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Abstract

Objectives: Female gender has been shown to negatively affect the outcomes of surgical bypass for peripheral arterial disease (PAD). We examined gender-related disparities in outcomes of endovascular PAD procedures in a large population-based study. **Methods:** We used discharge data from California hospitals to identify patients who had PAD interventions during 2005 to 2009. Logistic regression was used for 12-month reintervention, and Cox proportional hazard regression was used for amputation-free survival comparisons. **Results:** A total of 25 635 patients had endovascular procedures (11 389 [44.4%] women). Women were more likely than men (34.5% vs 30.1%, $P < .0001$) to have critical limb ischemia (CLI). Twelve-month reintervention rate in women was similar to men. Amputation-free survival was better among women than men (hazard ratio 0.84, 95% confidence interval [CI] 0.76-0.93, $P = .0006$). **Conclusion:** Despite presenting more frequently with CLI, women had better amputation-free survival than men following endovascular procedures. Future research should determine whether findings favor one type of PAD treatment modality over another for women.

Keywords

peripheral arterial, gender, endovascular, outcomes

Introduction

The numbers of endovascular procedures for peripheral arterial disease (PAD) have been exceeding the number of open surgical bypass procedures in the last decade.¹ According to a recent analysis of Medicare claims data, from 1996 to 2005, the number of percutaneous lower extremity arterial interventions exceeded the number of open surgical procedures with a contemporaneous 29% decrease in lower extremity amputation rates.¹ Despite the advances in treatment options, several recent reports have documented higher complication, amputation, and death rates in women compared to men following both open and endovascular lower extremity arterial revascularization procedures.^{2,3} However, there is still debate regarding whether women have worse outcomes following lower extremity arterial revascularization procedures compared to men.

Although multiple studies using administrative data have evaluated the temporal trends in PAD treatment and in-hospital outcomes in large diverse populations, few have access to or have reported longitudinal data on PAD interventions. Furthermore, considering the inherent learning curve for new technologies and

introduction of more advanced endovascular techniques and devices, few studies have focused on a more current large population database. In order to compare reintervention and amputation rates between open and endovascular PAD interventions with an emphasis on patient characteristics such as gender, age, race/ethnicity, and comorbidities, we have been using a large state-wide, all-payer database. The aim of this study was to evaluate gender-based differences in short- and mid-term outcomes of

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endovascular interventions for PAD affecting the lower limbs in a contemporary large population-based study.

Methods

We used the Patient Discharge Data (PDD) from California's Office of Statewide Health Planning and Development (OSHPD). The PDD is a population-based, all-payer database that allows longitudinal tracking within California of morbidity outcomes for all inpatient procedures performed at nonfederal hospitals. The PDD provides encrypted patient identifiers to link multiple admissions within California hospitals for each patient. The OSHPD is also linked to the death data file. We obtained approval from the state of California institutional review board to perform this study. We included all patients over the age of 35 who were admitted to a nonfederal California hospital with a primary or secondary diagnosis of atherosclerosis of lower extremities from 2005 to 2009. We used *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes 440.2, 440.21, 440.22, 440.23, and 440.24 to diagnose atherosclerosis of the lower extremities, specified by intermittent claudication, rest pain, ulceration, or ischemic gangrene to characterize the target population (Appendix A).

Subsequently, we used *ICD-9-CM* codes for open lower extremity bypass procedures (38.48-39.29) and endovascular procedures (39.50, 39.90, and 00.55) to link the cohort of patients with PAD as primary or secondary diagnosis to define our study population (Appendix A). This is necessary as the *ICD-9-CM* codes for noncoronary angioplasty and stenting are not anatomically specific. Since 2005, OSHPD has been collecting ambulatory surgery data, which identifies endovascular procedures by CPT codes (Appendix A). Compared to nondescript *ICD-9-CM* codes for noncoronary angioplasty and stenting, CPT codes for endovascular interventions such as angioplasty, atherectomy, and stenting are more anatomically specific. A look back exclusion period of 5 years prior to index admission was performed to remove any patients with previous bypass or major amputation from the cohort. This allowed us to identify as many first-time procedures in the group as possible. The OSHPD provides data on age, gender, race/ethnicity, insurance status, and chronic comorbid conditions. We categorized patients into non-Hispanic (NH) white, Hispanic, NH black, Asian/Native Hawaiian, and others. Furthermore, we used the Elixhauser comorbidity codes, which are derived from the *ICD-9-CM* codes for conditions present on admission (Appendix B).

We evaluated myocardial infarction (MI) rates within 30 days of the index procedure. One of the advantages of OSHPD is that it allows longitudinal follow-up of patients within California. We used *ICD-9-CM* codes 84.13-84.14, 84.15, 84.16, and 84.17 for major lower extremity amputation and excluded any amputations below the ankle. We captured 30-day perioperative amputation rate as well as amputation rate within 365 days. We have data on reinterventions (open or endovascular) performed within 1 year of the index procedure. Reinterventions were identified using the open and endovascular *ICD-9-CM* procedure codes linked to atherosclerosis of the lower extremity *ICD-9-*

CM codes. Because OSHPD is linked to the death data file, 30-day and 12-month death rates were obtained.

Statistical Analysis

Two-sided, Wilcoxon rank-sum test was used to compare age between men and women. We used the chi-square test to compare the distribution of PAD diagnosis between men and women. Furthermore, we used logistic regression to compare 12-month reintervention rates adjusting for age, race/ethnicity, insurance status (Medicare, Medi-Cal, County, Private, and Workers Comp/Government), comorbidities, severity of PAD, history of coronary artery angioplasty or bypass surgery, and history of carotid endarterectomy. History of coronary artery angioplasty or bypass surgery and history of carotid endarterectomy were used as potential factors for predicting poorer outcomes as they represent a more at-risk population. Cox proportional hazard regression⁴ was used for comparison of amputation-free survival between women and men controlling for age, race/ethnicity, insurance status (Medicare, Medi-Cal, County, Private, and Workers Comp/Government), comorbidities, severity of PAD, and history of coronary artery angioplasty or bypass surgery or history of carotid endarterectomy. A $P < .05$ was considered statistically significant. All statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

Results

Demographics, Patient Presentation, and Comorbidities

During 2005 to 2009, 41 507 individuals underwent open and endovascular PAD interventions in nonfederal California hospitals. A total of 25 635 (61.8%) patients had endovascular procedures: 11 389 (44.4%) were women and 14 246 (55.6%) were men (Table 1). In this study, women were older than men with a mean age of 73.2 years (range 35-105) compared to 70.1 years (range 35-102), respectively ($P < .0001$). Approximately 70.8% of the patients were older than 65 years of age. The majority of patients were NH white. In this study, 68.0% of the patients were NH white, 17.2% were Hispanic, 7.7% were black, 4.5% were Asian/Native Hawaiian, and 2.5% were coded as "others." The distribution of race/ethnicity between the sexes was statistically significant ($P < .0001$; Table 1).

Among patients undergoing endovascular procedures, claudication was the primary or secondary diagnosis of PAD in 9040 (35.3%) patients (Table 1). Critical limb ischemia (CLI) as defined by gangrene, ulceration or rest pain, was the diagnosis at admission in 8220 (32.1%) patients. The remaining 8375 patients had a diagnosis of aortic occlusive disease or miscellaneous atherosclerosis. The distribution of PAD diagnosis between the sexes was statistically significant ($P < .0001$) in which women were more likely than men (34.5% vs 30.1%) to present with CLI.

Perioperative Outcomes

In the endovascular group, 93 (0.7%) men and 85 (0.8%) women had an MI during admission or within 30 days of index

Table 1. Demographic and Baseline Comorbid Characteristics of Patients Who Underwent Endovascular Peripheral Arterial Disease Interventions in California Hospitals During 2005 to 2009.

	Women	Men	P Value
Mean age, years (median, range)	73.2 (74, 35-105)	70.1 (70, 35-102)	<.0001
Race			<.0001
Non-Hispanic white	7687 (67.5%)	9746 (68.4%)	
Black	1030 (9.0%)	949 (6.7%)	
Hispanic	1869 (16.4%)	2548 (17.9%)	
NH Asian/Native Hawaiian	561 (4.9%)	602 (4.2%)	
Other	242 (2.1%)	401 (2.8%)	
Diagnosis			<.0001
Critical limb ischemia	3927 (34.5%)	4293 (30.1%)	
Gangrene	1366 (12.0%)	1846 (13.0%)	
Ulceration	1533 (13.5%)	1602 (11.3%)	
Rest pain	1028 (9.0%)	845 (5.9%)	
Claudication	3651 (32.1%)	5389 (37.8%)	
Aortic atherosclerosis/misc	3811 (33.5%)	4564 (32.0%)	
Comorbidities			
Diabetes mellitus	3772 (33.1%)	5285 (37.1%)	<.0001
Renal failure	1437 (12.6%)	2170 (15.2%)	<.0001
Congestive heart failure	904 (7.9%)	1105 (7.8%)	.592
Hypertension	7497 (65.8%)	8810 (61.8%)	<.0001
Insurance status			<.0001
County/other indigent Programs	75 (0.7%)	143 (1.0%)	
Medicare	7792 (68.4%)	8741 (61.4%)	
Medi-Cal	652 (5.7%)	726 (5.1%)	
Private	2720 (23.9%)	4387 (30.8%)	
Workers Comp/Other Government/Other	149 (1.3%)	248 (1.7%)	

Table 2. The 30-Day Perioperative Outcomes of Patients Undergoing Endovascular Peripheral Arterial Disease Interventions in California Hospitals During 2005 to 2009.

	Women	Men	P Value
Myocardial infarction within 30 days	85 (0.8%)	93 (0.7%)	.648
Major amputation within 30 days	285 (2.5%)	430 (3.0%)	.004
All-cause mortality within 30 days	221 (1.9%)	206 (1.5%)	.024

procedure (women vs men odds ratio [OR] 1.14, 95% confidence interval [CI] 0.85-1.54, $P = .371$ without adjusting for any confounders). This remained statistically nonsignificant after adjusting for age, race/ethnicity, insurance status, comorbidities, severity of PAD, history of coronary artery angioplasty or bypass surgery, and history of carotid endarterectomy (women vs men OR 1.07, 95% CI 0.79-1.46, $P = .648$; Table 2). We found that 430 (3.0%) men and 285 (2.5%) women underwent major amputation within 30 days of admission (women vs men OR 0.83, 95% CI 0.71-0.96, $P = .013$ without adjusting for any confounders). After adjusting for confounders including age, race/ethnicity, insurance status, comorbidities, PAD severity, history of coronary artery angioplasty or bypass surgery, and history of carotid endarterectomy, the differences in major amputation within 30 days of admission was statistically significant (women vs men OR 0.78, 95% CI 0.65-0.92, $P = .004$).

Finally, 221 (1.9%) women and 206 (1.5%) men died during the 30-day perioperative period following the endovascular

procedure. The OR for death during the 30-day perioperative period was 1.35 in women (95% CI 1.11-1.63, $P = .002$ without adjusting for any confounders) compared to men. After adjusting for confounders including age, race/ethnicity, insurance status, comorbidities, PAD severity, history of coronary artery angioplasty or bypass surgery, and history of carotid endarterectomy, the OR for death during the 30-day perioperative period was 1.27 in women compared to men (95% CI 1.03-1.56, $P = .024$).

Mid-Term Outcomes: Reintervention

Overall, 8593 (33.5%) patients (3733 women and 4860 men) in the endovascular group underwent reintervention during the study period. This represented 32.8% of all women and 34.1% of all men who had an endovascular procedure. The majority of reinterventions, 6042 (70.3%), were endovascular, and 2551 (29.7%) reinterventions were open. The timing of reinterventions is presented in Table 3. There was no statistically significant difference between 12-month reintervention rate in women compared to men following endovascular procedures (women vs men; OR 0.96, 95% CI 0.91-1.01, $P = .149$) after adjusting for age, race/ethnicity, insurance status, comorbidities, PAD severity, and history of coronary artery angioplasty or bypass surgery, and history of carotid endarterectomy.

Among the 22 comorbidities we evaluated, diabetes mellitus and diabetes mellitus with complication were consistently

Table 3. Mid-Term Outcomes of Patients Who Underwent Endovascular Peripheral Arterial Disease Interventions in California Hospitals During 2005 to 2009 at 1 Year.

	Women	Men	P Value
Total number of patients requiring a reintervention within 365 days	3733 (32.8%)	4860 (34.1%)	.149
Open or combined open and endovascular reintervention	1044 (28.0%)	1507 (31.0%)	
Endovascular reintervention	2689 (72.0%)	3353 (69.0%)	
Major amputation within 365 days	689 (6.1%)	1028 (7.2%)	.0008
All-cause mortality within 365 days	1221 (10.7%)	1507 (10.6%)	.188
First reintervention admission day category			<.0001
0 to 60 days post anchor admission	1357 (36.4%)	2043 (42.0%)	
61 to 365 days post anchor admission	1721 (46.1%)	1992(41.0%)	
365+ days post anchor admission	655 (17.6%)	825 (17.0%)	
First reintervention admission day category			<.0001
0 to 60 days post anchor admission	1357 (36.4%)	2043 (42.0%)	
61 to 365 or 365+ days post anchor admission	2376 (63.7%)	2817 (58.0%)	

statistically significant for the likelihood of reintervention (diabetes mellitus: OR 1.20, 95% CI 1.13-1.28, $P < .0001$; diabetes mellitus with complication: OR 1.19, 95% CI 1.07-1.33, $P = .002$). Prior history of coronary artery angioplasty or bypass grafting or history of carotid endarterectomy also correlated with 12-month reintervention (OR 1.11, 95% CI 1.04-1.19, $P = .002$). Conversely, presence of congestive heart failure, paraplegia, electrolyte imbalance, weight loss, and neurological disorder correlated with the likelihood that the patient would not undergo reintervention.

Mid-Term Outcomes: Amputation and Mortality

Within 1 year of the endovascular procedures, 689 (6.05%) women and 1028 (7.22%) men underwent major amputation (Table 3). After adjusting for confounders including age, race/ethnicity, insurance status, comorbidities, PAD severity, history of coronary artery angioplasty or bypass surgery, and history of carotid endarterectomy, the difference in the distribution of major amputation within 365 days of admission for endovascular procedures between men and woman was statistically significant (women vs men; OR 0.82, 95% CI 0.73-0.92, $P = .0008$). Amputation-free survival was better among women than men (hazard ratio 0.84, 95% CI 0.76-0.93, $P = .0006$) following endovascular procedures (Figure 1, Kaplan-Meier estimate). We further evaluated amputation-free survival in patients with claudication and CLI. Among the patients with CLI, women continued to have better amputation-

free survival than men (Figure 2). There was no difference between the genders in the claudication group (Figure 3).

Discussion

Although the prevalence of PAD among men and women becomes nearly equivalent after the age of 65,^{5,6} women have been shown to be more likely than men to undergo amputation and less likely to undergo lower extremity arterial revascularization procedures for symptomatic PAD.^{7,2} Open bypass procedures declined by 36% among women and 30% among men in Florida, New Jersey, and New York during 1998 to 2007.² This trend of increasing decreasing open bypass procedures and increasing endovascular procedures is well known. However, in comparison to the number of studies evaluating gender-based differences in the outcomes of open surgical procedures for symptomatic PAD,⁸⁻¹² few studies have evaluated mid-term outcomes in endovascular PAD interventions.

We undertook this study to evaluate differences in short- and mid-term outcomes of endovascular therapy between men and women. This study is unique, as it represents a contemporary series of a diverse patient population with data from both inpatient and outpatient endovascular lower extremity arterial revascularization procedures. Endovascular procedures are increasingly favored by physicians and patients due to their less invasive nature and reduced lengths of stay. Furthermore, most institutions have adopted an endovascular first approach to treating PAD, with bypass surgery being reserved for failed endovascular therapy or no-option endovascular cases. The rise in the number of endovascular procedures is also attributed to its need for multiple endovascular procedures in patients to maintain patency. Finally, patients who may have been deemed too ill in the past to undergo lower extremity arterial bypass operations and were offered an amputation instead may now be offered endovascular intervention for limb salvage. This is best demonstrated by the decreased amputation rates among patients aged 85 years and older.¹³

As previously demonstrated,^{14,2} we found that women with symptomatic PAD are older and more frequently present with CLI, compared to men. Women are more likely to have asymptomatic disease and hence a delay in diagnosis, and later intervention may be why women present more often with CLI compared to men.¹⁵ It is unclear whether knowledge deficit or lack of screening for PAD in women contributes to their presentation with more advanced arterial occlusive disease.^{16,17} Although PAD is a known manifestation of systemic atherosclerosis and is associated with cardiovascular morbidity and mortality,¹⁸ it continues to be underdiagnosed in primary care clinics. Hirsch et al evaluated 6979 patients aged 70 years and older or aged 50 to 69 who had a history of smoking or diabetes mellitus.¹⁹ Although 83% of patients with PAD were aware of their PAD diagnosis, only 49% of the primary care physicians were aware of the diagnosis in this cohort.

Our study focused on outcomes of treatments between matched cohorts who underwent lower extremity arterial revascularization procedures for symptomatic PAD. In comparison,

Figure 1. Kaplan-Meier estimation of amputation-free survival function within 365 days following endovascular procedures.

Figure 2. Kaplan-Meier estimation of amputation-free survival function within 365 days following endovascular procedures for patients with critical limb ischemia.

many population-based studies have reported on the inequality in the number of procedures offered patients admitted for PAD-related diagnoses. Although nearly a third of our patient cohort underwent reintervention following endovascular procedures,

we found that women did not have more reinterventions than men. Short term, women had less reinterventions than men, but long-term, there were no differences in reintervention rates between the sexes.

Figure 3. Kaplan-Meier estimation of amputation-free survival function within 365 days following endovascular procedures for patients with claudication.

Single-center studies of gender differences in outcomes of endovascular lower extremity interventions have had conflicting findings.^{16,20-23} Several studies have shown equivalent outcomes of endovascular interventions between women and men, despite greater severity of PAD in women.^{16,20,24} A single-center evaluation of 351 angioplasties of lower extremity arteries (178 men and 173 women) over 10 years demonstrated an overall patency of 50%, 37%, and 26% at 1, 3, and 5 years, respectively.²⁰ Although univariate analysis suggested that sex, smoking, quality of distal run-off, and location of angioplasty were significant predictors of long-term patency, multivariate analysis revealed that gender was not a predictor of long-term durability of intervention. In contrast, Timaran et al reported that women who underwent external iliac artery stenting had reduced primary patency rates compared to men and were more likely to require subsequent aorto-iliac artery reconstruction.^{22,23} Furthermore, among patients undergoing iliac artery angioplasty and stenting for limb-threatening ischemia, women had significantly lower patency rates than men.

Although large population-based databases have evaluated the influence of gender on PAD outcomes, few have longitudinal follow-up. In our study, women had better amputation-free survival than men with endovascular PAD procedures. This is in contrast to many studies that have shown worse outcomes in women compared to men following all PAD interventions. Among 691 833 patients with PAD identified in the National Inpatient Sample (NIS) during 1998 to 2002, women were more likely than men to undergo an amputation.⁷ Furthermore, in an analysis of 2.4 million lower extremity inpatient PAD-related hospitalizations in New York, New Jersey, and Florida

from 1998 through 2007, women were less likely than men to undergo a lower extremity revascularization procedure.² The most pronounced difference in mortality rate was following open surgical procedures, with a mortality rate of 6.02% in women and 4.51% in men. In the endovascular group, Vouyouka et al found that mortality in women was 1.97% compared to 1.46% in men ($P = .0002$). This is similar to our findings of 1.9% mortality in women and 1.5% mortality in men in the 30-day perioperative period. One possible explanation for this finding has been that women presenting with symptomatic PAD are older than the men in the cohort.

There are inherent limitations in using administrative data. These include coding errors, incomplete, or missing data and lack of information on laboratory values, medication use, imaging studies, and restenosis rates. Certain comorbidities such as history of smoking are not coded consistently and can be largely inaccurate in administrative data. The OSHPD does not include data on Veterans Administration hospitals, which can represent up to 10% of all men who undergo PAD interventions.²⁵

In conclusion, we found that short-term women were less likely to undergo major amputation and were not more likely to have an MI compared to men. However, women were more likely than men to die in the 30-day perioperative period. Another important finding was that long-term, the reintervention rates for women were not different compared to men. Perhaps this reflects a lack of selection bias for reintervention based on gender. Women were found to be less likely than men to undergo major amputation in the year following endovascular intervention. Our research found that women have better mid-term outcomes than men following endovascular interventions

with better amputation-free survival. This may be secondary to lower amputation rates, lower event rates, and/or differences in life expectancy based on gender.

We need to better understand associations between gender and other risk factors, patient specific or hospital specific, which may affect outcomes of PAD interventions. Particularly, our goal should be to reduce the short-term mortality rate of PAD interventions in women. Further research may help us in predicting the most effective PAD treatment, whether open or endovascular, based on patient demographics and comorbidities.

Appendix A

Table A1. ICD-9-CM Codes for Primary/Secondary Diagnosis of Atherosclerosis of the Lower Extremities

440.20	Atherosclerosis of native arteries of the extremities, not specified
440.21	Atherosclerosis of native arteries of the extremities with intermittent claudication
440.22	Atherosclerosis of native arteries of the extremities with rest pain
440.23	Atherosclerosis of native arteries of the extremities with ulceration
440.24	Atherosclerosis of native arteries of the extremities with gangrene
440.29	Other atherosclerosis of native arteries of the extremities

Abbreviation: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Table A2. ICD-9-CM Codes for Endovascular Procedures

39.50	Percutaneous transluminal angioplasty (PTA) of noncoronary vessels
39.90	Insertion of non-drug-eluting peripheral (noncoronary) vessel stent(s)
00.55	Insertion of drug-eluting peripheral stent (s) of other peripheral vessels(s)

Abbreviation: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Table A3. ICD-9-CM Codes for Open Procedures

39.29	Other (peripheral) vascular shunt or bypass
38.08	Incision of vessel, embolectomy, thrombectomy
38.18	Endarterectomy
38.38	Resection of vessel with anastomosis
38.48	Resection of vessel with replacement

Abbreviation: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Table A4. A4. CPT Codes for Outpatient Percutaneous Procedures

35492	Transluminal peripheral atherectomy, percutaneous; iliac
35493	Transluminal peripheral atherectomy, percutaneous; femoral-popliteal
35495	Transluminal peripheral atherectomy, percutaneous; tibioperoneal trunk and branches
35473	Transluminal balloon angioplasty, percutaneous; iliac
35474	Transluminal balloon angioplasty, percutaneous; femoral-popliteal
35470	Transluminal balloon angioplasty, percutaneous; tibioperoneal trunk and branches
37205	Transcatheter placement, intravascular stent, percutaneous; initial vessel
37206	Transcatheter placement, intravascular stent, percutaneous; additional vessel
37220	Revascularization, endovascular, open or percutaneous, iliac artery, unilateral, initial vessel; with transluminal angioplasty
37221	with transluminal stent placement
37222	each additional ipsilateral iliac vessel; with transluminal angioplasty
37223	with transluminal stent placement(s)
37224	Revascularization, endovascular, open or percutaneous, femoral/popliteal artery(s), unilateral; with transluminal angioplasty
37225	with atherectomy
37226	with transluminal stent placement
37227	with transluminal stent placement and atherectomy
37228	Revascularization, endovascular, open or percutaneous, tibial/peroneal artery, unilateral, initial vessel; with transluminal angioplasty
37229	with atherectomy
37230	with transluminal stent placement
37231	with transluminal stent placement and atherectomy
37232	Revascularization, endovascular, open or percutaneous, tibial/peroneal artery, unilateral, each additional vessel; with transluminal angioplasty
37233	with atherectomy
37234	with transluminal stent placement
37235	with transluminal stent placement and atherectomy

Abbreviation: CPT, Current Procedural Terminology

Table A5. ICD-9-CM Codes for Major Amputations

84.10	Lower limb amputation, not otherwise specified
84.15	Amputation below knee
84.16	Disarticulation of knee
84.17	Amputation above knee
84.18	Disarticulation of hip
84.19	Abdominopelvic amputation

Abbreviation: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Appendix B

Table B1. Elixhauser Comorbidities.^a

Congestive Heart Failure	Valvular Disease
Pulmonary circulation disorders	Paralysis
Other neurological disorders	Chronic pulmonary disease
Diabetes, uncomplicated	Diabetes, complicated
Hypothyroidism	Renal failure
Liver disease	Rheumatoid arthritis/collagen vascular diseases
Coagulopathy	Obesity
Weight loss	Fluid and electrolyte
Blood loss anemia	Deficiency anemia
Alcohol abuse	Psychoses
Depression	Hypertension, complicated

^aDue to low frequency, peptic ulcer disease, AIDS/HIV, lymphoma, metastatic cancer, and solid tumor without metastasis were not included in our analyses.

Declaration of Conflicting Interests

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