Epidemiology and Prevention

Twenty-Year Analysis of Trends in the Incidence and In-Hospital Mortality for Lower-Extremity Arterial Thromboembolism

Ravikiran Korabathina, MD; Andrew R. Weintraub, MD; Lori Lyn Price, MAS; Navin K. Kapur, MD; Carey D. Kimmelstiel, MD; Mark D. Iafrati, MD; Syed M. Ali Tahir, MD

Background—Epidemiology data for lower-extremity arterial thromboembolism (LET) are limited and may result from either acute limb ischemia or an acute exacerbation of critical limb ischemia. Given marked changes in both diagnosis and therapy over the last 2 decades, we hypothesized that this time period would have witnessed reductions in both the incidence and in-hospital mortality of LET.

Methods and Results—Data from 1988 through 2007 from the National Hospital Discharge Survey were analyzed. All admissions for patients with LET were extracted, and the respective International Classification of Diseases, Ninth Revision, Clinical Modification codes were internally validated for both LET and acute limb ischemia. Descriptive statistics were used. The validity of the codes was good for identifying LET cases but poor for identifying acute limb ischemia cases because many of these acute presentations were attributable to critical limb ischemia. Over the 20-year span, there were 1.76 million cases of LET. The incidence of LET decreased significantly from 42.4 per 100,000 persons between 1988 and 1997 to 23.3 per 100,000 persons between 1998 and 2007. The in-hospital mortality for LET decreased significantly from 8.28% between 1988 and 1997 to 6.34% between 1998 and 2007, and male patients achieved greater mortality reduction compared with female patients. Treatments for acute limb ischemia showed decreasing use of surgical bypass and amputation and increasing rates of catheter-based thrombolysis.

Conclusions—Over the 20-year study period, there have been significant reductions in both LET incidence and in-hospital mortality. Unfortunately, LET admissions extracted from an administrative database comprise a diverse group of individuals, including those with acute and chronic forms of limb ischemia and iatrogenic arterial injury, limiting the true assessment of ALI incidence. (Circulation. 2013;128:115-121.)

Key Words: epidemiology ■ ischemia ■ peripheral vascular diseases ■ population groups
hospitals with an average length of stay for all patients of <30 days and those with a general specialty are included in the survey. These hospitals must also have ≥6 beds staffed for patient use. Each year, ≥1% of total hospital admissions from all over the country are abstracted and weighted to provide nationwide estimates. Information collected from each sampled hospital record includes age, sex, days of care, discharge status, and up to 7 discharge diagnoses and 4 procedures performed during that admission. These discharge diagnoses and procedures are listed according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Current Procedural Terminology codes that can provide more procedural details such as the specific artery treated and the surgical approach used (ie, percutaneous versus open repair) were not available.

All admissions with a diagnosis of LET based on the presence of the ICD-9-CM codes 444.0 (embolism and thrombosis of abdominal aorta), 444.81 (embolism and thrombosis of iliac artery), and 444.22 (arterial embolism and thrombosis of lower extremity) for any discharge diagnosis were extracted from the NHDS database. The ICD-9-CM codes for various comorbidities and procedures (see online-only Data Supplement for Appendices 1 and 2, respectively) were also extracted. All estimates were presented according to the accepted guidelines for the accuracy of NHDS data. Only absolute, unweighted estimates >60 were considered reliable. For incidence and mortality parameters, relative standard errors were calculated from the formulas provided in the NHDS 2000 data documentation. All absolute estimates were weighted according to the NHDS guidelines.

The primary outcome variables assessed were age-adjusted incidence and in-hospital mortality. For primary analysis purposes, the study period was divided into 2 decades (first decade, 1988–1997; second decade, 1998–2007). Because the 3 landmark, prospective, randomized trials that compared catheter-based thrombolysis with surgical revascularization for ALI were reported between 1994 and 1996, the first decade was considered the mainstream thrombolysis era and the second decade the mainstream thrombolysis time period. To clarify certain trends, the study period was further subdivided into 4 5-year time periods (1988–1992, 1993–1997, 1998–2002, and 2003–2007). Select analyses were also performed on the basis of sex and age (young, <65 years; elderly, ≥65 years).

Institutional Validation

The 3 candidate LET codes were subjected to an internal validation process at our institution. The institutional review board approved this study. The method of ICD-9-CM codes validation has been reported previously. Three ICD-9-CM codes, 444.0, 444.81, and 444.22, were validated for diagnostic accuracy in identifying cases of LET first and ALI next by performing a structured hospital record review. The hospital records of patients admitted to our institution with any of these 3 ICD-9-CM codes over the 2-year period from July 2008 to June 2010 were identified and reviewed by 3 individuals: 2 fellows and 1 attending in interventional cardiology. To resolve any discrepancies in patient categorization, a formal case review was conducted, and a consensus had to be reached by all 3 reviewers. The control subjects were the first 2 patients admitted on the first and last days of each month during the same 2-year period who did not have ICD-9-CM codes 444.0, 444.81, and 444.22 in their discharge records. For the purposes of validating LET, the definition used was the presence of an arterial flow–limiting stenosis or occlusion documented in the symptomatic limb by imaging studies (computed tomography angiography, magnetic resonance angiography, or ultrasonography), invasive angiography, or surgical pathology. For validating ALI, the following criteria were required:

1. The patient met Trans-Atlantic Inter-Society Consensus II definition of ALI: a sudden decrease in limb perfusion that causes a potential threat to limb viability secondary to a thrombotic or embolic event. Furthermore, the limb ischemia could not be related to a procedure or surgery (ie, graft thrombosis after lower-extremity bypass surgery).
2. The patient could be classified into 1 of the 4 clinical categories of ALI according to the Society for Vascular Surgery/International Society for Cardiac Vascular Surgery classification. These categories, which described the severity of ALI according to physical examination findings and Doppler signals, were as follows: viable (I), marginally threatened (IIa), immediately threatened (IIb), and irreversible (III).

Statistics

Baseline characteristics of study patients were summarized as frequencies and percentages for categorical variables and as means and medians for continuous variables. Data for continuous variables were compared by use of the Student t test and for categorical variables by use of the χ2 test. All statistical analyses were performed with SPSS version 18.0 (SPSS Inc, Chicago, IL). A value of P<0.05 was considered significant.

Results

Institutional Validation

On the basis of the single-center structured hospital record review, ICD-9-CM codes 444.0, 444.81, and 444.22 were present in a total of 69 records for patients >18 years of age during the defined 2-year cohort period. The majority of the patient records (43 of 69 admissions) contained ICD-9-CM code 444.22. The sensitivity and specificity of these 3 candidate codes for diagnosing LET based on the study definition were 98.5% and 95.0%, respectively, with a positive predictive value of 92.8% and a negative predictive value of 99.0%. The sensitivity and specificity of the 3 codes for diagnosing ALI according to the study criteria were 100% and 72.2%, respectively, with a positive predictive value of 46.4% and a negative predictive value of 100%. Only 32 of the 69 medical records met the study definition for ALI, with 28 records being classified as critical limb ischemia by the interventionalist or surgeon according to the procedural/operative note. In 4 additional cases, LET occurred immediately after aorto-bifemoral bypass surgery in 3 (ie, graft thrombosis) and after intra-aortic balloon pump placement in 1 (ie, iliac thrombosis). Of the 96 control patient records, LET was absent in 95 cases and confirmed in 1 case. ALI was absent in all control cases.

Study Population

In the NHDS database, 79% of LET admissions were coded with the ICD-9-CM code 444.22. The general characteristics of all LET admissions are shown in the Table. The mean age decreased by 1 year between decades. Women were older than men at hospital presentation in both decades. Elderly individuals approximated two thirds of the admissions in each decade. For comorbidities, only diabetes mellitus, cerebrovascular accident, chronic kidney disease, and aortic aneurysm/dissection showed a significant decrease from the first to the second decade. All other comorbidities showed an interdecade increase.

Outcomes

Of the estimated 664 million admissions throughout the United States during the 20-year study period, the total estimated admissions for LET were 1.76 million, comprising an overall age-adjusted incidence of 32.3 cases per 100,000 individuals. The overall age-adjusted incidence of LET decreased...
by 45% between the first and second study decades (42.4 cases per 100,000 individuals between 1988 and 1997 to 23.3 cases per 100,000 individuals between 1998 and 2007; \( P < 0.0001 \); Figure 1). A similar trend was observed for both sexes. In a 5-year time period analysis, the decrement in LET incidence between the first and second 5-year time periods was 32% (50.6 cases per 100,000 individuals between 1988 and 1992 to 34.6 cases per 100,000 individuals between 1993 and 1997; \( P < 0.0001 \)). LET incidence decreased by 25% between the second and third 5-year time periods (34.6 cases per 100,000 individuals between 1993 and 1997 to 25.9 cases per 100,000 individuals between 1998 and 2002 to 20.8 cases per 100,000 individuals between 2003 and 2007; \( P < 0.0001 \)).

Between 1988 and 2007, there were an estimated 132,983 in-hospital deaths for LET, accounting for an overall in-hospital mortality of 7.54%. The overall in-hospital mortality decreased by 23% between the 2 decades (8.28% between 1988 and 1997 to 6.34% between 1998 and 2007; \( P < 0.0001 \); Figure 2). The absolute mortality reductions between decades for the male and female cohorts were 2.25% and 1.65%, respectively. Over the entire study period, compared with the young, the elderly exhibited a significantly higher overall in-hospital mortality (elderly, 9.97%; young, 3.42%; \( P < 0.0001 \)).

### Table. General Characteristics of Admissions With the Primary Diagnosis of LET (ICD-9-CM 444.0, 444.81, and 444.22)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Men</td>
</tr>
<tr>
<td>Estimated total admissions, n</td>
<td>1,092,811</td>
<td>599,493</td>
</tr>
<tr>
<td>Age, mean (SD), y*</td>
<td>68 (14)</td>
<td>66 (13)</td>
</tr>
<tr>
<td>Elderly (≥65 y), %*</td>
<td>64.2</td>
<td>54.9</td>
</tr>
<tr>
<td>Mean (SD) length of stay, d*</td>
<td>11.0 (13.2)</td>
<td>10.5 (13.3)</td>
</tr>
<tr>
<td>Median length of stay, d*</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Comorbidities, %</td>
<td>[ICD-9-CM] indicates International Classification of Diseases, Ninth Revision, Clinical Modification; and LET, lower-extremity arterial thromboembolism. ( * P &lt; 0.0001 ) for between-decade comparisons for the total cohort, men, and women.</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation*</td>
<td>12.2</td>
<td>10.2</td>
</tr>
<tr>
<td>Coronary artery disease*</td>
<td>5.9</td>
<td>6.1</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>25.1</td>
<td>24.7</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>19.9</td>
<td>18.2</td>
</tr>
<tr>
<td>Dyslipidemia*</td>
<td>2.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Acute myocardial infarction*</td>
<td>4</td>
<td>4.3</td>
</tr>
<tr>
<td>Congestive heart failure*</td>
<td>10</td>
<td>5.3</td>
</tr>
<tr>
<td>Peripheral arterial disease*</td>
<td>19.5</td>
<td>19.5</td>
</tr>
<tr>
<td>Cerebrovascular accident*</td>
<td>4</td>
<td>3.4</td>
</tr>
<tr>
<td>Aortic aneurysm/dissection*</td>
<td>4.9</td>
<td>6.4</td>
</tr>
<tr>
<td>Acute kidney injury*</td>
<td>2</td>
<td>2.1</td>
</tr>
<tr>
<td>Chronic kidney disease*</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>Tissue loss*</td>
<td>13.2</td>
<td>12.4</td>
</tr>
<tr>
<td>Chronic obstructive lung disease*</td>
<td>2.3</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Procedures

During the 20-year study period, 72.2% of all individuals admitted for LET underwent a revascularization procedure (ie, surgical or catheter-based treatment); this rate was 3.7% higher for men compared with women (men, 73.9%; women, 70.2%; \( P < 0.0001 \)). The rates of surgical bypass showed a significant reduction between the first and second decades (36.6% versus 29.6%, respectively; \( P < 0.0001 \)), whereas the rates of catheter-based thrombolysis increased significantly for the same decade comparison (4.6% versus 7.1%, respectively; \( P < 0.0001 \)). Examination of the 5-year time periods shows that the rise in catheter-based thrombolysis was steady and significant between the third and fourth 5-year time periods (6.8% between 1998 and 2002 and 7.3% between 2003 and 2007;
ICD-9-CM coding for percutaneous angioplasty was available only from 1996 on, so the use rate during the first decade reflected only 2 years of data (Figure 3). Percutaneous angioplasty increased significantly between decades (11.8% between 1996 and 1997 to 15.4% between 1998 and 2007; \( P < 0.0001 \)), whereas the use of amputation decreased by 19% (9.0% between 1988 and 1997 versus to 7.3% between 1998 and 2007; \( P < 0.0001 \)).

**Discussion**

The major observations from this nationwide, multiyear study were marked changes in the incidence and in-hospital mortality of LET in the United States over the last 20 years. To the best of our knowledge, this is the largest retrospective analysis of admissions for severe limb-threatening ischemia.

Over the 20-year time period of the study, there was an almost 50% reduction in the overall age-adjusted incidence of LET from the first to the second decade. Although the greatest decrement in LET incidence occurred between the first and second 5-year time periods of the entire study period, there was still a significant reduction in incidence during the remaining 5-year time periods. According to the 2007 Trans-Atlantic Inter-Society Consensus II document, the annual incidence of ALI based on a few national registries and regional surveys is \( \approx 14 \) per 100,000 individuals.\(^2\) The finding from this study of an overall age-adjusted incidence of LET in the second decile of 23.3 per 100,000 persons is higher than this reference value. There is an overestimation of ALI incidence when an administrative database is used because the current ICD-9-CM coding system for LET does not distinguish between individuals with true ALI and those with an acute exacerbation of critical limb ischemia or with LET complicating nonemergent revascularization procedures.

To understand the temporal decrease in LET incidence, it is important to examine the origins of both embolism and thrombosis. Arterial emboli are predominantly cardiac in origin, with 2 of the largest single-center studies showing 86% of such events occurring in the presence of either coronary atherosclerosis or rheumatic heart disease.\(^{10,11}\) Atrial fibrillation was coexistent in >85% of these cases. The incidence of rheumatic heart disease has decreased significantly over the years. Although the age-adjusted prevalence of atrial fibrillation has increased significantly in the last 3 decades,\(^{11}\) there has been continued refinement of risk stratification models and a clear
demonstration of the reduction in embolic events with anti-thrombotic therapy for this condition. Furthermore, continued emphasis on timely revascularization for acute myocardial infarction has likely reduced the incidence of left ventricular mural thrombi as a substrate for embolism. In terms of thrombotic occlusions, which commonly occur in individuals with high atherosclerotic burden, there has been a continued evolution of pharmacological therapies for plaque stabilization. The increasing use of antihyperlipidemic therapy in patients with coronary artery disease and stroke has resulted in a reduction in total atherosclerosis burden. Furthermore, there has been a reported growth in the use of physiological screening tools for peripheral arterial disease, which may allow earlier identification of individuals with subclinical critical limb ischemia. The positive impact of surveillance imaging programs on graft patency has also been recognized. One can assume that the introduction of better interventional techniques, lower-profile equipment, and more reliable periprocedural anticoagulant therapies in recent years has probably lessened the likelihood of iatrogenic arterial injury and distal embolization. Although conjectural, all of these measures have likely contributed collectively to the decline in LET incidence.

This study confirms that LET continues to be a high-risk clinical condition. Despite advances in peripheral arterial disease screening, atherosclerosis recognition, medical therapy, and interventional techniques, the mortality reduction achieved between study decades has been only ≈25%. The absolute in-hospital mortality during the first study decade of 8.3% is comparable to the mortality rate of 9.3% reported previously for patients presenting with ALI between 1992 and 2000 using the Nationwide Inpatient Sample hospital database. The high-risk clinical profile of patients with LET alludes not only to the high rates of all-cause and cardiovascular mortality that generally characterize these individuals with polyvascular atherosclerosis but also to the high operative mortality that characterizes some of the invasive treatments for LET. In fact, more than one quarter of the patients admitted with LET in the present study were not considered candidates for any revascularization procedure, likely because of the presence of severe comorbidities or presentation with severe, prolonged ischemic time, making revascularization options prohibitive.

Male patients demonstrated a lower absolute mortality compared with female patients within each decade. This theme has been echoed in regional studies that have demonstrated a significantly higher mortality for women undergoing surgical revascularization for peripheral arterial disease. In this study, the older age at presentation for female patients likely contributed largely to this finding. Other proposed explanations for sex differences in outcome have included the delayed recognition of vascular disease in women as a result of the presumed atheroprotective effects of reproductive hormones and the prescription of fewer antiplatelet and lipid-lowering agents to treat atherosclerotic disease in women. In terms of anatomic factors, women have been noted to have smaller native and conduit vessel sizes, both of which have been correlated with poor surgical outcomes. Furthermore, a higher occurrence of periprocedural bleeding and infectious complications leading to higher morbidity and mortality has been demonstrated among female patients. Although men achieved a greater absolute mortality reduction compared with women between study decades (2.25% for men versus 1.65% for women), this difference does not appear to be clinically meaningful.

In the present study, nearly three quarters of all patients admitted for LET underwent an invasive revascularization procedure, with decreasing rates of surgical bypass and increasing rates of catheter-based thrombolysis between decades. This procedural trend is consistent with randomized, controlled data that emerged in the mid-1990s (ie, the midline time period in the present study) establishing clinical equipoise between these 2 management options as first-line therapy for ALI and the American College of Cardiology/American Heart Association guidelines recommending catheter-based thrombolysis with a Class I indication for those with the less severe Society for Vascular Surgery/International Society for Cardiac Vascular Surgery category I or IIa symptoms. These procedural trends may reflect the changing treatment preferences.
for thrombotic occlusions that have occurred over the last 2 decades. Interestingly, thromboembolectomy rates did not decrease between study periods, alluding to the continued efficacy of this procedure in rapidly restoring blood flow in acute lower-limb embolism. Amputation rates decreased during the mainstem catheter-based thrombolyis study decade (1998–2007) by ≈20%, which is congruent with the findings from randomized, controlled data that promulgated the efficacy of thrombolytic therapy in severe limb ischemia. This procedural trend is in contrast to the stable overall amputation rates for all comers with lower-extremity vascular disease observed in older studies. Unfortunately, making correlations between specific procedural trends found in this study and the lowering of in-hospital mortality becomes problematic, given the aforementioned limitations of the current ICD-9-CM coding system in not distinguishing embolism from thrombosis. The proper classification of patients by etiologic type is of critical importance because it guides the revascularization strategy. To the best of our knowledge, a standardized validation of LET codes for ALI has not been reported previously. The single-center internal validation revealed low specificity and positive predictive value for the 3 ICD-9-CM codes for LET in identifying cases of ALI. In fact, internal chart review confirmed that true cases of LET fell into the 3 distinct categories of ALI, acute exacerbation of critical limb ischemia, and iatrogenic causes after revascularization procedures, and this etiologic distribution pattern is likely reflected in the nationally representative administrative database. Furthermore, when looking at the timing from symptom onset to hospital admission, we see that only ≈70% of patients presented within 2 weeks of symptom onset. Furthermore, the majority of the remaining 30% of patients who presented with symptom duration >2 weeks exhibited category I ALI, suggesting viable tissue with no neurological deficits and audible arterial Doppler signals. As suggested previously, patients with a more subacute presentation of limb ischemia can be difficult to characterize, making efforts at evaluating ALI incidence challenging when an administrative data set is used.

Limitations

This study has several limitations. First, the use of an administrative database for the purposes of calculating incidence has certain drawbacks, as mentioned earlier. The NHDS database records discharges, not patients. Therefore, patients with repeated hospitalizations for the same diagnosis are not taken into account, leading to a possible overestimation of true incidence. In addition, only nonfederal hospitals are included in this database, so some underestimation of true incidence can occur. Second, the NHDS allows limited coding of secondary diagnoses, leading to an undercoding bias in which chronic diagnoses are omitted during acute hospitalizations. Third, the NHDS database does not provide information on pharmacological therapies such as heparin use that are instituted during the hospitalization or prescribed on discharge, so this crucial aspect of ALI care is not appreciated. Furthermore, Current Procedural Terminology codes, which can provide more procedural details such as the specific artery treated and the surgical approach used (ie, percutaneous versus open repair), were not available. Fourth, the impact of coding changes that occurred during the study period is difficult to ascertain, especially in regard to procedural trends. Finally, NHDS data on intermediate- or long-term outcomes of individuals are not available.

Disclosures

None.

References


Clinical perspective

The goal of this study was to use the National Hospital Discharge Survey administrative database to analyze the incidence, in-hospital mortality, and procedural trends for lower-extremity arterial thromboembolism across the entire United States over a 20-year time period. There is a paucity of epidemiological data on this clinical condition, which comprises a diverse group of both individuals with acute limb ischemia and those with an acute exacerbation of chronic limb ischemia and iatrogenic arterial injury. This large study encompassed a population of 1.76 million hospital admissions and represents the largest retrospective analysis of this high-risk patient population to date. We report a decrease in both age-adjusted incidence and in-hospital mortality of lower-extremity arterial thromboembolism over the specified time period for both male and female patients. An analysis of various procedural trends reveals decreasing use of surgical bypass and amputation and increasing rates of catheter-based thrombolysis to treat lower-extremity arterial thromboembolism. This study also alludes to the limitations in using an administrative database for analyzing the true incidence of acute limb ischemia, given the inability of this data set to distinguish acute limb ischemia from more chronic forms of limb ischemia.
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