 30 days after initiating SSA therapy. Markers for CaHD were identified using a predetermined list of medical and/or procedural claims based on the clinical experience of a practicing cardiologist. Case subjects had a documented medical/procedural claim for a marker of CaHD during the study period; control subjects had no markers for CaHD. Baseline characteristics were assessed during the pre-SSA treatment initiation period. Economic outcomes (health care resources and expenditures) were assessed in the follow-up period after SSA treatment initiation and compared between incident case subjects and control subjects. Descriptive statistics were used to assess demographic and clinical characteristics. Univariate and multivariate models were used to assess differences in health care resource use and costs between case subjects and control subjects.

Findings: A total of 654 patients met the eligibility criteria; 248 (38%) had a prevalent marker of CaHD and were excluded from the economic analysis. The analytic sample included 406 patients with CS, 185 (46%) of whom had an incident CaHD marker (case subjects) and 221 were controls. Baseline characteristics between the case subjects and control subjects were similar with the exception that case subjects tended to be older. Average health care resource use and costs were higher among case subjects (total costs, $51,825 vs $29,068; $P < 0.01$), driven by average hospital admissions (1.4 vs 0.7) with increased length of stay (4.3 vs 2.0 days), office visits (22.8 vs 19.8), and outpatient services (22.3 vs 15.4; all, $P < 0.05$).

Implications: CaHD may be common among patients with CS before initiating SSA therapy and within 2 years of starting SSA therapy, suggesting suboptimal control of serotonin production. Patients with CaHD incur substantial economic costs in addition to the clinical morbidity compared with patients with CS and no CaHD. (*Clin Ther.* 2019;41:1716–1723) © 2019 Published by Elsevier Inc.

Keywords: 5-HIAA, carcinoid heart disease, carcinoid tumor, malignant carcinoid syndrome, neuroendocrine tumors, serotonin.

INTRODUCTION

Neuroendocrine tumors (NETs) are rare but have increased in prevalence nearly 10-fold over the past 20

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years, largely due to improvements in detection and management.[1–3] A certain proportion of patients with NETs go on to develop carcinoid syndrome (CS), which is characterized by diarrhea, flushing, and nausea and may also include dyspnea, wheezing, and/or heart valve dysfunction.[4,5] When NETs metastasize to the liver, the high concentration of peptides, hormones, and other factors pass via the inferior vena cava to the right side of the heart, where serotonin receptors are stimulated, resulting in fibroblast proliferation (scarring of the heart's endocardium). The resultant damage is termed carcinoid heart disease (CaHD), which may develop in 70% of patients with NET and CS.[6–8] The likelihood of cardiac involvement in patients with CS may be as high as 50% by the time CS has presented clinically.[9]

The prognosis for patients with CaHD is poor, with 3-year survival less than one half that of peers without CaHD (31% vs 68%) as valvular dysfunction eventually progresses to right heart failure.[8,10] Patients experience shortness of breath, fatigue, ankle edema, and notable reductions in quality of life.[9,11] Somatostatin analogues (SSAs) are used for the medical management of CS symptoms but have shown no evidence of slowing the progression of CaHD.[12,13] Patients refractory to SSA therapy often receive a different formulation of SSA or escalated dosing beyond levels approved by the US Food and Drug Administration.[1,14]

The clinical burden of CaHD has been relatively well established given its impact on morbidity and mortality; however, the economic burden of CaHD has been less well characterized. Analyses of European registries have reported that patients with CaHD incur more than double the costs of peers without CaHD, attributed largely to valve replacement surgery, SSA therapy, and echocardiography.[15,16] There are no comparable studies available in the United States in recent years, leaving a substantial unmet need for research investigating the economic burden of CaHD in the United States. The objective of the current study was to determine the prevalence of CaHD among patients with CS before initiating SSA therapy and to investigate the incidence and incremental health care resource use and costs of CaHD markers among patients with CS receiving SSA therapy.

MATERIALS AND METHODS

This retrospective study investigated administrative claims for commercially insured adults receiving SSA therapy for CS between January 1, 2010, and December 31, 2016. Claims were evaluated for markers of CaHD such as tricuspid, pulmonary, aortic, or mitral valve–related disease. For the economic analyses, eligible patients had ≥1 medical claim for CS (*International Classification of Diseases, Ninth Revision,* code 259.2 or *International Classification of Diseases, Tenth Revision,* code E34.0) and no prevalent CaHD markers; had initiated SSA treatment; had no signs of acromegaly; were continuously enrolled in their health plan for at least 1 year before and for at least 30 days after initiating SSA therapy; and did not participate in a clinical trial during the analysis period. Claims for eligible patients were followed as long as they were observed in the dataset.

Patients with CS were identified in the Optum Clinformatics Data Mart claims database from Optum Insight (Eden Prairie, Minnesota), which is derived from a database of both commercial and Medicare Advantage administrative health claims for members of a large national managed care company affiliated with Optum. The population is geographically diverse, spanning all 50 states; it includes demographic and eligibility information, as well as linked medical and pharmacy claims from ~17 to 19 million annual covered lives for a total of >57 million unique lives over a 12-year period (2007–September 2018). All data were aggregated and de-identified under the Expert Determination method consistent with the Health Insurance Portability and Accountability Act of 1996 and managed according to Optum customer use agreements to protect confidentiality. Institutional review board approval was not required (exempt).

Cases were defined as patients with CS and a marker for CaHD based on the presence of one or more *International Classification of Diseases, Ninth Revision,* or *International Classification of Diseases, Tenth Revision,* diagnostic or procedural codes for tricuspid, pulmonary, aortic, or mitral valve involvement; edema or ascites; pleural effusions; congestive heart failure; diastolic heart failure; and/or

endomyocardial fibrosis (see the Supplemental Table in the online version at https://doi.org/10.1016/j.clinthera.2019.06.013). Prevalent case subjects were identified from the total CS cohort and removed from the analytic sample. Incident case subjects were then identified as those with a new CaHD marker identified during the study period. Control subjects had no evidence of any CaHD marker throughout the study period. Number and type of CaHD markers were recorded, along with demographic and clinical characteristics, including SSA therapy use and the 5 most prevalent comorbidities. Differences between case subjects and control subjects were investigated for health care resource utilization and costs related to outpatient office visits, other outpatient services, emergency department visits, hospital admissions, and prescriptions.

Descriptive statistics were used to examine demographic and clinical characteristics, SSA therapy use, and incident CaHD markers identified during the study period. Health care resource use and costs were annualized (per patient per year) and examined using measures of central tendency. Univariate and multivariate analyses were performed to investigate differences in baseline characteristics and health care resource use and costs between case subjects and control subjects. Univariate analyses used the Student's t test for continuous variables and χ^2 tests for categorical variables. Multivariate analyses of health resource utilization (encounters and length of stay) used generalized linear models with Poisson distribution and log link, and with gamma distribution and log link for direct costs, controlling for covariates of demographic characteristics (sex, race/ethnicity,

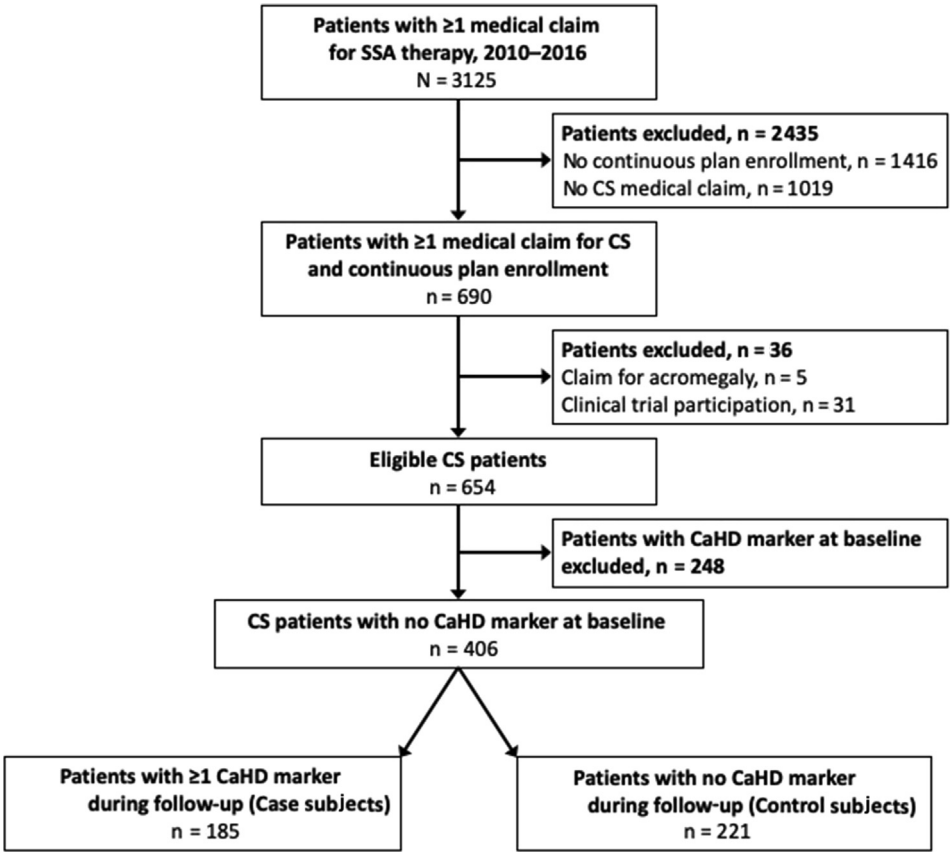

Figure 1. Patient attrition and identification of carcinoid heart disease (CaHD) case subjects and control subjects. CS = carcinoid syndrome; SSA = somatostatin analogue.

Table I. Demographic and clinical characteristics of the analytic sample.

Characteristic	Case Subjects (n = 185)	Control Subjects (n = 221)
Age, mean (SD), y	67* (11.8)	64 (12.9)
Female, no. (%)	97 (52.4)	114 (51.6)
Race/ethnicity, no. (%)		
White	126 (68.1)	159 (71.9)
Black	23 (12.4)	21 (9.5)
Asian	1 (0.5)	3 (1.4)
Hispanic	16 (8.7)	13 (5.9)
Missing or unknown	19 (10.3)	25 (11.3)
Region, no. (%)		
Northeast	17 (9.2)	20 (9.1)
South	85 (46.0)	102 (46.2)
Midwest	45 (24.3)	50 (22.6)
West	37 (20.0)	48 (21.7)
Unknown	1 (0.5)	1 (0.5)
Health insurance, n (%)		
Medicare	103 (55.7)	100 (45.3)
POS	61 (33.0)	80 (36.2)
HMO	7 (3.8)	10 (4.5)
PPO	0	2 (0.9)
Other	14 (7.6)	29 (13.1)
Charlson Comorbidity Index, mean (SD)	7.3 (3.6)	7.1 (3.5)
Top 5 comorbidities, no. (%)		
Malignant liver neoplasm	95 (51.4)	91 (41.2)
Abdominal pain, unspecified site	70 (37.8)	88 (39.8)
Hypertension	75 (40.5)	82 (37.1)
Hyperlipidemia	—	79 (35.8)
Benign carcinoid tumor, unspecified site	75 (40.5)	—
Other liver disorder, unspecified	72 (38.9)	77 (34.8)
Duration of follow-up, mean (SD), mo	35.2 (24.8)	25.5 (22.0)
SSA treatment use, no. (%)		
Received above-label SSA dose	27 (14.6)	31 (14.0)
Switched SSA therapy	18 (9.7)	12 (5.4)
Above-label or treatment change	40 (18.1)	36 (19.5)

HMO = health maintenance organization; POS = point-of-service; PPO = preferred provider organization; SSA = somatostatin analogue.
*$P = 0.004$ versus control subjects.

region, and health plan), age (continuous), and comorbidities (Charlson Comorbidity Index [CCI]). Multivariate analysis was also conducted to control for the length of follow-up time. Statistical analyses were performed by using SAS version 9.0 or higher (SAS Institute, Inc, Cary, North Carolina).

RESULTS

A total of 654 patients with CS met the initial eligibility criteria; 248 (38%) had a prevalent marker of CaHD and were excluded from the final analysis. The analytic sample included 406 patients with CS, 185 (46%) of whom had an incident CaHD marker (case subjects) and 221 (control subjects) who did not (Figure 1). Over the entire study period, this translates into 433 (66%) of 654 SSA-treated patients with CS and markers of CaHD. The average follow-up time was 35 months for case subjects and 26 months for control subjects. Demographic and clinical characteristics were similar between case subjects and control subjects with the exception of age: case subjects were older (mean age, 67 vs 64 years, respectively; $P = 0.004$) (Table I). Approximately one fifth (19%) of all patients received above-label dosing of SSA therapy (monthly dose octreotide LAR >30mg or lanreotide >120mg) or switched SSA treatment, including 20% of case subjects and 18% of control subjects. The average time to identification of a CaHD marker among case subjects was 16 months after initiation of SSA therapy. One half of all case subjects (45%) had at least 2 CaHD markers. Markers of right heart involvement were present in 20% of case

Table II. Markers of carcinoid heart disease (CaHD) among incident case subjects.

Variable	Case Subjects (n = 185)
Time to identification of first CaHD marker, mo	
Mean (SD)	15.9 (16.7)
Median (range)	10.0 (0–75.3)
No. of CaHD markers	
1	101 (54.6%)
2	53 (28.6%)
3	17 (9.2%)
4	7 (3.8%)
≥5	6 (3.2%)
Diagnostic claims	
Edema or ascites	130 (70.3%)
Pleural effusions	48 (25.9%)
Mitral valve disease, disorder, insufficiency, stenosis, incompetence, regurgitation	44 (23.8%)
Aortic valve disease, insufficiency, stenosis	28 (15.1%)
Tricuspid valve disease, stenosis, incompetence	26 (14.1%)
Congestive heart failure	24 (13.0%)
Diastolic heart failure	13 (7.0%)
Pulmonary valve disease, disorder, stenosis, incompetence, regurgitation	11 (5.9%)
Procedure claims	
Pulmonary valve replacement, repair, resection, revision	2 (1.1%)
Tricuspid valve replacement, repair, revision	2 (1.1%)

subjects and aortic or mitral valve involvement in 15% and 24% (Table II).

Health care resource use and costs were higher for case subjects than for control subjects, particularly those related to hospital admissions and outpatient visits (Table III). In univariate analyses, case subjects had significantly more hospital admissions (per patient per year), longer length of stay and higher costs, greater outpatient service use and costs, and total average costs ($51,825 vs $29,068; $P = 0.0005$). Results were consistent in the multivariate analyses controlling for age, sex, race, insurance plan, geographic region, and comorbidities in which case subjects had significantly more hospital admissions per year (+99%; $P < 0.0001$), longer length of hospital stay (+94%; $P < 0.0001$), more office visits (+17%; $P < 0.0001$), and higher total average costs (+$31,224; $P < 0.0001$). Health care costs tended to increase with the number of CaHD markers; however, the number of patients in the higher subgroups limited further analysis (Figure 2).

In the multivariate model, CCI, sex, Medicare insurance, and African–American race were significant predictors of health care costs (Table IV). Average total health care costs increased by 7% for every 1-point increase in CCI. Female subjects had 43% higher costs than male subjects, and Medicare enrollees had 34% lower costs compared with those with point-of-service plans. Results were consistent when the multivariate analysis also accounted for length of follow-up time among case subjects and control subjects; the exception was inpatient visits and costs, which were markedly higher for case subjects ($35,988 vs $25,379; $P = 0.0381$).

DISCUSSION

This retrospective study has shown a high prevalence and economic burden of CaHD among patients initiating SSA treatment for CS in the United States. More than one-third (38%) of initially identified patients with CS had an existing marker for CaHD, and one half (46%) of those with no CaHD marker at baseline developed one during the study period. In all, this outcome suggests that as many as two thirds (433 of 654 [66%]) of patients with CS receiving SSA therapy may have at least one marker for CaHD over a period of 2 to 3 years. On average, CaHD markers were identified within 16 months, and many patients went on to have more than one marker identified. These findings underscore the need for therapeutic agents that reduce the risk of developing CaHD in patients receiving SSA. Professional guidelines such as those of the North American Neuroendocrine Tumor Society and expert consensus from a multidisciplinary expert panel including oncologists and cardiologists have cited the importance of serotonin reduction in the potential to reduce or prevent CaHD and associated

Table III. Health care resource use and costs among incident carcinoid heart disease (CaHD) case subjects and control subjects.

Variable	Univariate Analysis		Multivariate Analysis:
	Case Subjects (n = 185)	Control Subjects (n = 221)	Difference Between Case Subjects Versus Control Subjects
Health care resource use, mean (SD)			
Hospital admissions	1.4* (3.0)	0.7 (1.9)	+98.5%†
Length of stay, d	4.3* (9.1)	2.0 (6.3)	+93.9%†
Outpatient office visits	22.8* (15.7)	19.8 (14.0)	+16.8%†
Other outpatient services	22.3* (20.0)	15.4 (18.4)	+41.7%†
ED visits	0.9 (1.9)	0.7 (2.3)	+3.4%
Prescriptions	38.6 (29.1)	33.2 (31.8)	+12.7%†
Health care costs, mean (SD)			
Total medical and pharmacy costs	$51,825* ($70,423)	$29,068 ($56,454)	+$31,224†
Hospital costs	$29,841* ($59,556)	$11,703 ($46,829)	+$5,916
Outpatient office visit costs	$2,005 ($3565)	$1,789 ($3442)	+$328
Other outpatient service costs	$6,881* ($11,062)	$4,524 ($7416)	+$2,704‡
ED costs	$223 ($1616)	$225 ($2672)	+$94
Prescription costs	$12,874 ($22,890)	$10,827 ($23,425)	+$3,492

ED = emergency department.
*$P < 0.05$ in univariate analyses.
†$P < 0.0001$.
‡$P = 0.001$.

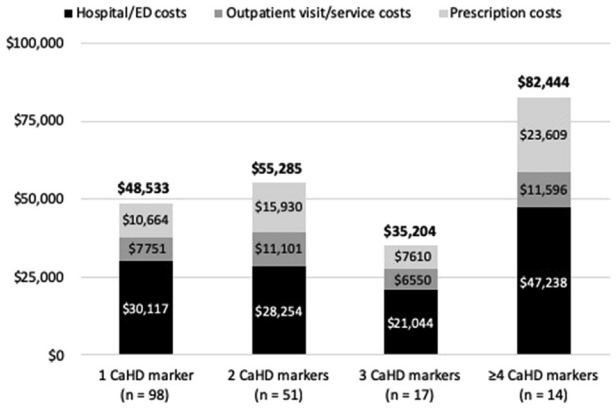

Figure 2. Mean annual health care costs per patient according to number of carcinoid heart disease (CaHD) markers. ED = emergency department.

complications.[17,18] Therefore, treatments reducing serotonin production may also contribute to reduced risk and clinical morbidity of CaHD in this population.

The majority of health care resources and associated costs were substantially higher among patients with CaHD compared with control subjects, particularly those costs related to hospital admissions and

Table IV. Significant predictors of total health care costs.

Significant Covariate	Log Estimates	Exponentiated Values
Charlson Comorbidity Index	0.0709	1.07
Female	0.3556	1.43
Medicare	−0.4167	0.66
Black	0.5596	1.75

outpatient care. The large differences in care requirements were driven largely by hospital admissions and length of stay. The total costs of care for patients with CaHD were more than double those of control subjects, a difference of more than $30,000 between average costs. As may have been expected given the lack of effective CaHD treatments, prescriptions were higher among CaHD case subjects but only incrementally more expensive ($3492 per patient). Comorbidities, sex, race, and insurance plan type were all significant predictors of total health care costs, with higher costs among female and black enrollees, and those with higher CCI, and lower costs among those with Medicare insurance compared with point-of-service plans.

There is little similar research to provide context for the findings from the current study. Björstad et al[16] reported that 6% of patients with CS (20 of 213) had a CaHD diagnosis in a small Swedish registry of gastroenteropancreatic neuroendocrine tumor patients between 2005 and 2013. Patients with CaHD received higher doses of SSA therapy and had higher health care resource use, translating to average costs of €6700 (approximately $7900 in 2018)[19] versus €2100 (approximately $2400) compared with those without CaHD. These estimates grew to €16,700 (approximately $19,600) and €7200 (approximately $8500) when SSA therapy was included. The high disparity of costs was attributed to SSA treatment, valve replacement surgery, and echocardiography. Lesén et al[17] conducted a similar analysis of Swedish registries, also reporting a 6% (20 of 312) incidence of CaHD and greater use of health care resources among patients with CaHD compared with those without, particularly for surgical interventions, examinations and imaging studies, outpatient visits, and medications.

The results of the current study should be interpreted with consideration of certain strengths and limitations. To our knowledge, this study is the first analysis of CaHD-specific health care resource use and costs among adults receiving treatment for CS in the United States. Initiation of SSA treatment as an indicator of medically managed disease over a 6-year study period was used to reliably identify patients with this rare condition. The linked medical and pharmacy administrative claims database provided information relevant to the US payer perspective of reimbursed care for patients with CS and CaHD. In turn, the nature of the claims database did not include detailed clinical information such as from medical charts, laboratory tests, or other diagnostic and prognostic measures, which inherently limited the clinical picture of included patients. The definitions of case subjects and control subjects were similarly limited to insurance claims rather than medical history and laboratory values. We calculated mean annualized per-patient health care resource use and costs; however, it is possible that variability in follow-up due to unobservable differences among case subjects and control subjects could have contributed to systematic differences in health resource use and associated costs, although we were unable to fully evaluate this consideration. The multivariate analysis controlling for length of follow-up time was consistent with the base case analysis, but it did show an even larger difference in inpatient use and costs between case subjects and control subjects than the base case comparison.

Overall, this study has reported the most recent estimates of CaHD prevalence and economic burden in the US population of adults with CS initiating SSA therapy, and reinforced the high unmet need for prevention, early detection, and clinical management.

CONCLUSIONS

CaHD is relatively common among patients with CS initiating SSA therapy and incurs substantial health care resource use and costs. Monitoring, timely diagnosis, and treatment beyond long-acting SSA therapy may reduce the burden of CaHD.

CONFLICTS OF INTEREST

This study sponsor, Lexicon Pharmaceuticals, Inc, participated in the design, conduct, analysis, and interpretation of findings.

VJN, RPO, PL, and SD were all employees of Lexicon Pharmaceuticals, Inc. when the study was conducted. JZ received research support from Lexicon Pharmaceuticals, Inc. related to this work.

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Drs. Joish, Perez-Olle, Lapuerta, and Zacks contributed to the conceptualization, methodology, supervision, writing review and editing; and Drs. Joish and Dharba contributed to data curation, formal analysis, methodology, administration, writing review and editing. All authors have contributed to the study, to development of the manuscript, and have approved the final article.

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APPENDIX

Table S1. Medical claim and procedural codes used to define marker(s) of CaHD.

Condition	ICD-9 Medical Claim Code	ICD-10 code Medical Claim Code
Tricuspid valve incompetence OR Tricuspid valve disease; Tricuspid valve stenosis	424.2	I36.0, I36.8
Pulmonary valve stenosis, disease, disorder, regurgitation, incompetence	424.3	I37.0
Aortic valve stenosis, disease, insufficiency	424.1	I35.0, I35.2
Mitral valve disease, insufficiency, incompetence, or regurgitation, stenosis, Mitral valve disorder	394.9, 397.8, 424.0	I34.0
Edema, or Ascites	782.3, 789.59	R60.1, R60.9, R18.8
Pleural Effusions	511.9	J91.8
Congestive heart failure	428.0	I50.814
Diastolic heart failure	428.3	I50.30
Endomyocardial Fibrosis	425.0	I42.3

Medical/ Surgical Procedure	ICD-9 Procedure Code	ICD-10 Procedure Code
Pulmonary valve Replacement OR Repair OR Resection OR Revision	35.03, 35.07, 35.08, 35.13, 35.25, 35.26, 35.82	Replacement: 02RH07Z, 02RH08Z, 02RH0JZ, 02RH0KZ, 02RH37H, 02RH37Z, 02RH38H, 02RH38Z, 02RH3JH, 02RH3JZ, 02RH3KH, 02RH3KZ, 02RH47Z, 02RH48Z, 02RH4JZ, 02RH4KZ Repair: 02QH0ZZ, 02QH3ZZ, 02QH4ZZ Resection: 02TH0ZZ, 02TH3ZZ, 02TH4ZZ Revision: 02WH07Z, 02WH08Z, 02WH0JZ, 02WH0KZ, 02WH37Z, 02WH38Z, 02WH3JZ, 02WH3KZ, 02WH47Z, 02WH48Z, 02WH4JZ, 02WH4KZ
Tricuspid valve Replacement OR Repair OR Revision	35.04, 35.14, 35.27, 35.28	Replacement: 02RJ07Z, 02RJ08Z, 02RJ0JZ, 02RJ0KZ, 02RJ37H, 02RJ37Z, 02RJ38H, 02RJ38Z, 02RJ3JH, 02RJ3JZ, 02RJ3KH, 02RJ3KZ, 02RJ47Z, 02RJ48Z, 02RJ4JZ, 02RJ4KZ Repair: 02QJ0ZG, 02QJ0ZZ, 02QJ3ZG, 02QJ3ZZ, 02QJ4ZG, 02QJ4ZZ Revision: 02WJ07Z, 02WJ08Z, 02WJ0JZ, 02WJ0KZ, 02WJ37Z, 02WJ38Z, 02WJ3JZ, 02WJ3KZ, 02WJ47Z, 02WJ48Z, 02WJ4JZ, 02WJ4KZ
Aortic valve Replacement OR Repair OR Revision	35.01, 35.05, 35.06, 35.11, 35.21, 35.22,	Replacement: 02RF07Z, 02RF08Z, 02RF0JZ, 02RF0KZ, 02RF37H, 02RF37Z, 02RF38H, 02RF38Z, 02RF3JH, 02RF3JZ, 02RF3KH, 02RF3KZ, 02RF47Z, 02RF48Z, 02RF4JZ, 02RF4KZ Repair: 02QF0ZJ, 02QF0ZZ, 02QF3ZJ, 02QF3ZZ, 02QF4ZJ, 02QF4ZZ Revision: 02WF07Z, 02WF08Z, 02WF0JZ, 02WF0KZ, 02WF37Z, 02WF38Z, 02WF3JZ, 02WF3KZ, 02WF47Z, 02WF48Z, 02WF4JZ, 02WF4KZ

Table S1. (*Continued*)

Medical/ Surgical Procedure	ICD-9 Procedure Code	ICD-10 Procedure Code
Mitral valve Replacement OR Repair OR Revision	35.02, 35.12, 35.23, 35.24, 35.97	Replacement: 02RG07Z, 02RG08Z, 02RG0JZ, 02RG0KZ, 02RG37H, 02RG37Z, 02RG38H, 02RG38Z, 02RG3JH, 02RG3JZ, 02RG3KH, 02RG3KZ, 02RG47Z, 02RG48Z, 02RG4JZ, 02RG4KZ Repair: 02QG0ZE, 02QG0ZZ, 02QG3ZE, 02QG3ZZ, 02QG4ZE, 02QG4ZZ Revision: 02WG07Z, 02WG08Z, 02WG0JZ, 02WG0KZ, 02WG37Z, 02WG38Z, 02WG3JZ, 02WG3KZ, 02WG47Z, 02WG48Z, 02WG4JZ, 02WG4KZ