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Morbidity and Mortality Caused by Cardiac Adverse Events after Revascularization for Critical Limb Ischemia

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Background: We assessed cardiac adverse events (AEs) after primary lower extremity arterial revascularization (LEAR) for critical lower limb ischemia (CLI) in order to evaluate the impact of cardiac AEs on the clinical outcome. We created an optimized care protocol concerning CLI patients' preoperative work-up as well as intra- and postoperative surveillance according to recent important literature and guidelines.

Methods: We conducted a prospective analysis of clinical outcome after LEAR using patient-related risk factors, comorbidity, surgical therapy, and AEs. This cohort was divided into patients with and without AEs. AEs were categorized according to predefined standards: minor, surgical, failed revascularization, and systemic. The consequences of AEs were reoperation, additional medication, irreversible physical damage, and early death.

Results: There were 106 patients (Fontaine III $n = 49$, 46%, and Fontaine IV $n = 57$, 56%) who underwent primary revascularization by bypass graft procedure ($n = 67$, 63%) or balloon angioplasty ($n = 39$, 37%). No difference in comorbidity was registered between the two groups. Eighty-four AEs were registered in 34 patients (32%). Patients experiencing AEs had significantly less antiplatelet agents (without AEs $n = 63$, 88%, vs. with AEs $n = 18$, 53%; $p = 0.000$) and/or β-blockers (without AEs $n = 66$, 92%, vs. with AEs $n = 16$, 47%; $p = 0.000$) compared to patients without AEs. The two most harmful consequences of AEs were irreversible physical damage ($n = 3$) and early death ($n = 8$). Sixty percent ($n = 9$) of systemic AEs were heart-related. The postprocedural mortality rate was 7.5%, with a 75% ($n = 6$) heart-related cause of death.

Conclusion: AEs occur in >30% of CLI patients after LEAR. The most harmful AEs on the clinical outcome of CLI patients were heart-related, causing increased morbidity and death. Significant correlations between prescription of β-blockers and antiplatelet agents and prevention of AEs were observed. A persistent focus on the prevention of systemic AEs in order to ameliorate the outcome after LEAR for limb salvage remains of utmost importance. Therefore, we advise the implementation of an optimized care protocol by discussing patients in a strict manner according to a predetermined protocol, to optimize and standardize the preoperative work-up as well as intra- and postoperative patient surveillance.

INTRODUCTION

Lower extremity peripheral arterial obstructive disease (PAOD) is a common syndrome that affects a large part of most adult populations in the Western world;[1-7] it affects about 5% of the population aged between 55 and 74 years.[8,9] The clinical manifestations of PAOD are a major cause of acute and chronic illness. In addition, PAOD is associated with decrements in functional capacity, decreased quality of life, and increased risk of death.

Patients undergoing primary lower extremity arterial revascularization (LEAR), for critical limb ischemia (CLI) represent a dynamic challenge for

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the anesthetist and the surgeon that extends beyond the intricacies of the planned operation. These patients frequently have arterial disease affecting several vascular beds and suffer from other significant comorbidities such as diabetes, respiratory disease, and renal disease. Also, CLI patients have an even greater risk of experiencing cardiovascular ischemic events.[10-13] Undergoing LEAR, they are at increased risk of life-threatening peri- and postoperative cardiac adverse events (AEs), such as myocardial infarction.[14-16] Fifty percent of patients operated for CLI die within 5 years,[11,17,18] mainly due to cardiovascular events.[19-21]

In order to improve the postoperative outcome of patients undergoing primary LEAR, the pre-, intra-, and postoperative hemodynamic optimization, cardiac management, and timely detection of postoperative AEs could be one of the main goals during endovascular or surgical definitive treatment of these high-risk CLI patients.

Prospective evaluation of AEs is helpful and necessary to obtain a good insight into the occurrence of AEs after treatment for CLI in vascular surgery; it can be used as an indicator of quality in surgery and care.[22-29] It is important to gain insight into the causes and consequences of AEs in patients after LEAR for CLI. Therefore, the objectives of the present study were (1) to assess the occurrence of AEs after LEAR for CLI and (2) to examine the impact of AEs on the clinical outcome of CLI patients' general health.

MATERIALS AND METHODS

Patients

A 2-year survey was performed on 106 consecutive patients without a history of LEAR or amputations. They were admitted for the first time with CLI and underwent primary LEAR. Criteria for inclusion in the study population was CLI, ischemic rest pain (Fontaine stage III) with a resting ankle pressure of <50 mm HG, and gangrene or nonhealing ischemic ulceration (Fontaine stage IV) with a resting ankle pressure of <70 mm HG. This corresponds 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[30,31] and the Trans-Atlantic Inter-Society Consensus (TASC) Document on Management of Peripheral Arterial Disease.[1,2] The included femoral popliteal lesions were according to TASC type B, C, or D for plaque morphology.[1,2] The cohort was divided into patients with AEs and without AEs during admission.

Risk Factors and Comorbidity

Risk factors and comorbidities were registered prospectively for all patients during their admission intake. Smoking, hypertension, cardiac disease, hyperlipidemia, diabetes mellitus, renal disease, pulmonary disease, carotid disease, and age were classified according to the SVS/ISCVS and TASC reporting standards. The risk factor and comorbidity management, according to TASC and American Heart Association/American College of Cardiology (AHA/ACC) reporting standards, was conducted by either a vascular specialist or a cardiologist preoperatively in the outpatient clinic or during admission before operation when urgent intervention was indicated. Also the body mass index (BMI)[32] of the patients was determined, divided into normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and adipose (>30 kg/m^2). Data on risk factors and comorbidities are listed in Table I.

Medication

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

Revascularization

The vascular treatment (LEAR) consisted of percutaneous transluminal angioplasties (PTAs) and bypass graft procedures. The PTAs were carried out by conventional balloon dilatation of the lesion with or without stent placement and under regional anesthesia. Patients were prescribed with a daily dose of acetylsalicylic acid/aspirin after the PTA was performed. The bypass graft procedure (BGP) was performed according to standard vascular techniques, using preferably reversed vein for femoral popliteal (supra- and infragenual) and crural BGPs and under general anesthesia. Patients were prescribed a daily dose of coumarin after the BGP was performed. The patency of a BGP 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 intervention were driven by the SVS/ISCVS and TASC reporting standards. The nonvascular treatment consisted of drainage/debridement, a minor amputation (defined as toe or foot amputation), and a major amputation (defined as an amputation above or below the level

Table I. Baseline characteristics of the total sample ($n = 106$) stratified by patients with and without AEs

Characteristics	Total	Without AE	With AE	*p*
Gender				0.987[a]
Male	56 (53)	38 (53)	18 (53)	
Female	50 (47)	34 (47)	16 (47)	
Age (years)				0.412[a]
<55	14 (13)	9 (13)	5 (15)	
55–69	30 (28)	23 (32)	7 (20)	
70–79	43 (41)	25 (35)	18 (53)	
>80	19 (18)	15 (21)	4 (12)	
BMI[32]				0.788[a]
Normal	60 (57)	41 (57)	19 (56)	
Overweight	40 (38)	26 (36)	14 (41)	
Adiposity	6 (6)	5 (7)	1 (3)	
Comorbidity				
Cardiac disease	52 (49)	32 (44)	20 (59)	0.167[a]
Pulmonary disease	33 (31)	21 (29)	12 (35)	0.525[a]
Renal disease	33 (31)	23 (32)	10 (29)	0.793[a]
Diabetes mellitus	44 (42)	23 (32)	11 (32)	0.426[a]
Hypertension	60 (57)	40 (56)	20 (59)	0.751[a]
Tobacco use	65 (61)	44 (61)	21 (62)	0.129[a]
Hyperlipidemia	46 (43)	34 (47)	12 (35)	0.247[a]
Carotid disease	24 (23)	13 (18)	11 (32)	0.101[a]
SVS-ISCVS risk score[30,31]				
Mean (SD)	0.78 (0.59)	0.74 (0.62)	0.87 (0.52)	0.299[a]
(min–max)	(0–2.3)	(0–2.3)	(0–2.1)	
Risk factors				
Median (SD)	3.0 (1.9)	3.0 (1.9)	3.5 (1.8)	0.270[b]
(min–max)	(1–8)	(1–8)	(1–8)	
Secondary prevention				
Antiplatelet agent	81 (76)	63 (88)	18 (53)	0.000[a]
ß-blocker	82 (77)	66 (92)	16 (47)	0.000[a]
HMG-CoA reductase inhibitor	91 (86)	61 (85)	30 (88)	0.628[a]

Data are presented as *n* and percentages, unless otherwise specified. SD, standard deviation.
[a]Chi-squared test.
[b]Mann-Whitney *U*-test.

of the knee). 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.[33-37] This definition differs from that used in other studies because it has been chosen with the explicit aim of excluding subjective judgment on cause and effect, as well as right and wrong. The definition of an AE is ''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 transfer 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.''[37] This definition did not change during the study period.

In 1993 a fully automated registration system (self-developed Microsoft Access application with an Oracle database as back-end) was implemented in the surgical department of the St. Elisabeth Hospital in Tilburg, The Netherlands. In 1995 total coverage was reached, and registration of AEs was also possible in the intensive care unit, operating room, emergency department, and outpatient clinic. Since 1995 the system has been based on an elaborated list of criteria developed by the ASN (Appendices I and II). AEs are registered immediately by

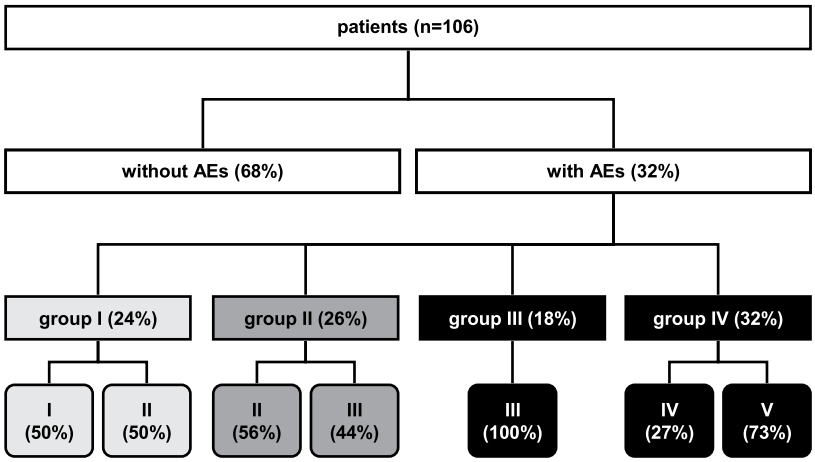


Fig. 1. Patients divided by the most important AEs that occurred during the postoperative period resulting in their consequences. All data are presented as percentages, unless otherwise specified. Group 1, minor; group 2, surgical; group 3, failed revascularization; group 4, systemic; I, no consequences; II, additional transfusion/medication; III, reoperation; IV, irreversible physical damage; V, death.

the physician who diagnoses them. The registered AEs are evaluated and discussed during a weekly meeting with all senior surgeons, surgical residents, and interns. As shown in Figure 1 and Appendix I, patients with 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. The review was retrospective, and this material was entered in a specifically designed computerized analysis database for vascular patients, developed in Access (Office XP from Microsoft, Redmond, WA). Statistical analyses were performed through a computerized software package, using Excel (Office XP from Microsoft) and SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL). Following completion of the data collection, univariate analyses were performed using chi-squared and unpaired Student's *t*-test. The secondary procedures and AEs were analyzed with the Mann-Whitney *U*-test. Univariate and multivariate analyses were performed using AEs (minor, surgical, systemic, and failed revascularization) as dependent variables, adjusting for gender, age, BMI, cardiac disease, pulmonary disease, renal disease, diabetes mellitus, hypertension, tobacco use, hyperlipidemia, carotid disease, SVS-ISVCS risk score, antiplatelet agents, β-blockers, and HMG-CoA reductase inhibitors. For all statistical analyses, $p < 0.05$ was considered statistically significant. The life-table analysis, constructed as described by SVS-ISCVS standards, was used to investigate differences in primary patency, secondary patency, limb salvage, and survival rates.

RESULTS

Patients, Risk Factors, and Comorbidity

A total of 56 men (53%) and 50 women (47%) underwent LEAR because of CLI. Mean ages were 72 and 70 years, respectively (range 47-93). Indication for LEAR was Fontaine III in 49 patients (44%) and Fontaine IV in 57 patients (56%). Mean duration of admission was 9 and 13 days, respectively (range 2-82). These patients suffered from cardiac disease ($n = 52$, 49%), pulmonary disease ($n = 33$, 31%), renal disease ($n = 33$, 31%), diabetes mellitus ($n = 39$, 38%), and hypertension ($n = 60$, 57%), resulting in a mean patient risk score of 0.8. In the patient group, 46 patients (43%) were overweight or obese. A summary of the risk factors and disease characteristics is listed in Table I; no significant differences in risk factors were found between patients with and those without AEs.

Medication

Univariate analysis. Concerning secondary prevention, a difference was present concerning prescription drugs: antiplatelet agents (total $n = 81$, 76%; without AEs $n = 63$, 88%, vs. with AEs $n = 18$, 53%; $p < 0.000$) and β-blockers (total $n = 82$, 77%; without AEs $n = 66$, 92%, vs. with AEs $n = 16$, 47%; $p < 0.000$). No difference was present concerning HMG-CoA reductase inhibitors (total $n = 91$, 86%; without AEs $n = 61$, 85%, vs. with AEs $n = 30$, 88%; $p = 0.628$). Concerning secondary prevention, 75-86% of CLI patients were on target with the TASC and AHA/ACC reporting guidelines.

Multivariate analysis. Not prescribing β-blockers and antiplatelet agents was associated with the occurrence of AEs (odds ratio [OR] = 0.017,

$p = 0.000$, and OR = 19.808, $p = 0.000$, respectively). Subsequently, not prescribing β-blockers was associated with the occurrence of the subcategory of systemic AEs (OR = 0.00, $p = 0.000$).

Revascularization

Primary procedures. Concerning the TASC type of femoral popliteal lesion stratified by patients with and those without AEs, no difference was seen (TASC B, without AEs $n = 26$, 36%, vs. with AEs $n = 13$, 38%; TASC C, without AEs $n = 12$, 17%, vs. with AEs $n = 4$, 12%; TASC D, without AEs $n = 34$, 47%, vs. with AEs $n = 17$, 50%; $p = 0.805$). Concerning the PTAs stratified by patients with or without AEs, no difference was seen (total $n = 39$, 37%; without AEs $n = 26$, 36%, vs. with AEs $n = 13$, 38%; $p = 0.345$). There was a total of 67 primary BGPs (63%): reversed vein in 57 (85%) and polytetrafluoroethylene (PTFE) in 10 (15%). Concerning the type of BGP stratified by patients with or without AEs, no difference was seen (femoral popliteal supragenual total $n = 16$, 15%, and without AEs $n = 12$, 17%, vs. with AEs $n = 4$, 12%; femoral popliteal infragenual total $n = 30$, 28%, and without AEs $n = 20$, 28%, vs. with AEs $n = 10$, 29%; femoral crural total $n = 21$, 20%, and without AEs $n = 14$, 19%, vs. with AEs $n = 7$, 21%; $p = 0.822$).

Secondary procedures. Secondary procedures occurred only in patients with AEs (total $n = 23$, 40%, $p = 0.000$; vascular $n = 8$, 35%, $p = 0.000$; nonvascular $n = 15$, 65%, $p = 0.000$). As listed in Table II, no difference ($p = 0.817$) was seen in primary LEAR (PTA $p = 0.345$, BGP $p = 0.822$) in all patients stratified by the occurrence of AEs. The total 30-day cumulative life-table primary and secondary patency rates of all BGPs and limb salvage rates were 89%, 97%, and 99%, respectively.

Adverse Events

Thirty-four patients (men $n = 18$, 53%, and women $n = 16$, 47%) experienced AEs. Sixty-five percent of the patients were 70 years or older. Indication for LEAR was Fontaine III in 13 (38%) and Fontaine IV in 21 (62%) patients.

As listed in Tables III and IV, a total of 48 AEs (during admission $n = 43$, 90%, and postdischarge in the outpatient clinic $n = 5$, 10%) were registered: 50% were categorized as minor/surgical and 50% as failed revascularization/systemic AEs, resulting in secondary procedures as listed in Table IV. In Figure 1, the AEs are related to their short-term outcomes. Minor AEs resulted equally in no consequence or in additional transfusion/medication. Surgical AEs resulted almost equally in additional transfusion/medication (56%) and in reoperation (44%) because of postoperative hemorrhage ($n = 2$) or wound drainage ($n = 2$). Patients categorized as failed revascularization underwent a reoperation to restore patency in 100% of cases. Five failed BGPs resulted in three embolectomies and two PTAs of the BGP and were performed to achieve assisted primary patency in the postoperative period. In two patients the reoperation was not successful and an amputation of the affected limb was needed (one below-knee and one above-knee).

As listed in Table III, patients undergoing minimally invasive revascularization procedures (PTA) as well as open surgical procedures (BGP) had an equal chance (total $n = 34$, 37%; PTA $n = 13$, 33%, vs. BGP $n = 21$, 31%; $p = 0.832$) of experiencing an AE. Also, no difference in the occurrence of the total AEs (PTA $n = 18$, 30%, vs. BGP $n = 30$, 62%; $p = 0.757$) was seen, stratified by types of primary LEAR.

All systemic AEs resulted in irreversible physical damage ($n = 3$, 27%) or, even worse, in the death of the patient ($n = 8$, 73%). Causes of death included arrhythmia ($n = 1$), cardiac arrest ($n = 2$), myocardial infarction ($n = 1$), cardiogenic shock ($n = 2$), hemorrhage ($n = 1$), and cerebrovascular accident ($n = 1$) and resulted in a 30-day overall mortality rate of 7.5%.

DISCUSSION

The primary goal of this study was to assess the occurrence of AEs after primary LEAR for CLI. The secondary goal of the study was to evaluate the impact of AEs on the clinical outcome of CLI patients' general health.

AEs are associated with poorer health outcomes for patients and increase the average estimated total costs in the treatment for PAOD.[38] The registration of AEs is a helpful tool to gain insight into the incidence and type of AEs that might occur after revascularization for CLI. It optimizes our awareness of all unwanted developments in the illness of the patients and in the treatment of illnesses that occurred in the vascular department and their (possibly preventable) causes. Furthermore, it gives us the opportunity to evaluate the quality of the work done and compare it with outcomes in the literature. However, uniformity of these AE registration systems is necessary, to compare the results between different health-care facilities.

Our results showed that 32% of the primary revascularized CLI patients underwent 48 AEs in

Table II. Summary of Fontaine and TASC classifications and primary and secondary procedures of all patients with primary CLI stratified by those with and without AEs

Characteristics	Total	Without AE	With AE	*p*
Fontaine classification[30,31]				0.257[a]
III	49 (46)	36 (50)	13 (38)	
IV	57 (54)	36 (50)	21 (62)	
TASC classification[1,2]				
Femoral popliteal lesions				0.805[a]
Type B	39 (37)	26 (36)	13 (38)	
Type C	16 (15)	12 (17)	4 (12)	
Type D	51 (48)	34 (47)	17 (50)	
Primary procedures	106 (82)	72 (100)	34 (60)	0.817[a]
PTA	39 (37)	26 (36)	13 (38)	0.345[a]
Femoral popliteal	67 (63)	46 (64)	21 (62)	
Type B lesion				0.822[a]
BGP	16 (15)	12 (17)	4 (12)	
Femoral popliteal SG	30 (28)	20 (28)	10 (29)	
Femoral popliteal IG	21 (20)	14 (19)	7 (21)	
Femoral crural				
Secondary procedures	23 (18)	0 (0)	23 (40)	0.000[b]
Vascular	8 (35)	0 (0)	8 (35)	0.000[b]
RoBGP	5 (17)	0 (0)	5 (17)	
RiBGP	1 (3)	0 (0)	1 (3)	
Hemorrhage	2 (7)	0 (0)	2 (7)	
Nonvascular	15 (65)	0 (0)	15 (65)	0.000[b]
Wound drainage	2 (7)	0 (0)	2 (7)	
Skin grafting	2 (3)	0 (0)	2 (3)	
Necrotectomy	3 (10)	0 (0)	3 (10)	
Minor amputation	6 (20)	0 (0)	6 (20)	
Major amputation	2 (7)	0 (0)	2 (7)	
Patients withsecondary procedures	16 (15)	0 (0)	16 (47)	0.000[a]

Data are presented as *n* and percentages, unless otherwise specified. SG, supragenual; IG, infragenual; RoBGP, revascularization of bypass graft; RiBGP, removal of infected bypass graft.
[a]Chi-squared test.
[b]Mann-Whitney *U*-test.

Table III. Summary of AEs of all patients with primary CLI: stratified by primary revascularization (PTA vs. BGP)

Characteristics	Total ($n = 106$)	PTA ($n = 39$)	BGP ($n = 67$)	*p*
Cause				
Minor other	8 (33)	5 (28)	3 (10)	0.247[a]
Surgical	16 (27)	7 (39)	9 (30)	0.338[a]
Systemic	15 (25)	6 (33)	9 (30)	0.738[a]
Failed revascularization	9 (15)	0 (0)	9 (30)	0.001[a]
Patients with AEs	34 (32)	13 (33)	21 (31)	0.832[a]
Total AEs	48 (100)	18 (38)	30 (62)	0.757[a]

Data are presented as *n* and percentages, unless otherwise specified.
[a]Mann-Whitney *U*-test.

the 30-day perioperative period. As outlined in Tables III and IV, 31% of the AEs were systemic, of which 47% were of cardiac cause. Cardiac AEs are the leading cause of morbidity and mortality in patients undergoing vascular surgery.[39] Numerous reports have also confirmed that patients undergoing vascular reconstruction have an increased risk of perioperative cardiac AEs.[40-42] As shown in Figure 1, profound impacts on patient morbidity and mortality were observed after systemic AEs; and these should be prevented during the pre-, peri-, and postoperative periods. It is

Table IV. AEs ($n = 48$) after primary revascularization for CLI of the total sample ($n = 106$)

Characteristics	
Minor	
Phlebitis	1 (2)
Urinary tract infection	6 (13)
Deep venous thrombosis	1 (2)
Total	8 (17)
Surgical	
Wound dehiscence	1 (2)
Wound infection	7 (15)
Hemorrhage	7 (15)
Other	1 (2)
Total	16 (33)
Failed revascularization	
BGP infection	1 (2)
Failed BGP	8 (17)
Total	9 (19)
Systemic	
Pneumonia	2 (4)
Respiratory failure	1 (2)
Arrhythmia	1 (2)
Cardiac arrest	2 (4)
Cardiogenic shock	3 (2)
Congestive heart failure	1 (2)
Myocardial infarction	2 (4)
Stroke	3 (4)
Total	15 (31)
Total AEs	48 (100)

Data are presented as *n* and percentages, unless otherwise specified.

important to stress that the cause of death was cardiac in 75% of the patients, resulting in a 30-day overall mortality rate of 7.5% compared to up to 3.9-8% mortality in the previous literature.[43-50]

There were no significant differences in risk factors, comorbidity, BMI, and Fontaine classification between patients with or without AEs. This could be explained by the fact that CLI is accompanied by extensive comorbid conditions in almost all patients.

Detailed analysis of variables correlated with the occurrence of AEs revealed that patients without AEs were treated more often with β-blockers compared to patient with AEs. Guidelines on perioperative care recommend that high-risk cardiac patients should receive a β-blocker.[3-5,51-55] However, available data also suggest that β-blockers are underused in patients undergoing revascularization,[56-59] which was also the case with the CLI patients suffering from cardiac AEs in this study. According to the literature,[51,60-66] the use of β-blockers 1 or 2 weeks prior to surgery and continuing beyond surgery is advised to achieve adequate heart rate control, ultimately resulting in a decrease of the incidence of perioperative cardiovascular AEs, and to offer long-term survival benefit. Also, the withdrawal of β-blockers prior to major surgery is associated with an increased incidence of cardiovascular morbidity and mortality. Furthermore, detailed analysis revealed that patients with antiplatelet agents experience fewer AEs compared to patients without this medication. The use of antiplatelet agents is indicated as secondary cardiovascular prevention in patients presenting with PAOD.[60,67-69] A patient who has withdrawn antiplatelet agents prior to the event has a worse outcome than one who either continues on antiplatelet agents or has never received this therapy.

No difference was seen in primary revascularization (PTA vs. BGP) in all CLI patients stratified by the occurrence of AEs. This indicates that the widely accepted hypothesis that minimally invasive revascularization procedures (PTA) are accompanied by fewer AEs compared to BGP should not be accepted. A possible explanation for the relatively high percentage of AEs in the PTA group could be the extensive comorbid status of the CLI patients with their subsequent susceptibility for hemodynamic imbalance after use of contrast agents. Another explanation could be found in the fact that in this study, in contrast to most AE studies, postdischarge AEs in the outpatient clinic were also included.

In order to reduce AEs and thereby patient morbidity and mortality, we suggest that the pre-, intra-, and postoperative cardiac management should be one of the main important goals during endovascular and surgical treatment of these high-risk CLI patients.

Preoperative Multidisciplinary Meeting

When considering a patient for revascularization, a careful preoperative clinical risk evaluation (Fig. 2) is essential. Extensive cardiac preoperative assessment and optimization according to the TASC and ACC/AHA guidelines is of utmost importance to reduce perioperative cardiac AEs. Second, as already stated, guidelines on perioperative care recommend that high-risk cardiac patients should receive a β-blocker.[3-5,51-55] Third, blood pressure-lowering therapy leads to reduction in cardiovascular events in patients with PAOD.[60,70-75] Fourth, the use of HMG-CoA reductase inhibitors may reduce the risk of perioperative myocardial infarction and the risk of major vascular events. Cessation of HMG-CoA reductase inhibitors is

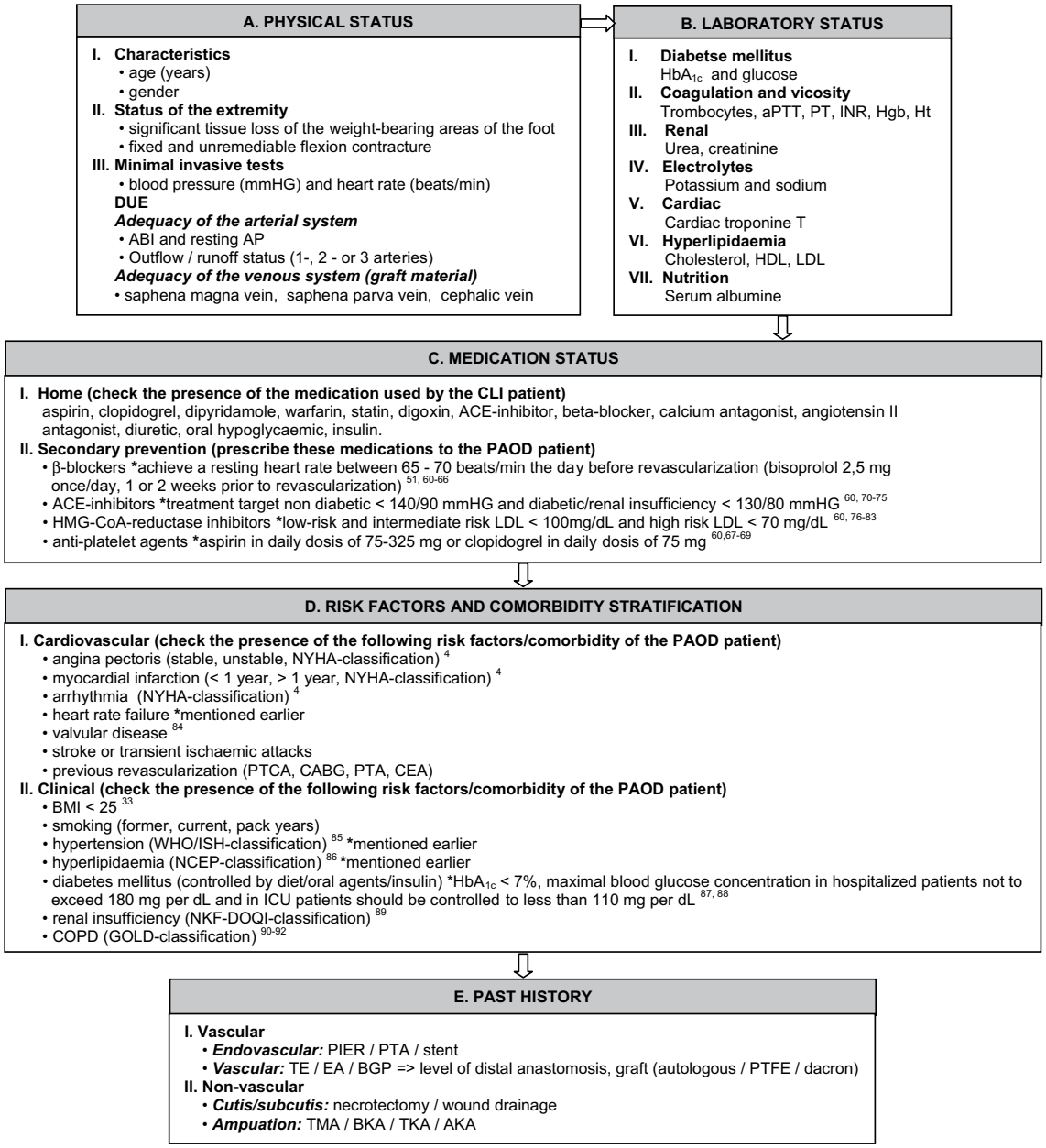
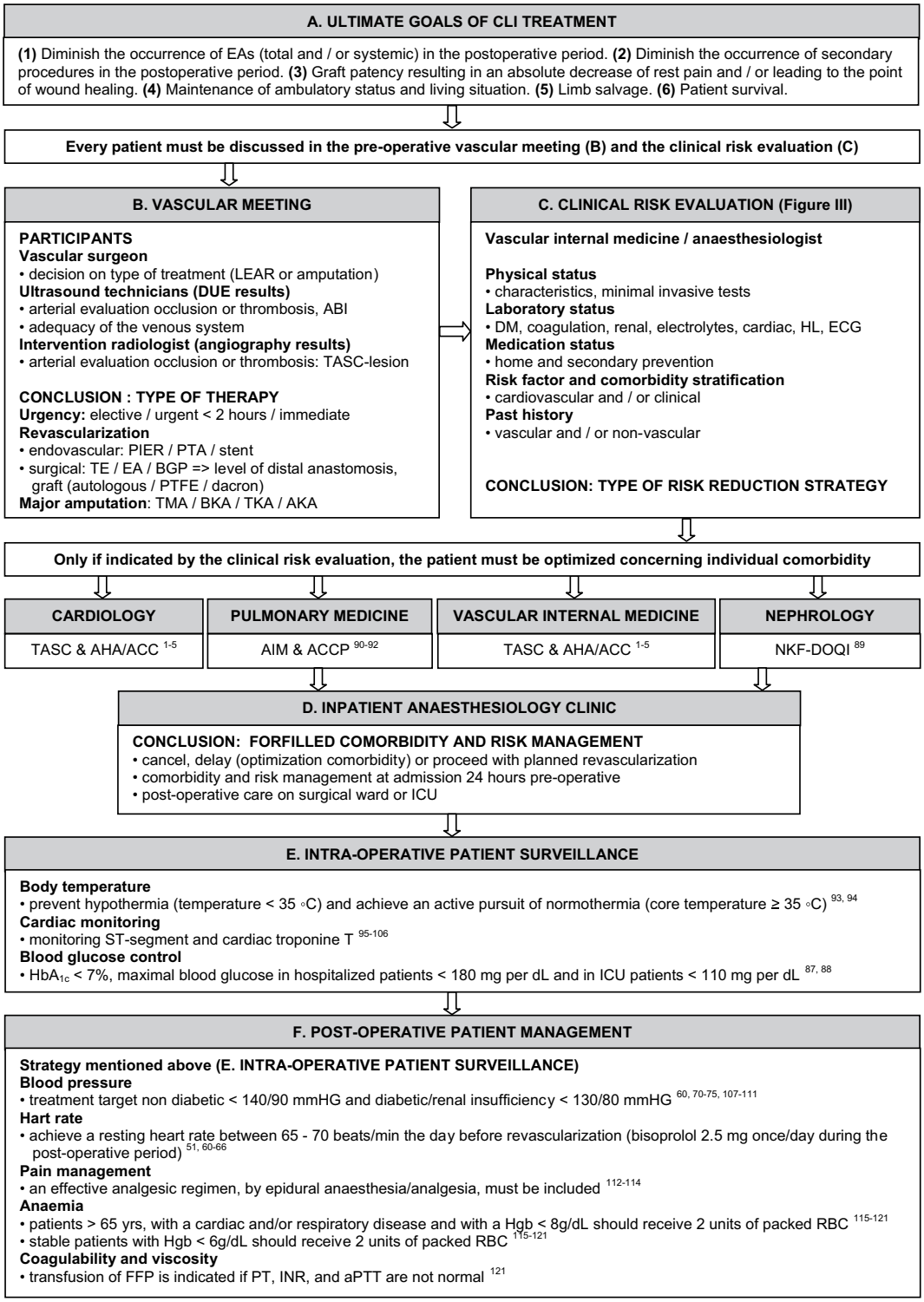


Fig. 2. Preoperative multidisciplinary meeting; clinical risk evaluation and subsequent risk-reduction strategies. aPTT, activated partial thromboplastin time; PT, prothrombin time; DUE, duplex ultrasound examination; ABI, ankle-brachial index; AP, arterial pressure; INR, international normalized ratio; Hgb, hemoglobin; Ht, hematocrit; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACE, angiotensin-converting enzyme; NYHA, New York Heart Association; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; PTA, percutaneous transluminal angioplasty; CEA, carotid endarterectomy; EA, endarterectomy; BGP, bypass graft; BMI, body mass index; WHO/ISH, World Health Organization/International Society of Hypertension; NCEP, National Cholesterol Education Program; ICU, intensive care unit; NKF-DOQI, National Kidney Foundation-Disease Outcomes Quality Initiative; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative on Obstructive Lung Diseases; TMA, transmetatarsal amputation; BKA, below-knee amputation; TKA, through-knee amputation; AKA, above-knee amputation; PIER, percutaneous intentional extraluminal revascularization; TE, thromboembolectomy; EA, endarterectomy.



PIER=Percutaneous intentional extraluminal revascularization; PTA=percutaneous transluminal angioplasty; TE=thromboembolectomy; EA=endarterectomy; BGP=bypass graft procedure; PTFE=polytetrafluoroethylene; TMA=transmetatarsal amputation; BKA=below knee amputation; TKA=through knee amputation; AKA=above knee amputation; DM=diabetes mellitus; HL=hyperlipidaemia; ECG=electrocardiogram; TASC=Trans Atlantic Inter-Society Consensus; AHA/ACC= the American College of Cardiology and the American Heart Association; AIM=annals of internal medicine clinical guidelines; ACCP= American College of Chest Physicians; NKF-DOQI=national kidney foundation-disease outcomes quality initiative; ICU=intensive care unit; Hgb=haemoglobin; RBC=red blood cells; FFP=fresh frozen plasma; aPTT=activated partial thromboplastin time; PT=prothrombin time; INR=international normalized ratio.

associated with significantly poorer outcomes compared to patients who continue their therapy or those who have never been on a HMG-CoA reductase inhibitor.[60,76-83] Fifth, the use of antiplatelet agents is indicated as secondary cardiovascular prevention in patients presenting with PAOD.

Intraoperative Patient Surveillance

The intraoperative patient surveillance is shown in Figure 3. First, prevent intraoperative hypothermia and myocardial ischemic burden; they are independent predictors of perioperative morbid cardiac AEs.[93-98] Intraoperative and postoperative ST-segment monitoring and troponin T release can be useful to monitor patients with single or multiple risk factors for coronary artery disease, with known coronary artery disease, or undergoing vascular surgery.[97-106] Second, hyperglycemia is an independent predictor of cardiovascular risk; the severity of hyperglycemia is directly related to mortality rate during myocardial ischemia.[107-111] Blood glucose concentration should be controlled during the perioperative period in patients with diabetes mellitus or acute hyperglycemia who are at high risk for myocardial ischemia when undergoing major revascularization procedures.[96,97]

Postoperative Patient Management

The postoperative patient management is shown in Figure 3. Because the majority of cardiac events in noncardiac surgical patients occur postoperatively, the postoperative period may be the time during which ablation of stress, adverse hemodynamics, and hypercoagulable responses are most critical. Epidural anesthesia/analgesia result in lower opiate dosages, a better ablation of the catecholamine response, and a reduction of hypercoagulability.[112-114] Second, anemia and hematocrit <28-30% impose stress on the cardiovascular system that may exacerbate myocardial ischemia and aggravate heart failure.[115-121] Third, hyperviscosity and hypercoagulability have also proven to be markers of poor prognosis.[1-5,121]

Limitations

Because of its retrospective nature, our study has limitations, which should be considered when interpreting the results. The number of patients in the present study does not permit further analyses in depth. Patients with previous surgical treatment for CLI were excluded in this study to reduce the influence of previous AEs on the outcome of the current treatment. The sample was composed exclusively of patients with CLI, and our results may not generalize to other patient samples. It should be appreciated that our results were obtained in one high-volume hospital and that cardiac event rates might differ in other centers.

CONCLUSION

AEs occur in >30% of CLI patients after LEAR. The most harmful AEs on the clinical outcome of CLI patients were heart-related, causing increased morbidity and death. Significant correlations between prescription of β-blockers and/or antiplatelet agents and prevention of AEs were observed. A persistent focus on the prevention of systemic AEs in order to ameliorate the outcome after LEAR for limb salvage remains of utmost importance.

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Fig. 3. Flowchart of preoperative multidisciplinary vascular meeting and clinical risk evaluation, intraoperative patient surveillance, and postoperative patient management. ABI, ankle-brachial index; LEAR, lower extremity arterial revascularization; PIER, percutaneous intentional extraluminal revascularization; PTA, percutaneous transluminal angioplasty; TE, thromboembolectomy; EA, endarterectomy; BGP, bypass graft procedure; PTFE, polytetrafluoroethylene; TMA, transmetatarsal amputation; BKA, below-knee amputation; TKA, through-knee amputation; AKA, above-knee amputation; DM, diabetes mellitus; HL, hyperlipidemia; ECG, electrocardiogram; TASC, Trans-Atlantic Inter-Society Consensus; AHA/ACC, American Heart Association/American College of Cardiology; AIM, *Annals of Internal Medicine* clinical guidelines; ACCP, American College of Chest Physicians; NKF-DOQI, National Kidney Foundation—Disease Outcomes Quality Initiative; ICU, intensive care unit; Hgb, hemoglobin; RBC, red blood cells; FFP, fresh frozen plasma; aPTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio.

American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society for Vascular Medicine and Biology, and the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. http://www.acc.org/clinical/guidelines/pad/index.pdf.
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Appendix I. Classification of AEs and explanation of causes

Category[a]	Cause of the AE[b] (groups 1–4)	Outcome (categories 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
(subcutis, muscles/ skeleton, hematology, vascular management)		V death

[a]These categories were further subdivided as listed in Appendix II.

[b]Explanation and definition of the causes of perioperative complications: *minor*, an AE such as urinary tract infection or 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 or 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 II. 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 ischaemic attack
- Neuropraxia

Renal
- Renal failure
- End-stage renal disease
- Urinary tract infection
- Urinary retention
- Pyelonephritis/hydronephritis

(Sub)Cutis
- Blister/ulcer
- Abscess
- Epidermiolysis
- 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
- Decreased 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, diagnosis, judgment, or technique
- Delay to OR, in MD response, or in diagnosis
- Incomplete hospital record

BGP = bypass graft procedure; PTA = percutaneous transluminal angioplasty; OR = operating room; MD = medical doctor.