Functional status as a prognostic factor for primary revascularization for critical limb ischemia

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Background: **Lower extremity arterial revascularization (LEAR) is the gold-standard for critical lower limb ischemia (CLI). The goal of this study was twofold. First, we evaluated the long-term functional status of patients undergoing primary LEAR for CLI. Second, prognostic factors of long-term functional status and survival after primary LEAR for CLI were assessed.**

Methods: **All primary LEAR procedures were analyzed. Patients were stratified by preoperative functional status: ambulatory (group I) vs nonambulatory (group II). Patients were followed-up after 3 and 6 years. Adverse events (AEs) were categorized according to predefined standards: minor, surgical, failed revascularization, and systemic. Associated patient demographic/clinical data were analyzed using univariate and multivariate methods.**

Results: **There were 106 LEAR patients (group I: n = 42, 40% vs group II: n = 64, 60%). Group II patients were significantly older (75 vs 62 years; $P = .00$), were classified ASA 3-4 more frequently (78% vs 52%; $P < .02$), had more cardiac disease (n = 42, 66% vs n = 10, 24%; $P = .00$), renal disease (n = 26, 41% vs n = 7, 17%; $P = .00$), diabetes (n = 36, 56% vs n = 8, 19%; $P = .00$), hypertension (n = 47, 73% vs n = 13, 31%; $P = .00$) and severe CLI (n = 42, 66% vs n = 18, 38%; $P < .01$). Group II patients had a higher incidence of death (65.6% vs 14.3%; $P = .00$), minor AEs (n = 38, 26% vs n = 10, 22%; $P = .00$), surgical AEs (n = 48, 33% vs n = 12, 26%; $P < .02$) and systemic AEs (n = 24, 86% vs n = 4, 9%; $P < .02$). Also more unplanned reinterventions occurred in group II (n = 148, 76% vs n = 47, 24%; $P = .00$). Nonambulatory status was a multivariate independent predictor of nonambulatory status after LEAR during 6 years follow-up (odds ration [OR[: 21.47; 95% confidence interval [CI]: 2.76-166.77; $P = .00$). Pulmonary disease (OR: 7.49; 95% CI: 2.17-25.80; $P = .00$), not prescribing β-blockers (OR: 4.67; 95% CI: 1.28-17.03; $P < .02$), nonambulatory status (OR: 22.99; 95% CI: 6.27-84.24; $P = .00$), and systemic AEs (OR: 9.66; 95% CI: 1.84-50.57; $P < .01$) were independent predictors of death. Functional status was not improved in group II after long-term follow-up.**

Conclusion: **Nonambulatory patients suffer from extensive comorbid conditions. They are accompanied with an increased occurrence of AEs, unplanned reinterventions, and poor long-term survival rates. Successful LEAR did not improve their functional status after 6 years. This emphasizes that attempts for limb salvage must be carefully considered in these patients. (J Vasc Surg 2010;51:360-71.)**

With aging of the population and improved medical care, vascular physicians face an ever increasing number of elderly patients with progressed forms of peripheral arterial occlusive disease (PAOD).[1] There will be approximately between 500 and 1000 new cases of critical lower limb ischemia (CLI) every year in a European or North American population of 1 million, and the prevalence has been estimated to be 1 per 2500 inhabitants.[2,3] These patients represent about 1% of the total number of patients with PAOD.[2,3] They frequently have arterial disease affecting several vascular beds and suffer from other significant comorbidities such as diabetes mellitus, respiratory disease, and renal disease.

The treatment options of CLI patients can broadly be classified into optimal medical management and invasive treatment. The optimal medical management often consists of lifestyle modification (smoking cessation, dietary management, and supervised walking exercise) and medical comanagement (lipid-lowering agents, antiplatelet agents, heart rate and blood pressure regulation).[2-6] It has been shown to be effective in decreasing the risk of cardiovascular morbidity and improving long-term survival.[2-4,7,8] The invasive treatment consists of vascular (endovascular and/or surgical treatment) and nonvascular (drainage, minor and major amputations) treatment.

The primary goals of CLI treatment are to relieve ischemic pain, heal ischemic ulcers, prevent limb loss, improve patient function and quality of life (QOL), and prolong patient survival. However, most CLI patients have a tremendous disease burden, with poor baseline function, including loss of functional status and ability to live independently. Their prognosis is associated with their multiple comorbid diseases, which may also influence the patient's QOL[2,9] and functional status. The 5-year survival of these CLI patients is relatively poor and compares with patients with cancer (≤50%).[10,11]

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Extensive lower extremity arterial revascularization (LEAR) in patients with CLI is indicated for patients who are independently functioning without extensive comorbid conditions. However, LEAR in nonambulatory CLI patients with extensive comorbid conditions without a likelihood that they will benefit functionally in terms of maintaining or improving ambulatory status and pain relief remains questionable. In selected high-risk patients, a primary major amputation after CLI is thought by some to be a better option rather than sequential hospital admissions with reinterventions, wound complications, and weeks of hospitalization due to failed revascularization attempts,[2,3,12-17] a topic that was addressed previously by Moore et al[18,19] in the 1980s.

The purpose of this study was twofold. First, we attempted to determine the outcome of functional status and patient survival undergoing primary LEAR for CLI. Second, we attempted to assess which prognostic factors may be of importance in determining functional status and survival after primary LEAR.

METHODS

Patients

This study was evaluated and approved by the institutional review board. All 106 consecutive patients without a history of LEAR or amputations were included. Criteria for inclusion was critical limb ischemia (CLI); ischemic rest pain (Fontaine stage 3) with a resting AP $<$ 40 mm Hg; and gangrene or nonhealing ischemic ulceration (Fontaine stage 4) with a resting AP $<$ 60 mm Hg, corresponding with categories 4, 5, and 6 of the Society of Vascular Surgery/North American Chapter of the International Society for Cardiovascular surgery (SVS/ISCVS) standards[6] and according to the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC)[2,3] guidelines. In case of in diabetic patients, CLI was diagnosed by clinical findings in combination with signs of diminished perfusion and radiologic diagnostics (computed tomography angiography/digital subtraction angiography). The included femoral popliteal lesions were according to the TASC-classification type B, C, or D for plaque morphology.[2,3]

Functional status

As listed in Appendix I, online only, the functional status was evaluated according to the functional independence measure.[20] It was determined before (inclusion period: January 2001 till January 2003) and after (3 years and 6 years) primary LEAR. The patients were followed up at the time of their death to determine their functional status.

Risk factors and comorbidity

Risk factors, the American Society of Anesthesiologists (ASA) classification,[21] and body mass index (BMI)[22] were registered prospectively during the admission intake. Risk factor classification and management was according to the SVS/ISCVS standards, TASC, and AHA/ACC[4,23] guidelines.

Medical comanagement

Medication use according to the TASC and AHA/ACC reporting standards was listed by the patients at baseline. Prescribed drugs recorded for purposes of analysis were reviewed and classified according to the following categories: antiplatelet agents, β-blockers, and HMG-CoA-reductase inhibitors.

Invasive treatment of CLI

As listed in Table II, revascularization was divided in primary LEAR and unplanned reinterventions. LEAR was divided in percutaneous transluminal angioplasties (PTAs) and bypass graft procedures (BGPs). PTAs were carried out by conventional balloon dilatation of the lesion with or without stent placement and were performed under local anesthesia with or without sedation. Bypass graft procedures (BGP) were performed according to standard vascular techniques, using preferably reversed vein for femoral popliteal (supra- and infragenual) and crural BGPs. The BGP patency was determined by duplex ultrasound examination and ankle-brachial indices in all patients 4 weeks after LEAR. The definition of primary and secondary patency, the decision to intervene and the type of reintervention were driven by the SVS/ISCVS and TASC reporting standards. All operations were performed by or under the supervision of a vascular surgeon.

Adverse events

In The Netherlands, the Association of Surgeons of the Netherlands (ASN) has agreed on one common definition of Aes.[24] This definition (Appendix II, online only) differs from that used in other studies because it has been chosen with the explicit aim of excluding subjective judgment on cause and effect, and right and wrong. This definition did not change during the study period. As listed in Appendices II and III, online only, the AEs were subdivided into four groups: minor, surgical, failed revascularization, and systemic.

Registration and statistical analysis

Patient information was registered prospectively in an electronic patient file (Oracle database) used for all patients during their admission intake. Statistical analyses were performed through a computerized software package, using SPSS 16.0 for Windows. Patient characteristics, reinterventions, and AEs were analyzed with the Mann-Whitney U-Test. Univariate analyses (χ^2 and unpaired Student *t* test) and multivariate logistic regression models (Cox regression) were conducted. The Kaplan-Meier survival method was used to calculate the time curve of the cumulative primary and secondary patency, limb salvage, and patient survival rates determined at regular intervals after primary LEAR. The log-rank test was used for comparison of these survival rates. For all statistical

Table I. Patient characteristics of all patients with primary CLI stratified by functional status prior to LEAR

Characteristics	*Total*	*Group I*	*Group II*	P *value*
Gender				.13[a]
Male	56 (53)	26 (62)	30 (47)	
Female	50 (47)	16 (38)	34 (53)	
Age				
Mean, years	70	62	75	.00[a]
(Min;max), years	(47;93)	(47;85)	(55;93)	
BMI				.09[a]
Normal	60 (57)	27 (64)	33 (52)	
Overweight	40 (38)	15 (36)	25 (39)	
Obesity	6 (6)	0 (0)	6 (9)	
ASA-classification				<.02[a]
Classification 2	34 (32)	20 (48)	14 (22)	
Classification 3	68 (64)	21 (50)	47 (73)	
Classification 4	4 (4)	1 (2)	3 (5)	
Comorbidity				
Cardiac disease	52 (49)	10 (24)	42 (66)	.00[a]
Pulmonary disease	33 (31)	13 (31)	20 (31)	.97[a]
Renal disease	33 (31)	7 (17)	26 (41)	<.01[a]
Diabetes mellitus	44 (42)	8 (19)	36 (56)	.00[a]
Hypertension	60 (57)	13 (31)	47 (73)	.00[a]
Tobacco use	65 (61)	23 (55)	32 (50)	.00[a]
Hyperlipidemia	46 (43)	26 (62)	20 (31)	.00[a]
Carotid disease	24 (23)	7 (17)	17 (27)	.23[a]
SVS/ISCVS				
Risk factors				
Median (SD), n	3.4 (1.8)	2 (1.8)	4 (1.8)	.01[b]
(Min;max), n	(1;8)	(1;8)	(1;8)	
Risk score				
Mean (SD)	0.78 (0.56)	0.50 (0.54)	0.97 (0.55)	.00[a]
(Min;max)	(0.0;2.3)	(0.0;1.8)	(0.1;2.3)	
Secondary prevention				
Antiplatelet agent	81 (76)	30 (71)	51 (80)	.33[a]
β-blocker	82 (77)	32 (76)	50 (78)	.82[a]
HMG-CoA-reductase inhibitors	91 (86)	36 (86)	55 (86)	.97[a]
ABI at baseline mean (SD)	0.46 (0.22)	0.47 (0.21)	0.45 (0.22)	.17[b]
Fontaine-classification				<.01[a]
Classification 3	48 (45)	26 (62)	22 (34)	
Classification 4	58 (55)	16 (38)	42 (66)	
TASC-classification				
Femoral popliteal lesions				.23[a]
Type B lesion	39 (37)	19 (45)	20 (31)	
Type C lesion	16 (15)	7 (17)	9 (14)	
Type D lesion	51 (48)	16 (38)	35 (55)	

LEAR, Lower extremity arterial revascularization; *CLI,* critical limb ischemia; *group I,* independent; *group II,* dependent; *ASA,* American society of anesthesiologists; *BMI,* body mass index; normal, BMI 18.5-24.9 kg/m^2; overweight, BMI 25.0-29.9 kg/m^2; obesity, BMI > 30 kg/m^2; *SVS-ISCVS,* Society of Vascular Surgery/North American Chapter, International Society of Cardiovascular Surgery; *ABI,* ankle-brachial index; *TASC,* Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease.
Data are presented as n and (%), unless otherwise specified.
[a]χ^2 test.
[b]Mann-Whitney test.

analyses, *P* value <.05 was considered to be statistically significant.

RESULTS

Patients' characteristics

Comorbidity. Fifty-six men (53%) and 50 women (47%) underwent LEAR (Table I). Forty-two (40%) represented group I and 64 (60%) group II. Mean age was 70 (range 47-93) years (group I: 62 range 47-85 years vs group II: 75 range 55-93 years, $P = .00$). There was a difference concerning the ASA-classification; 68% of all patients (n = 72) were ASA 3-4 (group I: n = 22, 52% vs group II: n = 50, 78%, $P < .02$). There was no difference with regard to the BMI, 44% of all patients (n = 46) were overweight or obese (group I: n = 15, 36% vs group II: n = 31, 48%, $P = .09$). Concerning the comorbidity, more patients in group II suffered from cardiac disease ($P = .00$), renal disease ($P < .01$), diabetes mellitus ($P = .00$), and hypertension ($P = .00$). More patients in group I were current smokers ($P = .00$) and suffered

Table II. Summary of primary LEAR and unplanned reinterventions of all patients with primary CLI stratified by functional status after LEAR

Characteristics	*Total*	*Group I*	*Group II*	P *value*
Primary LEAR	106 (35)	42 (40)	64 (60)	.10[a]
PTA	39 (37)	20 (47)	19 (30)	<.01[a]
Femoral popliteal: type B lesion	39 (37)	20 (47)	19 (30)	
BGP	67 (63)	23 (55)	45 (70)	.07[a]
Femoral popliteal SG	16 (15)	7 (17)	9 (14)	
Femoral popliteal IG	30 (28)	12 (29)	18 (28)	
Femoral crural	21 (20)	3 (7)	18 (28)	
Unplanned reinterventions	195 (65)	47 (24)	148 (76)	.00[b]
Vascular	89 (46)	31 (66)	58 (38)	.13[b]
RoBGP	28 (14)	12 (26)	16 (57)	
RiBGP	2 (1)	0 (0)	2 (1)	
PTA	28 (14)	7 (15)	21 (14)	
BGP	22 (11)	11 (23)	11 (7)	
Hemorrhage	9 (5)	1 (2)	8 (5)	
Nonvascular	106 (54)	16 (34)	90 (61)	<.01[b]
Wound drainage	9 (5)	2 (4)	7 (5)	
Skin grafting	8 (4)	2 (4)	6 (4)	
Necrotectomy	40 (21)	8 (17)	32 (22)	
Minor amputation	37 (19)	4 (9)	33 (22)	
BKA	3 (2)	0 (0)	3 (2)	
AKA	9 (5)	0 (0)	9 (6)	
Patients with reinterventions	58 (55)	15 (36)	43 (67)	.00[a]
Total interventions	301 (100)	89 (30)	212 (70)	.00[b]

CLI, Critical limb ischemia; *LEAR,* lower extremity arterial revascularization; *BGP,* bypass graft procedure; *SG,* supragenual; *IG,* infragenual; *PTA,* percutaneous transluminal angioplasty; *group I,* ambulatory; *group II,* nonambulatory; *RoBGP,* revascularization of bypass graft; *RiBGP,* removal infected bypass graft; *BKA,* below knee amputation; *AKA,* above knee amputation.
Data are presented as *n* and (%), unless otherwise specified.
[a]χ^2 test.
[b]Mann-Whitney test.

from hyperlipidemia P = .00). Resulting in a mean patient SVS-ISCVS risk score of 0.78 (group I: 0.50 vs group II: 0.97, P = .00).

Medical comanagement. With respect to the medical comanagement (Table I), no difference was identified: antiplatelet agents (group I: n = 30, 71% vs group II: n = 51, 80%, P = .33), β-blockers (group I: n = 32, 76% vs group II: n = 50, 78%, P = .82), and HMG-CoA-reductase inhibitors (group I: n = 36, 86% vs group II: n = 55, 86%, P = 0.97). Between 75% and 86% of the patients were on target of the TASC and AHA/ACC reporting guidelines concerning the medical comanagement.

Peripheral arterial occlusive disease. There was a difference concerning the Fontaine-classification (Table I): 45% (n = 45) were classified Fontaine 3 and 55% (n = 58) Fontaine 4 (Fontaine 3: group I: n = 26, 62% vs group II: n = 22, 34% and Fontaine 4: group I: n = 16, 38% vs group II: n = 42, 66% P < .01). There was no difference (Table I) concerning the TASC type of femoral popliteal lesion (TASC B: group I: n = 19, 45% vs group II: n = 20, 31% and TASC C: group I: n = 7, 17% vs group II: n = 9, 14% and TASC D: group I: n = 16, 38% vs group II: n = 35, 55%, P = .23).

Invasive treatment of CLI

Primary LEAR. There was a difference with regard to PTAs (n = 39, 37%), (group I: n = 20, 47% vs group II: n = 19, 30%, P < .01). A total of 67 primary BGPs (64%): reversed vein was used in 57 (85%) and PTFE was used in 10 BGPs (15%). There was no difference (Table II) concerning BGPs (femoral popliteal SG group I: n = 7, 17% vs group II: n = 9, 14% and femoral popliteal IG group I: n = 12, 29% vs group II: n = 18, 28% and femoral crural group I: n = 3, 7% vs group II: n = 18, 28%, P = .07).

Reinterventions. There was a difference (Table II) among the patients who underwent reinterventions (group I: n = 15, 36% vs group II: n = 43, 67%, P = .00). There was also a difference in all reinterventions (total: n = 195, 65%; group I: n = 47, 24% vs group II: n = 148, 76%, P = .00; vascular: n = 89, 46%; group I: n = 31, 66% vs group II: n = 58, 38%, P = .13 and nonvascular: n = 106, 54%; group I: n = 16, 34% vs group II: n = 90, 61%, P < .01). All major amputations (BKA: n = 3, 2% and AKA: n = 9, 6%) occurred in group II patients.

In hospital adverse events. One hundred ninety-two AEs (Table III) occurred in 62 patients (58%). There was a difference with regard to the patients who underwent AEs (group I: n = 14, 33% vs group II: n = 48, 75%, P = .00). There was also a difference in the total of AEs (group I: n = 46, 24% vs group II: n = 146, 76%, P = .00; minor: n = 48, 25%; group I: n = 10, 22% vs group II: n = 38, 26%, P = .00; surgical: n = 60, 31%; group I: n = 12, 26% vs group II: n = 48, 33%, P < .02; systemic: n = 28, 15%; group I: n = 4, 9% vs group II: n = 24, 86%, P <.02).

Functional status

Before primary LEAR, 40% of the patients (42 of 106) were ambulatory and 60% (64 of 106) were nonambulatory (Table IV, Figs 1 and 2).

Follow-up at 3 years. Forty-three percent (n = 46) were ambulatory, 30% (n = 32) nonambulatory, and 27% (n = 28) died (Figs 1, 2, and 3). Of the 42 (40%) ambulatory patients before LEAR, 38 (90%) remained ambulatory, two (5%) worsened to nonambulatory status, and two (5%) were not alive at 3 years. Of the 64 (60%) nonambulatory patients before LEAR, 30 (47%) remained nonambulatory, eight (13%) improved their status to ambulatory, and 26 (41%) were not alive at 3 years. Overall, preoperative ambulatory status was maintained in 87% (n = 68) of survivors, worsened in 2.6% (n = 2), and improved in 10% (n = 8) of survivors at 3 years.

Follow-up at 6 years. Thirty-three percent (n = 35) were ambulatory, 22% (n = 23) were nonambulatory, and 45% (n = 48) had died (Figs 1, 2, and 3). Of the 42 (40%) ambulatory patients before LEAR, 35 (83%) remained ambulatory, one (2%) worsened to the nonambulatory status, and six (14%) were not alive at 6 years. Of the 64 nonambulatory patients (60%) before LEAR, 22 (34%) remained nonambulatory and 42 (66%) were not alive at 6

Table III. Summary of adverse events of all patients with primary CLI stratified by functional status prior to LEAR

Characteristics	*Total*	*Group I*	*Group II*	P *value*
Minor	48 (25)	10 (22)	38 (26)	.00[b]
Line infection	1 (1)	0 (0)	1 (1)	
Urinary tract infection	13 (7)	3 (7)	10 (7)	
Blister/ulcer	2 (1)	0 (0)	2 (1)	
Other miscellaneous	6 (3)	1 (2)	6 (4)	
Delay to operation room	8 (4)	0 (0)	8 (5)	
Delay to medical doctor	5 (3)	3 (7)	2 (1)	
Error in judgment	5 (3)	1 (2)	4 (3)	
Incomplete hospital record	7 (4)	2 (4)	5 (3)	
Surgical	60 (31)	12 (26)	48 (33)	<.02[b]
Wound infection	25 (13)	4 (9)	21 (14)	
Wound dehiscence	6 (3)	2 (4)	4 (3)	
Hemorrhage	18 (9)	5 (11)	13 (9)	
Gangrene	10 (5)	0 (0)	10 (7)	
Other	1 (1)	1 (2)	0 (0)	
Failed revascularization	56 (29)	20 (43)	36 (25)	<.16[b]
Failed BGP	46 (24)	19 (41)	27 (18)	
Failed PTA	10 (5)	1 (2)	9 (6)	
Systemic	28 (15)	4 (9)	24 (86)	<.02[b]
Respiratory Insufficiency	2 (1)	0 (0)	2 (1)	
Pneumonia	3 (2)	1 (2)	2 (1)	
Arrhythmia	3 (2)	0 (0)	3 (2)	
Cardiac arrest	3 (2)	1 (2)	2 (1)	
Cardiogenic shock	3 (2)	0 (0)	3 (2)	
Congestive heart failure	4 (2)	0 (0)	4 (3)	
Myocardial infarction	4 (2)	0 (0)	4 (3)	
Shock	1 (1)	1 (2)	0 (0)	
Septicemia	2 (1)	0 (0)	2 (1)	
Stroke	3 (2)	1 (2)	2 (1)	
Patients				
With adverse events	62 (58)	14 (33)	48 (75)	.00[a]
Who died during follow-up	48 (45)	6 (14)	42 (66)	.00[a]
Total adverse events	192 (100)	46 (24)	146 (76)	.00[b]

LEAR, Lower extremity arterial revascularization; *group I,* ambulatory; *group II,* nonambulatory; *BGP,* bypass graft procedure; *PTA,* percutaneous transluminal angioplasty.
Data are presented as n and (%), unless otherwise specified.
[a]χ^2 test.
[b]Mann-Whitney test.

Table IV. Functional status of all patients prior primary LEAR and during follow-up: 3 years and 6 years

Prior primary LEAR		*After 3 years of follow-up*			*After 6 years of follow-up*		
Status	*Total*	*Ambulatory*	*Nonambulatory*	*Died*	*Ambulatory*	*Nonambulatory*	*Died*
Ambulatory	42 (40)	38 (90)	2 (5)	2 (5)	35 (76)	5 (11)	6 (13)
Nonambulatory	64 (60)	8 (13)	30 (47)	26 (41)	0 (0)	18 (56)	14 (44)
Total	106 (100)	46 (43)	32 (30)	28 (27)	35 (45)	23 (29)	20 (26)

LEAR, Lower extremity arterial revascularization.
Data are presented as n and (%), unless otherwise specified.

years. Overall, preoperative ambulatory status was maintained in 98% (n = 57) and worsened in 2% (n = 1) of the survivors at 6 years.

Predictive factors

Table V and Fig 3 list the relationship between patient characteristics and functional and living status after LEAR.

Functional status. BMI, diabetes mellitus, and nonambulatory status were significantly correlated with nonambulatory status after 6 years. Including these variables in the multivariate analysis, only nonambulatory status (OR: 21.47; 95% CI: 2.76-166.77; P = .00) remained an independent predictive risk factor for postoperative nonambulatory status.

Long-term survival. ASA-3, Fontaine-4, cardiac, pulmonary, renal, and carotid disease, diabetes mellitus, hypertension, not prescribing β-blockers, nonambulatory status, the occurrence of reinterventions, and AEs were significantly correlated with early death 6 years after LEAR. Including these variables in the multivariate analysis, pul-

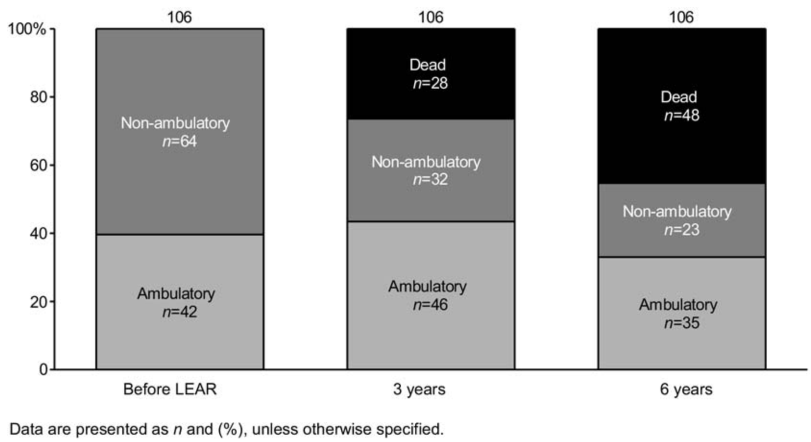


Fig 1. Functional status of all critical lower limb ischemia (CLI) patients stratified by functional status before primary LEAR and during follow-up (3 and 6 years).

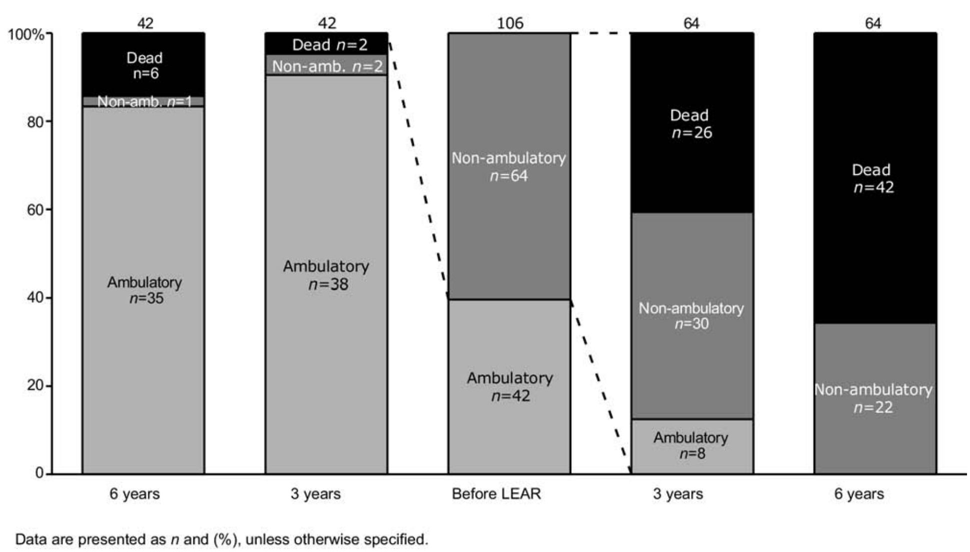


Fig 2. Functional status of all critical lower limb ischemia (CLI) patients stratified by functional status before primary lower extremity arterial revascularization (LEAR) and during follow-up (3 and 6 years).

monary disease (OR: 7.49; 95% CI: 2.17-25.80; $P = .00$), not prescribing β-blockers (OR: 4.67; 95% CI: 1.28-17.03; $P < .02$), nonambulatory status (OR: 22.99; 95% CI: 6.27-84.24; $P = .00$), and systemic AEs (OR: 9.66; 95% CI: 1.84-50.57; $P < .01$) remained independent predictive risk factors for early death.

Patency, limb salvage, and survival. The AE "failed revascularization" occurred 56 times (group I: n = 20, 43% vs group II: n = 36, 35%, $P < .16$) in these series. There was no difference (Table VI) concerning primary patency rates of all PTAs after 6 years (all: 87.7%; group I: 95.7% vs group II: 82.4%, $P = .63$). There was also no difference (Table VI) concerning primary and secondary patency rates of all BGPs after 6 years (all: 52.6%; group I: 77.4% vs group II: 35.7%, $P = .25$) and (all: 77.6%; group I: 87.9% vs group II: 72.2%, $P = .30$), respectively.

There was a difference concerning limb salvage rates of all limbs (Table VI and Fig 4) after 6 years (all: 87.5%; group I: 100% vs group II: 85.2%, $P < .03$).

Forty-eight patients died (≤30 days: n = 8, 28%; <30 days and 3 years]: n = 20, 42%; <3 - and 6 years]: n = 20, 42%) after LEAR (Tables VI and VII). There was a difference (Table VI and Fig 5) concerning the patient survival rates after 6 years (all: 59.2%; group I: 87.8% vs group II: 38.6%, $P = .00$).

DISCUSSION

Contemporary care of CLI consists of near universal attempts of LEAR. The overall decision for limb salvage must consider not only the foot and the technical aspects of LEAR but also the patient's comorbidity and expected outcomes.[25] This information can and must have serious

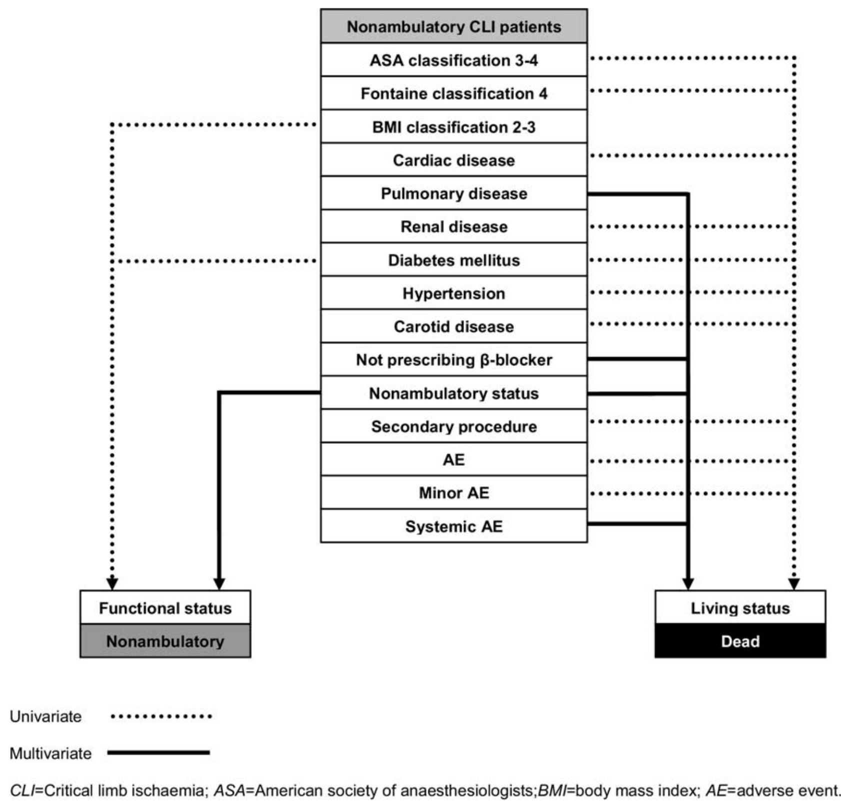


Fig 3. Univariate and multivariate positive predicting factors of functional (nonambulatory) and living status (death).

influence on the decision concerning which exact therapy is the best approach for each individual CLI patient. This study was conducted to obtain insight in functional status and long-term survival after LEAR in CLI patients. Furthermore, several important prognostic factors influencing functional status and survival in this specific patient population were assessed.

Functional status prior LEAR: ambulatory vs nonambulatory

Patient characteristics. Assessing patients' characteristics reveals that the nonambulatory patients were high-risk patients suffering from extensive comorbid conditions and severe CLI. Compared with the ambulatory patients, the nonambulatory patients were characterized by a higher SVS/ISCVS risk score and ASA classification 3-4 at time of LEAR. They were older, suffered from cardiac disease, renal disease, hypertension, hyperlipidemia, and diabetes mellitus. Also, most of the nonambulatory patients in this study were diagnosed with Fontaine classification 4, the most severe form of CLI.

Reintervention and adverse events after primary LEAR for CLI. Almost all reinterventions in the postoperative period were performed in the nonambulatory patient group. The reintervention and AE rate in the nonambulatory patient group is significantly higher compared with the ambulant patient group. This is due to the more severe comorbid condition of these patients. However, the high reintervention rate in the nonambulatory patients implicates an increased risk of new AEs, total length of stay, increased morbidity, and health care costs. Furthermore, these reinterventions and AEs result in an increased physical and mental burden for the CLI patient. The risk of postoperative AEs is directly related to preoperative general health status and presence of severe comorbidity.[26] Reports have also confirmed that patients undergoing LEAR have an increased risk of perioperative cardiac AEs.[27,28]

Limb salvage. Results of the traditional measures of outcome of LEAR were primary and secondary patency rates of 52.6% and 77.6%, respectively, and a total limb salvage rate of 87.5%. They were in correspondence with findings in other reports.[2,29-31]

Important to stress is that the limb salvage in the nonambulatory patients was significantly worse after 6 years; all unplanned major amputations only occurred in these patients.

Functional status and long-term survival after primary LEAR for CLI

In this study, at time of primary LEAR, 40% of the CLI patients were ambulatory and 60% non ambulatory. After long-term follow-up (6 years), 48 patients died (45%) and

Table V. Univariate and multivariate Cox regression analysis of CLI patient characteristics predicting for functional and living status

Characteristics	*Univariate regression*			*Multivariate regression*		
	OR	*95% CI*	P *value*	*OR*	*95% CI*	P *value*
Functional status Nonambulatory						
BMI						
Overweight/obesity	13.00	(2.03-82.96)	.02			
Comorbidity						
Diabetes mellitus	2.74	(1.06-7.10)	.04			
Functional status						
Nonambulatory	21.47	(2.76-166.77)	.00	21.47	(2.76-166.77)	.00
Living status						
Death						
ASA-classification						
Classification 3	3.05	(1.36-6.83)	.01			
Fontaine-classification						
Classification 4	2.09	(0.95-4.59)	.06			
Comorbidity						
Cardiac disease	3.80	(1.69-8.52)	.00			
Pulmonary disease	3.61	(1.51-8.61)	.00	7.49	(2.17-25.80)	.00
Renal disease	3.61	(1.51-8.61)	.00			
Diabetes mellitus	2.23	(1.04-4.90)	.04			
Hypertension	2.52	(1.13-5.61)	.02			
Carotid disease	3.12	(1.19-8.14)	.02			
Secondary prevention[a]						
β-blocker	2.47	(0.97-6.31)	.05	4.67	(1.28-17.03)	<.02
Functional status						
Nonambulatory	11.45	(4.18-31.33)	.00	22.99	(6.27-84.24)	.00
Secondary procedures	2.46	(1.11-5.43)	.03			
Adverse events	3.69	(1.60-8.49)	.00			
Minor	3.01	(1.36-6.96)	.02			
Systemic	15.35	(3.32-70.87)	.00	9.66	(1.84-50.57)	<.01

LEAR, Lower extremity arterial revascularization; *CLI,* critical limb ischemia; *OR,* odds ratio; *CI,* confidence interval; *ASA,* American Society of Anesthesiologists; *BMI,* body mass index.
Data are presented as *n* and (%), unless otherwise specified.
[a]Not prescribing medication concerning secondary prevention.
Univariate analysis was performed using χ^2 test and unpaired Student *t* test. A multivariate logistic regression model was fitted that was based on all patient characteristics that had a *P* value <.05 in the univariate analysis. The effect of patient characteristics, secondary prevention, functional status, reinterventions and AEs on the patients' functional and living status and AEs were assessed using the Cox regression model to estimate odds ratios (OR) and their 95% confidence intervals (CI).

for those patients who survive, 60% was ambulatory and 40% nonambulatory after primary LEAR.

Ambulatory. Ambulatory status at time of LEAR in CLI patients is a positive predicting factor concerning long-term functional status.[12,29,32-34] This was also the finding in our study; the status of patients who were ambulatory prior to LEAR (40%) was rarely worsened by LEAR after 3 and 6 years, respectively. Also most of the patients in this group (86%) were alive after 6 years.

Nonambulatory. The findings of this study implicate that the majority of non ambulant patients with satisfactory technical outcome after LEAR, including limb salvage, will experience no improvement in functional status. These findings are in agreement with the literature.[29,32,33] In this study, the patients' nonambulatory status at time of LEAR was an independent predictive risk factor of functional status after 6 years. Also, BMI (overweight/obesity) and DM were correlated with nonambulatory status after 6 years. Although there may be compelling reasons to consider LEAR in nonambulatory patients, our results suggest that such procedures should be considered carefully, as return to ambulatory status is almost never achievable. Therefore, the consideration for LEAR in most of these patients should be to improve the QOL by decreasing pain level, sleep problems, and heal foot lesion in patients with CLI.[35,36]

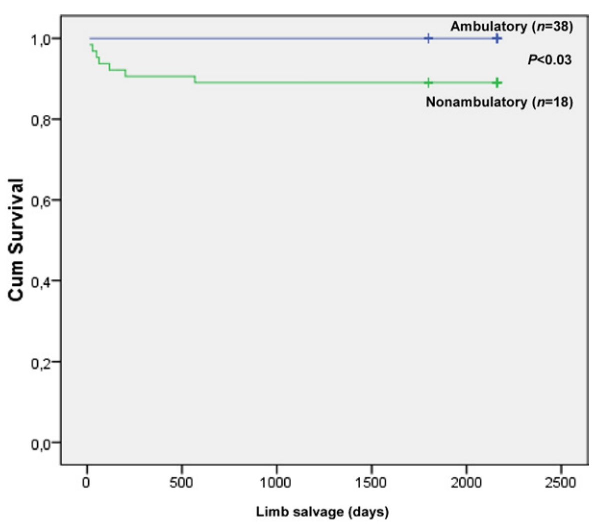
Prognostic factors for survival after primary LEAR for CLI

Many studies have described increased mortality after LEAR for CLI with risk factors such as diabetes, smoking, cardiac disease, and cerebrovascular atherosclerosis.[11,29,30,37,38] In this study, cardiac, pulmonary, carotid, and renal disease, DM, and hypertension were correlated with early death. The severity of limb ischemia is also an important predictor of death rates.[39] In this study, there was also a correlation between the severity of ischemia (Fontaine classification 4) and early death. Patients' nonambulatory status at time of LEAR, not prescribing a β-blocker, and the occurrence of systemic AEs were inde-

Table VI. Cumulative life-table primary and secondary patency rates, limb salvage, and patient survival rates stratified by preoperative functional status

	1 month	*6 months*	*12 months*	*24 months*	*36 months*	*48 months*	*60 months*	*72 months*
BGP								
Primary patency								
All	91 (87.6)	76 (78.3)	66 (71.2)	60 (63.8)	50 (63.8)	43 (63.8)	42 (52.6)	31 (52.6)
Group I	34 (100)	31 (93.5)	29 (90.3)	28 (77.4)	24 (77.4)	23 (77.4)	23 (77.4)	22 (77.4)
Group II	57 (82.5)	45 (73.8)	37 (63.8)	32 (59.6)	26 (59.6)	20 (59.6)	19 (35.7)	9 (35.7)
Secondary patency								
All	91 (93.3)	81 (85.1)	72 (81.6)	69 (79.1)	63 (79.1)	56 (79.1)	55 (77.6)	50 (77.6)
Group I	34 (100)	33 (93.3)	31 (90.9)	30 (87.9)	29 (87.9)	28 (87.9)	28 (87.9)	27 (87.9)
Group II	57 (90.9)	48 (81.2)	41 (77.3)	39 (75.2)	34 (75.2)	28 (75.2)	27 (72.2)	23 (72.2)
PTA								
Primary patency								
All	65 (96.8)	59 (96.8)	57 (91.6)	52 (89.8)	47 (89.8)	44 (87.8)	43 (87.8)	36 (87.8)
Group I	26 (100)	25 (100)	25 (100)	24 (100)	24 (100)	23 (95.7)	22 (95.7)	21 (95.7)
Group II	39 (94.7)	34 (94.7)	32 (85.7)	28 (82.4)	23 (82.4)	21 (82.4)	21 (82.4)	15 (82.4)
Limb salvage								
All	106 (95.1)	93 (90.9)	85 (89.8)	82 (87.5)	73 (87.5)	65 (87.5)	64 (87.5)	56 (87.5)
Group I	42 (100)	41 (100)	41 (97.6)	40 (97.6)	40 (95.1)	39 (95.1)	39 (92.7)	38 (87.8)
Group II	64 (100)	52 (92.0)	44 (89.9)	42 (85.2)	33 (85.2)	26 (85.2)	25 (85.2)	18 (85.2)
Patient survival								
All	106 (100)	98 (95.9)	94 (93.9)	92 (86.7)	85 (78.6)	77 (77.6)	76 (69.4)	68 (59.2)
Group I	42 (100)	41 (100)	41 (97.6)	40 (97.6)	40 (95.1)	39 (95.1)	39 (92.7)	38 (87.8)
Group II	64 (100)	57 (93.0)	53 (91.2)	52 (78.9)	45 (66.7)	38 (64.9)	37 (52.6)	30 (38.6)

BGP, Bypass graft procedure; *PTA,* percutaneous transluminal angioplasty; *group I,* ambulatory; *group II,* nonambulatory.
Data are presented as at risk and (%), unless otherwise specified.
The Kaplan-Meier survival method was used to calculate the time curve of the cumulative primary - and secondary patency, limb salvage and patient survival rates determined at regular intervals: 1-, 6-, 12-, 24-, 36-, 48-, 60- and 72-months after primary LEAR. The log-rank test was used for comparison of these survival rates.



Data are presented numbers at risk (%), unless otherwise specified.

Fig 4. Kaplan-Meier curve of the cumulative limb salvage rates of all limbs stratified by preoperative ambulatory (n = 42, 40%) and nonambulatory (n = 64, 60%) status after 6 years follow-up.

pendent predictive risk factors for early death. The latest AHA/ACC guidelines[4,23] on perioperative care recommend initiating β-blocker treatment in patients with one or more cardiovascular clinical risk factors. As stated in the literature,[40] the occurrence of reinterventions (major amputations) after primary LEAR was associated with significantly worse long-term survival. The previously reported 5-year survival rate for CLI patients ranged from 12% to 64%, with a mean of 45% to 60%.[29,31-33] The survival rate of the patients in this study of 59.2% at 6 years is similar to multiple previous reports, with a 30-days mortality rate of 7%.

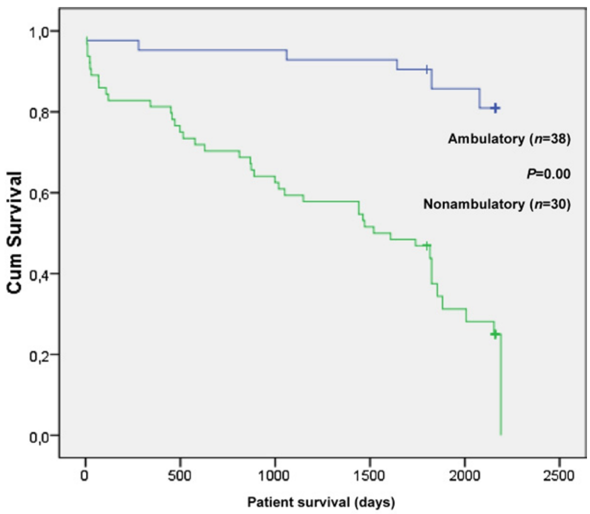
Table VII. Causes of death during follow-up: 30 days, 3, and 6 years

Cause of death	*Total*	*30 days*	*3 years*	*6 years*
Cardiac	17 (35)	6 (35)	8 (47)	3 (18)
Pulmonary	3 (6)	0 (0)	3 (100)	0 (0)
Renal	2 (4)	0 (0)	1 (50)	1 (50)
Cerebral	2 (4)	1 (33)	0 (0)	1 (50)
Hemorrhage	3 (6)	1 (33)	0 (0)	2 (67)
Malignancy	2 (4)	0 (0)	0 (0)	2 (100)
Unknown	19 (40)	0 (0)	8 (42)	11 (58)
Total patients died	48 (100)	8 (16)	20 (42)	20 (42)

Data are presented as n and (%), unless otherwise specified.

Evaluation of the optimal treatment of CLI: primary LEAR - or major amputation

Nonambulatory patients have a significant decreased chance of ambulatory status after LEAR due to their comorbidity, the occurrence of Aes, and reinterventions. LEAR is preferable to primary major amputation in cost as well as in allowing the patient to regain functional life.[41-43] However, the overall decision for limb salvage must also



Data are presented numbers at risk (%), unless otherwise specified.

Fig 5. Kaplan-Meier curve of the cumulative patient survival rates stratified by preoperative ambulatory (n = 42, 40%) and nonambulatory (n = 64, 60%) status after 6 years follow-up.

consider the patient's comorbidity and expected outcomes.[25] Careful consideration should be focused on chances of successful revascularization with subsequent relief of pain and limb salvage vs repeated failed revascularization attempts inducing increased patient morbidity and ultimately major amputation. The ongoing topic of controversy is primary LEAR vs primary major amputation, particularly in patients with CLI.[12-14] As noted in the TASC guidelines, there are patients who will benefit from primary amputation rather than extensive LEAR. Subgroups of the CLI patients currently undergoing extensive limb salvage efforts may be better served with primary amputation. Recent studies demonstrate that there appears to be no difference in QOL or functional outcome between primary LEAR and major amputation during follow-up.[14-16] Also, in selected high-risk patients an early primary major amputation may be preferred above weeks of hospitalization to undergo repeated revascularization attempts and wound treatment attempting to heal distal wounds. If subgroups of CLI patients are better served by primary amputation, how can they be identified? Several variables are to be taken into account when deciding the type of treatment (primary LEAR or major amputation) in case of CLI, such as: functional status and independence, mental status (e.g. dementia), comorbidity, pain, wound status (e.g. size and complexity in the foot), fixed and unremediable flexion contracture,[4,23] technical issues of LEAR, nutritional status and life expectancy. If salvage of a leg can keep it functional for assisted transfers from bed to chair, rather than have a patient who is a "dead lift" bedridden person who cannot easily transfer to a chair, LEAR is good treatment option. Limb salvage will continue to be the overriding goal for most CLI patients referred to vascular therapy, but a subset of these patients is clearly better served with a primary major amputation.

Limitations and strength of the study

Several remarks have to be made concerning potential limitations of this study. This study is limited by the relative small cohort of high-risk patients who were referred to a single center. Furthermore, since patients with previous surgical treatment of CLI were excluded in this study, results of our study cannot be extrapolated in this specific patient category. However, to the best of our knowledge, this is the first study to compare functional status before and long-term (3 and 6 years) after LEAR for CLI with detailed analysis of prognostic factors of morbidity and mortality in this specific patient population.

CONCLUSION

Patients with good functional status before LEAR almost universally maintain this status 6 years after primary LEAR. Preoperative nonambulatory high-risk comorbid CLI patients infrequently experience improvement in functional status after LEAR, they frequently experience AEs and reinterventions, and have especially poor long-term survival rates, emphasizing that attempts at limb salvage must be carefully considered in these patients. Within our multivariate analysis, we identified nonambulatory as an independent predictive risk factor for post LEAR nonambulatory status. Also pulmonary disease, not prescribing β-blockers, nonambulatory status, and systemic AEs were independent predictive risk factors for early death. Surgeons and CLI patients should consider these variables to inform decision making when considering revascularization in these high-risk settings.

AUTHOR CONTRIBUTIONS

Conception and design: HC, JH, EJ
Analysis and interpretation: HC, JH, EJ
Data collection: HC, EJ
Writing the article: HC, JH, EJ, DP, JF
Critical revision of the article: HC, JH, DP, JF
Final approval of the article: JH, JF
Statistical analysis: HC
Obtained funding: Not applicable
Overall responsibility: JF

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Appendix I, online only. Functional status (mobility/type of transfer and locomotion) classified according to the functional independence measure

Group	*Definition of the functional status*
Ambulatory group I	Another person is not needed to complete an activity Included independent/outside, restricted/indoors, and assisted (with cane or walker).
Nonambulatory group II	The patient can at least put forth half or more of the energy to complete an activity or the patient puts forth less than half the energy, requires maximal or total assistance, or even worse, the activity is not performed at all Included wheelchair dependent or bed-bound patients.

Appendix II, online only. Classification of AEs and an explanation of the causes of these AEs

Category[a]	*Cause of the AE*[b] *(group 1-4)*	*Outcome (category I-V)*
Cardiac	1 minor	I no consequence
Pulmonary	2 surgical	II additional transfusion/medication
Neurology	3 failed revascularization	III reoperation
Renal	4 systemic	IV irreversible physical damage
(Sub)cutis		V death
Muscles/skeleton		
Hematology		
Vascular		
Management		

AE, Adverse event.

[a]General definition of an AE.

An unintended and unwanted event or state occurring during or following medical care, that is so harmful to a patient's health that (adjustment of) treatment is required or that permanent damage results. The AE may be noted during hospitalization, until 30 days after discharge or transferee to another department. The intended result of treatment, the likelihood of the adverse outcome occurring, and the presence or absence of a medical error causing it, is irrelevant in identifying an adverse outcome.

[b]Explanation and definition of the causes of perioperative AEs.

Minor: an AE such as: urinary tract infection, deep venous thrombosis.

Surgical: an AE due to surgical treatment, such as: abscess, wound infection, wound necrosis, wound dehiscence, hemorrhage.

Failed revascularization: when a primary bypass graft occluded, or at risk for occlusion and surgical or endovascular reintervention was performed. It was also defined when an anatomical arterial segment occluded after a PTA was performed on that same segment.

Systemic: potential life threatening AEs, such as: pneumonia, respiratory failure, arrhythmia, cardiac arrest, cardiogenic shock, congestive heart failure, myocardial infarction, shock, stroke.

Appendix III, online only. Subdivision of specific AE categories

- Cardiac
  - Congestive heart failure
  - Arrhythmia
  - Cardiac arrest
  - Myocardial infarction
  - Endocarditis/pericarditis
  - Cardiogenic shock
  - Hypertension/hypotension
  - Tachycardia/bradycardia
- Pulmonary
  - Respiratory insufficiency
  - Aspiration/pneumonia
  - Pleural fluid
  - Atelectasis
  - Embolism
- Neurology
  - Cerebrovascular accident
  - Transient ischemic attack
  - Neuropraxia
- Renal
  - Renal failure
  - End-stage renal disease
  - Urinary tract infection
  - Urinary retention
  - Pyelonefritis/hydronefritis
- (Sub)cutis
  - Blister/ulcer
  - Abscess
  - Epidermolysis
  - Seroma
  - Cellulites
  - Wound hematoma
  - Wound infection
  - Wound dehiscence
  - Necrosis/unexpected tissue loss
- Muscles/skeleton
  - Compartmental syndrome
  - Osteomyelitis
- Hematology
  - Spontaneous hemorrhage
  - Heparin induced thrombocytopenia
  - Transfusion reaction
  - Decrease hemoglobin
  - Thrombosis from ATIII, or protein C or S deficiency
  - Septicemia
  - Fluid and electrolytes
- Vascular management
  - Line infection
  - Deep venous thrombosis
  - Infection BGP
  - Stenosis BGP/anatomical segment after PTA
  - Occlusion BGP/anatomical segment after PTA
  - Anastomotic pseudoaneurysm/anatomical segment after PTA
  - Hemorrhage
- General management
  - Error in medication/in diagnosis/in judgment/in technique
  - Delay to OR/in MD response/in diagnosis
  - Incomplete hospital record

BGP, Bypass graft procedure; *PTA,* percutaneous transluminal angioplasty; *OR*, operating room; *MD,* medical doctor.