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Contemporary Revascularization Strategies and Outcomes Among Patients With Diabetes With Critical Limb Ischemia

Insights From the National Inpatient Sample

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ABSTRACT

OBJECTIVES The purpose of this study was to evaluate temporal trends in the frequency of revascularization and associated outcomes in patients with diabetes mellitus and critical limb ischemia (CLI).

BACKGROUND Little is known about outcomes following revascularization for CLI in patients with diabetes mellitus.

METHODS Temporal trends in hospitalization for CLI among patients with diabetes were determined using the 2002–2015 National Inpatient Sample database. Propensity score matching was used to compare patients who underwent revascularization with those who did not and, separately, to compare those who underwent endovascular versus surgical revascularization. The main study outcome was in-hospital mortality.

RESULTS The analysis included 1,222,324 hospitalizations. The number of hospitalizations for CLI among patients with diabetes increased over time ($p_{trend} < 0.001$). There was an increase in the use of lower extremity revascularization, paralleled by a decline in in-hospital mortality during the study period. In the matched cohort, patients who were revascularized had lower in-hospital mortality (odds ratio [OR]: 0.68; 95% confidence interval [CI]: 0.63 to 0.72) and major amputation (OR: 0.25; 95% CI: 0.24 to 0.27) compared with those who were treated medically. Compared with endovascular revascularization, those who underwent surgical revascularization had higher rates of in-hospital mortality (OR: 1.18; 95% CI: 1.04 to 1.35) but lower rates of major amputation (OR: 0.75; 95% CI: 0.70 to 0.81). Major bleeding, blood transfusion, post-operative infection, respiratory complications, discharges to nursing facility, and longer length of hospital stay were also more common among those who underwent surgery.

CONCLUSIONS In this national analysis of patients with DM and CLI, we demonstrated an increase in hospitalization for CLI among patients with diabetes in the United States. Although in-hospital mortality decreased over time regardless of the treatment strategy used, this outcome occurred less frequently among those who underwent revascularization than not. Compared with surgical revascularization, endovascular revascularization was associated with lower in-hospital mortality but higher rates of major amputation. (J Am Coll Cardiol Intv 2021;14:664–74) © 2021 by the American College of Cardiology Foundation.

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Critical limb ischemia (CLI) is the most severe manifestation of peripheral artery disease (PAD), with presentations ranging from rest pain to gangrene (1). The mortality rates associated with CLI exceed 20% at 6 months and are higher among those who do not undergo revascularization (2,3). Diabetes mellitus (DM) is a major risk factor for PAD, and patients with DM tend to have more extensive and progressive arterial disease (4,5). Importantly, DM is the strongest risk factor for infragenicular atherosclerotic arterial disease, which is closely linked with the development of CLI and consequent need for major amputations (4,5). The American College of Cardiology/American Heart Association guidelines provide a Class 1 recommendation for endovascular or surgical revascularization, when possible, to minimize tissue loss in patients with CLI (6). However, there is clinical equipoise around the optimal revascularization approach for patients with CLI, including those with DM. The BEST-CLI (Best Endovascular Versus Best Surgical Therapy in Patients With CLI) trial is an ongoing large multicenter, open-label, randomized trial comparing endovascular versus surgical therapy in patients with CLI that should shed light on the relative safety and effectiveness of both revascularization modalities including patients with DM (7). At present, there is a paucity of real-world data on the frequency with which revascularization is used, the preferred modalities, and the associated outcomes in this cohort. To better address these knowledge gaps, we evaluated hospitalized patients with DM and CLI using a large national administrative claims database.

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METHODS

DATA SOURCE. The National Inpatient Sample (NIS) database is the largest inpatient database in the United States, part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality. The NIS is derived from billing data submitted by hospitals to statewide data organizations. It contains information on demographic and clinical characteristics as well as resource use obtained from discharge abstracts. Unweighted data from the NIS contain more than 7 million hospital stays each year, representing an approximate 20% sample of annual hospital discharges in the United States. Using validated sample weights, weighted data from the NIS contain more than 35 million annual discharges, which represents a national estimate of total annual hospital discharges in the United States (8). The NIS includes all patients, including those covered by Medicare, Medicaid, and private insurance and the uninsured. For Medicare, the NIS includes Medicare Advantage patients, a population that is often missing from Medicare claims data but constitutes as many as 30% of Medicare beneficiaries (8). The NIS reports data using the International Classification of Diseases; the International Classification of Diseases-9th Edition (ICD-9) was used until September 2015, after which the International Classification of Diseases-10th Edition was instituted. Data from the NIS have been used to describe health care utilization, access, charges, quality, and outcomes (9,10). This study was deemed exempt by the Institutional Review Board at the University of Texas Medical Branch, as data are deidentified and publicly available.

STUDY POPULATION. The study flow is outlined in Figure 1. The NIS database for 2002 to 2015 was queried to identify hospitalizations with primary ICD-9 diagnostic codes for CLI (11). Hospitalizations with secondary diagnostic codes for DM were then identified. ICD-9 codes used to define clinical characteristics appear in Supplemental Table 1. Data for 2015 were analyzed by quarter, and discontinuity in the frequency of available study variables was identified across ICD-9 and International Classification of Diseases-Tenth Edition coding systems. Therefore, only ICD-9 codes were used, and data beyond September 2015 were not included. Per HCUP regulations, trend analysis for covariate and outcome prevalence was conducted by dividing that observed in the first 3 quarters of 2015 by 0.75 to estimate overall annual prevalence (12).

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
CLI = critical limb ischemia
DM = diabetes mellitus
ESRD = end-stage renal disease
HCUP = Healthcare Cost and Utilization Project
HD = hemodialysis
ICD-9 = International Classification of Diseases-9th Revision
IQR = interquartile range
MI = myocardial infarction
NIS = National Inpatient Sample
OR = odds ratio
PAD = peripheral artery disease

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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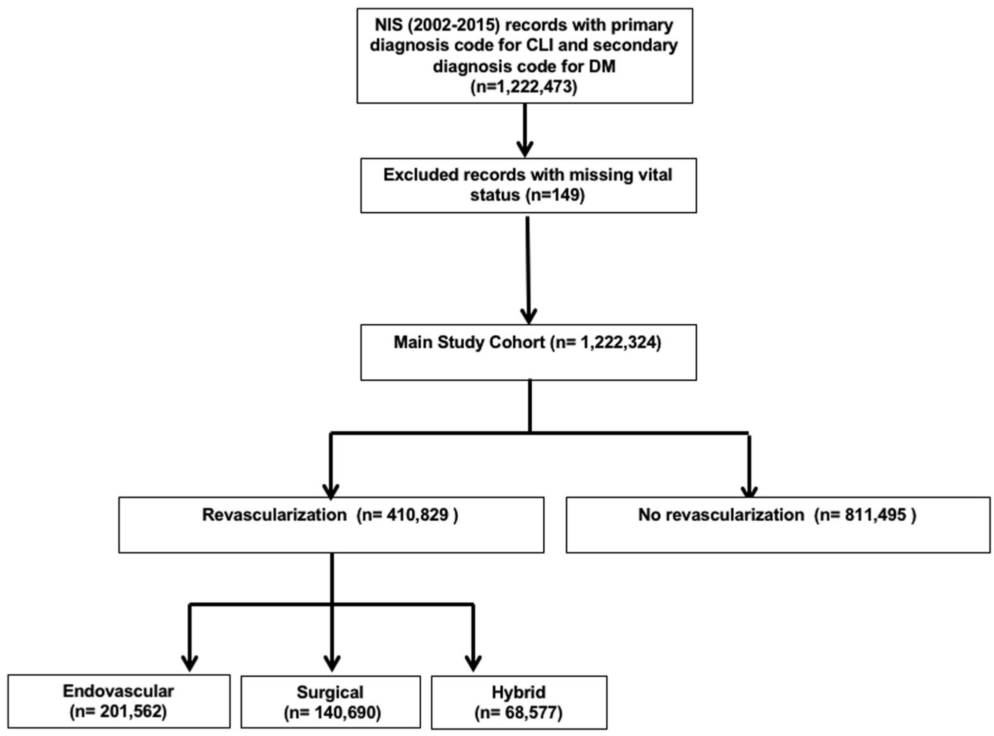
FIGURE 1 **Study Flow Diagram**



Flow diagram on how the study cohort was identified. CLI = critical limb ischemia; DM = diabetes mellitus; NIS = National Inpatient Sample.

LOWER EXTREMITY REVASCULARIZATION. Endovascular (balloon angioplasty, atherectomy, or stent placement), surgical, and combined endovascular and surgical (i.e., hybrid) revascularization approaches were defined using ICD-9 procedure codes, listed in Supplemental Table 1 (13).

OUTCOMES. In-hospital outcomes were evaluated for patients who underwent revascularization versus those who did not and, in a secondary analysis, for those who underwent endovascular versus surgical revascularization. The primary outcome of interest was in-hospital mortality. Secondary outcomes included major amputation, minor amputation, postoperative infection, major bleeding, respiratory complications, acute stroke, acute kidney injury, length of hospital stay, and total hospital costs. We estimated hospital costs by adjusting for inflation using the U.S. Bureau of Labor Statistics Consumer Price Index to the current year as the index base. Temporal trends for these outcomes were also examined. Inpatient outcomes were abstracted and reported using ICD-9 and Clinical Classifications Software codes as reported by HCUP (Supplemental Table 1).

STATISTICAL ANALYSIS. Categorical variables are expressed as frequencies and percentages and were compared using the chi-square test. Continuous variables are expressed as mean ± SD or median (interquartile range [IQR]) depending on their distribution and were compared using Student's *t*-test or the Mann-Whitney *U* test as appropriate. Propensity score methodology was used to match hospitalizations 1:1 for patients who underwent revascularization versus those who did not, as well as to match endovascular versus surgical revascularization. Nearest neighbor matching was used, using a caliper width of 0.2 (MatchIt R package) (14). The propensity score was calculated from 26 patient- and hospital-related variables, including those from the PREVENT III risk score for predicting amputation-free survival (age ≥75 years, chronic anemia, coronary artery disease, end-stage renal disease [ESRD] on hemodialysis [HD], and tissue loss) (15) (Supplemental Table 2). Linear regression analysis was used to evaluate temporal trends in hospitalizations for CLI and DM.

All analyses were conducted using the complex sample feature of SPSS and appropriate weighting samples to account for hospital clustering, weights, and stratification in accordance with HCUP regulations. SPSS version 24.0 (IBM, Armonk, New York) and R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analyses. Associations were considered significant if the p value was ≤0.05.

RESULTS

There were 1,222,473 hospitalizations between 2002 and 2015 with a primary diagnosis of CLI and a secondary diagnosis of DM. After excluding those with missing vital status (n = 149), the final cohort included 1,222,324 hospitalizations. Of those, revascularization was performed in 410,829 (28%) (**Figure 1**).

PATIENTS. Baseline patient characteristics by revascularization status are shown in **Table 1**. Before matching, those who did not undergo revascularization were more likely to have coagulopathy, obesity, chronic kidney disease, ESRD on HD, chronic liver disease, anemia, heart failure, valvular heart disease, pulmonary circulation disorders, and tissue loss. Those undergoing revascularization were more likely to have hypertension, coronary artery disease, prior myocardial infarction (MI), prior coronary artery bypass grafting, and prior stroke. Patients were less likely to undergo revascularization at smaller and rural hospitals. After matching, standardized differences were <10% for all characteristics, suggesting that covariates were well balanced across comparison groups (Supplemental Figure 1).

Baseline patient characteristics by revascularization modality are shown in **Table 2**. Before matching, those undergoing surgical revascularization were less likely to be women and less likely to have coagulopathy, obesity, hypertension, chronic kidney disease, ESRD on HD, chronic liver disease, anemia, heart failure, prior stroke, pulmonary circulation disorders, and tissue loss. Those undergoing surgical revascularization were more likely to have chronic lung disease, prior MI, and prior coronary artery bypass grafting. Surgical treatment was offered more often in larger hospitals and in the Northeast. Endovascular treatment was also more common in the South. After matching, standardized differences were <10% for all matching characteristics, suggesting that covariates were well balanced across comparison groups (Supplemental Figure 2).

OUTCOMES. Revascularization versus none. In-hospital outcomes according to whether patients underwent revascularization versus no revascularization in the unmatched cohort appear in Supplemental Table 3. After propensity matching, patients who underwent revascularization had lower rates of in-hospital mortality (1.9% vs. 2.8%; odds ratio [OR]: 0.68; 95% confidence interval [CI]: 0.63 to 0.72; p < 0.001), major amputation (6.7% vs. 20.8%; OR: 0.25; 95% CI: 0.24 to 0.27; p < 0.001), acute stroke (0.7% vs. 0.8%; OR: 0.87; 95% CI: 0.78 to 0.98; p = 0.02), infection (2.1% vs. 2.3%; OR: 0.90; 95% CI: 0.84 to 0.96; p = 0.01), and discharge to a nursing facility (34.0% vs. 37.9%; OR: 0.85; 95% CI: 0.83 to 0.87; p < 0.001) but higher rates of acute MI (3.6% vs. 3.0%; OR: 1.18; 95% CI: 1.12 to 1.25; p < 0.001), major bleeding (13.8% vs. 7.3%; OR: 2.03; 95% CI: 1.96 to 2.10; p < 0.001), blood transfusion (20.9% vs. 14.7%; OR: 1.53; 95% CI: 1.48 to 1.58; p < 0.001), minor amputation (19.3% vs. 13.7%; OR: 1.47; 95% CI: 1.43 to 1.52; p < 0.001), and respiratory complications (0.5% vs. 0.3%; OR: 1.87; 95% CI: 1.58 to 2.21; p < 0.001) compared with those who were not revascularized. The incidence of acute kidney injury was not different between the revascularization and no-revascularization groups (12.2% vs. 12.5%; OR: 0.97; 95% CI: 0.94 to 1.00; p = 0.06) (**Figure 2**). Those undergoing revascularization had longer lengths of hospital stay (median 7 days (IQR: 2 to 12 days] vs. 6 days [IQR: 3 to 10 days]; p < 0.001) and higher hospital costs (median $18,130 [IQR: $11,257 to $29,162] vs. $7,964 [IQR: $4,541 to $14,352]; p < 0.001) compared with those who did not undergo revascularization. Among those who did not undergo revascularization, in-hospital mortality was similar among those who underwent amputation (major or minor) versus no amputation (2.7% vs. 2.9%; OR: 0.93; 95% CI: 0.85 to 1.02; p = 0.18) (Supplemental Tables 4 and 5).

Surgical versus endovascular revascularization. In-hospital outcomes according to whether patients underwent endovascular versus surgical revascularization in the unmatched cohort appear in Supplemental Table 6. After propensity matching, those undergoing surgical revascularization had higher rates of in-hospital mortality (1.9% vs. 1.6%; OR: 1.18; 95% CI: 1.04 to 1.35; p = 0.01), minor amputation (20.2% vs. 19.2%; OR: 1.07; 95% CI: 1.02 to 1.12; p = 0.01), major bleeding (15.3% vs. 10.0%; OR: 1.63; 95% CI: 1.54 to 1.72; p < 0.001), blood transfusion (26.9% vs. 12.9%; OR: 2.50; 95% CI: 2.33 to 2.68; p < 0.001), infection (2.9% vs. 1.2%; OR: 2.40; 95% CI: 2.11 to 2.74; p < 0.001), respiratory complications (0.8% vs. 0.2%; OR: 4.06; 95% CI: 3.02 to 5.46; p < 0.001), and discharge to a nursing facility (37.6% vs. 28.7%; OR: 1.50; 95% CI: 1.42 to 1.57; p < 0.001) but lower rates of major amputation (5.4% vs. 7.0%; OR: 0.75; 95% CI: 0.70 to 0.81;

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TABLE 1 Baseline Characteristics Before and After Propensity Matching on the Likelihood of Revascularization

	Unmatched Cohort			Matched Cohort		
	Any Revascularization (n = 410,829)	No Revascularization (n = 811,495)	p Value	Any Revascularization (n = 408,539)	No Revascularization (n = 406,314)	p Value
Age, yrs	68.5 ± 11.4	68.2 ±12.7	<0.001	68.48 ± 11.435	67.81 ± 12.694	<0.001
Female	172,143 (41.90)	332,713 (41.00)	<0.001	171,164 (41.90)	169,045 (41.60)	0.24
Race						
White	221,082 (62.79)	424,690 (61.20)	<0.001	220,361 (62.80)	216,480 (61.50)	0.07
Black	68,356 (19.41)	140,775 (20.28)		68,194 (19.40)	71,421 (20.30)	
Hispanic	43,822 (12.45)	93,744 (13.51)		43,718 (12.50)	46,831 (13.30)	
Other races	18,825 (5.35)	34,781 (5.01)		18,782 (5.40)	17,027 (4.80)	
Coagulopathy	12,453 (3.00)	28,172 (3.50)	<0.001	12,430 (3.00)	12,668 (3.10)	0.38
Obesity	42876 (10.40)	116,496 (14.40)	<0.001	42,781 (10.50)	43,245 (10.60)	0.29
Hypertension	324,786 (79.10)	595,278 (73.40)	<0.001	322,911 (79.00)	319,174 (78.60)	0.03
Hypothyroidism	37,862 (9.20)	82,946 (10.20)	<0.001	37,750 (9.20)	38,170 (9.40)	0.30
Chronic kidney disease	150,242 (36.60)	322,406 (39.70)	<0.001	149,694 (36.60)	153,428 (37.80)	<0.001
ESRD on HD	41,264 (10.10)	86,315 (10.70)	<0.001	41,259 (10.10)	42,683 (10.50)	0.02
Chronic liver disease	6,058 (1.50)	19,092 (2.40)	<0.001	6,029 (1.50)	6,231 (1.50)	0.324
Chronic lung disease	82,751 (20.10)	163,698 (20.20)	0.870	82,244 (20.10)	79,787 (19.60)	0.016
Anemia	118,067 (28.70)	263,116 (32.40)	<0.001	117,635 (28.80)	120,297 (29.60)	0.001
Heart failure	48,561 (11.80)	216,089 (26.60)	<0.001	48,325 (11.80)	51,104 (12.60)	<0.001
Valvular heart disease	12,991 (3.20)	48,349 (6.00)	<0.001	12,950 (3.20)	20,621 (5.10)	<0.001
Coronary artery disease	215,860 (52.50)	367,780 (45.30)	<0.001	214,500 (52.50)	208,941 (51.40)	<0.001
Prior ICD	10,170 (2.50)	16,294 (2.00)	<0.001	10,094 (2.50)	8,944 (2.20)	0.001
Prior cardiac pacemaker	14,586 (3.60)	29,863 (3.70)	0.870	14,549 (3.60)	14,258 (3.50)	0.57
Prior MI	50,979 (12.40)	72,680 (9.00)	<0.001	50,480 (12.40)	46,732 (11.50)	<0.001
Prior PCI	35,334 (8.60)	48,009 (5.90)	<0.001	35,028 (8.60)	31,857 (7.80)	<0.001
Prior CABG	72,565 (17.70)	108,256 (13.30)	<0.001	72,133 (17.70)	62,982 (15.50)	<0.001
Prior stroke	24,887 (6.10)	38,948 (4.80)	<0.001	24,738 (6.10)	21,326 (5.20)	<0.001
Smoking	68,034 (16.60)	80,535 (9.90)	<0.001	67,074 (16.40)	59,502 (14.60)	<0.001
Pulmonary circulation disease	5,204 (1.30)	24,176 (3.00)	<0.001	5,181 (1.30)	5,642 (1.40)	0.03
Tissue loss	326,031 (79.70)	654,278 (81.00)	<0.001	325,686 (79.70)	329,174 (81.00)	<0.001
Hospital bed size						
Small	40,289 (9.80)	99,152 (12.20)	<0.001	40,201 (9.80)	39,562 (9.70)	0.94
Medium	99,319 (24.20)	209,475 (25.90)		99,066 (24.20)	98,485 (24.20)	
Large	270,062 (65.90)	500,862 (61.90)		269,272 (65.90)	268,267 (66.00)	
Hospital region						
Northeast	85,770 (20.90)	159,030 (19.60)	<0.001	169,500 (20.90)	83,993 (20.70)	0.769
Midwest or North Central	96,435 (23.50)	194,627 (24.00)		192,223 (23.40)	96,654 (23.80)	
South	158,949 (38.70)	318,644 (39.30)		314,920 (38.70)	156,978 (38.60)	
West	69,679 (17.00)	139,191 (17.20)		138,211 (17.00)	68,690 (16.90)	
Hospital teaching status						
Rural	24,628 (6.00)	91,865 (11.30)	<0.001	24,603 (6.00)	27,307 (6.70)	0.01
Urban nonteaching	154,308 (37.70)	339,222 (41.90)		154,019 (37.70)	150,376 (37.00)	
Urban teaching	230,734 (56.30)	378,402 (46.70)		229,916 (56.30)	228,631 (56.30)	
Length of stay, days	7 (4–13)	6 (3–10)	<0.001	7 (2–12)	6 (3–10)	<0.001

Values are mean ± SD, n (%), or median (interquartile range).

CABG = coronary artery bypass grafting; ESRD = end-stage renal disease; HD = hemodialysis; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; PCI = percutaneous coronary intervention.

TABLE 2 Baseline Characteristics Before and After Propensity Matching on the Likelihood of Surgical Versus Endovascular Revascularization

	Unmatched Cohort			Matched Cohort		
	Surgical (n = 140,690)	Endovascular (n = 201,562)	p Value	Surgical (n = 140,342)	Endovascular (n = 141,724)	p Value
Age, yrs	68.17 ± 11.21	68.73 ± 11.75	<0.001	68.18 ± 11.20	68.67 ± 11.67	<0.001
Female	57,420 (40.80)	86,688 (43.00)	<0.001	11,998 (40.90)	12,264 (41.80)	0.03
Race						
White	75,348 (65.20)	104,801 (59.30)	<0.001	15,717 (65.00)	15,618 (61.60)	<0.001
Black	22,142 (19.20)	35,781 (20.20)		4,660 (19.30)	4,785 (18.90)	
Hispanic	12,1616 (10.90)	25,423 (14.40)		2,660 (11.00)	3,471 (13.70)	
Other races	5,404 (4.70)	10,830 (6.10)		1,127 (4.70)	1,483 (5.80)	
Coagulopathy	3,651 (2.60)	5,884 (2.90)	0.01	764 (2.60)	744 (2.50)	0.69
Obesity	12,190 (8.70)	23,056 (11.40)	<0.001	2,532 (8.60)	2,623 (8.90)	0.18
Hypertension	107,185 (76.20)	162,016 (80.40)	<0.001	22,305 (76.10)	22,479 (76.70)	0.22
Hypothyroidism	11,118 (7.90)	20,621 (10.20)	<0.001	2,297 (7.80)	2,427 (8.30)	0.10
Chronic kidney disease	39,170 (27.80)	89,647 (44.50)	<0.001	8,147 (27.80)	8,658 (29.50)	<0.001
ESRD on HD	7620 (5.40)	28401 (14.10)	<0.001	1,581 (5.40)	1,675 (5.70)	0.19
Chronic liver disease	1,793 (1.30)	3,112 (1.50)	0.01	374 (1.30)	397 (1.40)	0.37
Chronic lung disease	30,362 (21.60)	34,699 (17.20)	<0.001	6,324 (21.60)	5,720 (19.50)	<0.001
Anemia	34,683 (24.70)	63,906 (31.70)	<0.001	7,229 (24.70)	7,525 (25.70)	0.02
Heart failure	16,729 (11.90)	25,959 (12.90)	0.01	3,518 (12.00)	3,508 (12.00)	0.94
Valvular heart disease	4,936 (3.50)	6,425 (3.20)	0.04	1,033 (3.50)	828 (2.80)	<0.001
Coronary artery disease	72,312 (51.40)	105,186 (52.20)	0.08	15,026 (51.20)	14,905 (50.80)	0.29
Prior ICD	2,683 (1.90)	5,614 (2.80)	<0.001	554 (1.90)	602 (2.10)	0.23
Prior cardiac pacemaker	4,373 (3.10)	7,959 (3.90)	<0.001	906 (3.10)	948 (3.20)	0.37
Prior MI	18,161 (12.90)	22,408 (11.10)	<0.001	3,750 (12.80)	3,504 (11.90)	<0.001
Prior PCI	10,843 (7.70)	17,850 (8.90)	<0.001	2,243 (7.60)	2,313 (7.90)	0.32
Prior CABG	25,428 (18.10)	33,575 (16.70)	<0.001	5,289 (18.00)	4,776 (16.30)	<0.001
Prior stroke	6,500 (4.60)	13,479 (6.70)	<0.001	1,322 (4.50)	1,876 (6.40)	<0.001
Smoking	24,480 (17.40)	27,833 (13.80)	<0.001	5,074 (17.30)	4,752 (16.20)	<0.001
Pulmonary circulation disease	1,374 (1.00)	3,103 (1.50)	<0.001	288 (1.00)	314 (1.10)	0.36
Tissue loss	107845 (77.00)	170342 (84.80)	<0.001	22,569 (77.00)	23,630 (80.60)	<0.001
Hospital bed size						
Small	13,360 (9.50)	20,505 (10.20)	<0.001	2,975 (10.10)	2,881 (9.80)	034
Medium	31,777 (22.60)	51,364 (25.60)		6,594 (22.50)	7,135 (24.30)	
Large	95,273 (67.90)	129,088 (64.20)		19,755 (67.40)	19,308 (65.80)	
Hospital region						
Northeast	32,410 (23.00)	39,231 (19.50)	<0.001	6,619 (22.60)	5,892 (20.10)	<0.001
Midwest or North Central	31,920 (22.70)	48,085 (23.90)		6,537 (22.30)	7,001 (23.90)	
South	51,907 (36.90)	81,173 (40.30)		11,007 (37.50)	11,916 (40.60)	
West	24,454 (17.40)	33,074 (16.40)		5,161 (17.60)	4,515 (15.40)	
Hospital teaching status						
Rural	8,512 (6.10)	11,409 (5.70)	0.56	1,777 (6.10)	1,824 (6.20)	0.82
Urban nonteaching	53,488 (38.10)	76,215 (37.90)		11,268 (38.40)	11,131 (38.00)	
Urban teaching	78,411 (55.80)	113,332 (56.40)		16,279 (55.50)	16,369 (55.80)	
Length of stay, days	8 (4–14)	7 (2–12)	<0.001	8 (4–14)	6 (2–12)	<0.001

Values are mean ± SD, n (%), or median (interquartile range).
Abbreviations as in Table 1.

$p < 0.001$) and acute kidney injury (9.4% vs. 13.2%; OR: 0.69; 95% CI: 0.65 to 0.73; $p < 0.001$) and similar rates of acute MI (3.3% vs. 3.4%; OR: 0.95; 95% CI: 0.86 to 1.06; $p = 0.36$) and acute stroke (0.6% vs. 0.7%; OR: 0.89; 95% CI: 0.73 to 1.09; $p = 0.25$) compared with those undergoing endovascular revascularization (Figure 3). Compared with endovascular revascularization, those undergoing surgical revascularization had longer lengths of hospital stay (median 8 days [IQR: 4 to 14 days] vs. 6 days [IQR: 2

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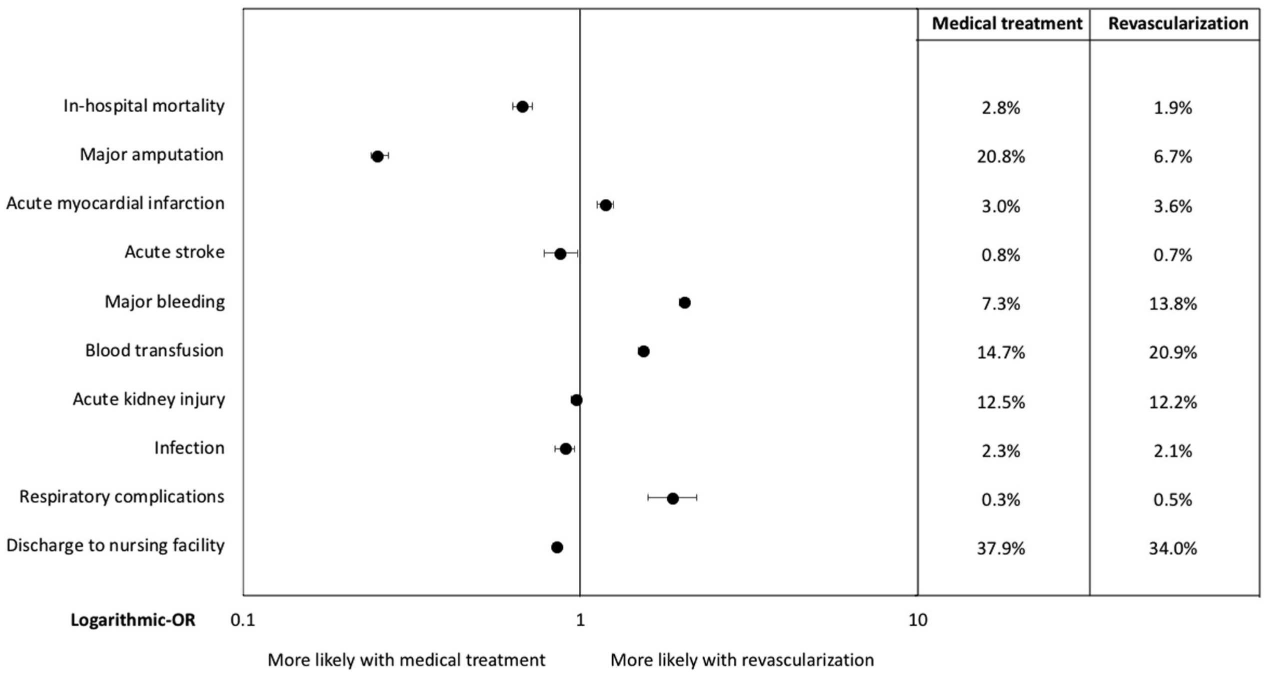
FIGURE 2 In-Hospital Outcomes Following Revascularization Versus Medical Treatment



Forest plot comparing in-hospital outcomes following revascularization versus medical treatment after propensity matching. OR = odds ratio.

to 12 days]; $p < 0.001$) but lower hospital costs (median $16,016 [IQR: $9,991 to $26,151] vs. $17,902 [IQR: $11,275 to $28,084]; $p < 0.001$).

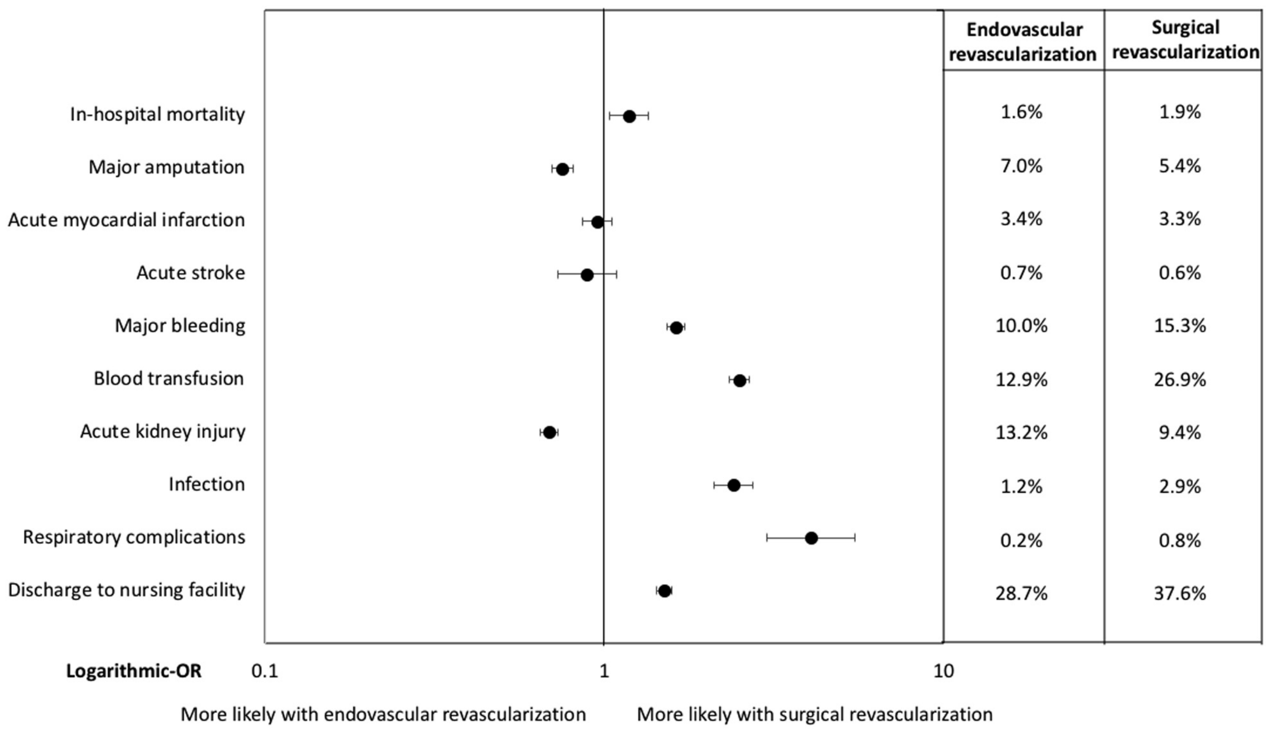
TEMPORAL TRENDS IN HOSPITALIZATION AND OUTCOME. Over the study period, the total number of hospitalizations for CLI increased (from 84,047 in 2002 to 103,293 in 2015; $p_{trend} < 0.001$), as did the proportion of CLI hospitalizations involving patients with DM (from 50.3% in 2002 to 55.3% in 2015; $p_{trend} < 0.001$) (Central Illustration). The percentage of patients who underwent lower extremity revascularization using any modality increased during that time interval (from 27.4% in 2002 to 36.7% in 2015; $p_{trend} < 0.001$). The percentage of endovascular revascularization procedures increased (from 5.3% in 2002 to 21.5% in 2015; $p_{trend} < 0.001$), surgical revascularization decreased (from 19.9% in 2002 to 7.6% in 2015; $p_{trend} < 0.001$), and that for hybrid revascularization increased (from 2.3% in 2002 to 7.7% in 2015; $p_{trend} < 0.001$). The propensity-adjusted yearly rates of in-hospital mortality fell significantly during the same interval for patients treated medically (from 3.4% in 2002 to 2.8% in 2015p $p_{trend} = 0.01$) with endovascular therapy (from 2.9% in 2002 to 1.2% in 2015; $p_{trend} = 0.01$) or with surgery (from 2.3% in 2002 to 1.1% in 2015; $p_{trend} = 0.01$) (Central Illustration).

DISCUSSION

In this observational analysis inclusive of ~1.2 million hospitalizations for CLI among patients with DM, the main study findings were as follows: 1) hospitalizations for patients with CLI and DM increased over time; 2) the proportion of patients treated with lower extremity revascularization increased, while that for medical therapy alone decreased over time; 3) the proportion of patients treated with endovascular revascularization became greater while that for surgical revascularization became smaller over time; 4) those who were revascularized had lower in-hospital mortality and major amputation than those who were not; and 5) of those who were revascularized, surgery was associated with higher in-hospital mortality but lower major amputation than endovascular therapy.

We observed an increasing number of hospitalizations for CLI among patients with DM over our study period. This novel finding occurred despite concomitant advances in secondary preventive measures, such

FIGURE 3 In-Hospital Outcomes Following Surgical Versus Endovascular Revascularization



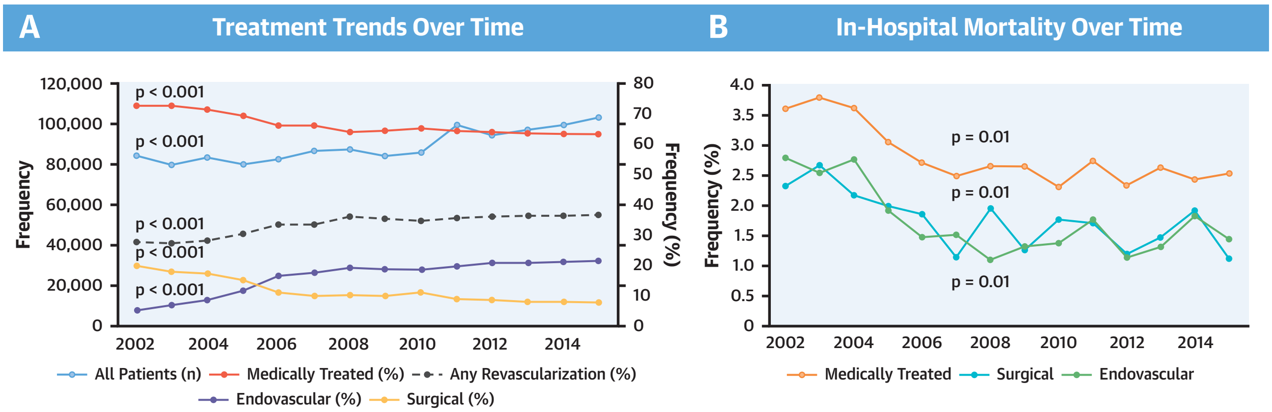
Forest plot comparing in-hospital outcomes following surgical versus endovascular revascularization after propensity matching. OR = odds ratio.

as wider use of statins and novel antidiabetic medications (16,17). The increase in CLI-related hospitalizations is likely multifactorial. For example, it might have been related to the increased prevalence of DM or to the longer duration that patients are living with DM (i.e., more opportunity for hospitalization) (18,19). In addition, substantial efforts have been made by cardiovascular organizations to educate health care providers regarding identification and early referral of patients with CLI for specialty care (20). Future efforts should be directed at improving public awareness about PAD symptoms and implementing early preventive measures before the development of CLI in high-risk patient subgroups.

Revascularization for CLI has been associated with lower rates of limb loss in prior studies (21,22), and although the rate of revascularization increased over time, only 28% of patients underwent revascularization in our analysis. Similar rates have been demonstrated in other registry analyses (1,23). In an analysis of California statewide data including 87,816 patients admitted with CLI, only 19.1% underwent surgical or endovascular revascularization (1). Similarly, a recent analysis of 20,938 veterans hospitalized for CLI demonstrated that 40% underwent revascularization within 90 days of the index hospitalization (23). Further research is warranted to identify predictors of revascularization in patients with CLI, including those with DM.

Our observation that the use of endovascular revascularization has increased and that surgical revascularization has decreased over time has been made by others (21,22,24). These trends are interesting considering that equipoise remains regarding the optimal revascularization modality for CLI, a hypothesis that is currently under investigation in the BEST-CLI trial. BEST-CLI is an ongoing large, multicenter, open-label randomized trial comparing endovascular versus surgical therapy in patients with CLI who are eligible for either modality (7). Although BEST-CLI and other ongoing trials might provide answers about optimal revascularization modalities for patients with CLI in general, they are not adequately powered to detect outcome differences in the subgroup of patients with DM (7). Accordingly, large registry analyses such as ours will be required to

CENTRAL ILLUSTRATION Temporal Trends in Hospitalization Rates, Treatment Strategies, and In-Hospital Mortality



Elbadawi, A. et al. J Am Coll Cardiol Intv. 2021;14(6):664–74.

(A) Hospitalization rates and treatment rendered over time. The **gray line** represents all revascularization (i.e., endovascular treatment, surgical treatment, and hybrid treatment [not presented in this figure]). **(B)** In-hospital mortality over time by treatment rendered.

assess treatment-associated outcomes in this patient population for the time being.

It is encouraging that in-hospital survival improved over the 15-year study period, irrespective of the primary treatment chosen. Studies have consistently shown an association between revascularization and improved survival among all comers with CLI (22,25). Our analysis now extends these observations to those with DM. We found that patients who were not revascularized had higher in-hospital mortality and major amputation. The observed superior survival with revascularization persisted after adjustment for patient characteristics, including the severity of CLI as estimated by the PREVENT III score, a validated tool for stratifying patients with CLI by the risk for amputation-free survival (15). Although it remains possible that medically treated patients were sicker and therefore more likely to experience worse outcomes, we believe that the association between revascularization and improved outcome is plausible, as the groups were well matched following propensity score matching. Other factors may have contributed to improved outcomes among all patients, including more frequent use of guideline-directed medical therapies such as antiplatelet agents and statins (25), improved wound care, and management of DM (26). In an analysis using a Medicare claims database, quality of DM care in outpatient settings was significantly associated with limb salvage among patients with DM undergoing lower extremity revascularization (27). In contrast, compared with medically treated patients, those undergoing revascularization had higher rates of acute MI, which likely resulted from procedure-related hemodynamic perturbations occurring in patients with concomitant coronary atherosclerosis. Similarly, revascularization was associated with higher rates of bleeding, vascular complications, and blood transfusion, which may have resulted from greater periprocedural use of anticoagulant and antiplatelet agents.

Although prior observational studies of patients with CLI have found no difference in outcome between surgical and endovascular approaches (22,24), ours is the largest study to date comparing these revascularization modalities in patients with DM and CLI. We believe that the higher observed in-hospital mortality with surgery compared with endovascular therapy might be explained by the higher rates of bleeding, infection, and respiratory complications that occurred with the former; it is not likely that these observed differences resulted from underlying differences in the prevalence of adverse clinical characteristics given that propensity score matching appeared successful. It is possible that the higher rate of major amputations among patients undergoing endovascular revascularization was related to an inherent higher risk among patients offered endovascular therapy compared with surgery.

However, given that propensity score analysis should have accounted for such differences in baseline risk, it is also plausible that patients with DM and extensive end-stage atherosclerosis might benefit more from surgical than endovascular reconstruction in restoration of blood flow (4). Finally, it is possible that endovascular revascularization was performed ahead of planned amputation in an effort to minimize the extent of tissue loss; the NIS does not capture intended treatment strategy, making it difficult to rule out this possibility. Interestingly, we found a slightly lower median cost of stay among those treated with surgical compared with endovascular approaches despite the higher rates of complications and longer hospital stay with the former. Such difference might be related to differential procedural costs; however, this hypothesis could not be verified using the available data.

STUDY LIMITATIONS. First, despite the use of propensity score matching, we cannot exclude the possibility that confounding, or bias influenced our findings; in particular, it may not be possible to completely adjust for these factors as they relate to comparisons of endovascular and surgical revascularization. Also, it is possible that survivor bias played a role, whereby sicker patients with CLI died before any consideration was given to revascularization, and those who underwent revascularization survived whatever morbidity led to their admission.

Second, as an administrative claims database, the NIS is liable to documentation and coding errors. Nevertheless, the NIS has been extensively validated internally and externally. Annual data quality assessments are performed to maintain internal validity of the NIS database (24). Estimates, clinical characteristics and procedural data from the NIS have been externally validated against data from the American Hospital Association Annual Survey Database, the National Hospital Discharge Survey, and the Med-PAR inpatient database from Centers for Medicare and Medicaid Services (28,29).

Third, our analysis ended in September 2015, and trend analysis data for covariate and outcome prevalence were extrapolated through the end of the year. Because hospitalization numbers were increasing and outcomes were improving over time, it is possible that this extrapolation led to an underestimation of CLI hospitalizations and an overestimation of mortality rates for all treatment modalities in 2015.

Fourth, the NIS provides only in-hospital data; it remains possible that the longer term outcomes, such as limb salvage, associated with the treatment strategies under study would differ from those observed in the hospitalized patients in our study cohort.

Fifth, many useful data are not available for analysis, including imaging data, prescription of guideline-directed medications, laboratory results, procedural details (e.g., extent of PAD, reason for selecting one modality over another, details on bypass grafts or endovascular devices), timing of in-hospital outcomes with respect to timing of procedure, length of stay and cost of treatment at nursing facilities to which patients were discharged, and the quality of follow-up DM or wound care. Future studies might take such factors into account to provide greater insight.

Finally, the group of patients who underwent hybrid revascularization represents a heterogenous group. We were unable to determine whether the second revascularization procedure performed in those patients was planned or performed for salvage following a procedural complication. Despite the aforementioned findings, we believe that our study addresses important knowledge gaps regarding patients with CLI and DM.

CONCLUSIONS

In this national analysis of patients with DM and CLI, we observed that hospitalizations increased over time. Absence of revascularization was associated with higher in-hospital mortality and major amputation. Compared with endovascular therapy, surgical revascularization was associated with higher in-hospital mortality but lower major amputation. Randomized data comparing surgical with endovascular revascularization among patients with CLI are forthcoming.

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Dr. Drachman is a consultant to Abbott Vascular, Boston Scientific, Broadview Ventures, and Cardiovascular Systems. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? There is a paucity of real-world data on hospitalization trends for patients with DM and CLI and on outcomes associated with available treatment strategies.

WHAT IS NEW? Hospitalizations for CLI increased among patients with DM over time. The use of lower extremity revascularization increased during the study period. In-hospital mortality declined over time, regardless of treatment strategy used. Surgical revascularization was associated with higher in-hospital mortality but lower major amputation compared with endovascular therapy.

WHAT IS NEXT? Further studies evaluating long-term outcomes following revascularization of patients with DM with CLI are needed.

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KEY WORDS critical limb ischemia, diabetes mellitus, endovascular revascularization, surgical revascularization

APPENDIX For supplemental tables and figures, please see the online version of this paper.