Current challenges in the treatment of chronic limb threatening ischaemia

CURRENT CHALLENGES IN THE TREATMENT OF CHRONIC LIMB THREATENING ISCHAEMIA

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Chapter 1

General introduction and outline of the thesis

Introduction

Peripheral arterial disease (PAD) is a major health care problem in our modern Western world with a reported prevalence of 15%, rising up to 30% in older populations.[1,2] It is characterized by arterial insufficiency due to stenosis or occlusion of major systemic arteries, most commonly in the lower limbs and most commonly caused by atherosclerosis. Depending on their symptoms, patients with PAD can be divided in two categories: Intermittent Claudication (IC) and Chronic Limb Threatening Ischaemia (CLTI). In addition, the Rutherford classification is a commonly used staging system to further specify the severity of ischaemic symptoms. Rutherford stage 1-3 refer to IC, defined as classical pain symptoms in the lower extremities which are exercise-dependent and can be relieved by resting. CLTI represents the advanced stage of PAD (Rutherford stage 4-6), defined as ischemic rest pain and/or tissue necrosis, and is associated with a high risk of limb loss and mortality.[3,4]

For patients with symptoms of IC a conservative treatment approach, including best pharmaceutical care, lifestyle changes and walking exercises, is always the first choice. In contrast, revascularization is the cornerstone of the treatment of patients with CLTI, aiming to preserve a functional limb and to relieve ischemic rest pain. Both surgical and endovascular revascularization as well as hybrid combinations of both approaches play a key role and are subject of research worldwide. From all patients with PAD, about 10% develop CLTI symptoms and should therefore be offered endovascular or surgical revascularization.[5] Endarterectomy and lower extremity bypass are the main surgical techniques whereas angioplasty and stenting using a variety of devices are the endovascular techniques to revascularize the affected limb. The decision which intervention to use is based on a range of different factors and in modern practice an “endovascular-first” strategy is commonly accepted.[4, 6-9] On the other hand, the leading randomized controlled trial (BASIL trial) in this field compared both strategies and concluded that a surgical bypass should be offered to all patients with a life expectancy of more than two years.[10]

However, not all patients are suitable for any kind of intervention, especially in the frail group of patients aged >80 years (octogenarians). The treatment of octogenarians with CLTI is not as straightforward as in younger patients.[11] Severe co-morbidities, such as cardiovascular or chronical kidney diseases, lead to an increased vulnerability for adverse events or make patients even unfit for surgical or endovascular intervention. Furthermore, the clinical benefits of a revascularization approach might be limited as well in these patients, because of various comorbidities and worse general health condition.[11] Alternative treatment options are conservative treatment (best pharmacological and wound care) or primary amputation of the affected limb. Data on the effectiveness of the different treatment approaches in octogenarians are rare and despite the increasing number of affected octogenarians, there is no consensus about the optimal management of these patients.[11] This is a topic of major importance for both the individual patient and our public health care system. Due to the overall aging of the population and high rates of metabolic syndrome and smoking, the prevalence of both PAD and CLTI is expected to further increase, leading to an increasing number of octogenarians with CLTI and to a significant economic impact. [3, 4, 12] Understanding CLTI and its treatment strategies is therefore essential to be able to provide best medical care for affected patients of all age groups.[4, 6]

Another major challenge in the treatment of patients with CLTI is the management of postoperative infections. Despite all preventive methods, surgical site infections (SSI), most commonly in the groin, are a frequently seen postoperative complication, especially in patients undergoing surgical revascularization. It is a serious complication that may lead to graft infection with increased risk of subsequent amputation and mortality. In recent nationwide studies, 11% of all patients were diagnosed with a SSI within 30 days after surgical revascularization.[13, 14] Mortality rates ranging from 6-75% and amputation rates ranging from 22-75% are reported in the literature.[15] Although deep groin infections are a frequently seen complication in vascular surgery, the optimal treatment regimen remains controversial. Coverage of the groin with a vascularized upper leg muscle flap is described to have positive effects on groin healing. The sartorius muscle flap (SMF) and the rectus femoris muscle flap (RFF) are the most commonly

used muscles for this procedure. Whether one of both techniques is more effective in groin coverage is not known yet.[16, 17]

However, ideally, the incidence of SSIs would be reduced in the first place. Major advances in reducing the incidence of SSIs have been made by improvement of operating room ventilation and sterilization methods, by antiseptic precautions of surgeon and patient and the use of antibiotic prophylaxis, but more effective SSI prevention in vascular surgery is absolutely needed.[18-20] One promising concept is the local sustained prophylactic antibiotic delivery in the operated groin using collagen implants. For this purpose, resorbable gentamicin-containing collagen implants are available and have achieved promising results within the field of cardiac surgery.[21, 22] It can be hypothesized that the use of gentamycin-implants can also reduce SSIs following vascular surgery.

Outline of the thesis

This thesis is divided into two parts and describes both literature and clinical studies addressing two important challenges for revascularization of patients suffering from Chronic Limb Threatening Ischaemia (CLTI).

In **Part I** the effectiveness of revascularization in octogenarians with CLTI was assessed. Differences in clinical outcomes between octogenarians and patients younger than 80 years were first analysed in a systematic review and meta-analysis (**Chapter 2**). Second, mortality and major amputation rates of both age groups were investigated in a retrospective cohort study (**Chapter 3**).

Part II focuses on surgical site infections after revascularization, a challenging and frequently seen complication. Both treatment and prevention strategies were investigated. First, the effectiveness of muscle flap coverage for deep groin infection was analysed in a systematic review (**Chapter 4**). Second, the outcomes of rectus femoris flaps were assessed in a retrospective cohort study (**Chapter 5**) and compared with the outcomes of sartorius muscle flaps (**Chapter 6**). Finally, with the aim to prevent surgical site infections of the groin, a

prospective randomized controlled trial analysed the effectiveness of gentamicin-implants in reduction of groin infections following vascular surgery (**Chapter 7**).

Chapter 8 summarizes the main results and conclusions presented in this thesis and lastly, future perspectives and implications for further research and clinical applications are depicted in **Chapter 9**.

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Chapter 2

Mortality and Major Amputation after Revascularisation in Octogenarians Versus Non-Octogenarians with Chronic Limb Threatening Ischaemia: A Systematic Review and Meta-Analysis.

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Abstract

Objective: The aim of this systematic review and meta-analysis was to assess the clinical outcomes after revascularisation in octogenarians with chronic limb threatening ischaemia (CLTI).

Methods: This was a systematic review and meta-analysis, in which the Medline, Embase, and Cochrane Library databases were searched systematically by two independent researchers. Meta-analyses were performed to analyse one year mortality, one-year major amputation, and one year amputation free survival (AFS) after revascularisation. Pooled outcome estimates were reported as percentages and odds ratio (OR) with 95% confidence intervals (CI). In addition, sensitivity and subgroup analyses were performed and the quality of evidence was determined according to the GRADE system.

Results: The review includes 21 observational studies with patients who were treated for CLTI. Meta-analysis of 12 studies with a total of 17 118 patients was performed. A mortality rate of 32% was found in octogenarians (95% CI 27-37%), which was significantly higher than in the non-octogenarians (17%, 95% CI 11-22%/OR 2.52, 95% CI 1.93-3.29; GRADE: “low”). No significant difference in amputation rate was found (octogenarians 15%, 95% CI 11-18%; non-octogenarians 12%, 95% CI 7-14%; GRADE: “very low”). AFS was significantly lower in the octogenarian group (OR 1.55, 95% CI 1.03-2.43; GRADE: “very low”). In a subgroup analysis differentiating between endovascular and surgical revascularisation, amputation rates were comparable. For octogenarians, those treated conservatively had a mortality rate significantly higher than those treated by revascularisation (OR 1.76, 95% CI 1.19-2.60; GRADE: “very low”). No significant difference in mortality rate was found between primary amputation and revascularisation in octogenarians (OR 0.70, 95% CI 0.24-2.03; GRADE: “very low”).

Conclusion: In octogenarians with CLTI, a substantial one-year mortality rate of 32% was found after revascularisation. The amputation rates were comparable between both age groups. However, only low-quality evidence could be obtained supporting the results of this meta-analysis because only observational studies were available for inclusion.

Introduction

More than 200 million people worldwide are suffering from peripheral arterial disease (PAD) of the lower extremities, a significant healthcare problem which can lead to chronic limb threatening ischaemia (CLTI).[1,2] CLTI is associated with a high risk of limb loss if limb perfusion is not restored successfully,[3,4] therefore, endovascular or surgical revascularisation is the key treatment for patients with CLTI.[4-6] The effectiveness of different revascularisation techniques has been reported extensively in the literature. Much effort has been made to investigate whether one method of revascularisation is more effective than another one; however, the effectiveness of revascularisation among different age groups has been assessed in remarkably few studies. Meta- analyses comparing outcomes of octogenarians with younger patients have been performed in other fields of vascular surgery such as abdominal aortic aneurysm repair but not for CLTI.[7,8]

Based on the literature, it can be hypothesised that treatment of octogenarians with CLTI might not be as straightforward as in younger patients. Various comorbidities in these patients might limit the clinical benefits of a revascularisation approach.[9,10] To the present authors' knowledge, there is no systematic review addressing this problem and comparing the outcomes of octogenarians after revascularisation with the outcomes of patients aged <80 years. This experience is crucial as there is an increasing number of octogenarians suffering from CLTI because of the overall ageing of the population.[9,10]

The aim of this systematic review and meta-analysis was to analyse the differences in clinical outcomes, such as major amputation and overall survival after revascularisation between octogenarians and patients aged <80 years.

Methods

A systematic review was performed based on the Preferred and Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) statement.[11,12]

Literature search and study selection

The Medline, Embase, and Cochrane Library databases were searched systematically by two independent authors (L.W. and C.N.) for articles related to the effectiveness of revascularisation techniques in octogenarians. The literature search strategy is presented in Appendix 1. The last search was performed in February 2019. The retrieved records were screened on title, abstract, and result tables by both researchers, and eligibility assessment was performed following the inclusion and exclusion criteria described below. In addition, the reference lists of included studies were screened for relevant publications. Conference proceedings and the grey literature were not searched. In the event of discrepancy between the two researchers, all decisions were based on consultation of a third independent researcher (B.M.).

Inclusion and exclusion criteria

Studies were included in the systematic review if they met the following criteria, irrespective of the epidemiological design: 1) studies involving patients with objective evidence of PAD and CLTI; 2) all types of primary revascularisation with no distinction made between various endovascular or open techniques; 3) studies reporting limb salvage, major amputation, or mortality after one year follow up as primary or secondary outcome; and 4) studies that defined a separate group of patients aged < 80 years. Studies that did not differentiate in their results between octogenarians and patients aged >80 years, were excluded from the meta-analysis.

Data extraction and quality assessment

Two independent authors (L.W. and C.N.) completed the data extraction regarding the study characteristics, study methods, patient characteristics, type of interventions, and the study outcomes. For studies presenting their outcomes as one year survival and/or limb salvage rates, these out- comes were converted into one year mortality rates and/or major amputation rates.[15-17,21,23,25,27-32,34] Data from Kaplan Meier curves were extracted using the software WebPlotDigitizer 4.2.[33,34] In addition, before performing the meta-analysis, the number of events was calculated using the outcome rates and cohort sizes given in the article for nine studies.[20-23,27,31-34] In the other three studies all required data were given.[10,19,24]

To assess the methodological quality of each study, the Newcastle Ottawa Scale (NOS) was used, a scale system based on three domains: selection of study groups (0-4 points), comparability (0-2 points), and assessment of outcomes (0-3 points).[13] In this scale system, a maximum of 9 points can be reached. A score from one to three points is categorised as low quality, four to six points as unclear/ moderate quality, and seven to nine points as high quality.

Statistical analysis

The primary outcome measures used in this meta-analysis were one year mortality, one-year major amputation, and one year amputation free survival (AFS). Pooled outcome estimates of all 21 studies were presented as percentage and as odds ratio (OR) with associated 95% confidence intervals (CI). Comparative meta-analysis was performed including 12 studies that compared the clinical outcomes of octogenarians with patients aged <80 years. To account for interstudy heterogeneity, random effects modelling using the Mantel-Haenszel method was used. Heterogeneity among studies was assessed by I^2 statistics (I^2 values < 50% = low heterogeneity; I^2 values 50-75% = moderate heterogeneity; I^2 values > 75% = significant heterogeneity). Sensitivity analyses were performed for larger studies (>100 patients per age group) and for studies with a NOS ≥ score 7. Funnel plots were not used for assessment of publication bias as the recommended minimum of 10 studies per outcome was not reached. In addition, a subgroup analysis was performed for patients treated conservatively in the included studies and for patients treated by primary amputation. Furthermore, intergroup comparisons in the octogenarian group were performed and mortality in octogenarians was compared between revascularisation and conservative treatment and primary amputation, respectively. Again, random effects' modelling was used and heterogeneity was assessed by I^2 statistics. Pooled estimates were reported as OR with 95% CI. Subgroup analysis was also performed, differentiating between endovascular and surgical revascularisation. All statistical calculations were performed using the meta-analysis software Review Manager 5.3 and Stata Version 14.1. A p value of < .050 represented statistical significance.

Quality of evidence

The quality of evidence and strength of recommendation was assessed for all outcomes using the GRADE system (grading of recommendation assessment, development, and evaluation) and its five parameters14 (Appendix 2). The strength of evidence can be “high”, “moderate”, “low”, or “very low”. For observational cohort studies, the rating starts per definition at “low” quality. The presence of one or more serious limitations therefore resulted in a “very low” quality evidence. A summary of findings table was produced including the three primary outcomes and the outcomes of the associated sensitivity analyses.

Results

Study selection

After removing duplicates, the search yielded 1 296 articles, which were screened on title, abstract, and on result tables if necessary. In addition, four relevant articles were identified from the manual search of the reference lists.[15,16,19,28] Finally, 21 articles were included in the systematic review. Details of the study selection process and reasons for exclusion are documented in the flow chart (Fig. 1).

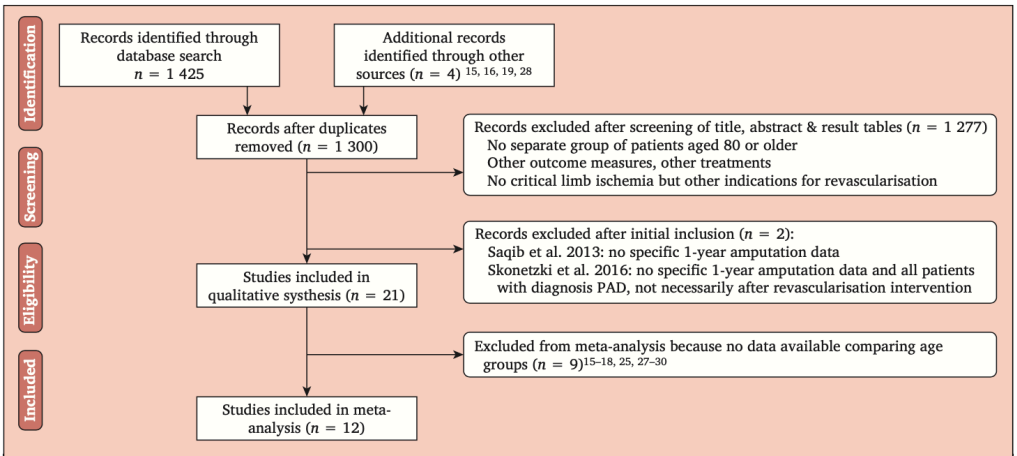

Figure 1. PRISMA flow chart illustrating the study selection process of this systematic review and meta-analysis.

Study characteristics and patient demographics

The final systematic review included 21 studies, published between 2004 and 2018.[10,15-34] Among the 21 studies, 19 were retrospective cohort studies and two had a prospective study design.[19,32] A summary of included article study characteristics and the NOS scores are provided in Table 1.

Table 1. Summary of studies included in this systematic review on revascularisation in octogenarians, including study design, characteristics, and risk of bias

Study	Study period	Location	Study design	Number of institutions	Type of intervention	Total patients	≥80 years	Follow up − mo	NOS score
Arvela 2011[15]	2000–2007	Finland	R	Single	Endo, surgery	584	584	24*	5
Atar 2005[16]	1996–2002	Israel	R	Single	Endo	38	38	12	4
Ballotta 2010[17]	1995–2007	Italy	R	Single	Surgery	197	197	74 (1–137)*	5
Baubeta 2017[33]	2008–2013	SWE	R	Swedvasc	Endo, surgery	10 617	4 629	32.4†	6
Biasi 2017[18]	2010–2014	UK	R + P	Single	Endo, surgery	120	120	–	4
Brosi 2007[19]	1999–2004	CHE	P	Single	Endo, surgery, conservative	376	150	12	8
Dermody 2015[20]	2003–2013	USA	R	VSGNE	Surgery	3 371	702	12	6
Domenick 2012[21]	2004–2010	USA	R	Single	Endo	201	78	8.7 ± 7.3*	4
Dosluoglu 2009[22]	2001–2007	USA	R	Single	Endo, surgery	344	89	25.0 ± 19.2*	7
Gillgren 2011[23]	2006–2008	SWE	R	Single	Endo	112	53	18 (12–24)†	5
Klaphake 2018[24]	2006–2013	NL	R	Single	Endo, surgery, conservative	428	175	37.2 (0–108)†	7
Lejay 2012[25]	2003–2008	France	R	Single	Endo, surgery	167	167	33.1*	6
de Leur 2012[10]	2006–2009	NL	R	Single	Endo, surgery, conservative	191	72	–	4
Mathur 2015[26]	2003–2010	UK	R	Single	Endo	478	196	26.9 ± 0.54*	4
Nehler 1993[27]	1981–1991	USA	R	Single	Surgery	88	88	24.5*	4
Rodriguez 2016[28]	2002–2013	Spain	R	Single	Surgery, conservative	53	53	–	3
Salas 2004[29]	1999–2000	UK	R	Single	Endo	98	98	Range 12–42	5
Shirasu 2016[34]	2006–2013	Japan	R	Single	Surgery	106	19	29 ± 22*	6
Steunenberg 2016[30]	2012–2015	NL	R	Single	Endo, surgery, conservative	36	36	7†	3
Uhl 2016[31]	2007–2015	GER	R	Single	Surgery	270	92	31 (0.1–92)†	7
Uhl 2017[32]	2013–2014	GER	P	27 vascular centres	Endo	624	221	–	7

Endo = endovascular revascularisation; NOS = Newcastle–Ottawa quality assessment scale; P = prospective cohort study; R = retrospective cohort study; Swedvasc = data from the Swedish National Quality Registry for Vascular Surgery; VSGNE = all centres participating in the Vascular Study Group of New England; CHE = Switzerland; GER = Germany; NL = The Netherlands; SWE = Sweden; UK = United Kingdom; USA = United States of America; – = data not available.

* Data presented as mean, mean (range) or mean ± standard deviation.

† Data presented as median or median (range).

In total, five of the 21 studies were considered to be of higher methodological quality (≥ 7 points). Six studies investigated endovascular revascularisation only,[16,21,23,26,29,32] six studies investigated surgical revascularisation only,[17,20,27,28,31,34] and nine analysed both techniques.[10,15,18,19,22,24,25,30,33] In addition, in five studies a subgroup of patients was treated conservatively and four studies investigated outcomes after primary amputation as well.[10,19,24,28,30] The number of participants ranged from 36 to 10 617 patients. The octogenarian group sizes ranged from 19 to 4629 patients. A total of 18 517 patients was included in this

review. Gender, Rutherford classification, and comorbidities per study are summarised in Table 2.

Table 2. Summary of patient characteristics of studies included in this systematic review on revascularisation in octogenarians

Study	Total – *n*		Male – %		Rutherford 5/6 – %		Heart failure – %		Kidney failure – %		Pulm. Disease – %		CAD – %	
	Patients	≥80 years	<80 years†	≥80 years	<80 years†	≥80 years	<80 years†	≥80 years	<80 years†	≥80 years	<80 years†	≥80 years	<80 years†	≥80 years
Arvela 2011[15]	584	584		30		77		–		–		15		72
Atar 2005[16]	38	38		63		82		39		18		8		55
Ballotta 2010[17]	197	197		68		82		–		2		20		33
Baubeta 2017[33]	10 617	4 629	49*		–*		28*		7*		14*		20*	
Biasi 2017[18]	120	120		56		63		–		–		–		–
Brosi 2007[19]	376	150	68	43	83	81	–	–	–	–	–	–	–	–
Dermody 2015[20]	3 371	702	68	56	–	–	–	–	–	–	–	–	–	–
Domenick 2012[21]	201	78	60*		–	–	–	–	24	13	–	–	58	71
Dosluoglu 2009[22]	344	89	99*		40	44	–	–	0	12	26	17	59	73
Gillgren 2011[23]	112	53	34*		52*		21*		17*		–*		25*	
Klaphake 2018[24]	428	175	52*		59*		29*		18*		–*		–*	
Lejay 2012[25]	167	167		–		23		–		–		–		–
de Leur 2012[10]	191	72	60	29	43	56	56	58	8	11	–	–	–	–
Mathur 2015[26]	478	196	59*		68*		–*		7*		–*		48*	
Nehler 1993[27]	88	88		53		94		–		–		–		31
Rodriguez 2016[28]	53	53		–		–		–		–		–		–
Salas 2004[29]	98	98		37		63		–		–		–		14
Shirasu 2016[34]	106	19	77	79	89	86	–	–	69	21		–	52	42
Steunenberg 2016[30]	36	36		25		83		–		–		19		–
Uhl 2016[31]	270	92	76	35	64	75	–	–	6	1	–	–	41	35
Uhl 2017[32]	624	221	69	51	78	78	–	–	12	6	–	–	44	52

Data are presented as %, unless stated otherwise. CAD = coronary artery disease; Kidney failure = dialysis dependent; Pulm. disease = chronic pulmonary disease; – = data not available.

* Data inseparable between patients <80 years and ≥80 years.

† Empty cells indicate studies not including patients <80 years.

Primary outcomes

Twelve of the 21 studies, including 17 118 patients, compared the outcomes after revascularisation between age groups and were selected for inclusion in the comparative meta-analysis. The other nine studies only involved one age group (octogenarians) and were therefore excluded from the meta-analysis[15-18,25,27-30] (Fig. 1). The individual results of all studies and pooled outcome estimates are presented in Table 3. The outcomes of the comparative meta-analysis are summarised in Fig. 2 and Tables 4 and 5.

Table 3. Individual results of studies included in this systematic review with meta-analysis, depicting one year mortality, major amputation, and/or amputation free survival (AFS) rate for octogenarians and non-octogenarians

Study	One year mortality – %			One year major amputation – %			One year AFS – %		
	<80 years†	≥80 years	p*	<80 years†	≥80 years	p*	<80 years†	≥80 years	p*
Arvela 2011[15]		34.4			–			58.6	
Atar 2005[16]		–			14.8			–	
Ballotta 2010[17]		9			4			88	
Baubeta 2017[33]	–	–		14	17		–	–	
Biasi 2017[18]		32			–			62	
Brosi 2007[19]	OS: 16.5 Endo: 23.8	OS: 37.4 Endo: 31.7	.044	OS: 17 Endo: 19.7	OS: 11.8 Endo: 18.2	NS NS		–	
Dermody 2015[20]	5.9–9.5	25.7	<.001	12.6–23.5	13.1	<.001	68.5–74.7	58.8	.007
Domenick 2012[21]	–	–		15.6	5.6	.03	–	–	
Dosluoglu 2009[22]	OS: 22 ± 4 Endo: 21 ± 3	OS: 35 ± 5 Endo: 39 ± 6	NS .019	OS: 39 ± 11 Endo: 18 ± 3	OS: 23 ± 9 Endo: 7 ± 3	NS .015	–	–	
Gillgren 2011[23]	–	–		–	–		77	57	NS
Klaphake 2018[24]	OS: 16 Endo: 21	OS: 32 Endo: 36		–	–		–	–	
Lejay 2012[25]		OS: 26 Endo: 32			OS: 9 Endo: 6			–	
de Leur 2012[10]	OS: 19 Endo: 15	OS: 50 Endo: 24	<.01 NS	OS: 9 Endo: 7	OS: 17 Endo: 15		–	–	
Mathur 2015[26]		–			–		73–78	73	
Nehler 1993[27]		27			6			–	
Rodriguez 2016[28]		44			20			50	
Salas 2004[29]		29			–			–	
Shirasu 2016[34]	13	6		6	5		16	10	
Steunenberg 2016[30]		60			–			–	
Uhl 2016[31]	12.7	31	<.001	12.5	12.4	NS	–	–	
Uhl 2017[32]	–	–		10	5	.01	75	77	NS
Pooled meta-analysis (95% CI)	17 (11–22) I^2 = 91%	32 (27–37) I^2 = 66%		15 (11–18) I^2 = 89%	12 (7–14) I^2 = 79%		69 (58–81) I^2 = 96%	64 (54–74) I^2 = 90%	

Data are presented as mean or mean ± standard deviation, unless stated otherwise. To account for interstudy heterogeneity, random effects modelling was used to calculate pooled outcome estimates. NS = not significant; OS = open surgery; Endo = endovascular; CI = confidence interval; I^2 = statistical heterogeneity assessed by I^2 statistics; AFS = amputation free survival.

* p values of < .050 represent statistical significance.

† Empty cells indicate studies not including patients <80 years.

Mortality. Seven of the 12 studies included in the meta- analysis reported one year mortality data (1 238 octogenarians, 3 695 non-octogenarians).[10,19,20,22,24,21,32,34] The pooled mortality rate was 32% in the octogenarian group (95% CI 27-37%; I^2 = 66%) and 17% in the non-octogenarian group (95% CI 11-22%; I^2 = 91%). Comparative analysis showed a significantly increased one year mortality rate in the octogenarian group (OR 2.52, 95% CI 1.93-3.29; Fig. 2A). Low heterogeneity was found among the studies (I^2 = 44%, p = .10). A significantly increased mortality rate was found in octogenarians treated by both endovascular and surgical revascularisation (Appendix 3). Significance was maintained in the sensitivity analyses for both larger studies and low risk of bias studies (NOS ≥ 7; Table 5). The GRADE quality rating was “low” for this outcome (Table 4).

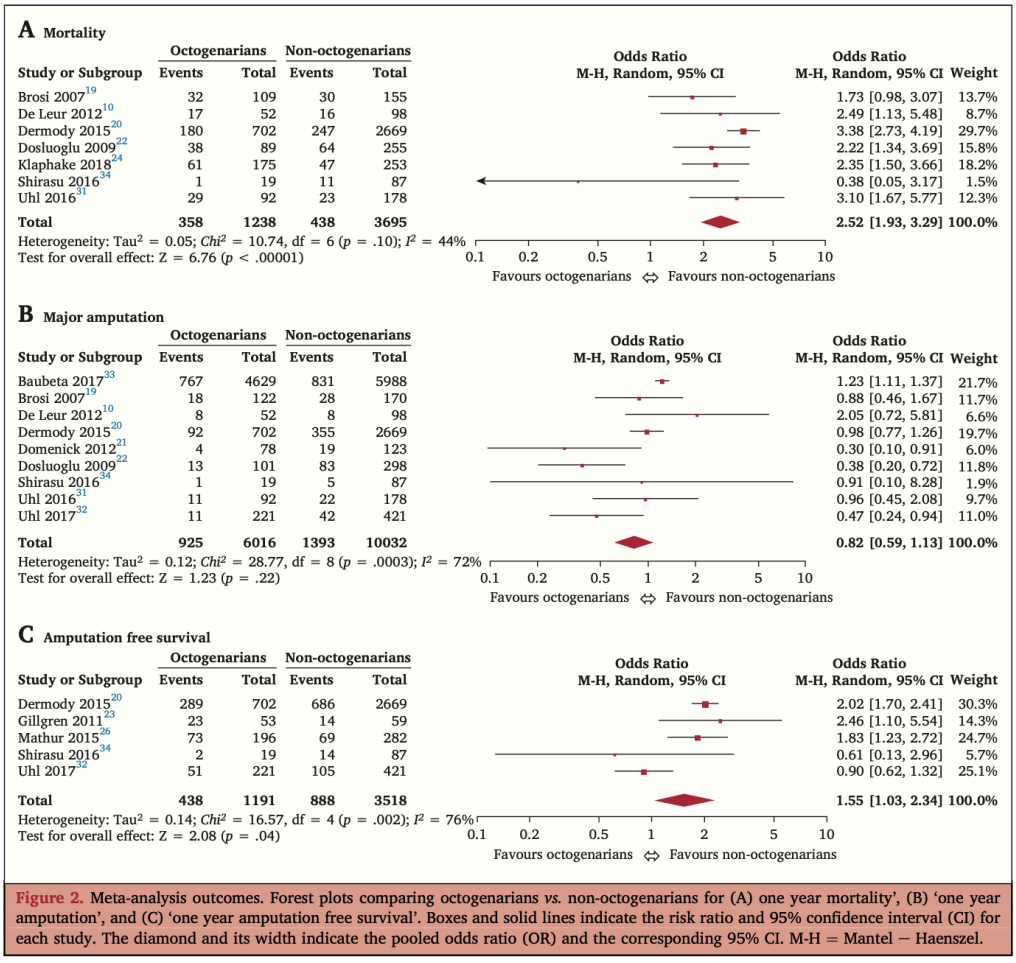

Figure 2. Meta-analysis outcomes. Forest plots comparing octogenarians *vs.* non-octogenarians for (A) one year mortality', (B) 'one year amputation', and (C) 'one year amputation free survival'. Boxes and solid lines indicate the risk ratio and 95% confidence interval (CI) for each study. The diamond and its width indicate the pooled odds ratio (OR) and the corresponding 95% CI. M-H = Mantel – Haenszel.

Major amputation. Eight studies reported one-year major amputation data (6 016 octogenarians, 10 032 non-octogenarians).[10,19-22,31-34] The pooled amputation rate was 12% in the octogenarians (95% CI 7-14%; I^2 = 79%) and 15% in the non-octogenarians (95% CI 11-18%; I^2 = 89%). In comparative analysis, no significant difference was found between age groups (Fig. 2B). Heterogeneity among the studies was moderate (I^2 =72%, p < .001). In a subgroup analysis differentiating between endovascular and surgical revascularisation, amputation rates were comparable among age groups, and no difference in amputation rate was found within the octogenarian group between treatments (Appendix 3). The difference in amputation rates did

become statistically significant when analysing studies with NOS ≥ 7 only (OR 0.61, 95% CI 0.39-0.96; Table 5). The GRADE rating was “very low” for this outcome (Table 4).

Amputation free survival. Five studies reported data on one-year AFS (1 191 octogenarians, 3 518 non- octogenarians).[20,23,26,32,34] Pooled AFS was 64% for octogenarians (95% CI 54-74; I^2 = 90%) and 69% for non-octogenarians (95% CI 58-81%; I^2 = 96%). Comparative analysis revealed a significantly lower one-year AFS in octogenarians (OR 1.55, 95% CI 1.03-2.34) (Fig. 2C). Heterogeneity was significant (I^2 = 76%, p = .002). Significance was lost in the sensitivity analysis for larger studies. Sensitivity analysis for high quality studies (NOS ≥ 7) could not be performed, because only one study reached this high methodological quality (Table 5). The GRADE rating was “very low” for this outcome (Table 4).

Table 4. Assessment of the quality of outcomes evidence of this meta-analysis on outcome after revascularisation in octogenarians using the GRADE system (grading of recommendations assessment, development, and evaluation)

	Studies (patients)	1. Risk of bias	2. Inconsistency	3. Indirectness	4. Imprecision	5. Publication bias	Overall quality of evidence
Primary outcomes	12 (17 118)						
Mortality	7 (4 933)	No	No	No	No	–	Low
Amputation	8 (16 048)	Yes	Yes	No	No	–	Very low
Amputation free survival	5 (4 709)	Yes	Yes	No	No	–	Very low
Outcomes subgroup analysis							
Mortality (Cons)	3 (313)	Yes	No	Yes	Yes	–	Very low
Mortality (Amp)	2 (63)	Yes	No	Yes	Yes	–	Very low
Mortality 80+ (Cons *vs.* Revasc)	3 (496)	Yes	No	Yes	Yes	–	Very low
Mortality 80+ (Amp *vs.* Revasc)	2 (254)	Yes	No	Yes	Yes	–	Very low

Risk of bias was assessed by sensitivity analyses if possible. Inconsistency = I^2 > 50%. Indirectness = restriction regarding applicability. Imprecision = total number events less than 300. Publication bias not assessed with funnel plots, as < 10 studies per outcome. Amp = primary amputation; Cons = conservative treatment; Revasc = revascularisation.

Table 5. Summary of findings for the primary outcomes of the meta-analysis and the performed sensitivity analyses combined with the GRADE rating

Sensitivity analysis*	Studies (patients) – *n*	≥80 years	<80 years	I^2 †	*p*	OR (95% CI)	Quality of evidence
Mortality							
All studies	7 (4 933)	1238	3695	44%	.10	2.52 (1.93–3.29)	Low
Larger studies	3 (4 063)	986	3077	66%	.050	2.56 (1.73–3.80)	
NOS ≥ 7	4 (1 306)	465	841	0%	.60	2.28 (1.76–2.96)	
Amputation							
All studies	8 (16 048)	6016	10 032	72%	<.001	0.82 (0.59–1.13)	Very low
Larger studies	5 (15 321)	5775	9546	82%	<.001	0.80 (0.56–1.15)	
NOS ≥ 7	4 (1 603)	536	1067	42%	.16	0.61 (0.39–0.96)	
Amputation free survival							
All studies	5 (4 709)	1191	3518	76%	.002	1.55 (1.03–2.34)	Very low
Larger studies	3 (4 491)	1119	3372	86%	<.001	1.52 (0.94–2.46)	
NOS ≥ 7	1 (642)	221	421	–	–	0.90 (0.62–1.32)	

CI = confidence interval; OR = odds ratio.
* Larger studies = including only studies with >100 patients per age group. Newcastle-Ottawa Scale (NOS) ≥7 = including only studies with NOS ≥7.
† I^2 = heterogeneity assessed by I^2 statistics.

Subgroup analysis and intergroup comparisons

The outcomes of the subgroup analysis for conservative treatment and primary amputation are summarised in Fig. 3. The GRADE quality rating was "very low" for all outcomes of the subgroup analysis (Table 4).

Mortality after conservative treatment. Three of the 10 studies included in the meta-analysis reported mortality data after conservative treatment as well (160 octogenarians, 153 non-octogenarians).[10,19,24] Low heterogeneity was found among the studies (I^2 = 0%, p = .42). Comparative analysis showed a significantly increased mortality rate in octogenarians (OR 3.00, 95% CI 1.80-5.00; Fig. 3A).

Mortality after primary amputation. Two studies reported mortality after primary amputation (27 octogenarians, 36 non-octogenarians).[10,24] Heterogeneity was again low (I^2 = 0%, p 1⁄4 .46). No significant difference was found between age groups (Fig. 3B).

Conservative treatment vs. revascularisation in octogenarians. In three studies, 160 octogenarians were treated conservatively and 336 underwent revascularisation.[10,19,24] Low heterogeneity was found (I^2 = 0%, p = .42) and the mortality rate was significantly higher among those treated conservatively (OR 1.76, 95% CI 1.19-2.60; Fig. 3C).

Primary amputation vs. revascularisation in octogenarians. In two studies, 27 octogenarians were treated by primary amputation and 227 octogenarians underwent revascularisation.[10,24] The heterogeneity between studies was low (I^2 = 12%, p = .29) and no significant difference in one year mortality rate was found between groups (Fig. 3D).

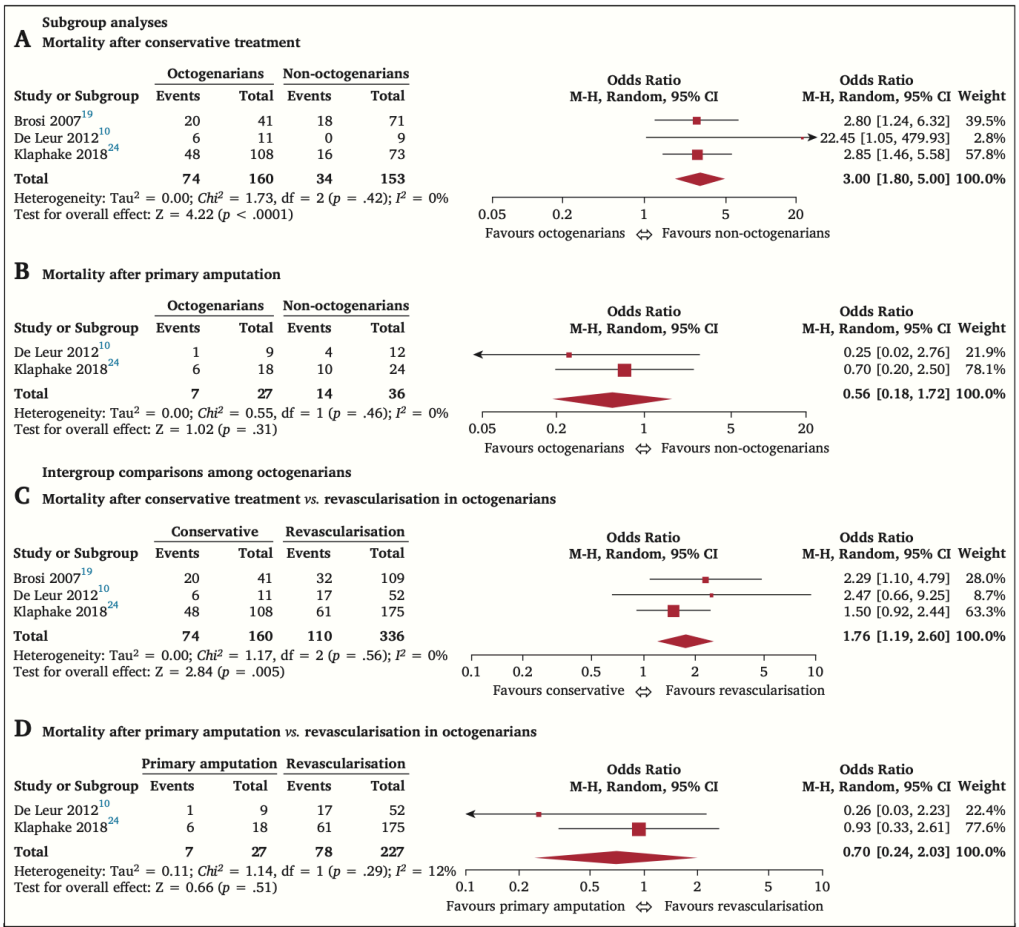

Figure 3. Subgroup analyses and intergroup comparison. Forest plots comparing octogenarians and non-octogenarians for one year mortality after (A) conservative treatment or (B) primary amputation. In addition, forest plots comparing the one year mortality in octogenarians after revascularisation with (C) conservative treatment or (D) primary amputation, respectively. Boxes and solid lines indicate the risk ratio and 95% confidence interval (CI) for each study. The diamond and its width indicate the pooled Odds ratio (OR) and the corresponding 95% CI. M-H = Mantel – Haenszel.

Discussion

Despite the increasing number of octogenarians with CLTI, there is no agreement on the optimal management of these patients. In this systematic review and meta-analysis, the effectiveness of revascularisation in octogenarians was assessed. Advanced age is a well-known risk factor in cardiovascular diseases and therefore it was hypothesised that it would influence the outcomes of revascularisation. However, as randomised clinical trials will never be ethically justifiable, this

large sample size meta-analysis attempted to ensure methodologically valid verification of a generally believed expectation. Indeed, an important one-year mortality rate of 32% was found in octogenarians. This outcome is of major importance for clinical practice to inform patients and colleagues adequately during the decision-making process on any intervention in this fragile patient group.

No significant difference was found regarding the amputation rates between age groups, suggesting that the amputation rate in octogenarians was probably underestimated because of the high mortality rate. As described above, the finding of a higher mortality rate in octogenarians is not surprising; however, the substantial mortality rates found in the individual studies and in the meta- analysis need to be addressed in clinical practice and may justify a more conservative approach. However, only low and very low-quality evidence could be reached supporting the results of this meta-analysis as only observational studies were available for inclusion. An important short-coming of the existing literature is that data on the clinical outcomes of conservative treatment of CLTI are limited. These results would be extremely valuable in decision making, putting assumed benefits of revascularisation into perspective, especially for a frail patient group like octogenarians. In this review, five studies mentioned clinical outcomes after conservative treatment, reporting inconsistent results.[10,19,24,28,30] In a recent study by Santema et al., the authors concluded that revascularisation was not required in all patients with CLTI, because of similar overall survival and AFS rates found in their study.[35] However, differences between octogenarians and non-octogenarians were not analysed. Data on clinical outcomes of primary amputation in patients with CLTI are limited as well and described in two studies only, describing comparable mortality rates after primary amputation and revascularisation.[10,24]

When comparing the mortality rates in octogenarians after revascularisation with the outcomes after conservative treatment in the subgroup analysis of the present meta- analysis, there was significantly increased survival after revascularisation (OR 1.76, 95% CI 1.19-2.60). These findings suggest that the survival of octogenarians was slightly improved by revascularisation, despite the high mortality rate found in the primary analysis. Primary amputation achieved comparable survival rates to revascularisation in octogenarians. However, the number of conservatively treated patients in the included studies was limited. In addition, selection bias

might have influenced these outcomes as patients in poor clinical condition are more likely to undergo conservative treatment. The small number of studies reporting conservative treatment of CLTI and their conflicting results, underline the lack of knowledge within this field. None of the included and described studies performed a quality-of-life analysis. This information would be of major importance to be able to discuss whether revascularisation is always the optimal management of octogenarians with CLTI.

A recent meta-analysis of endovascular abdominal aortic aneurysm repair outcomes in octogenarians did find higher mortality rates in octogenarians (9% in octogenarians vs. 4% in non-octogenarians), but concluded that such mortality was still acceptable and an appropriate therapeutic approach.[7] However, it should be acknowledged that elective aortic aneurysm repair is a preventive intervention to avoid rupture and therefore is not indicated in patients with limited life expectancy. Revascularisation in CLTI patients is performed in symptomatic patients, a totally different clinical situation, and therefore may not also be indicated in patients with limited life expectancy. The mortality rate of 32% in octogenarians after revascularisation found in the present meta-analysis is an important message, which needs to be discussed to reach adequate informed consent. However, as the mortality rate in conservatively treated octogenarians was even higher in this limited analysis, revascularisation may be lifesaving in a selected population of octogenarians. Additionally, there is growing evidence that certain selected patients may be appropriately treated by primary amputation or conservative treatment, which should be addressed in the clinical decision making. In this frail population, it is clear that the focus should be more on the quality of life gained by a therapeutic approach. Steunenberg et al. did not find significant differences in six month mortality in octogenarians after endovascular, surgical, or conservative treatment, but observed in all patients a significantly increased quality of life at six months, including conservatively treated patients.[36]

A recently published study on multi- disciplinary approach and conservative treatment of patients with mild to moderate ischaemia and tissue loss reported an impressive limb salvage rate of 89.3% at long term follow up.[37] Future high quality research should aim to further define factors to select patients for conservative vs. revascularisation management. An individual revascularisation approach based on specific clinical and anatomic patterns should be initiated for octogenarians, in the context of the current Global Vascular Guidelines on the Management

of CLTI.[38] These guidelines also recently introduced the new terminology chronic limb threatening ischaemia (CLTI) rather than chronic limb ischaemia (CLI) to adequately address the broad and heterogeneous group of patients with varying degrees of ischaemia. It is important to note that the new terminology was used throughout this article according to the recommendations, whereas included studies used CLI since they were published before the new guidelines.

Limitations and quality of evidence

Regarding the strength of the evidence supporting the results of this meta-analysis, several limitations have to be considered, and the results should therefore be interpreted with caution. First, no randomised controlled trials (RCTs) were available for inclusion. In addition, 19 of the 21 studies were retrospective cohort studies, increasing the risk of information bias. The current Global Vascular Guidelines on the Management of CLTI also stressed that high quality data on "evidence-based revascularisation" is limited.[38] Only five studies reached high methodological quality and therefore low risk of bias in this review. Four of the studies were published >10 years ago. Differences in life expectancy could have influenced the results; however, as most studies were published rather recently, this was not expected to be of major impact. Another limitation when comparing octogenarians with non-octogenarians is the inconsistency in the non-octogenarian group, in which comorbidities of a 40-year-old CLTI patient may differ significantly from those of a 78-year-old CLTI patient. Despite concurrent results in most sensitivity analyses, the quality of evidence for most out- comes was "very low", as the GRADE rating for observational studies starts per definition at "low" quality. In particular, the outcomes of the subgroup analysis should be interpreted with caution because of the small number of patients, leading to imprecision and indirectness. As mentioned, selection bias is an issue in this subgroup analysis. Furthermore, any bias in the selection and data extraction of the studies or in the quality assessment of the study design cannot be ruled out, despite two independent reviewers performing these processes. Publication bias was not assessed because the recommended minimum of 10 studies per outcome was not reached.

Future perspectives

More than 1000 octogenarians and more than 3500 non-octogenarians per outcome were included in this meta-analysis. However, only observational cohort studies could be included leading to low quality evidence supporting the results of the meta-analysis. In addition, data on clinical outcomes after conservative management and primary amputation in patients with CLTI are limited. Additional studies are needed to provide more solid results and to determine the optimal management of octogenarians with CLTI. Outcomes after revascularisation have to be compared with outcomes after conservative treatment or primary amputation and standardised study designs and end points should be used as promoted by the current Global Vascular Guidelines on the Management of CLTI.[38] These results should also be used to develop adequate risk scores, enabling appropriate patient selection. Furthermore, quality of life studies should be performed to decide whether revascularisation interventions are always indicated in this group of frail patients.

Conclusion

In octogenarians with CLTI, a substantial one-year mortality rate of 32% was found after revascularisation, significantly higher than in patients aged <80 years. However, only low-quality evidence could be reached supporting the results of the present meta-analysis as only observational studies were available for inclusion. The high mortality in octogenarians after revascularisation for CLTI needs to be addressed in the (outpatient) clinic during decision making on any intervention in this fragile patient group. As conservatively treated octogenarians had an even slightly higher mortality rate in this limited analysis, revascularisation may be still life saving in selected octogenarians. The focus should be more on whether patient quality of life is improved by a therapeutic approach rather than increasing physical health and life expectancies of octogenarians. Appropriate patient selection is of major importance and an individual therapeutic approach should be initiated for every octogenarian. Additional studies should further investigate differences in clinical outcomes, including quality of life studies, to determine the optimal management of octogenarians with CLTI. The small number of studies reporting on conservative treatment of CLTI underlines the lack of knowledge within this field.

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Chapter 3

Mortality in Octogenarians With Chronic Limb Threatening Ischaemia After Revascularisation or Conservative Therapy Alone

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Currently, there is no consensus about the optimal management of octogenarians with chronic limb threatening ischaemia (CLTI).[1,2] In this retrospective study clinical outcomes in octogenarians with CLTI were analysed. Patients with CLTI (Rutherford categories 4, 5, and 6) treated at the authors' institution from 2011 to 2017 were reviewed retrospectively. Local ethics committee approval was obtained. Treatment was divided in three groups: endovascular or surgical revascularisation with optimal wound care and medical management, or conservative treatment alone. Primary outcomes were one year mortality, major amputation, and procedure related (30 day) mortality. Clinical success was analysed by comparing toe pressures and wound healing during follow up. Data analysis was performed in SPSS Statistics version 24 (IBM, Armonk, NY, USA). Chi square tests, independent samples t tests, and multivariable Cox regression analysis were done, and p values < .05 were considered to be statistically significant. A total of 329 patients were treated for CLTI (126 octogenarians, 203 non-octogenarians). Of these, 107 octogenarians and 183 non-octogenarians were revascularised, and 19 octogenarians and 20 non-octogenarians were treated conservatively. One year follow up data were analysed for all patients; mean duration of follow up was 29.4 +- 22.4 months. Of the octogenarians, the one year mortality rate was significantly higher (44% vs. 18%; p < .001), whereas the major amputation rates were equal (11% vs. 11%; p = .87). Irrespective of treatment group, the octogenarian mortality rate was twice as high as that of non-octogenarians (Table 1). Procedure related mortality was not significantly different between the two age groups. In both age groups, a significant improvement in mean toe pressure was found after revascularisation (octogenarians: 25 mmHg vs. 53 mmHg, p = .002; non-octogenarians: 29 mmHg vs. 61 mmHg, p < .001). Wound healing was achieved in 69% of octogenarians and 78% of non-octogenarians (p = .082). Wound healing was highest after surgical revascularisation in both age groups (octogenarians 83%, non-octogenarians 85%; p = .92), followed by endovascular revascularisation (71% vs. 81%; p = .13) and conservative treatment (48% vs. 48%; p = .37). Age > 80 years, dialysis, Rutherford category 5/6, and heart failure were predictors of mortality in Cox regression analysis, resulting in a one year mortality rate of 58% after revascularisation when all risk factors were present. Age > 80 years had the strongest correlation with death after endovascular and surgical revascularisation in the Cox regression model (hazard ratio 2.21, 95% confidence interval 1.51-3.23) after correcting for the confounder Rutherford

category and confounding comorbidities such as heart failure and dialysis. Analysis of the main outcomes separated by Rutherford category showed that the clinical outcomes were statistically significantly worse in patients with CLTI Rutherford category 5/6 (mortality 33% vs. 14%, $p < .001$; major amputation 14% vs. 4%, $p = .005$) compared with Rutherford category 4 patients.

In this study, a high one year mortality rate of 44% and a median survival of 1.7 years was found in octogenarians after revascularisation for CLTI. The finding of a higher mortality rate may not be surprising, but the confirmation of such a poor life expectancy, regardless of treatment approach, underlines that the benefit of an intervention may be limited and that clinical decision making is not straightforward. Several relevant clinical predictors of mortality after revascularisation were identified and should be taken into account during the clinical decision-making process on any intervention in octogenarians. There is recent evidence that selected patients may be appropriately treated by primary amputation or conservative treatment as well.[3,4] In this limited analysis, the mortality rate of conservatively treated octogenarians was also high, but no major amputations were performed. Wound healing was achieved in half of conservatively treated patients. However, the subgroup of conservatively treated patients was much smaller and the statistical power of these analyses was limited. Owing to the retrospective design of this study it was not possible to collect sufficient data to perform quality of life (QoL) studies. QoL data are of major importance to determine the optimal management of octogenarians with CLTI. The authors believe that limb salvage is able to contribute to a high QoL, which should be the major therapeutic goal, especially in elderly patients. Steunenberg et al.[3] prospectively analysed QoL in combination with mortality in two age groups (70-79 and >80 years) of patients with CLTI and all patients showed significantly increased QoL results at six months, including conservatively treated patients. A recently published study on a multidisciplinary approach of conservative treatment of patients with mild to moderate ischaemia and tissue loss reported an impressive limb salvage rate of 89.3% at the mid-term follow up.[4] Recently, the PROCLION Registry (Prospective Registration of Critical Leg Ischaemia Out- comes in the Netherlands), a multicentre observational study on outcomes of patients with CLTI in the Netherlands has been initiated, comparing clinical outcomes and QoL after conservative treatment with outcomes after revascularisation. Hopefully, this registry will also

provide sufficient information on elderly patients, and hence recommendations for optimal management (conservative vs. revascularisation) of octogenarians with CLTI, in addition to the current Global Vascular Guidelines on the Management of CLTI.[5]

In conclusion, double mortality rates were found in octogenarians with CLTI after revascularisation, regardless of the technique used, which underlines the need to focus mostly on QoL of these patients because of the limited lifesaving or prolonging effect of these revascularisations. It was possible to demonstrate that initial conservative treatment and delaying revascularisation with close follow up is a safe treatment option in selected patients.

Table 1. Baseline characteristics and clinical outcomes in octogenarians (≥80 years) and non-octogenarians (<80 years) with chronic limb threatening ischaemia

	Octogenarians (n = 126)	Non-octogenarians (n = 203)	p value*
Age − years	86 ± 4.0	67 ± 9.1	
One year mortality	55 (44)	36 (18)	<.001
Endovascular revascularisation	36/87 (41)	19/122 (16)	<.001
Surgical revascularisation	9/18 (50)	11/58 (19)	.009
Conservative treatment	10/21 (48)	6/23 (26)	.21
One year major amputation	14 (11)	22 (11)	.87
Endovascular revascularisation	13/87 (15)	17/122 (14)	1.0
Surgical revascularisation	1/18 (6)	5/58 (9)	1.0
Conservative treatment	0/21 (0)	0/23 (0)	1.0
Procedure related (30 day) mortality	13 (10)	10 (5)	.15
Endovascular revascularisation	9/87 (10)	6/122 (5)	.17
Surgical revascularisation	4/18 (22)	4/58 (7)	.085
Wound healing	87 (69)	159 (78)	.082
Endovascular revascularisation	62/87 (71)	99/122 (81)	.13
Surgical revascularisation	15/18 (83)	49/58 (84)	.92
Conservative treatment	10/21 (48)	11/23 (48)	.37

Data are presented n (%) or as mean ± standard deviation.
*Differences between the two age groups were assessed by chi square tests for categorical data.

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Chapter 4

A systematic review on the use of muscle flaps for deep groin infection following vascular surgery

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Abstract

Objective: The aim of this systematic review is to assess potential differences in effectiveness (graft loss and limb loss) be- tween the sartorius muscle flap (SMF) and the rectus femoris muscle flap (RFF) coverage technique for deep groin wound infection following vascular surgery. Our hypothesis was that RFF reconstruction is more effective in groin coverage.

Methods: The PubMed, Embase, and Medline databases were systematically searched by two independent researchers for articles reporting effectiveness of both muscle flaps in the treatment of groin infections following vascular surgery. After quality assessment using the Newcastle-Ottawa Scale and Methodological Index for Non-Randomized studies (MINOR) scores and data extraction, individual results of the included studies were reviewed. Weighted pooled outcome estimates were calculated.

Results: A total of 17 studies comprising 544 SMF reconstructions and 238 RFF reconstructions were included. The pooled flap survival rate was 100% in both groups, with a pooled amputation rate of 0% and 2%, respectively. In the RFF group, a pooled 30-day mortality rate of 0% was found, compared with 1% in the SMF group. Pooled graft loss rates were 2% in the RFF group and 21% in the SMF group. Only one head-to-head comparison between both muscle flaps was performed, finding no significant differences.

Conclusions: Deep groin infection after vascular surgery can be treated with debridement and local muscle flap coverage. In this systematic review, superiority of either muscle flap on amputation or mortality rates was not demonstrated; however, there was a lower rate of vascular graft loss after RFF reconstruction. These conclusions are based on low-quality evidence because of limited data. Local muscle flap reconstruction using both techniques is effective in the treatment of infected groin wounds, achieving good results in a fragile group of patients. Therefore, anatomical and patient characteristics, which were not assessed in this analysis, are critical in the decision-making process on which muscle flap reconstruction is the best treatment option for an individual patient.

Introduction

Deep groin wound infections following various vascular interventions are an important health care problem with potentially limb- and even life-threating consequences for the patient. Mortality rates resulting from deep vascular wound infections range from 6% to 75% and limb loss rates range from 22% to 75%.[1,2] The groin is the most common site for postoperative graft infections in vascular surgery, and infection of a vascular graft leads to an increased risk of bacteremia.[3-5] Effective management of infected groin wounds is therefore of major importance to save limb and life of the patient. Traditional wound management includes administration of systemic antibiotics and removal of the infected vascular graft, followed by revascularization with an extra-anatomic bypass if necessary.[4,6,7] Because of severe morbidity and mortality rates associated with this procedure, surgeons have been searching for an alternative approach to manage deep groin infections.[7] Since 1976, coverage of the groin with a vascularized upper leg muscular flap has been described as an additional approach, and there is growing evidence of possible benefits of this approach.[2,4,8,9]

Muscle flap coverage has positive effects on groin healing because of an increased blood flow with enhanced delivery of oxygen, nutrients, and antibiotics to the infected area and because of immediate elimination of dead space.[3,10,11] The sartorius muscle flap (SMF) and the rectus femoris muscle flap (RFF) are the most commonly used muscles[3,4]; however, both have advantages and disadvantages, whereas a randomized comparison was never performed. The large volume of the rectus femoris muscle, the more reliable blood sup- ply provided by the profundal femoral artery, and the easy mobilization are theoretical advantages of the RFF reconstruction. An increased risk of donor site morbidity is a potential disadvantage.[3]

Although deep groin wound infections are a challenging and frequently seen complication in vascular surgery, remarkably little evidence is available in the literature on the optimal treatment regimen. The theoretical advantages of the RFF compared with the SMF have not yet been reflected in true clinical benefits.[3] It can be hypothesized that the RFF reconstruction is more effective in groin coverage because of the larger volume of the muscle, the greater distance to the infected area, and the more reliable blood supply. However, only studies with limited patient numbers have analysed the outcomes of muscle flaps in this setting. To our

knowledge, no systematic review has addressed this topic and collation of the evidence from smaller studies is needed. Therefore, the aim of this systematic review was to assess the differences in outcomes between the SMF and the RFF used for deep groin wound reconstruction in patients with postoperative deep wound infections following vascular interventions.

Methods

A systematic review was performed based on the Preferred and Reporting Items for Systematic Reviews and Meta-Analyses statement.[12,13]

Literature search and study selection. The PubMed, Embase, and Medline databases were searched systematically by two independent researchers (L.W. and J.C.) for articles related to the effectiveness of both muscle flaps for groin wound reconstruction in treating groin infections following vascular surgery. The following search terms were used: groin infection, prosthetic graft infection, vascular infection, surgical wound infection, groin wound complications, muscle flap, groin wound reconstruction, surgical flap, rectus femoris muscle, sartorius muscle, muscle flap transposition, antibiotics, extra-anatomic bypass, obturator bypass, graft excision, muscle flap survival, limb salvage, amputation, survival, and graft preservation. The literature search strategy is presented in the Appendix (online only). The last search was performed in March 2019. The retrieved records were screened on title, abstract, and result tables. Both re- searchers performed eligibility assessment following the inclusion and exclusion criteria described in the following section. Reviews and case reports with fewer than six cases and articles published in languages different from English, Dutch, German, or Polish were excluded. In addition, the reference lists of included studies were screened for relevant publications. In case of any discrepancy between the two researchers, all decisions were based on consultation of a third independent researcher (B.M.E.M.).

Inclusion and exclusion criteria. Studies were included in this systematic review if they complied with the following criteria, irrespective of the epidemiological design: (1) studies treating

patients with groin wound infections following vascular surgery; (2) studies using the SMF and/or the RFF as part of their treatment strategy; and (3) studies reporting flap survival, amputation rates, or overall survival as primary or secondary outcome. Studies that used other muscle flaps or did not differentiate between the two muscle flaps regarding clinical outcomes were excluded. Groin reconstruction resulting from other causes than previous vascular surgery (such as lymph node excision) were excluded as well.

Data extraction and quality assessment. Two independent researchers (L.W. and B.M.) completed the data extraction regarding the study characteristics, the study methods, type of interventions, and the outcomes of the studies. All required data were present in the published articles. To assess the methodological quality, the Newcastle-Ottawa Scale (NOS) was used for comparative studies and the Methodological Index for Non-Randomized studies (MINOR) score was used for noncomparative studies. The NOS is a scale system based on three domains: selection of study groups (0-4 points), comparability (0-2 points), and assessment of outcomes (0-3 points).[13,14] A maximum of 9 points can be reached. In this scale system, a score from 1 to 3 points was categorized as low quality, 4 to 6 points was categorized as un- clear/moderate quality, and 7 to 9 points was categorized as high quality. The MINOR score is a scale system as well, in which a maximum score of 16 points can be reached.[15] A score from 1 to 6 points was categorized as low quality, 7 to 11 points was categorized as unclear/moderate quality, and 12 to 16 points was categorized as high quality.

Statistical analysis. Because the only two articles that directly compared both muscle flap techniques appeared to be from the same group and had overlapping study periods, no comparative statistical analysis was performed. It is likely that both study populations are largely overlapping. Instead, the metaprop_one command was used in Stata version 14.1 to calculate weighted pooled outcome proportions using a random-effects model without comparing both techniques in an actual meta-analysis. Pooled outcome estimates were presented as percentages with 95% confidence interval. Statistical heterogeneity was assessed using the I^2 statistic (I^2 values < 50% = low heterogeneity; I^2 values 50%-75% = moderate heterogeneity; I^2 values > 75% = significant heterogeneity).

Results

Study selection

After removing duplicates, the search yielded 3551 articles that were first screened on title and abstract. After this screening, 45 articles eligible for review remained. After full-text screening of these 45 articles, 17 were finally included in this systematic review. The flow chart illustrates this study selection process and reasons for exclusion (Fig 1).

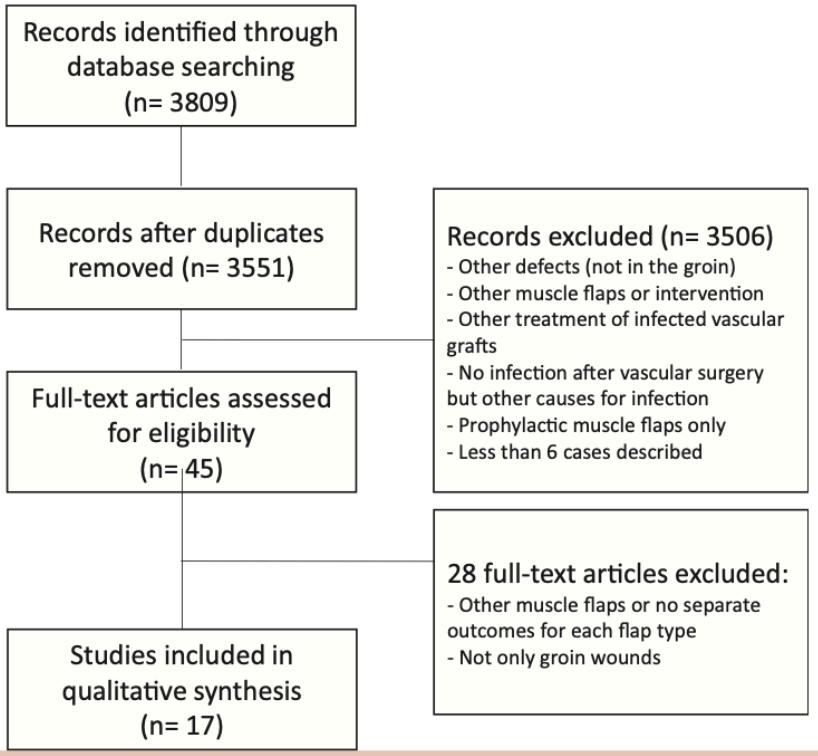

Fig 1. Flow chart illustrating the study selection process.

Study characteristics

The 17 included articles were published between 1994 and 2017.[2,3,9,10,16-28] Two studies were case reports[18,19]; the other 15 were retrospective cohort studies. A summary of the most

important study characteristics of the included articles and the methodological scores is provided in Table I. Four studies were classified as comparative studies and all four were considered to be of higher methodological quality (NOS score > 7 points).[3,9,23,28] The other 13 studies had a noncomparative study design; therefore, the MINOR score was used for quality assessment. None of these studies were considered to be of high methodological quality. The number of patients ranged from 7 to 244 patients.

Table I. Summary of included studies, study design characteristics, and risk of bias

Study	Study period	Location	Study design	Number of institutions	Total patients	SMF	RFF	Follow-up, months	NOS score	MINOR
Mirzabeigi 2017[3]	2005-2014	USA	R	Single	184	108	86	Not given	7/9	
Fischer 2013[9]	2005-2011	USA	R	Single	244	68	69	Not given	7/9	
Alkon 2005[16]	1999-2003	USA	R	Single	33	–	37	Not given		7/16
Armstrong 2007[17]	1994-2006	USA	R	Single	86	89	–	Mean 52 (12-132)		9/16
Colwell 2004[18]	1998-2002	USA	C	Single	9	5	4	2-24		–
Galland 2002[19]	–	UK	C	Single	7	8	–	7-30		–
Graham 2002[20]	1991-2000	South Africa	R	Single	21	18	–	36 (1-96)		9/16
Landry 2009[21]	2005-2008	USA	R	Single	20	21	–	Mean 9.5 ± 10.5		8/16
Meland 1994[22]	–	USA	R	Single	20	9	13	Mean 41 (14-120)		9/16
Nelson 2014[23]	2010-2011	USA	R	Single	43	–	27	Not given	7/9	
Ryu 2016[24]	2000-2009	Korea	R	Single	30	29	–	Mean 14.1 (1-56)		9/16
Schutzer 2015[25]	1996-2001	USA	R	Single	50	50	–	18		9/16
Seify 2006[26]	1989-2001	USA	R	Single	22	16	2	Mean 23		8/16
Taylor 1996[27]	1992-1995	USA	R	Single	10	7	–	Median 5 (1-18)		8/16
Töpel 2011[28]	2007-2010	GER	R	Single	53	34	–	6.4	7/9	
Verma 2015[2]	2000-2009	India	R	Multi	68	72	–	Mean 52 ± 42		11/16
Wu 2006[10]	2000-2004	USA	R	Single	19	10	–	30 (5-45)		9/16

C, Case report; *NOS*, Newcastle-Ottawa quality assessment scale; *R*, retrospective cohort study; *RFF*, rectus femoris muscle flap; *SMF*, sartorius muscle flap.
Colwell and Galland have no scores because they are case reports.

Treatment characteristics

Ten studies reported outcomes after SMF reconstruction only,[2,10,17,19-21,24,25,27,28] two studies after RFF reconstruction only,[16,23] and five studies reported outcomes of both types of interventions.[3,9,18,22,26] Only one research group performed a head-to-head comparison of both

muscle flaps in a larger study population of more than 100 patients.[3,9] In all studies, 929 patients underwent a total of 946 muscle flap reconstructions. Only eight infections were treated without muscle flap reconstruction.[27] A subgroup of 164 flaps was excluded from this systematic review because other muscle flaps were used for reconstruction (n = 16) or the muscle flap reconstruction was performed for other indications than infection (n = 20) or in a prophylactic setting (n = 128).[9,10,20,22-24,26-28] Therefore, the systemic review finally involved 782 muscle flaps. Of these, 544 SMF reconstructions and 238 RFF reconstructions were performed.

Patient characteristics

The mean age of the patients ranged from 59 to 74 years. Two studies did not describe the mean age of their study population.[17,25] The included studies involved 569 males and 360 females. Furthermore, 587 wounds contained prosthetic material and 479 wounds were found to be culture positive for microorganisms. In three studies, baseline characteristics regarding prosthetic material and/or positive wound cultures were not presented.[2,10,24] Only one research group directly compared both muscle flaps and compared the baseline characteristics of both study groups as well.[3,9] The authors described that more patients with coronary artery disease and obesity were found in the RFF group. Furthermore, more positive wound cultures were found in this group.[3]

Clinical presentation

Nine studies only involved patients with deep graft infections in the groin, classified as Szilagyi III infections in seven studies.[2,10,16-18,20,26-28] The other studies did not specify the type of infection or treated patients for groin infections without graft involvement as well (Table II). The timing of infection was specified in nine studies and the rates of early infections (within 4 months after initial vascular surgery) ranged from 10% to 100%.[2,3,17-20,22,24,26] Initial graft preservation was attempted in varying extent between the different studies. In three studies, all grafts stayed primarily in situ.[19,21,28] Seven studies did not clearly state the percentage of primarily graft excision. In the other seven studies, the graft was immediately excised in 10% to 95% of all cases.[16-18,20,22,26,27] In addition, five studies described whether the graft was replaced by additional revascularization.[16-18,20,27]

Table II. Summary of baseline and intraoperative characteristics of the included studies

Study	Total patients	SMF	RFF	Prosthetic material	Positive culture	Timing of infection	Type of infection	Primary graft excision	Additional revascularization
Mirzabeigi 2017[5]	184	108	86	57%	41%	100% early	Szilagyi II and III	NS	NS
Fischer 2013[9]	244	68	69	41%	38%	ND	Infections 35% Drainage 35% Seromas 14%	NS	NS
Alkon 2005[16]	33	–	37	77%	89%	ND	Szilagyi III	5/23 (22%)	EAB = 1
Armstrong 2007[17]	86	89	–	100%	97%	10% early	Szilagyi III	83/89 (97%) 46% partial 51% total	EAB = 4 Autologous = 57 PTFE = 2 Rifampin-PTFE = 20
Colwell 2004[18]	9	5	4	67%	100%	100% early	Szilagyi III	2/9 (22%)	Graft replaced = 2
Galland 2002[19]	7	8	–	100%	63%	38% early	Pus in all wounds	0%	No
Graham 2002[20]	21	18	–	100%	86%	62% early	Szilagyi III	2/21 (10%)	PTFE = 1 Autologous = 1
Landry 2009[21]	20	21	–	81%	67%	ND	Infection 38% Hematoma/seroma 43% Pseudoaneurysm 19%	0%	No
Meland 1994[22]	20	9	13	100%	92%	90% early	Szilagyi I-III	7/20 (35%)	ND
Nelson 2014[23]	43	–	27	48%	33%	ND	Infection 48% Hematoma/seroma 26% Lymphocele 26%	NS	NS
Ryu 2016[24]	30	29	–	–	70%	83% early	Infection	NS	ND
Schutzer 2015[25]	50	50	–	50%	100%	ND	Major wound necrosis or infection	NS	ND
Seify 2006[26]	22	16	2	42%	65%	56% early	Graft infection	12/18 (67%)	ND
Taylor 1996[27]	10	7	–	100%	76%	ND	Szilagyi III	2/7 (29%)	PTFE = 2
Töpel 2011[28]	53	34	–	70%	71%	ND	Szilagyi III	0%	No
Verma 2015[2]	68	72	–	76%	–	40% early	Szilagyi III	NS	ND
Wu 2006[10]	19	10	–	–	–	ND	Perigraft/graft infection	ND	ND

EAB, Extra-anatomic bypass; *early wound infection*, within 4 months after initial surgery; *ND*, not described; *NS*, not stated; *PTFE*, polytetrafluoroethylene; *RFF*, rectus femoris muscle flap; *SMF*, sartorius muscle flap; *Szilagyi I*, infection involves only the dermis; *Szilagyi II*, infection extends into the subcutaneous tissue but does not invade the arterial implant; *Szilagyi III*, the arterial implant is involved in the infection.

Outcomes

Different outcome measures were used in the included studies (Table III).

Flap survival. Overall flap survival rate was described in 13 studies, ranging widely from 29% to 100% after SMF reconstruction and from 62% to 100% after RFF reconstruction. In the majority of the articles (nine studies), a flap survival rate of more than 95% was found for both muscle flap operations. The weighted pooled flap survival rate was 100% in both groups (SMF: 95% confidence interval [CI] 99-100; I^2 = 63% and RFF: 95% CI 100-100; I^2 = 62%).

Limb loss. Amputation rates were described in 16 studies, ranging from 0% to 38% after SMF reconstruction and from 0% to 25% after RFF reconstruction. In six studies, no amputations were

performed at all. The weighted pooled amputation rate was 2% (95% CI, 0-4; I^2 = 458%) in the RFF group and 0% (95%CI, 0-0; I^2 = 70%) in the SMF group.

Thirty-day mortality. Thirty-day mortality rates were analysed in nine studies, ranging from 0% to 15%. In three studies, no deaths were recorded within the first 30 days. In the RFF group, a weighted pooled 30-day mortality rate of 3% (95% CI, -1 to 2; I^2 = not calculated) was found, compared with 1% (95% CI, 0-3; I^2 = 57%) in the SMF group.

Vascular graft loss. Finally, graft loss was described in 11 studies, ranging from 0% to 100% for SMF reconstruction and from 0% to 22% after RFF reconstruction. Graft loss was defined as secondary excision of the vascular graft in a reintervention after previous muscle flap coverage. The weighted pooled graft loss rate was 2% (95% CI, -1 to 5; I^2 = 78%) in the RFF group and 21% (95%CI, -17 to 59; I^2 = 100%) in the SMF group.

Head-to-head comparison. Only Fischer et al and Mirzabeigi et al directly compared the effectiveness of both interventions in their study population. Limb loss and vascular graft loss, as separate outcomes, were not significantly different be- tween both muscle flaps (Table III).[3,9] However, when analysing a combined endpoint, a significant difference in overall major limb-related complications (graft loss, limb loss, or reoperation) was found. Fischer et al reported a significant lower major limb related complication rate of 2.9% when the RFF was used, compared with 13.2% after using the SMF.[9]

Table III. Individual results of included studies

	Muscle flap survival		Amputation rate			30-day mortality rate		Graft loss		
Study	**SMF**	**RFF**	**SMF**	**RFF**	**SD**	**SMF**	**RFF**	**SMF**	**RFF**	**SD**
Mirzabeigi 2017[5]			4%	6%	NS[a]			16%	22%	NS[a]
Fischer 2013[9]			7%	3%	NS[a]			7%	1%	NS[a]
Alkon 2005[16]		100%		8%			15%		17%	
Armstrong 2007[17]	100%		0%			2%		100%		
Colwell 2004[18]	100%	100%	0%	25%		0%	0%	0%	0%	
Galland 2002[19]	75%		13%			0%		38%		
Graham 2002[20]	94%		29%							
Landry 2009[21]	95%		0%					0%		
Meland 1994[22]	78%	62%								
Nelson 2014[23]				0%					0%	
Ryu 2016[24]	97%		3%			3%		3%		
Schutzer 2015[25]	98%		12%			12%				
Seify 2006[26]	100 %	100%	38%	0%						
Taylor 1996[27]	29%									
Töpel 2011[28]	97%		7%			3%		12%		
Verma 2015[2]			0%					13%		
Wu 2006[10]	100%		0%			0%				
Pooled (95% CI)	100% (99-100)	100% (100-100)	0% (0-0)	2% (0-4)		1% (0-3)	0% (–1 to 2)	21% (–17 to 59)	2% (–1 to 5)	

NS, Not significant; *RFF*, rectus femoris muscle flap; *SD*, significant difference; *SMF*, sartorius muscle flap.
Weighted pooled outcome estimates were calculated using random-effects meta-analysis of proportions in Stata version 14.1.
[a]Outcomes of the only head-to-head comparison available in the literature.

Discussion

The management of severe groin wound complications following vascular interventions remains challenging for vascular surgeons.[26] Although there is growing evidence supporting possible benefits of muscle flap coverage compared with traditional wound management, there is no high-level comparison data available.[2-4,8,9] Furthermore, no true clinical benefits favouring either the SMF or the RFF technique have been described. In this systematic review, the differences in clinical outcomes between both muscle flaps were assessed.

A total of 17 studies were included in this systematic review, reporting wide ranges of flap survival, amputation rates, graft loss, and/or 30-day mortality as outcome measures. The overall consensus was highly positive regarding the effectiveness and safety of muscle flap reconstruction in complex groin wounds, independent from the technique used. Only Taylor et al came to a negative conclusion regarding muscle flap reconstructions in general because of the high local failure rate of 78% in their study.[27] They treated seven patients with an SMF, one patient with a rectus abdominis flap, and another patient with a tensor fascia flap.

The described results suggest a tendency to lower complication rates after using an RFF in comparison to an SMF. After pooling the results, flap survival, limb loss, and 30-day mortality rates were comparable between both groups. In contrast, vascular graft loss was much lower in the RFF group; however, most studies were based on rather small study populations and the SMF was performed twice as often as the RFF. Statistical heterogeneity was found to be moderate or significant for all outcomes. In addition, there was a high heterogeneity between the study populations regarding clinical presentation and extent of initial graft excision vs preservation. These factors could influence the outcomes of muscle flap coverage for infected vascular grafts making it difficult to combine the outcomes of the different studies. Only one research group with larger study populations of more than 100 patients directly compared the effectiveness of both muscle flap interventions, finding no significant differences regarding limb loss or graft loss.[3,9] However, Fischer et al did report significantly better results after RFF coverage when analysing a combined endpoint. The available data are limited and of rather poor quality and a comparative meta-analysis could not be performed. Therefore, we were not able to reveal superiority of either muscle flap, but we were able to demonstrate that muscle flap coverage in general was effective in the management of complex groin wounds.

SMF vs RFF. In the literature, numerous potential advantages and disadvantages have been described for both muscle flaps, but the current available data do not support a clear clinical benefit of one over the other. A major theoretical advantage of using the SMF for reconstruction is that no second soft-tissue defect is required for harvesting the donor flap, which can potentially lead to added morbidity. Another theoretical argument, which might be of concern when using the RFF, is development of a functional limitation in knee extension and strength loss of the operative leg; however, Sbitany et al found no noticeable decrease of quadriceps strength following rectus femoris harvesting.[29] Other studies also did not find significant functional donor-site morbidity.[30,31] A very low donor-site complication rate was also found in the present review.[9,16,23] It can be argued that the greater volume of the muscle and the longer distance to the affected area in the groin are primarily favouring the use of RFF. In addition, the SMF has a more challenging blood supply because it depends on multiple sources of vascularization. It receives segmental blood supply from the superficial femoral artery (SFA) and the proximal part of the muscle receives blood supply from other vessels in this area as well.[32,33]

The SFA is often compromised in patients with peripheral artery disease.[3,4,10,11] However, Töpel et al directly assessed the impact of SFA occlusion on the outcome of SMF reconstruction and did not find an increased risk of flap loss.[28] More important, risk of muscle flap necrosis is increased when the posteromedially entering vascular pedicles are not preserved during mobilization of the muscle flap. To avoid flap necrosis, the SMF should only be mobilized laterally and then twisted into the groin wound.[33] Some studies suggest using the SMF for smaller defects and the RFF if larger, more complex wounds are present, or if skin is needed in the transfer.[9,18] Mirzabeigi et al propose using SMF as first-line approach because of being less invasive without a requirement of a second soft-tissue defect.[3] Finally, Fischer et al suggest also considering the SMF in prophylactic settings to prevent groin com- plications in patients who are at high risk for groin wound infections.[9]

To minimize the risk of donor-site morbidity and functional deficits in knee extension after RFF reconstruction, Nelson et al developed a minimally invasive approach for flap harvest.[23] Standard lighted retractors, commonly used in breast reconstruction, were used for this approach. The outcomes of this approach were compared with the standard incision; no differences in complication rates and operative time were observed.[23]

Limitations. Several limitations have to be considered when interpreting the results of this systematic review. No randomized controlled trials are available until now and most of the included studies are based on rather small study populations. All studies had a retrospective study design, increasing the risk of information bias. In addition, most of the included studies were of moderate methodological quality. The SMF was performed more often than the RFF (544 SMF vs 238 RFF) procedure. A large range of different outcome measures were used and often not specifically defined. All of these limitations influenced the interpretation of the results. To minimize bias, two independent reviewers performed this systematic review. Nevertheless, any bias in the selection and data extraction or in the quality assessment of the study design cannot be ruled out.

Conclusion

Muscle flap coverage is effective in the management of deep groin wound infections after vascular surgery, achieving good results in a fragile group of patients. In this systematic review, superiority of either muscle flap on amputation or mortality rates was not demonstrated. Vascular graft loss rates were lower after RFF reconstruction; however, these conclusions are based on low- quality evidence. We would recommend performing muscle flap coverage according to the specific preference and experience of the surgical team as well as anatomical and patient characteristics, which were not assessed in this analysis. Additional studies are needed to provide more solid results and to be able to draw more robust scientific conclusions.

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Chapter 5

Outcome of rectus femoris muscle flaps for groin coverage after vascular surgery

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Abstract

Objective: The aim of this retrospective cohort study was to investigate the outcome of rectus femoris muscle flaps (RFFs) for deep groin wound complications in vascular surgery patients and to compare the outcome with a cohort of sartorius muscle flaps (SMFs) because the RFF is a promising alternative technique for groin coverage.

Methods: All RFFs and SMFs performed by vascular surgeons in a regional collaboration in The Southern Netherlands were retrospectively reviewed. Primary outcomes were muscle flap survival, overall and secondary graft salvage, and limb salvage. Secondary outcomes were 30-day groin wound complications and mortality, donor site and vascular complications, 1-year amputation-free survival, overall patient survival, impaired knee extensor function, and length of hospital stay.

Results: A total of 96 RFFs were performed in 88 patients (mean age, 68 years; 67% male) and compared with a cohort of 30 SMFs in 28 patients (mean age, 64 years; 77% male). At a mean follow-up of 29 months and 23 months, respectively, comparable flap survival (94% vs 90%), secondary graft salvage (80% vs 92%), and limb salvage (89% vs 90%) rates were found. The 30-day mortality rates were 12% and 17%, respectively, and the 1-year amputation-free survival was comparable between treatment groups (71% vs 68%).

Conclusions: This study presents a large series of RFFs for deep groin wound complications after vascular surgery. We demonstrate that muscle flap coverage using the rectus femoris muscle by vascular surgeons is an effective way to manage complex groin wound infections in a challenging group of patients, achieving similarly good results as the SMF.

Introduction

Deep groin infections after vascular surgery are a major health care problem with limb-threatening and even life- threatening consequences.[1,2] Despite efforts to prevent surgical site infections, incidences of these deep infections range from 4% to 43%.[3-6] Moreover, mortality and amputation rates are up to 6% to 75% and 22% to 75%, respectively.[1,2]

A commonly used classification system for wound infections was proposed by Szilagyi et al.[7] Grade I describes a superficial infection with involvement of the dermis alone, whereas a grade II infection extends to the subcutaneous tissue. A grade III infection affects the vascular graft with an increased risk of bacteraemia and blowout.[7] Traditional wound management of these grade III wound infections includes administration of systemic antibiotics and removal of the infected vascular graft, followed by revascularization with an extra-anatomic bypass if necessary.[7-9] Since 1980, coverage of the groin with a vascularized sartorius muscle flap (SMF) has been described as an additional step to antibiotics and surgical debridement and graft removal if necessary because of high morbidity and mortality rates associated with the traditional procedure.[10] SMF coverage is beneficial because of increased blood flow with enhanced delivery of oxygen, nutrients, and antibiotics to the infected area and because of immediate elimination of dead space.[11-14]

The rectus femoris muscle flap (RFF) was introduced in 1989 as a promising alternative technique for groin coverage with several theoretical advantages, such as the greater volume of the muscle and the longer distance between the muscle origin and the affected area in the groin.[15] Often, after extensive debridement of an infected groin wound, a large defect remains that can be filled more adequately with the bulky RFF. In addition, the RFF most frequently has a more sufficient blood supply provided by the profunda femoris artery, in contrast to the SMF, which is dependent on the often-compromised superficial femoral artery. Risk of muscle flap necrosis is increased when the SMF is used and mobilization of the muscle flap is not performed adequately, preserving the posteromedially entering vascular pedicles. A disadvantage of the RFF could be the second tissue defect resulting from harvest of the rectus femoris muscle.[11,14,16,17]

The decision as to whether the SMF or the RFF is chosen for muscle flap coverage mostly depends on preference and experience of the surgeon and hospital. Even though a recent study did not demonstrate superiority of the RFF over the SMF in clinical effectiveness,[16] we hypothesized that the RFF reconstruction is more effective in groin coverage because of the advantages described before. In our regional collaboration, the RFF has become the preferred method of muscle flap coverage of debrided infected groins after vascular surgery. The aim of this study was to describe our experience with the RFF and to compare it with a cohort of SMF coverage for groin wound complications in vascular surgery.

Methods

A prospectively collected cohort of muscle flaps was retrospectively reviewed in three hospitals forming a regional collaboration in the southern part of The Netherlands (European Vascular Center Aachen- Maastricht/MUMC, VieCuri Hospital Venlo, and Maxima Medical Center Veldhoven [MMC]). Approval of the local ethical committee was obtained before the start of this study. Because of the retrospective character of this study, patient informed consent was not obtained. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies were followed. Vascular patients with RFFs or SMFs were retrospectively analysed. In the MMC, all muscle flaps performed after 2001 were included. In Venlo and in the European Vascular Center, inclusion started in 2008 and 2011, respectively.

Study population and data collection. Similar patient inclusion and exclusion criteria were used in all three centres. Included were all individuals who received an RFF or SMF performed by a vascular surgeon. Patients undergoing a muscle flap reconstruction in the groin for reasons other than a vascular surgery-related indication or undergoing another type of muscle flap reconstruction were excluded. RFFs and SMFs were performed as salvage flaps for groin complications. Electronic medical record systems were used to identify patients' demographics and comorbidities. Baseline characteristics (age, sex), risk factors, and comorbidities (diabetes mellitus [type 1 and type 2], smoking, body mass index, hypertension, hypercholesterolemia, history of cardiac disease, chronic obstructive pulmonary disease, and chronic kidney disease [glomerular filtration rate <30 mL/min/1.73 m^2]) were recorded. In addition, operative

characteristics (history of prior groin surgery, underlying nonautologous graft, indication for flap transposition, surgical procedures, wound cultures) and clinical outcomes (complications and reinterventions within 30 days, flap survival, graft loss, major amputation, survival, length of hospital stay, and function of the leg) were recorded. An amputation proximal to the ankle joint was defined as major amputation and therefore as limb loss. In this study, graft loss was differentiated into primary and secondary graft loss. In case of primary graft loss, the vascular graft was removed primarily within the same operation as the muscle flap coverage. In case of secondary graft loss, graft salvage was primarily intended but the vascular graft had to be removed during follow-up in a reintervention.

Surgical technique and decision-making. Vascular surgeons of all four hospitals were proficient in the harvest and use of the RFF and SMF. After surgical debridement of the groin wound, a decision was made to perform either flap. The operating surgeons also made the decision between arterial graft preservation and graft excision at the moment of debridement. In general, each location had a preferred muscle coverage technique, which was mostly the RFF. Only in one center (the MMC) were both flaps performed. In the MMC, the SMF was used in cases of small defects after debridement and limited dead space. In Aachen (one of two locations of the European Vascular Center), the SMF was the preferred technique and surgeons at this location performed only the SMF, regardless of the wound defect and infection burden.

For RFF coverage, one or two smaller longitudinal mid-anterior incisions were made extending over the distal two-thirds of the thigh. The rectus femoris muscle was identified, followed by disinsertion from the patellar bone attachment from its fascial connections. The lateral femoral circumflex artery was identified and preserved. The muscle flap was reversed in a distal to proximal approach and passed into the groin wound through a subcutaneous tunnel connecting the harvest site to the groin wound and fixed with resorbable sutures (Fig). Depending on the groin defect, the surgeon decided whether to close the wound in layers over a suction drain in the harvest site or whether to initiate vacuum-assisted closure (VAC) therapy. The donor site was managed by a layered wound closure as well. All RFFs were procedures without a cutaneous harvest component. Including debridement and washout time, the RFF is generally completed within 60 minutes. The technique is also presented in detail with an intraoperative video in a recent publication by Ryer et al.[18]

For SMF harvest, the groin wound incision was extended farther laterally and the fascia was incised, exposing the sartorius muscle. The superior margin of the muscle was detached, and the segmental branches of the superficial femoral artery on the underside of the muscle were identified. The muscle is turned around and placed in the groin wound. In general, drains were used and the wound was closed in layers. Again, the surgeon decided whether VAC therapy should be initiated. Including debridement and washout time, the SMF is generally a slightly shorter intervention compared with the RFF because there is no second donor site to close. All muscle flaps were performed at the same time as the groin debridement.

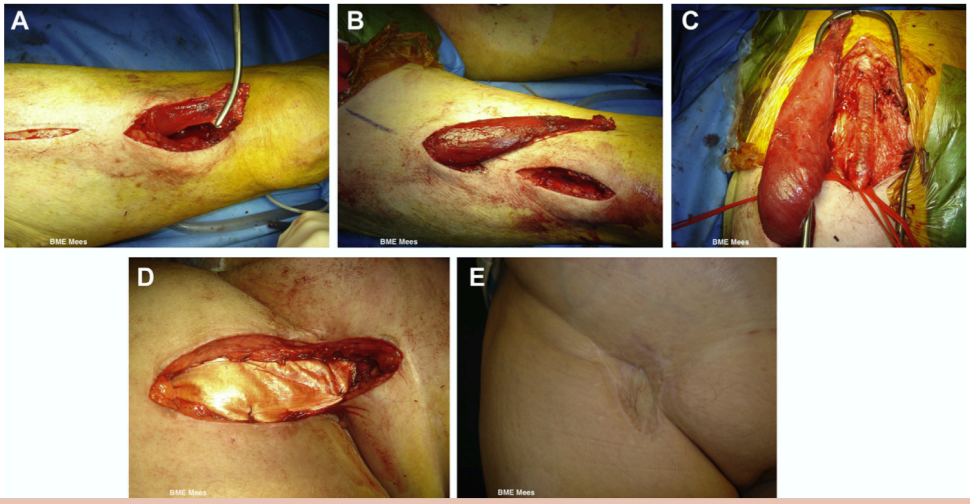

Fig. Illustration of muscle flap coverage using the rectus femoris muscle. **A,** Longitudinal midanterior incisions are made. **B,** The rectus femoris muscle is detached from its patellar insertion. **C,** The muscle flap is passed to the groin wound through a subcutaneous tunnel to cover the vascular graft. **D,** Muscle flap coverage resulted in immediate elimination of dead space. **E,** Complete wound healing was achieved.

Study end points. Primary outcomes were muscle flap survival, graft salvage, and limb salvage. Secondary out- comes were groin wound complications within 30 days (infection, bleeding, or seroma), donor site and vascular complications within 30 days, 30-day mortality, overall amputation-free survival, and patient survival. In addition, morbidity due to impaired muscle power of the knee extensor and length of hospital stay were analysed as secondary outcomes. At follow-up visits, patients were asked whether they had any diminished strength in the leg that was operated on, and any impaired muscle function was documented. Date of last clinical

contact or death was used to calculate the follow-up period per patient. Overall flap survival, graft salvage, and limb salvage were reported for the whole follow-up period.

Statistical analysis. All statistical analyses were performed with SPSS Statistics 24 (IBM Corp, Armonk, NY). Standard descriptive statistics were used for demographic data and baseline characteristics. Categorical data were expressed as counts and percentages, continuous data as mean in combination with the standard deviation. Data analysis was also performed comparing the two groups (RFF vs SMF). Differences between the groups were assessed by c^2 tests. To compare the means of continuous variables, independent samples t-tests were used. Patient survival was analysed using Kaplan-Meier plots, and differences between treatment groups were assessed by the log-rank test. P values of <.05 were considered statistically significant. The SMF group was smaller than the RFF group, which may have reduced the statistical power of all comparative analyses.

Results

During the 17-year study period, a total of 96 RFFs were performed in 88 patients (European Vascular Center, n = 41; VieCuri, n = 21; MMC, n = 34). Baseline patient characteristics are shown in Table I. Two- thirds of patients were male (67%). The mean age was 68 years, and 11 patients were older than 80 years. Severe cardiovascular and pulmonary comorbidities were frequently observed. In addition, almost half (46%) had a body mass index >25 kg/m^2. Also, almost half of the patients were smokers (46%), and 34% of all patients were diagnosed with diabetes.

Table I. Baseline characteristics of 88 patients undergoing 96 rectus femoris muscle flaps (RFFs)

Age at surgery, years	68 ± 9.8 (36-88)
Age >80 years	11 (12)
Sex	
Female	32 (33)
Male	64 (67)
Risk factors and comorbidities	
Diabetes	33 (34)
Smoking	44 (46)
Body mass index, kg/m^2	26 ± 5.3
Body mass index >25 kg/m^2	44 (46)
Hypertension	70 (75)
Hypercholesterolemia	72 (76)
History of cardiac disease	37 (39)
Chronic obstructive pulmonary disease	29 (31)
Chronic kidney disease	6 (6)

Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation (range).

Most patients had a history of prior groin surgery, and most of the groin wounds involved nonautologous graft material (98%; Table II). Details about prior groin operations and their indications are presented in Table II. Two patients were intravenous drug abusers, presenting with infected femoral pseudoaneurysms without a history of prior groin surgery. The average number of previous operations in the groin of interest was 2.5 (range, 0-6). Mean time between the last vascular operation involving the groin and muscle flap reconstruction was 8 months (range, 0-80 months). Bilateral groin coverage in one operation was performed in six patients. Two patients received bilateral muscle flaps in two separate operations during the study period. All muscle flaps were urgent interventions for a vascular surgery-related complication. More than half of the patients presented with classic symptoms of deep groin infection, such as purulent drainage (66%). Other symptoms were bleeding, hematoma, and false aneurysm. During the RFF operations, the vascular graft was removed in 39 of 90 groins with prosthetic graft material in situ (43%). In 11 of these cases, the graft was removed without reconstruction; in 17 cases, the nonautologous graft material was replaced with venous material; and in the remaining 11 cases, nonautologous graft material was used again after primary graft excision.

The 17 venous grafts (10 venous patch and 7 venous bypass) were placed in the groin. The 11 nonautologous grafts were tunnelled extra-anatomically through a sterile field around the infected groin. Nonautologous graft material was used in these patients because a novel vascular bypass reconstruction was necessary to prevent deep limb ischemia due to insufficient collateralization, and there was no venous conduit available of sufficient quality. The newly placed prosthetic bypass graft was extra-anatomically tunnelled outside the infected area. A total of 66 wound cultures were positive for microorganisms. Different microorganisms were isolated from the culture, as shown in Table III. In 9 cases, no wound culture specimen was taken, and in the other 21 cases, the wound cultures remained negative. VAC therapy was initiated in 41 cases (46%).

Table II. Operative characteristics of groins undergoing a rectus femoris muscle flap (RFF) reconstruction (N = 96)

Bilateral groin coverage	6
History of prior groin surgery	94 (98)
No. of previous groin operations	2.5 ± 1.5 (0-6)
Index operation before muscle flap transposition	
Inflow procedures (aorta-bifemoral bypass, femoral-femoral crossover bypass)	31
Isolated groin operation (femoral endarterectomy [thromboendarterectomy], endovascular procedures, thrombectomy bypass, or combinations)	32
Outflow procedure (supragenicular bypass, infragenicular bypass)	15
Combined inflow-outflow procedure	16
Indication for last vascular intervention	
Peripheral artery disease	74
Abdominal aortic aneurysm	6
False aneurysm groin	13
Popliteal aneurysm	1
Time until muscle flap transposition, days	234 ± 507 (1-2473)
Underlying type of vascular graft	
No graft	2
Venous graft	4
Bovine patch	23
Polytetrafluoroethylene	13
Dacron	42
Silver Graft	10
Omniflow	2
Infectious symptoms before flap transposition	
Purulent drainage	63 (66)
Blowout	10 (10)
Bleeding	8 (8)
Hematoma	3 (3)
False aneurysm	12 (13)
Primary graft excision	39 (43)
Without reconstruction	11 (28)
With reconstruction with venous material	17 (44)
With reconstruction with prosthetic material	11 (28)
VAC therapy	41 (46)
Positive wound cultures	66 (73)

VAC, Vacuum-assisted closure.
Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation (range).

Table III. Microbiology of 66 positive wound cultures

	No. isolated
Gram-positive bacteria	45
Staphylococcus spp	
S. aureus	15
S. epidermidis	4
S. warneri	1
S. lugdunensis	1
MRSA	2
Streptococcus spp	
S. faecalis	8
S. haemolyticus	1
Finegoldia magna	2
Gram-negative bacteria	21
Pseudomonas spp	7
Enterobacteriaceae	8
Bacteroides fragilis	3
Nonbacterial	4
Candida albicans	4

MRSA, Methicillin-resistant *Staphylococcus aureus*.

Study end points. The clinical outcomes of our cohort of RFFs are presented in Table IV. An overall flap survival rate of 94% was achieved in this study after a mean of 29 months (range, 0-151 months). As described before, primary graft excision was performed in 39 cases of the RFF group. Of the remaining 51 vascular grafts, 10 grafts had to be removed in a reintervention during follow-up (secondary graft salvage, 80%). At the end of follow-up, 41 of the 90 grafts were still in situ, resulting in an overall graft salvage rate of 46%. An overall limb salvage rate of 89% was achieved in this study. There was no significant difference in major amputation rates between primary graft excision (5/39 patients [13%]) and initial graft preservation (7/55 patients [13%]; P = .56). After primary graft excision, 3 of 11 nonreconstructed patients underwent major amputation during follow-up (27%) compared with 2 of 17 patients with venous reconstruction (12%) and 0 of 11 patients with nonautologous reconstruction. Therefore, the small subgroup of non- reconstructed patients did not have a higher rate of limb loss (P = .16). Mortality rates of 12% and 24% were found at 30-day and 1-year follow-up, respectively. During the first 30 days, five patients died of ongoing infection and sepsis. In these

five patients, arterial graft preservation was attempted in three cases. The other patients died of heart failure (n = 4) or other unrelated causes of death (n = 2, pneumonia and stroke). The 1-year amputation- free survival rate was 71%. Ongoing wound infection was described most often as a complication within 30 days (20%). Most of the patients who suffered from ongoing wound infection were managed with graft preservation (14/19 patients with this complication). Interestingly, the donor site complication rate in the RFF group was low. Only two patients developed bleeding at the donor site. Donor site morbidity due to impaired muscle power of the knee extensor after muscle flap coverage was reported in only two cases.

RFF vs SMF. During the same study period, a total of 30 SMFs were performed in 28 patients (European Vascular Center, n 1⁄4 23; MMC, n = 7). Baseline patient characteristics and operative characteristics of both groups are shown in Supplementary Tables I and II (online only). Flap survival, graft salvage, and limb salvage rates were comparable between groups (Table IV). The Kaplan- Meier plot for survival showed no significant difference in survival rate between treatment groups (Supplementary Fig, online only). The mean survival after operation was 2.9 years in the SMF group and 3.0 years in the RFF group. Differences in 30-day complication rates were not statistically significant as well. However, the inequality of the group sizes has to be considered in interpreting the results of all comparative analyses.

Table IV. Clinical outcomes of the performed rectus femoris muscle flap (*RFF*) reconstructions compared with the performed sartorius muscle flap (*SMF*) reconstructions

	RFF (n = 96)	SMF (n = 30)	*P* value[a]
Overall flap survival	86 (94)	26 (90)	.45
Graft salvage			
Overall graft salvage	41/90 (46)	11/25 (44)	.81
Secondary graft salvage	41/51 (80)	11/12 (92)	.69
Overall limb salvage	84 (89)	26 (90)	1.00
Mortality			
30 days	11 (12)	5 (17)	.53
1 year	23 (24)	6 (24)	1.00
1-year amputation-free survival	67 (71)	17 (68)	.81
Groin wound complications (30 days)			
Ongoing wound infection	19 (20)	4 (13)	.42
Bleeding	10 (11)	2 (7)	.73
Seroma	5 (5)	1 (3)	1.00
Vascular complications[b] (30 days)	13 (14)	5 (17)	.77
Donor site complications (30 days)			
Wound infection	0	0	1.00
Bleeding	1	0	1.00
Morbidity due to impaired muscle power	2 (3)	–	
Length of hospital stay, days	21 (3-239)	31 (9-77)	.06
Follow-up, months	29 ± 29 (0-151)	23 ± 26 (0-100)	.37

Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation (range) or median (range).
[a]Differences between the two treatment groups were assessed by χ^2 tests (in case of categorical data) or independent samples *t*-test and Mann-Whitney *U* test (in case of continuous data).
[b]Any kind of revascularization for critical limb ischemia.

Discussion

The management of groin wound complications after vascular interventions remains challenging for vascular surgeons worldwide.[19] This study presents a large series of RFFs for groin coverage in vascular surgery patients and compares the outcomes with SMFs. We demonstrate that the RFF technique is an effective way to manage deep groin defects after debridement for infection. An overall flap survival rate of 94%, secondary graft salvage rate of 80%, and limb salvage rate of 89% were attained in this study with a mean follow-up of >2 years. These outcomes in the RFF group were comparable to the outcomes of a cohort of SMFs. It must be appreciated that the performed salvage flaps were urgent interventions, underscoring the severity of infections and clinical condition before muscle flap coverage. The 30- day mortality rate of 12% underlines that patients with groin wound infections represent a challenging group of patients for the vascular surgeon with a poor prognosis.[1,2]

A few differences in baseline and operative characteristics were found between treatment groups (Supplementary Tables I and II, online only). VAC therapy was initiated more often in the

SMF group than in the RFF group. This difference is most likely due to a difference in local protocol. Most SMFs were performed in the Aachen, Germany, location of the European Vascular Center Aachen-Maastricht, where VAC therapy is used in a more standard fashion.

It is not surprising that the groin is the most common site for severe postoperative infections after vascular surgery.[11] The majority of peripheral vascular interventions are performed through an inguinal access. The groin harbours an unfavourable wound environment because of the rich lymphatic anatomy and potential for a large dead space.[2,16] Peri genital contamination can also contribute to an active groin wound infection with nonviable soft tissue and gross contamination.[11,16] In addition, multiple risk factors for wound infections, such as advanced age, smoking, and diabetes mellitus, are often found in patients undergoing vascular surgery.[2,16] The baseline characteristics of our study population with high percentages of diabetes and smoking and a high body mass index support this contention. This could also have contributed to the relatively high rate of local groin wound complications after muscle flap coverage. Ongoing infection and bleeding were reported most often but did not lead to flap loss in most patients. Furthermore, in the literature, comparable local complication rates are reported as well. Mirzabeigi et al[16] performed a relatively large muscle flap study in the United States and reported a complication rate of 34%.

Previously, only a few studies have reported on the use of the RFF for deep groin wound infections. Mirzabeigi et al[16] reported 94% limb salvage and 78% graft salvage when using the rectus femoris muscle for reconstruction. Fischer et al[13] reported limb salvage and graft salvage rates of 99% and 97%, respectively. Other reported limb and graft salvage rates are down to 75% and 65%, respectively.[20,21] Our results for limb salvage and graft salvage are comparable to the results reported by Mirzabeigi et al.[16] The graft salvage rate reported by Fischer et al[13] is high in comparison with the literature and our outcomes. Their graft loss salvage was calculated as a percentage of the whole study population, even though only half of the patients had a prosthetic graft in situ. Our study presents the largest European series of RFFs after vascular surgery. Even in comparison with the studies of Mirzabeigi et al[16] and Fischer et al,[13] who directly compared the RFF with the SMF in the United States, we were able to analyse more patients after RFF. Besides the large size of our study cohort and the multicentre character, this study also offers an originality that all muscle flaps were performed by vascular surgeons and not by

plastic and reconstructive surgeons as in the previous studies. In the most recent series of Ryer et al,[18] the experience of vascular surgeons in performing RFFs was also described, showing excellent results in a single-center study of 23 patients. In our series, we were able to confirm these same good results on a larger scale and in a significantly older population. Finally, whereas most studies were single-center reports on the single RFF technique, our study had the possibility of comparing the RFF technique with the SMF technique in the same center.

The donor site complication rate found in our study was low. In comparison, Fischer et al[13] described a donor site complication rate of 7.5% in their study. The possible risk of donor site morbidity and functional deficits in knee extension after RFF reconstruction is one of the greatest considerations in choosing another muscle flap technique; however, our study indicates that added morbidity due to harvesting of the donor muscle is a rarity. In addition, the mild decrease in muscle strength did not result in a serious disease burden in these patients. In concordance, Sbitany et al[22] showed that no noticeable decrease of quadriceps strength was found as a result of rectus femoris harvest. Other studies did not find significant functional donor site morbidity as well.[23,24]

To date, superiority of either muscle flap has not been demonstrated. According to our experience, most training centres or vascular surgeons use either technique as a standard approach. In our centres, all vascular surgeons are able to perform the RFF technique lege artis, which is also a necessity because an important amount of these operations has to be performed outside office hours. Vascular surgeons, when trained in a center with SMF as the preferred technique, were unfamiliar with the RFF technique and were subsequently trained in-house to perform RFF coverage.

Only two retrospective cohort studies with >100 patients directly compared the effectiveness of both techniques and found no significant differences.[13,16] Our study also demonstrated clinical success rates equal to those of the SMF. However, only studies with limited patient numbers have analysed the outcomes of muscle flaps in this setting. Another alternative technique for groin coverage is the gracilis muscle flap. Dua et al[25] recently evaluated a gracilis muscle flap technique and concluded that it should be considered a primary form of muscle coverage for groin complications. In our centres, gracilis muscle flaps were not performed primarily in patients with groin complications.

For the treatment of vascular graft infections, VAC therapy can be of importance as well. This negative pressure wound therapy eliminates interstitial fluid, modulates the wound surface, and promotes the formation of granulation tissue.[2,26] Dosluoglu et al[27] managed a small number of early groin wound infections with wound debridement, antibiotics, and VAC therapy only and achieved good results regarding graft preservation. In addition, Verma et al[2] described the use of VAC therapy after muscle flap coverage with the SMF to assist in wound closure. As described before, in our study, the surgeon decided whether VAC therapy should be initiated according to the groin defect. In our study, 46% of our RFFs and 86% of the SMFs were temporarily covered with a VAC device.

Limitations. A shortcoming of the study that has to be addressed is the retrospective character. All possible disadvantages of this design, such as recall bias and missing data, may be present. Although this study is one of the larger reported series, the results and conclusions presented are not yet supported by prospective data. Furthermore, we have struggled with unequal group sizes because the SMF was performed much less often than the RFF in our centres. This inequality resulted in a ratio of 3:1 in comparing the RFF with the SMF. This may have reduced the statistical power and influenced the interpretation of the results. In one center, both flaps were performed; in the MMC, the SMF (seven cases) was used in small defects after debridement and limited dead space. Therefore, for these patients, selection bias probably could have played a role. However, the majority of SMFs (23 cases) were performed as the preferred technique in Aachen, regardless of the wound defect and infection burden.

Future perspectives. Numerous potential advantages and disadvantages are described for both muscle flaps. Our study underlines that the RFF technique is an effective way to manage deep groin defects. However, to prove that this technique is superior to other muscle flaps regarding the clinical outcomes, additional prospective studies or even a randomized comparison is needed. Especially for large tissue defects, it is likely that the RFF with its larger volume is the most effective way to cover the groin.

Conclusion

This study presents a large series of RFF coverage after complications of vascular surgery and demonstrates an effective management of deep groin wound infections, with excellent results regarding limb salvage and graft salvage in a population of challenging patients with an otherwise poor prognosis. These outcomes were comparable to the outcomes in a cohort of SMF coverage. Both techniques can be safely performed, depending on the preference and experience of the surgical team. The RFF should be used preferentially to cover large tissue defects, whereas the SMF could be used to cover smaller defects in the groin.

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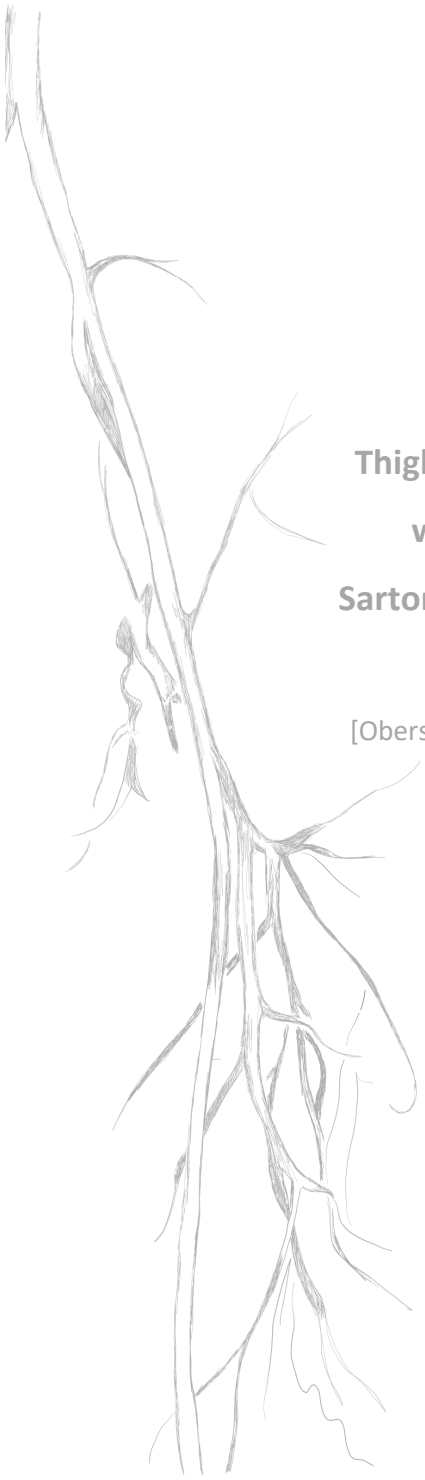

Chapter 6

Thigh muscle flaps for postoperative inguinal wound complications in vascular surgery: Sartorius muscle versus rectus femoris muscle

[Oberschenkelmuskellappen bei inguinalen postoperativen Komplikationen in der Gefäßchirurgie – Musculus sartorius vs. Musculus rectus femoris]

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Abstract

Background. Inguinal wound complications often cause postoperative morbidity and also mortality following vascular surgical interventions. The aim of this study was to report experiences and a comparison of the outcomes using rectus femoris muscle flaps (RFF) and sartorius muscle flaps (SMF).

Material and methods. A retrospective study was performed at two locations of a cross- border vascular center and all muscle flap interventions performed at the two centres within the vascular surgery department were reviewed. Primary outcomes were muscle flap survival, graft salvage and major amputations.

Results. A total of 44 RFFs were performed in 39 patients (mean age 67 years, 73% males) and 25 SMFs in 24 patients (mean age 64 years, 76% males). Wound infections were the most common indications for muscle flap reconstruction. At a mean follow-up of 24 months (±24) and 17 months (±20), respectively, comparable flap survival rates (91% vs. 84%), wound healing rates (72% vs. 83%), graft salvage (65% vs. 73%) and amputation rates (9% vs. 8%) were found.

Conclusion. Muscle flap reconstruction is an effective way to cover groin defects resulting from deep wound infections after vascular surgery, achieving good results in a high-risk group of patients. No differences were found between SMF and RFF regarding amputation and graft loss. Both techniques can be safely performed, depending on the preference and experience of the surgical team. The RFF technique should be preferentially used to cover large tissue defects, whereas the SMF procedure can be preferred to cover smaller defects in the groin.

Background

Postoperative wound complications in the groin are a common reason for postoperative morbidity and mortality after vascular surgery [1, 2]. Despite all efforts to prevent infection of the surgical site, incidences of 4–43% are reported in the literature [3–6]. Particularly deep prosthesis infections represent one of the most severe complications in vascular surgery due to the high mortality and amputation rates between 6–75% and 22–75%, respectively [1, 2]. For various reasons, the groin is an unfavorable wound environment and therefore most frequently affected by postoperative infections in vascular surgery [2, 7, 8]. The best-known classification of postoperative wound infections according to Szilagy describes three categories [9]. Grade I includes superficial infection confined to the skin, whereas Grade II infection also extends to the subcutaneous tissue. A grade III infection ultimately affects also the vascular prosthesis and leads to an increased risk of bacteremia [9]. The traditional therapeutical approach involves the administration of systemic antibiotics and removal of the infected vascular prosthesis, followed by reconstruction if necessary [9–11]. Since 1976, covering the groin area with a thigh muscle flap has been described as an additional approach, since high morbidity and mortality rates have been reported even with the traditional therapeutic strategy [8, 12–14]. These muscle flaps cover the large tissue defects caused by the infection itself and by surgical debridement. In addition, muscle flap surgery has positive effects on the healing process due to increased blood flow with increased supply of oxygen, nutrients and antibiotics to the infected area [7, 14]. Various muscle flaps for wound reconstruction in the groin area are described in the literature. Sartorius muscle flap is the most frequently used and described procedure worldwide. However, using the rectus femoris muscle flap is a promising alternative procedure with several advantages. Despite the second soft tissue defect required for rectus femoris muscle flap removal, the greater volume of the muscle and the greater distance to the affected infected area in the groin are primarily beneficial for the treatment of complex groin wound infections. In addition, the sartorius flap can only be mobilized from the lateral side due to the segmental blood supply through the superficial femoral artery, which is often itself damaged in patients with atherosclerosis. The rectus femoris muscle flap has a more reliable blood supply through the deep femoral artery [7, 8, 14, 15]. The decision which muscle to use to cover the groin

depends mainly on the preference and experience of the hospital and the surgeon performing the operation. Although deep wound infections in the groin have been a difficult and common complication for decades, the optimal therapeutic strategy is still very unclear. A randomized trial comparing the sartorius muscle flap and the rectus femoris muscle flap was never carried out [7].

The aim of this study was therefore to report on our experience with the use of the rectus femoris muscle flap and the sartorius muscle flap for complications of the deep groin in vascular surgery.

Methods

In this retrospective, single center study we analyzed all patients who were treated with one of the two muscle flaps at the two locations of a cross-border vascular center between 2006 and 2017. Approval of the local ethics committee was obtained before starting this study. Patients who received a muscle flap in the groin for reasons other than vascular surgery or who were treated with other muscle flaps were excluded.

Data collection

As already mentioned, all data was collected retrospectively. The hospitals' electronic health records were used to identify demographic data and comorbidities. In addition, various operative characteristics and clinical results were recorded. All amputations above the ankle were defined as major amputations and therefore limb loss. A distinction was made between primary and secondary loss of the vascular prosthesis. Secondary loss of the vascular prosthesis occurred when reintervention to secondary vascular prosthesis removal was required.

Surgical techniques

All muscle flap operations analyzed were performed by vascular surgeons. The inguinal wounds were usually examined microbiologically and antibiotic therapy started. The wounds were extensively surgically debrided. The selection of the muscle flap was made by the surgeon and was always based on an assessment of the wound size and the resulting soft tissue defect as

well as the assessment of the suitability of the local muscle flaps. The wounds were assessed subjectively and no volume measurements or specific blood supply studies were performed.

To remove the rectus femoris muscle, an additional longitudinal incision is made in the middle of the thigh, which extends over the distal two-thirds of the thigh (Fig. 1). The rectus femoris muscle is identified and detached from its distal attachment to the patella and from its fascial connections. The leading lateral femoral artery is identified and preserved. The muscle flap is raised in a distal-proximal way and inserted into the groin wound through a subcutaneous tunnel that connects the removal site and the groin wound. Depending on the tissue defect, the wound is closed in layers using suction drainage or a vacuum-assisted closure (VAC) therapy is initiated. The donation site is also provided with a layered wound closure. Including extensive cleaning and rinsing of the wound, rectus femoris muscle flap surgery generally takes 30–60 minutes.

For the sartorius muscle flap, the incision of the groin wound is first lengthened laterally and the fascia incised, which exposes the sartorius muscle. The proximal edge of the muscle is peeled off and the segmental branches of the superficial femoral artery on the dorsal side of the muscle are identified. The muscle is turned over and placed in the groin wound. Again, either VAC therapy is initiated or the wound is closed in layers using suction drainage. Sartorius muscle flap surgery, including cleaning and rinsing, is generally performed within 30–60 minutes.

Postoperatively, the initiated antibiotic therapy was adjusted based on the microbiological results and usually continued for several weeks, first intravenously and then in oral form. These decisions were always made in close collaboration with infectious specialists. The patients could usually be mobilized again after a few days and leave the hospital after sufficient further wound healing so that outpatient wound care is possible. Regular wound controls took place first in the inpatient and later in the outpatient setting until the groin wounds had healed.

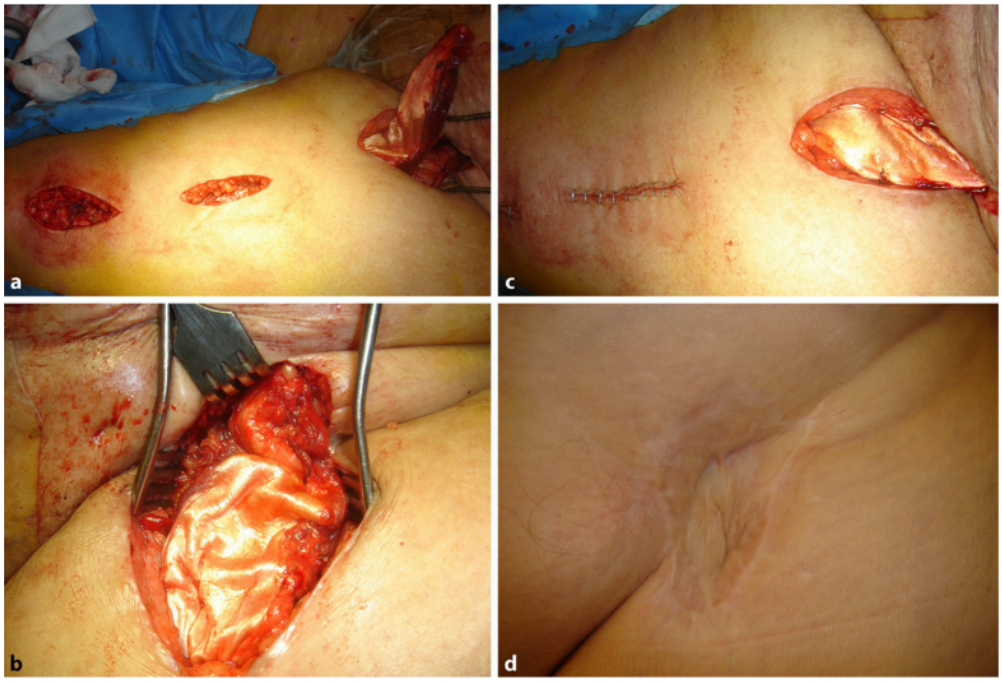

Figure 1: Illustration of muscle flap coverage using the rectus femoris muscle. a: Longitudinal midanterior incisions are made. b: The muscle flap is passed to the groin wound through a subcutaneous tunnel to cover the vascular graft. c: Muscle flap coverage resulted in immediate elimination of dead space. The donation site is provided with layered wound closure d: Complete wound healing was achieved.

Study endpoints

The primary endpoints were muscle flap survival, salvage of the vascular prosthesis, and major amputations. Secondary endpoints were wound healing, local wound complications within 30 days, and rectus femoris site complications, vascular complications and patient survival. In addition, the morbidity due to impaired muscle strength of the knee extensor after rectus femoris removal and the length of hospital stay were analyzed as secondary endpoints. The date of the last clinical contact was used to calculate the follow-up period per patient.

Statistical analysis

All statistical analyses were performed with SPSS Statistics 24 and the two treatment groups (RFF versus SMF) were compared with each other. Standard descriptive statistics were used for demographic data and comorbidities. Categorical data were presented as percentages, continuous data as mean combined with the standard deviation (SD). The differences between the two groups were assessed using $\chi 2$ tests. Independent sample t-tests were used to compare the means of the continuous variables. P-values of <0.05 were considered to be statistically significant.

Results

During the study period, a total of 44 rectus femoris muscle flaps were performed in 39 patients and a total of 25 sartorius muscle flaps were performed in 24 patients. The mean follow-up period was 24 months (± 24) in the rectus femoris group and 17 months (± 20) in the sartorius group. The demographic data of all patients are shown in Table 1 and the operative characteristics in Table 2.

Table I: Baseline characteristics

	M. rectus femoris (n=39) 44 flaps	**M. sartorius (n=24)** 25 flaps	**p-value**
Age at surgery	67 ± 9,6 (36-86)	65 ± 16,0 (26-85)	0,34
Age > 80 years	7%	20%	0,13
Sex			0,77
Female	27%	24%	
Male	73%	76%	
Comorbidities			
Diabetes	36%	36%	0,98
Smoking	43%	60%	0,18
Body mass index, kg/m^2	28,5 ± 5,4	25,1 ± 3,9	0,58
Body mass index > 25kg/m^2	58%	48%	0,42
Hypertension	77%	76%	0,94

Hypercholesterolemia	86%	44%	<0,001
History of cardiac disease	39%	36%	0,83
COPD	21%	32%	0,29
Chronic kidney disease	5%	44%	<0,001

Categorial variables are presented as number (%). Continuous variables are presented as mean ± standard deviation (range). Differences between both treatment groups were assessed using $\chi 2$ tests (categorial variables) or independent sample t-tests (continuous variables). COPD = Chronic obstructive pulmonary disease.

In both groups, more than two-thirds of the patients were male (73% and 76%, respectively). The mean age in the rectus femoris group was 67 years (± 9.6) and in the Sartorius group 65 years (± 16.0). The investigated comorbidities were often present in this study population and only few significant differences between the two groups were found (Table 1). In the rectus femoris group, more patients were treated for hypercholesterolemia (86% vs. 44%, p <0.001), while more patients in the sartorius group suffered from chronic kidney failure (5% vs. 44%, p <0.001).

Operative characteristics

Almost all of the patients in this study population had a history of previous groin surgeries (98% and 88%). Most of the groin wounds contained non-autologous material (98% vs. 84%). Deep wound infections in the groin were the most common indication for muscle flap surgery in both groups (48% and 56%). More than half of all patients required emergency surgery (57% and 56%). In both groups, more than half of all wound cultures were positive for microorganisms (64% and 72%). During rectus femoris operations, the vascular prosthesis was removed from 17 of the 43 groins with non-autologous material in situ (40%). In 6 of these cases the prosthesis was removed without reconstruction, in 5 cases the non-autologous prosthesis material was replaced by venous material, and in the remaining 6 cases non-autologous material was used again. During the sartorius operations, the original vascular prosthesis was removed from 10 of the 21 groins with non-autologous material in situ (48%) and replaced in 3 cases with venous material and in 4 cases with non-autologous material. More than half of all patients required VAC therapy (56% and 81%).

Table II: Operative characteristics

	M. rectus femoris (n=44)	**M. sartorius (n=25)**	**p-value**
History of prior groin surgery	98%	88%	0,13
Number of prior operations (range)	2,6 (0-6)	2,3 (0-6)	0,50
Time until muscle flap, days	322	96	0,10
Non-autologous material in situ	98%	84%	0,05
Indication for muscle flap			0,27
Wound infection	48%	56%	
Blowout	21%	4%	
Bleeding	2%	12%	
Hematoma	5%	8%	
False aneurysm	18%	12%	
Prophylactic	7%	8%	
Emergency operation	57%	56%	0,95
Primary graft excision	40% (n=17)	48% (n=10)	0,79
Without reconstruction	6	3	
With reconstruction with venous material	5	3	
With reconstruction with prosthetic material	6	4	
VAC-therapy	56%	81%	0,05
Positive wound cultures	64%	70%	0,48

Categorial variables are presented as number (%). Continuous variables are presented as mean (range). Differences between both treatment groups were assessed using $\chi 2$ tests (categorial variables) or independent sample t-tests (continuous variables). VAC = Vacuum-assisted closure.

Study endpoints

The clinical results after muscle flap surgery are shown in Table 3. During an average follow-up period of 24 months (± 24), 91% of the RFF remained vital and during an average follow-up period of 17 months (± 20) in the sartorius group, 84% of all SMF remained vital. Wound healing, loss of the vascular prosthesis, amputations, and mortality were also comparable between the two treatment groups. A total of 65% and 73% of the remaining vascular prostheses could be

obtained. In the rectus femoris group, only one amputation was required within the first 30 days and 4 patients died from recurrent infection and sepsis. In the sartorius group, one amputation was required within the first 30 days. One patient died from bleeding and another from an unrelated cause. In both groups, recurrent wound infections were most frequently described as a local complication of the groin wound (34% vs. 12%).

Table III: Study end points

	M. rectus femoris (n=44)	**M. sartorius (n=25)**	**p-value**
Overall flap survival	91%	84%	0,45
Graft salvage	65%	73%	0,52
Major amputations	9%	8%	1,00
Mortality			
30 days	9%	12%	0,70
1 year	48%	56%	0,94
Groin wound complications (30 days)			
Ongoing wound infection	34%	12%	0,05
Bleeding	12%	8%	1,00
Seroma	7%	0%	0,55
Flap necrosis	9%	4%	0,65
Complete wound healing	72%	83%	0,30
Vascular complications (30 days)[a]	16%	20%	0,75
Donor site complications (30 days)	2%	-	
Wound infection	1		
Impaired muscle strength	4%	-	
Length of hospital stay, days	27 ± 20	41 ± 26	0,02
Follow-up, months	24 ± 24 (0-83)	17 ± 20 (0-73)	0,27

Categorial variables are presented as number (%). Continuous variables are presented as mean (range). Differences between both treatment groups were assessed using $\chi 2$ tests (categorial variables) or independent sample t-tests (continuous variables). [a] Any kind of revascularization for critical limb ischemia.

Interestingly, the donor site complication rate was very low in the rectus femoris group. Only one patient developed a complication at the donor site (2%) and only one case reported impairment of muscle strength. The mean length of hospital stay was significantly shorter in the rectus femoris group than in the sartorius group (27 ± 20 days vs. 41 ± 26 days, p = 0.02).

Discussion

The treatment of complications of the inguinal wound after vascular surgery is still a challenge for vascular surgeons worldwide [16]. This retrospective study at two locations of a cross-border vascular center compares the results of the rectus femoris muscle flap with the results of the sartorius muscle flap. We were able to show that muscle flap surgery is an effective procedure to cover deep defects after infection of the inguinal wound and we were able to demonstrate good results with both techniques in terms of amputations and vascular prosthesis salvage.
In this study, with an average follow-up period of 2 years, 91% of all rectus femoris muscle flaps and 84% of all sartorius muscle flaps were vital at the last patient contact. Serious complications such as loss of the vascular prosthesis, amputations, and mortality were rare in both treatment groups. In addition, more than half of all patients required emergency surgery, which shows the severity of the infections and the clinical presentations. For the vascular surgeon, patients with deep infections in the groin represent a difficult group of patients with a poor prognosis [1, 2]. Our study shows that muscle flap surgery with both muscles resulted in acceptable mortality and amputation rates that were low compared to the mortality and morbidity rates after traditional wound management [11]. The only significant difference between the two groups was a shorter length of hospital stay in the rectus femoris group. This difference is most likely due to general differences between the health care systems of Germany and the Netherlands. The use of the rectus femoris muscle flap is preferred in the Dutch part of the vascular center, while the sartorius muscle flaps were performed in Aachen. Statistics show that the average length of stay in German hospitals in 2016 was 7 days and in the Netherlands 5 days [17, 18]. It is therefore not surprising that this trend can also be seen in our study.

Inguinal wound infections

The groin is the region most commonly affected by postoperative infections [8]. The majority of peripheral vascular interventions are performed by an inguinal approach. It is known, however, that the groin is a rather unfavorable wound environment due to its lymphatic anatomy, the potential for a large tissue defect, and postoperative adipose tissue and skin necrosis [2, 7]. In addition, the direct proximity of this area to the heavily contaminated anogenital region also contributes to an increased risk of wound infections [7, 8]. In addition, several comorbidities are often present in vascular surgery patients, such as B. diabetes mellitus, which are additional risk factors for wound infections [2, 7]. Diabetes, nicotine abuse, and a high body mass index (BMI) were also common in our study population, which increased the risk of wound infections. This could have contributed to the relatively high rate of local complications after muscle flap surgery. Recurring infection and bleeding were reported most frequently, but did not result in muscle flap loss in the majority of patients. In addition, comparable complication rates are reported in the literature. Mirzabeigi et al. conducted a relatively large muscle flap study in the USA and the authors reported a complication rate of 34% [7]. Although our study found a tendency towards a higher complication rate in the rectus femoris group, the difference was not statistically significant and the long-term clinical outcomes were comparable in both treatment groups.

Results of the muscle flaps

Few studies in the literature have focused on the results of rectus femoris muscle flap surgery for deep groin wounds. Mirzabeigi et al. reported amputations in 5.8% of cases and 21.6% loss of vascular prosthesis [7]. Fischer et al. reported amputation and prosthesis loss rates of 1.4% and 2.9%, respectively [13]. Other amputation rates range up to 25% and prosthesis loss rates up to 35% [19, 20]. Mirzabeigi et al. also reported comparable complication rates after using the sartorius muscle, while Fischer et al. reported a significantly lower overall complication rate of 2.9% (loss of prosthesis, amputation, or reintervention) when using the rectus femoris muscle, compared with 13.2% after using the sartorius muscle [7, 13]. In our study, there were no differences between the two treatment groups with regard to the primary endpoints. Interestingly, however, the complication rate of the rectus femoris removal site found in our

study was very low. In comparison, Fischer et al. reported a complication rate of 7.5% in their study [13]. The possible risk of additional morbidity from the second soft tissue defect and functional deficits in knee extension after rectus femoris muscle flap surgery is one of the greatest potential disadvantages. Our study shows that additional morbidity due to the removal of the muscle was a rarity. In addition, Sbitany et al. showed that the muscle strength in their study did not noticeably decrease after rectus femoris muscle flap surgery [21]. Further studies also found no significant functional impairment [22, 23]. A disadvantage of sartorius muscle flap surgery is the more complex blood supply. The sartorius muscle is supplied with segmental blood from the superficial femoral artery (SFA) and in the proximal part of the muscle also from other vessels in this area [24, 25]. Blood flow through the SFA is often compromised in patients with peripheral arterial disease [7, 8, 14, 15]. Toepel et al. assessed the influence of an SFA occlusion on the result of sartorius muscle flap surgery and found no increased risk of muscle flap loss [26]. It is much more important that the risk of muscle lobe necrosis is increased if the vascular pedicels entering posteromedially are not preserved during mobilization of the sartorius muscle. To avoid flap necrosis, only a small segment of the sartorius muscle should be mobilized laterally and then twisted into the groin wound [25].

Alternative procedures for plastic-surgical defect coverage in the groin, such as the gracilis muscle flap, the tensor fasciae latae (TFL) flap or the contralateral rectus abdominis flap, can also be used after vascular surgery [27–30]. However, validated clinical data on any form of groin defect coverage are very limited, mostly based on case reports and studies with small patient populations. By Dua et al., recently, the gracilis muscle flap technique was evaluated with 100% wound healing as a result, so it was concluded that this procedure should be considered as the primary procedure for groin defect coverage [27]. The rectus femoris and sartorius muscle flaps offer the advantages of less invasiveness, especially compared to the TFL and contralateral rectus abdominis flaps, that they can usually be used by the vascular surgeon themselves and for most groin defects that occur in vascular surgery are of sufficient size.

Limitations

A limitation of the present study is its retrospective character. All possible disadvantages of this design, such as missing data and memory distortion, can be present. In addition, the study

population is relatively small. Due to the retrospective nature of this study, no randomization was performed and we found significantly more patients with chronic kidney failure in the sartorius group. This different distribution of a risk factor for impaired wound healing can influence the results.

Future perspectives

As discussed above, numerous potential advantages and disadvantages are described for both types of muscle flaps. The decision which muscle flap to use to cover the groin currently depends mainly on the preference and experience of the hospital and the operating surgeon. The data currently available do not support a clear clinical advantage for either method, but no prospective or randomized controlled studies are available. In our study, both muscle flaps were equivalent in terms of clinical results. Further prospective studies should therefore investigate whether one of the two muscle flaps is superior to the other in terms of clinical results.

Conclusion

Muscle flap surgery is effective to cover groin defects caused by deep infections after vascular surgery, with good results in a difficult and vulnerable group of patients. No differences were found between the rectus femoris and sartorius muscle flaps with regard to amputations and loss of the vascular prosthesis. We therefore recommend performing the muscle flap depending on the preferences and experience of the surgical team. In our opinion, however, it makes sense to master both techniques, since the rectus femoris muscle flap is particularly suitable for covering large tissue defects and the sartorius muscle flap can be used for smaller defects.

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Chapter 7

Gentamicin Containing Collagen Implants and Groin Wound Infections in Vascular Surgery: A Prospective Randomised Controlled Multicentre Trial

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Abstract

Objective: The aim of this study was to assess the effectiveness of gentamicin containing collagen implants in the reduction of surgical site infections (SSIs) in patients undergoing an inguinal incision for vascular surgery.

Methods: Prospective blinded randomised controlled multicentre trial (RCT), performed in four hospitals in The Netherlands and Belgium. This study included 288 patients who underwent an inguinal incision for primary arterial repair (femoral endarterectomy, femorofemoral or femoropopliteal bypass, aortobifemoral bypass, thrombectomy, embolectomy, endovascular aneurysm repair) between October 2012 and December 2015. Patients were randomised to receive a gentamicin implant (study group) or no implant (control group). The calculated sample sizes of 304 patients per group were not reached. Primary outcome was SSI incidence after six weeks. Secondary outcomes were time to onset of infection, length of hospital stay, allergic reactions, treatment with antibiotics, need for re-admission, re-operation and mortality.

Results: One hundred fifty-one patients were allocated to the study group (mean age 69 ± 9.2 years) and 137 patients were allocated to the control group (mean age 70 ± 10.4 years). Both groups were homogeneous regarding baseline and intra-operative characteristics. Gentamicin implants did not result in a significant overall reduction of SSIs in the study group (7% vs. 12%, $p = .17$). In a post hoc analysis comparing two study sites with low (<10%) and two study sites with high (>10%) infection rates in the control group, gentamicin implants significantly reduced SSIs in high risk centres (22% vs. 1%, $p < .001$), whereas there was no significant effect in low risk centres (13% vs. 7%, $p = .30$). There were no allergic reactions and all secondary outcomes were comparable between groups.

Conclusion: Gentamicin implants did not result in a significant overall reduction of SSIs in this RCT. Gentamicin implants did reduce the incidence of SSIs in high risk centres and may be a valuable adjunct to improve outcomes in such vascular centres with a high incidence of wound infections. However, the limitation of not reaching the calculated sample sizes should be considered.

Introduction

Surgical site infections (SSIs) following vascular interventions are an important healthcare problem, with a serious impact on patients' morbidity and mortality and increased healthcare costs due to longer hospital stays.[1,2] In the literature, a wide variation in the incidence of SSIs following vascular surgery is described, varying from 4% to 43% in retrospective studies.[3-6] In a recent prospective multicentre study, the authors estimated the average costs per patient of developing a SSI at 3220 euro.[3]

SSIs following vascular surgery, defined as wound infections within 30 days after operation or within one year if an implant was used, are associated with several independent predictive factors, most importantly obesity and infra-inguinal intervention.[3,4,6-9] Major advances in reducing the incidence of SSIs have been made by improved operating room ventilation, sterilisation methods, antiseptic precautions of surgeon and patient and antibiotic prophylaxis.[7,10-13] However, despite these preventive methods, SSIs remain a substantial cause of morbidity, associated with an increased risk of removal of the vascular prosthesis and subsequent amputation.[1,7]

More effective SSI prevention in vascular surgery is needed. Local delivery of antibiotics within the surgical incision has the potential to combine higher target site concentrations with a reduced risk of systemic side effects and nephrotoxicity.[14] Collagen represents a favourable matrix for such an on-site drug delivery, because it is completely biodegradable and does not require subsequent removal. Furthermore, the positive effects of local antibiotics on wound healing and homeostasis have been described.[1,14,15]

The application of resorbable gentamicin containing collagen implants to prevent SSIs has been assessed in different studies, but without consistent results.[2,14] Three systematic reviews, two with meta-analysis, analysed the effectiveness of gentamicin implants in SSI reduction and in all three studies a protective effect and a reduced SSI rate was reported.[1,2,14] Importantly, only Hussain et al. focused on vascular surgery patients and no randomised controlled trials (RCTs) were available for inclusion in this systematic review.[1] Therefore, additional randomised studies are required for further investigation of the effectiveness of gentamicin implants in vascular

surgery.[1] In 2014, a prospective pilot study with 60 vascular surgery patients confirmed SSI reduction in the groin incision, but again validation in a multicentre RCT was still necessary.[16] There is clearly a lack of knowledge about the effectiveness of gentamicin implant application in vascular surgery. The greatest body of evidence can be found within the field of cardiac surgery.[2] Based on the promising results of these studies and the pilot study it can be hypothesised that the use of gentamicin implants can reduce SSIs following vascular surgery as well.[16] To confirm this hypothesis, a randomised multicentre trial was initiated. The aim was to assess the effectiveness of gentamicin containing collagen implants in SSI reduction in patients with peripheral arterial occlusive disease following vascular surgery via an inguinal incision.

Materials and methods

A prospective, randomised controlled trial was performed in four hospitals in The Netherlands (Maastricht University Medical Centre (MUMC), Zuyderland Medical Centre in Heerlen, the Elisabeth-TweeSteden Hospital in Tilburg) and Belgium (Leuven University Hospital). Ethical Committee approval was obtained, and the trial is registered in the Netherlands Trial Register with the following code: NTR3754. The gentamicin implants used in this study were funded by EUSA Pharma.

A total of 288 patients were included between October 2012 and December 2015. All patients provided informed consent before inclusion in this study, in accordance with the principles of the Declaration of Helsinki and the Medical Research Involving Human Subjects Act. The CONSORT Statement for reporting randomised controlled trials (CONsolidated Standards Of Reporting Trials) was followed (Fig. S1).

Study population

All patients undergoing first longitudinal inguinal incision for primary arterial repair were eligible to participate in this study: more precisely all patients undergoing a femorofemoral bypass, femoral endarterectomy, femoropopliteal bypass, aortobifemoral bypass, thrombectomy, embolectomy, combinations of these operations or patients undergoing endovascular aneurysm repair. For all operations, the groin incision was the study incision of interest. For

bilateral groin incisions for vascular surgery, the right groin was included in the study and the left groin was excluded. All patients were operated in one of the participating hospitals described above. Patients were 18 years or older, and both sexes were included. Patients with a known sensitivity or allergy to gentamicin and patients being either pregnant or breast feeding were excluded from this study. Patients with previous groin operations were also excluded.

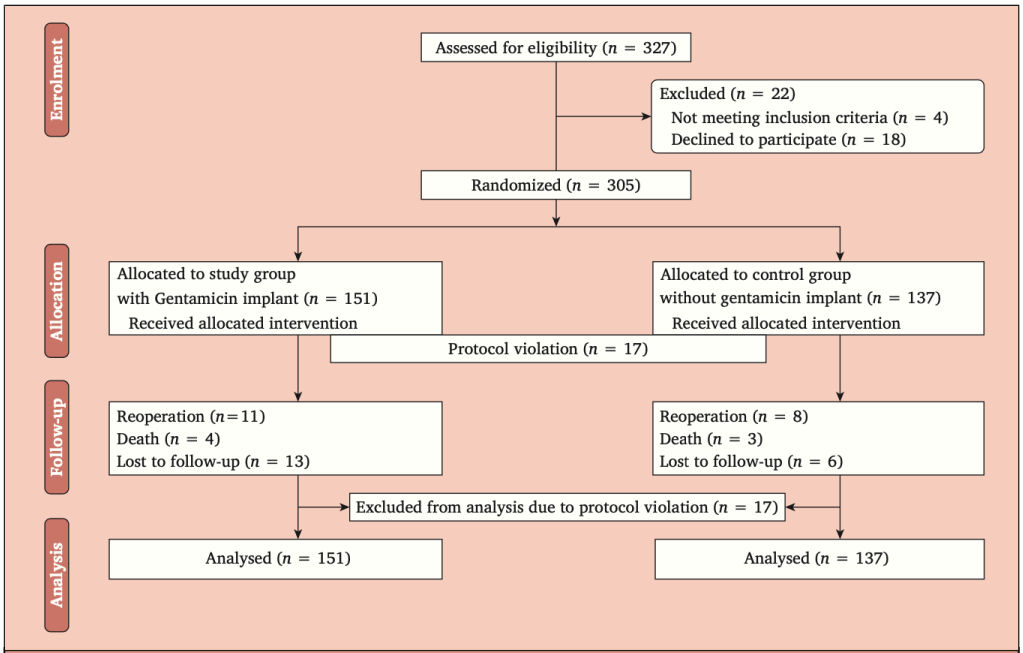

Figure 1. Flowchart illustrating the study enrolment process and follow up according to the CONSORT Statement. Statistical analysis following intention to treat analysis. Protocol violation = not able to reveal the randomisation group of 17 patients at the moment of statistical analysis; therefore, these patients had to be excluded after randomisation.

Study design and randomisation

An external statistician, who was not involved in the enrolment or assessment of the patients, coordinated randomisation. Randomisation was stratified for study site. A computer based randomised block design was used for randomisation. Patients were allocated in a blinded fashion to one of two groups: the treatment group received a gentamicin containing collagen implant (study group) and the other group did not (control group). Numbered blinded envelopes were placed in the operating rooms, containing a notification whether the patient was allocated to the study or the control group and a standard clinical registration form that was completed by the surgeon. The envelopes were opened at the end of the operation, immediately before

wound closure. The observer assessing the wound post-operatively in the outpatient clinic was blinded to the allocation. Therefore, both the wound assessors and the patients were blinded, only the surgeon was not. For registering the baseline characteristics before operation and for follow up of the groin wound and clinical condition of the patient post-operatively, a standard clinical registration form was used.

Treatment

The allocated study group received a gentamicin containing collagen implant, whereas the control group did not. The implants (Garacol® 130 mg) were made available by EUSA Pharma, United Kingdom (€112.87 per implant). This flat absorbable bovine collagen implant of 10 x 10 x 0.5 cm contained a dose of 130 mg gentamicin. The aminoglycoside gentamicin has antimicrobial activity against Pseudomonas aeruginosa, E. coli, Proteus spp., Klebsiella spp., Enterobacter spp., Serratia spp., Providencia spp., Acinetobacter spp. and Citrobacter spp., Morganella spp., S. aureus., Staphylococcus spp., Str. Viridans, Enterococcus spp., Mycobacterium spp. It was implanted in the wound in the subfascial plane before closure of the groin incision. All surgeons in the four participating centres were trained to perform the implantation of the gentamicin implant in a standardised way, according to the study protocol. There was no specific dissection technique instructed; the dissection itself was performed according to the preferences of the operating surgeon, following the generally accepted and practiced techniques in vascular surgery. The implant was sealed under a running facial suture with absorbable material. Skin closure was performed with absorbable suture material intracutaneous. Independent of this study treatment, the standard pre-operative protocol for the prevention of SSIs was applied in both groups in each participating hospital. This included standard operating room protocols, applying prophylactic pre-operative anti- biotics (MUMC: 1 x 2 g cefazoline intravenously, 30 min before operation; Heerlen, Tilburg and Leuven: amoxicillin/ clavulate or amoxicillin, 30 min before operation), standard skin care and aseptic skin care of patient and surgeon.

Follow up and data collection

The study follow-up period was six weeks. Patients were examined on day 1 post-operatively, on discharge and two, four and six weeks after operation respectively. As described above, a standard clinical registration form was used. Up to week 6 after discharge, wound healing was also recorded using photography. Gender, age at intervention, body mass index (BMI), smoking in the past five years, use of antibiotics within 30 days before operation and the comorbidities (diabetes mellitus type 1 and 2, chronic kidney disease (glomerular filtration rate (GFR) < 30 mL/min/ 1.73 m^2), history of hypertension or use of antihypertensive medication, history of hypercholesterolaemia or use of statins) were collected as general baseline characteristics. Collected intra-operative characteristics were type of operation, operation duration, use of prosthetic material, blood loss and length of incision (in cm). Wound assessment was performed at the pre-set time points up to six weeks of follow up and wound infections meeting the criteria for SSIs as described by the Centres for Disease Control and Prevention (CDC) were analysed as SSI.[17,18] Therefore, patients with a positive wound culture or documented purulent drainage were classified to have a SSI and the time until infection was documented. Wound cultures were not taken routinely but in clinically suspicious cases due to symptoms such as redness or wound dehiscence.

Study endpoints

The primary outcome was the overall incidence of SSIs, according to the CDC definitions. Secondary outcomes were length of hospital stay (in days), allergic reactions, treatment with antibiotics, need for re-admission and re-operation and mortality during follow up. In addition, the mean time until infection was analysed.

Statistical analysis

A sample size calculation was performed, expecting 15% SSIs in the control group and 50% fewer in the study arm receiving the gentamicin implant. With a confidence level of 5% and statistical power of 80%, the calculated sample size was 304 patients per group.

All statistical analyses were performed with SPSS Statistics 24. Data analysis was performed comparing both groups (with gentamicin implant vs. without gentamicin implant) and by

intention to treat analysis. Owing to protocol violation, the allocated randomisation group of all patients at the moment of statistical analysis could not be revealed; therefore, few patients had to be excluded after randomisation (n = 17). Descriptive statistics were presented for the baseline characteristics. Categorical data were expressed as percentages, continuous data as mean with the standard deviation (SD). Differences in patient characteristics and outcomes between the two age groups were assessed by Chi-squared tests. To compare the means of continuous variables, independent samples t tests were used. Outcome analysis was stratified for centre of inclusion. The primary outcome was also analysed in a post hoc subgroup analysis for study sites with low (<10%) and high (>10%) incidence of infection in the control group because of significant heterogeneity in treatment effect between study sites. The endpoint remained the same, namely "surgical site infection" as was defined in the overall analysis, making the study design suitable for this subgroup comparison as well. In addition, a post hoc sensitivity analysis was performed excluding patients with endovascular interventions only (n = 34). Time to infection was analysed using Kaplan Meier plots and differences between study groups were assessed by the log rank test. A p value < .05 was considered statistically significant.

Results

A total of 288 patients/groins were analysed in this randomised controlled trial performed between October 2012 and December 2015. According to the sample size calculation, 304 patients should have been included per group. These numbers were not reached. Details of the study enrolment and allocation process and reasons for exclusion or dropout are shown in the flow chart according to the CONSORT Statement (Fig. 1). Follow up was six weeks and the loss to follow up rate was 15.6%, equally distributed between groups. A total of 151 patients received a gentamicin implant (study group) and 137 patients did not (control group).

Baseline characteristics

The patient baseline characteristics are shown in Table 1 and no significant differences were found between groups. The mean age was 69 years in the study group and 70 years in the control group. The study population was predominantly male (70% study group and 72% control

group). Patients were balanced regarding all risk factors and comorbidities analysed at baseline. Regarding the intra-operative characteristics, no significant differences were found between groups. In both groups, half of the patients were operated for isolated femoral endarterectomy, thrombectomy and/or embolectomy (50%). The use of prosthetic material, the mean operation time and the mean incision length were comparable between groups.

Table 1. Baseline characteristics of patients with an inguinal incision for primary arterial repair treated without (control group) or with gentamicin containing collagen implant (study group)

Characteristic	Study group (n = 151)	Control group (n = 137)
Age – years (range)	69 ± 9.2 (43–87)	70 ± 10.4 (38–90)
Male sex	105 (70)	99 (72)
Risk factors and comorbidity		
Body mass index – kg/m^2	26.0 ± 4.5	26.1 ± 3.9
Diabetes mellitus (type I and II)	45 (30)	36 (27)
Smoking	64 (43)	55 (41)
Chronic kidney disease – GFR <30 mL/min/1.73 m^2	15 (10)	14 (10)
Arterial hypertension and/or antihypertensive medication	108 (73)	105 (77)
Hypercholesterolaemia and/or statin medication	124 (83)	107 (79)
Pre-operative antibiotics – 30 days	10 (7)	12 (11)
Operative characteristics		
Type of operation		
Endarterectomy – thrombectomy or/and embolectomy	76 (50)	68 (50)
Supragenicular bypass	34 (23)	33 (24)
Infragenicular bypass	14 (9)	13 (10)
Aorta/axillobifemoral bypass	9 (6)	7 (5)
Endovascular aortic aneurysm repair	18 (12)	16 (11)
Use of prosthetic material	110 (83)	98 (77)
Operation time – min	165 ± 73	160 ± 74
Incision length – cm	7.9 ± 2.1	7.9 ± 2.7
Blood loss – mL	486 ± 674	543 ± 798

Data are presented as mean ± standard deviation or n (%). Differences between the two treatment groups were assessed by chi-squared tests (in case of categorical data) or independent sample t-test (in case of continuous data). There were no statistically significant differences between study groups. GFR = glomerular filtration rate.

Primary outcome

The outcomes for both groups are shown in Table 2. The use of a gentamicin implant was not associated with a significant overall reduction of SSIs. The overall wound infection rate was 7% in the study group and 12% in the control group (p = .17). Because of a significant heterogeneity in treatment effect between study sites a subgroup analysis was performed. Two centres had higher risks for infection in the control group (19% and 25%) than two other centres with a lower risk (6% and 9%). In the two centres with a high SSI incidence in the control group (>10%), a greater reduction in SSIs by means of the gentamicin implants was found, reaching statistical significance (1% vs. 22%, p < .001; Table 3). In the two centres with low incidence of infection in the control group, this effect was not observed. In the sensitivity analysis, excluding patients

with an endovascular aortic aneurysm repair (n = 34), all findings were consistent with the results of the primary analysis.

Table 2. Primary and secondary outcomes of patients with an inguinal incision for primary arterial repair treated without (control group) or with gentamicin containing collagen implant (study group)

Outcome	Study group (n = 151)	Control group (n = 137)	p value*
Total wound infections	11 (7)	17 (12)	.17
Length of hospital stay − d	6 ± 5.2	7 ± 6.3	.06
Post-operative antibiotics	27 (21)	30 (25)	.55
Re-admission	9 (7)	10 (8)	.81
Re-operation	11 (8)	8 (7)	.64
Death	4 (3)	3 (3)	1.00

Data are presented as mean ± standard deviation or n (%).
* Differences between the treatment groups were assessed by chi-squared tests (in case of categorical data) or independent sample t test (in case of continuous data), stratified for the centre of inclusion.

Table 3. Subgroup analysis for the primary outcome of patients with inguinal incision for primary arterial repair treated without (control group) or with gentamicin containing collagen implant (study group). Centres at high risk of infection in the control group (19% and 25%) and centres with low baseline risk of infection (6% and 9%)

Outcome	Study group	Control group	p value*
High risk centres (>10% infections in the control group)			
Number of patients	72	51	
Total wound infections	1 (1)	11 (22)	<.001
Low risk centres (<10% infections in the control group)			
Number of patients	79	85	
Total wound infections	10 (13)	6 (7)	.30

Data are presented as mean ± standard deviation or n (%).
* Differences between the two treatment groups were assessed by chi-squared tests, stratified for the centre of inclusion.

Secondary outcome

The mean time to infection was comparable in both groups (20 ± 10.7 days vs. 20 ± 11.6 days, p = .93). In Kaplan Meier analysis, the difference between groups was not statistically significant (Fig. 2). A total of 17 wound cultures were taken in each group (11% study group vs. 13% control group, p = .74). In the control group, all wound cultures were positive, whereas in the study group there were only 10 positive wound cultures (p = .09). Regarding the other secondary outcomes, mean length of hospital stay was comparable between the study group and the control group (6 ± 5.2 and 7 ± 6.3 days, p = .06). No allergic reactions were observed in either group and no significant differences were found in the secondary outcomes, antibiotics, re-admission or re-operation. Mortality rates were 3% in both groups.

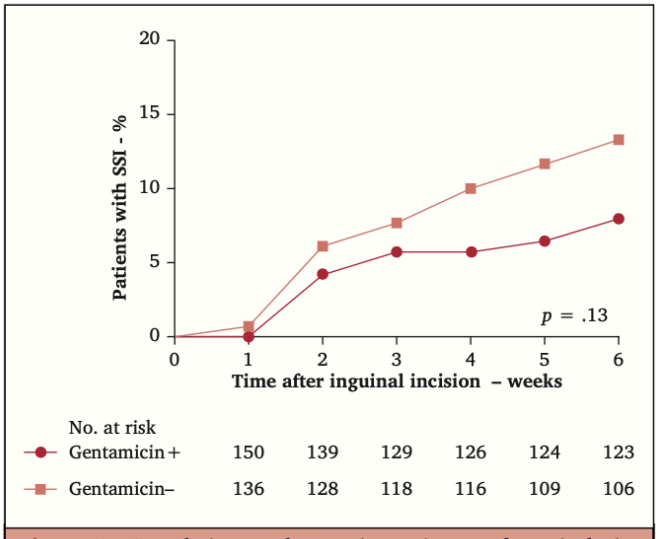

Figure 2. Cumulative Kaplan–Meier estimate of surgical site infection (SSI; according to the Centres for Disease Control and Prevention definition) rates after inguinal incision for primary arterial repair treated without (Gentamicin -) or with gentamicin containing collagen implant (Gentamicin +). Differences in infection rates between groups, assessed by the log rank test, stratified for centre of inclusion, were not statistically significant ($p = .13$).

Discussion

SSIs following vascular surgery remain a major healthcare problem and reduction of SSIs and more effective SSI prevention in vascular surgery are absolutely needed.[1-3] In the present randomised controlled trial, no significant reduction of SSIs was achieved using gentamicin implants in patients undergoing an inguinal incision for vascular surgery. Overall wound infection rates of 7% and 12% were found in the respective allocation arms, which is comparable to the literature.[3-6] Interestingly, in two centres with high incidence of infection in the control group, a greater reduction in SSIs was found in the study group, reaching statistical significance. The results were less promising than hypothesised based on the results of the pilot study of Costa Almeida et al. In their prospective study of 60 vascular surgery patients, no SSI occurred in the implant group, compared with six infections in the control group and this difference was found to be significant. In addition, length of hospital stay was also significantly reduced.[16] These

results could not be validated in the multicentre randomised controlled trial. There was an essential difference in patient characteristics, since Costa Almeida et al. only included non-diabetic and non-obese patients. In the current study, only in a subgroup with high risk of infection was there a significant reduction in SSIs. This post hoc subgroup analysis was performed because a significant heterogeneity in treatment effect between study sites was found during statistical analysis. Two centres had a remarkably higher SSI incidence in their control group (19% and 25%) than the two other centres (6% and 9%). An incidence of SSIs greater than 10% in the control group was therefore defined as a high risk centre. Subgroup analysis showed a significant difference in infection rate in these high risk centres. In the analysis, operating time was not different between study sites and not correlated with the incidence of infection. The two low risk centres did not have a higher proportion of endovascular aortic aneurysm repairs and the results of the sensitivity analysis excluding these endovascular interventions were consistent with the results of the primary analysis, making any influence unlikely. In addition, incision length and the use of prosthetic material were not associated with surgical site infections either. Also baseline characteristics (gender, age > 80 years, BMI > 25, smoking and diabetes) did not show any correlation with the outcome and were not un- evenly distributed between study sites. One reason might be differences in peri-operative tissue handling by different operators, but no attempt has been made to correlate infection with surgeon. Also, differences in operating room facilities or more operations performed by assistant surgeons could have influenced the outcomes. In conclusion, an explanation for the difference in SSI incidence based on the data provided could not be found.

In a systematic review, Hussain et al.[1] analysed five clinical studies, involving 109 patients, and all reviewed publications demonstrated that the SSI rate was reduced by prophylactic use of gentamicin implants.[19-21] However, all the included studies involved very small study populations and were rather dated. The present randomised controlled trial is the largest series to date. Despite presenting the largest clinical trial to date on this matter, the calculated sample sizes were not reached due to slow enrolment, even though it was a multicentre design. This could explain why the overall reduction in SSIs did not reach statistical significance. In larger study populations this clear trend might have reached statistical significance. Also, the reduction

in hospital stays almost reached statistical significance in this study and might have become significant in larger study groups.

Limitations

There are a number of limitations that should be considered. First, all results of this study should be interpreted with caution, since the required 304 patients per group was not reached. Another drawback is the multicentre nature of the study. However, this multicentre set up is also advantageous since the external validity is higher compared with a single centre set up. The severity of the SSI was not assessed due to insufficient standardisation of wound assessment and interpretation difficulties across centres. Wound assessment and classification are clinical and rather subjective decisions. All forms of serous leakage, seroma or cellulitis with an intact dermis are widely interpretable. One physician might interpret local erythema or serous leakage as clinical wound infection, whereas another physician might interpret it as regular variant of the healing process. The aim was to make the assessment of wound healing as objective as possible by using photography and judgement by a second, independent physician. Unfortunately, assessment of wound healing using photos appeared un- reliable due to factors such as lighting conditions. Finally, CDC definitions were used, since positive wound cultures and purulent drainage could be analysed more objectively.

Despite all limitations described above, on the positive side both groups were homogeneous at baseline. No con- founding factors were found regarding the baseline intra- operative characteristics. No allergic reactions or other adverse side effects were observed, underlining that gentamicin implants can used safely.

Future perspectives

The promising results of previous studies could not be validated in this multicentre randomised controlled trial. A reduction in SSIs was found; however, only statistically significant in a subgroup at high risk of infection. Additional studies with adequate group sizes to reach adequate statistical power would be needed to further confirm these results. Objective wound assessment by a restricted number of physicians is of major importance to obtain valid results. A control group receiving a collagen implant without gentamicin would be of interest as well,

since collagen itself is known to have positive effects on wound healing and homeostasis.[1,14,15] In addition, further research has to be focused on cost effectiveness analysis as well. Even if a significant decrease in infection rate and hospital stay were to be observed, it would still be necessary to assess a possible reduction of the health care costs as well.

Conclusion

The use of gentamicin implants did not result in a significant overall reduction of SSIs. However, a significant reduction in the incidence of SSIs was found in high risk centres (>10% infections in the control group) but not in low risk centres. The use of gentamicin implants may therefore be a valuable adjunct to improve outcomes in vascular centres with a high incidence of wound infections, however, the limitation of not reaching the calculated sample sizes should be considered.

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Chapter 8

Summary and conclusion

More and more patients are suffering from Chronic Limb Threatening Ischaemia (CLTI) with high risk of major amputation and mortality and several crucial aspects regarding the optimal management of these patients are unclear. Numerous revascularization techniques have been developed in the last decades. An impressive variability in primary treatment choices for patients with CLTI can be found in the literature, underlining the lack of knowledge and treatment uniformity. Understanding CLTI and its treatment strategies is however essential to be able to provide the best medical care for affected patients.[1-4] To overcome two of the shortcomings of the existing literature this thesis focuses on the effectiveness of revascularization in octogenarians with CLTI (**Part I**) and on the management of surgical site infections (SSIs) as complication after revascularization (**Part II**).

Revascularization in octogenarians (Part I)

Revascularization is the cornerstone of the treatment of patients with CLTI. In octogenarians however, the clinical benefits of a revascularization approach might be limited. Advanced age is a well-known risk factor in cardiovascular diseases and it was expected that it would influence the outcomes of revascularization. However, considering the fact that randomised clinical trials will never be ethically justifiable, we attempted to ensure methodological valid verification of a generally believed expectation with a meta-analysis with large sample size. **Chapter 2** describes the outcomes of this systematic review and meta-analysis on the effectiveness of revascularization in octogenarians. We were able to include more than 17000 patients with CLTI and found an important 1-year mortality rate of 32% in octogenarians after revascularization, which was significantly higher than in non-octogenarians (17%). Amputation rates were not significantly different, whereas AFS was significantly lower in the octogenarian's group as well. These outcomes were confirmed in our retrospective cohort study of 329 patients with CLTI as described in **Chapter 3**. A 1-year mortality rate of 44% in octogenarians and 18% in patients younger than 80 years were found, while amputation rates were comparable. In this study, age ≥ 80 years, dialysis, Rutherford category 5/6 and heart failure were predictors of mortality in Cox-regression analysis, resulting in a 1-year mortality rate of 58% in case all four risk factors were present. These outcomes are of major importance for clinical practice to inform patients

and colleagues adequately during the decision-making process on any intervention in this fragile patient group. As a consequence, appropriate patient selection is essential and our predictive factors may help in the decision-making whether patients will benefit from revascularization or not. Conservative treatment could be considered in certain patients as well, since there is growing evidence that selected patients may be appropriately treated with primary amputation or conservative treatment.[5,6] In our retrospective cohort, the mortality rate of conservatively treated octogenarians was also relevant, but no major amputations were performed in the conservatively treated group. An individual therapeutic approach should be initiated, focused on the quality of life of these patients.

Surgical site infections after revascularization (Part II)

Surgical site infection (SSI) can be a serious complication following revascularization that may lead to graft infection with increased risk of subsequent amputation and mortality. Both treatment and prevention strategies were investigated in this thesis. The management of severe groin wound complications remains challenging for vascular surgeons, although there is growing evidence that support the benefits of muscle flap coverage as effective treatment approach in a challenging patient population with otherwise a poor prognosis. **Chapter 4** describes the outcomes of our systematic review on the effectiveness of two muscle flap coverage techniques for deep groin infection (rectus femoris muscle flap (RFF) versus sartorius muscle flap (SMF)). Superiority of either muscle flap on amputation or mortality rates was not demonstrated, but we were able to demonstrate that muscle flap coverage in general was effective in the management of complex groin wounds. Graft loss rates were lower after RFF reconstruction, but these conclusions were based on low- quality evidence.

These outcomes were confirmed in two retrospective cohort studies. As described in **Chapter 5**, low rates of limb loss, graft loss and mortality were demonstrated in a cohort of 88 patients undergoing 96 RFFs. This study presents the largest worldwide series of RFFs and the results demonstrate that the RFF technique is an effective way to manage deep groin defects resulting from debridement for infection. **Chapter 6** compares our own outcomes of RFFs and SMFs and equal results on amputation, mortality and graft loss rates were found with both techniques.

Therefore, it can be concluded that local muscle flap reconstruction using both techniques is effective in the treatment of infected groin wounds, achieving good results regarding limb salvage and graft salvage in a challenging patient population. Therefore, we would recommend performing the type of muscle flap coverage according to the specific preference and experience of the surgical team as well as anatomical and patient characteristics, the latter were not assessed in this thesis. The RFF could be used preferentially to cover large tissue defects, whereas the SMF could be preferred to cover smaller defects in the groin.

Finally, **Chapter 7** describes our prospective randomized controlled trial, aiming to prevent femoral SSIs in the first place, using gentamicin implants following vascular surgery via inguinal incision. In this multicentre trial, 288 patients were randomized to either receive a gentamicin-implant or not. Interestingly, the effect of gentamicin implants on SSI rate differed significantly between study sites. Gentamicin implants significantly reduced the incidence of SSIs in high-risk centres (>10% infections in the control group), but had no effect in low-risk centres. Therefore, preventive use of gentamycin-implants in the groin after vascular surgery cannot be routinely advised based on current evidence, but the use of gentamicin implants may be a valuable adjunct to improve outcomes in vascular centres with a high incidence of wound infections.

Conclusion

The research performed in this thesis adds to the debate about the optimal management of patients with CLTI and important steps were made towards a better understanding of CLTI and its treatment strategies. Two current challenges in the management of patients with CLTI were assessed and three main conclusions can be made:

1. Revascularization in octogenarians with CLTI is associated with a substantial high mortality rate. Appropriate patient selection is of major importance and an individual therapeutic approach should be initiated, focused on the quality of life of these patients.

2. Deep groin infections after revascularization can be effectively managed using muscle flap coverage in addition to debridement. Anatomical and patient characteristics are critical in the decision-making process which muscle flap reconstruction is the best treatment option for an individual patient.

3. Preventive use of gentamycin-implants after femoral vascular surgery cannot be routinely advised, but should be considered in vascular centres with a high incidence of wound infections in the groin.

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Chapter 9

Discussion and future perspectives

Important steps were made towards a better understanding of CLTI. Two current challenges in the treatment of CLTI were extensively investigated: revascularization of octogenarians and surgical site infection as complication after revascularization. However, several aspects should be further investigated to be able to provide the best medical care for all affected patients.

Conservative treatment of CLTI and quality of life

As already highlighted in the introduction of this thesis, revascularization is the cornerstone of the treatment of patients with CLTI. The high mortality rates in octogenarians described in this thesis suggest however that revascularization might not be indicated in all octogenarians and that a more conservative approach may be justified in this friable patient group. Unfortunately, data on clinical outcomes of conservative treatment of CLTI and of primary amputations are very limited. Only few studies mention clinical outcomes after conservative treatment, reporting inconsistent results. In our limited analysis, the mortality rate of conservatively treated octogenarians was also high. However, there are studies available concluding that conservative treatment is non-inferior to revascularization in terms of mortality and that revascularization was not required in all patients with CLTI.[1-6] The results of these studies focus on objective outcome measurements such as mortality and limb salvage. We think however that quality of life and pain relief should be the major therapeutic goals in this group of patients and available data on these outcomes are very scare. Only Steunenberg et al. prospectively analysed quality of life in combination with mortality in two age groups (70-79 and >80 years) of patients with CLTI and all patients showed significant increased quality of life results at six months, including conservatively treated patients.[7] A recently published study on multidisciplinary approached conservative treatment of patients with mild to moderate ischemia and tissue loss reported an impressive limb salvage rate of 89.3% at mid-term follow-up.[8] These results are extremely valuable in the decision-making, putting assumed benefits of revascularization into perspective, especially for a frail patient group like octogenarians.

Additional studies should therefore further investigate outcomes after conservative treatment and primary amputation, including quality of life studies, to determine the optimal management of octogenarians with CLTI. Recently, a multicentre observational study on outcomes of CLTI

patients in the Netherlands has been initiated, comparing clinical outcomes and quality of life after conservative treatment to outcomes after revascularization. Hopefully, this registry will provide sufficient information on elderly patients as well, and hence recommendations for optimal management (conservative versus revascularization) of octogenarians with CLTI. Until results of this future research are available, an individual revascularization approach based on specific clinical and anatomic patterns should be used for octogenarians, in the context of the current Global Vascular Guidelines on the Management of CLTI.[9]

Appropriate patient selection for revascularization

As described above, conservative treatment may be considered in selected patients with CLTI, but therefore, appropriate patient selection and risk assessment are required. Predictive risk models can be useful to assess the risk of an intervention and to decide whether a patient will benefit from it. Several predictive risk models have been developed for patients with CLTI, aiming to predict amputation and/or mortality after revascularization. Their use in clinical practice is however limited.[10-14] In this thesis, the combination of the factors octogenarian, Rutherford category 5/6, heart failure and dialysis was associated with a 1-year mortality rate of 58% after revascularization. This outcome underlines the importance of including these factors in future predictive risk models to identify patients who may not benefit from revascularization. Optimizing the treatment of octogenarians with CLTI therefore, also needs adequate risk scores validated for those parameters described above, enabling appropriate patient selection.

Prevention of surgical site infections after revascularization

We were not able to validate the promising results of previous studies on the effectiveness of gentamicin containing collagen implants in the reduction of surgical site infections in our multicentre randomized controlled trial.[15-18] A reduction in surgical site infections was only found in a subgroup with high risk for infection. We were not able to reach the required group

sizes as calculated in the power calculation, which could explain that the overall difference was not statistically significant. Additional studies with adequate group sizes to reach adequate statistical power would be needed to further confirm these results. Ideally, the control group would receive a placebo collagen-implant without gentamycin, since collagen itself is known to have positive effects on wound healing and homeostasis.[15, 18, 19] In addition, further research has to be focused on cost-effectiveness analysis as well. Even if a significant decrease in infection rate and in-hospital days would have been observed, it is still necessary to assess to what extent these effects result in a reduction of the health care costs as well. Based on current evidence preventive use of gentamycin-implants cannot be routinely advised.

Muscle flap coverage for deep groin infection

In our studies, superiority of either muscle flap on amputation or mortality rates was not demonstrated. In addition to the discussion which type of muscle flap coverage is the most effective one, the value of performing muscle flaps in a prophylactic setting is an interesting area for further research. Fisher et al. found significantly less groin wound complications in patients receiving a prophylactic flap after initial open vascular surgery involving the femoral arteries through groin incision.[20] The authors developed the so-called Penn Groin Assessment Scale for risk stratification and clinical decision making whether a prophylactic flap should be considered, including obesity, smoking, the use of a prosthetic graft and previous groin operations as preoperative risk factors.[21] In addition, there is an ongoing discussion about whether muscle flaps should be performed by vascular surgeons or by plastic and reconstructive surgeons. To our opinion, this debate should not be linked to the educational background of the surgeon itself, but to the experience of the surgical team on this area and muscle flap coverage should be performed by experienced surgeons in a regular matter.

Alternative therapies for patients with CLTI

As described above, traditional conservative treatment and primary amputation are treatment choices that have to be explored in future studies. Moreover, different alternative therapies are

under research for patients with CLTI who may be not suitable for revascularization. Hyperbaric oxygen therapy aims to increase wound healing by inspiring oxygen in a compression chamber leading to a suggested increase in oxygen supply to the ischemic tissue. Another approach is therapeutic angiogenesis using growth factors and stem cell therapies to stimulate growth of new blood vessels.[22, 23] Finally, so called venous arterialization, describing a concept of using the venous bed as an alternative conduit for perfusion with arterial blood, is believed to be another alternative technique for limb salvage.[24] Although consideration of hyperbaric oxygen therapy in selected patients is already advocated by current guidelines, research on these alternative therapies is still in its infancy and additional studies are absolutely needed.[22, 23, 25]

Health care costs already increased during the last decades and the financial load of the health care system will further increase because of the overall aging and increased life expectancy. Questions about cost effectiveness are therefore of importance in current research, also in CLTI treatment. As described above, cost-effectiveness analysis of the use of gentamycin implants is needed, but cost-effectiveness analysis of CLTI treatment approaches in general is of interest as well. The literature indicates that endovascular treatment is less expensive in the short-term, but there is a lack of knowledge about the cost-effectiveness of conservative treatment approaches and especially long-term data are missing.[25, 27]

In conclusion, additional studies on quality of life and outcomes after conservative treatment are needed to determine the optimal management of octogenarians with CLTI. In addition, appropriate patient selection using validated risk scores is of major importance to optimize the treatment of octogenarians. Before the use of gentamycin-implants could be routinely advised in prevention of surgical site infections, additional studies with greater group sizes and cost-effectiveness analyses would be needed. Finally, different alternative therapies for patients with CLTI could be a last option for limb salvage in the future.

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Nederlandse samenvatting

Steeds meer patiënten lijden aan perifeer arterieel vaatlijden en kritieke ischemie van de onderste ledematen (CLTI) met een hoog risico op amputatie en mortaliteit en verschillende belangrijke aspecten met betrekking tot de optimale behandeling van deze patiënten zijn onduidelijk. In de afgelopen decennia zijn een groot aantal revascularisatie-technieken ontwikkeld. Er heerst echter onduidelijkheid over welke behandelingskeuze voor welke patiënt op welk moment de meest geschikte is. Een universeel gelden behandelingsconcept voor patiënten met CLTI mist tot nu toe in de literatuur.[1-4] Om twee van de tekortkomingen van de actuele literatuur te overwinnen, richt dit proefschrift zich op de effectiviteit van revascularisatie in tachtigplussers met CLTI (**deel I**) en op de behandeling van postoperatieve wondinfecties als complicatie na revascularisatie (**deel II**).

Revascularisatie bij tachtigplussers (deel I)

Revascularisatie is de hoeksteen van de behandeling van patiënten met CLTI. Bij tachtigplussers kunnen de klinische voordelen van een revascularisatiebenadering echter beperkt zijn. Oudere leeftijd is een bekende risicofactor bij hart- en vaatziekten en de verwachting was dat dit de uitkomsten van revascularisatie zou beïnvloeden. Gezien het feit dat gerandomiseerde klinische onderzoeken op dit wetenschappelijk gebied nooit ethisch verantwoord zullen zijn, hebben wij geprobeerd om een methodologisch valide verificatie van een algemeen aangenomen verwachting te bevestigen door een meta-analyse met een grote steekproefomvang. **Hoofdstuk 2** beschrijft de resultaten van deze systematische review en meta-analyse over de effectiviteit van revascularisatie bij tachtigplussers. Wij waren in staat om meer dan 17.000 patiënten met CLTI op te nemen en vonden een belangrijk 1-jaars sterftecijfer van 32% bij tachtigplussers na revascularisatie, wat significant hoger was dan bij niet-tachtigjarigen (17%).

Deze uitkomsten werden bevestigd in onze retrospectieve cohortstudie van 329 patiënten met CLTI zoals beschreven in **Hoofdstuk 3**. Een 1-jaars sterftecijfer van 44% bij tachtigplussers en 18% bij patiënten jonger dan 80 jaar werd gevonden, terwijl de amputatiecijfers vergelijkbaar waren. In deze studie waren leeftijd ≥ 80 jaar, dialyse, Rutherford categorie 5/6 en hartfalen voorspellers van mortaliteit in Cox-regressieanalyse, resulterend in een sterftecijfer van 58% indien alle risicofactoren aanwezig waren. Deze uitkomsten zijn van groot belang voor de

klinische praktijk om patiënten en collega's tijdens het besluitvormingsproces adequaat te informeren over elke interventie in deze kwetsbare patiëntengroep. Nauwkeurige patiëntselectie is van groot belang en onze voorspellende factoren kunnen helpen bij de vraag of patiënten baat zullen hebben van een revascularisatie of niet. Conservatieve behandeling kan ook worden overwogen bij geselecteerde patiënten, aangezien er steeds meer aanwijzingen zijn dat geselecteerde patiënten met primaire amputatie of conservatieve behandeling adequaat behandeld kunnen worden.[5,6] In onze beperkte analyse was het sterftecijfer van conservatief behandelde tachtigplussers eveneens hoog, maar er werden geen amputaties doorgevoerd.

Postoperatieve wondinfecties na revascularisatie (deel II)

Een postoperatieve wondinfectie in de lies kan een ernstige complicatie zijn na revascularisatie, mogelijk leidend tot transplantaatinfectie met een verhoogd risico op daaropvolgende amputatie en mortaliteit. In dit proefschrift zijn zowel behandelings- als preventiestrategieën onderzocht. De behandeling van deze ernstige complicaties van de lieswonden blijft een uitdaging voor vaatchirurgen. Tegenwoordig zijn er steeds meer aanwijzingen voor positieve effecten van het bedekken van de geïnfecteerde lieswond met een spierflap. **Hoofdstuk 4** beschrijft de uitkomsten van onze systematische review over de effectiviteit van spierflapbedekking voor diepe liesinfectie (rectus femoris spierflap (RFF) versus sartorius spierflap (SMF)). Superioriteit van spierflap met betrekking tot amputatie of sterftecijfers werd niet aangetoond, maar we konden aantonen dat spierflapbedekking in het algemeen effectief was in de behandeling van complexe lieswonden.

Deze uitkomsten werden bevestigd in twee retrospectieve cohortstudies. Zoals beschreven in **Hoofdstuk 5** werden lage percentages ledemaatverlies, transplantaatverlies en mortaliteit gevonden in een cohort van 88 patiënten die 96 RFF's ondergingen. Deze studie presenteert de grootste reeks RFF's en de resultaten tonen aan dat de RFF-techniek een effectieve manier is om diepe liesdefecten na chirurgisch debridement te behandelen. **Hoofdstuk 6** vergelijkt onze uitkomsten van RFF's en SMF's en vergelijkbare resultaten werden gevonden met beide technieken. Daarom kan worden geconcludeerd dat lokale spierflapreconstructie met behulp van beide technieken effectief is in de behandeling van geïnfecteerde lieswonden, waarbij

goede resultaten worden behaald met betrekking tot ledemaat- en transplantaatbehoud in een uitdagende patiëntenpopulatie met een slechte prognose. Onze aanbeveling is om het type spierflapbedekking te kiezen op basis van de specifieke voorkeur en ervaring van het chirurgische team, evenals anatomische en patiëntkenmerken, die niet zijn beoordeeld in dit proefschrift. De RFF zou bij voorkeur kunnen worden gebruikt om grote weefseldefecten te bedekken, terwijl de SMF de voorkeur zou kunnen hebben om kleinere defecten in de lies te bedekken.

Ten slotte beschrijft **Hoofdstuk 7** onze prospectieve gerandomiseerde studie met het doel dit soort postoperatieve wondinfecties te voorkomen door implantatie van een gentamicine-matje in de lies incisie op het einde van de vaatchirurgische ingreep. In deze multicenter trial werden 288 patiënten gerandomiseerd om al dan niet een gentamicine-matje te krijgen. Interessant is dat het effect van gentamicine-matjes op het aantal postoperatieve wondinfecties significant verschilde tussen de onderzoeks-ziekenhuizen. Gentamicine-implantaten verminderden de incidentie van postoperatieve wondinfecties significant in hoog-risico centra (> 10% infecties in de controlegroep), maar hadden geen effect in laag-risico centra. Daarom kan preventief gebruik van gentamycine-implantaten niet routinematig worden geadviseerd op basis van de huidige gegevens. Het gebruik van gentamicine-matjes zou wel een waardevol hulpmiddel in vasculaire ziekenhuizen met een hoge incidentie van wondinfecties kunnen zijn om de resultaten te verbeteren.

Conclusie

De onderzoeken die in dit proefschrift werden uitgevoerd, dragen bij aan de discussie over de optimale behandeling van patiënten met CLTI en er zijn belangrijke stappen gezet naar een beter begrip van CLTI en de behandelingsstrategieën. Twee huidige uitdagingen in de behandeling van patiënten met CLTI werden benaderd en er kunnen drie belangrijke conclusies worden getrokken:

1. Revascularisatie bij tachtigplussers gaat gepaard met een aanzienlijk hoog sterftecijfer. Nauwkeurige patiënten selectie is van groot belang en er moet voor iedere

patiënt een individuele therapeutische benadering worden gekozen, gericht op de kwaliteit van leven van deze patiënten.

2. Postoperatieve liesinfecties na revascularisatie kunnen effectief worden behandeld met behulp van een spierflapbedekking na chirurgisch debridement. Anatomische en patiëntkenmerken zijn van cruciaal belang in het besluitvormingsproces over de vraag welke spierflapbedekking de beste behandelingsoptie is voor een individuele patiënt.

3. Preventief gebruik van gentamycine-implantaten kan niet routinematig worden geadviseerd, maar moet worden overwogen in vasculaire centra met een hoge incidentie van wondinfecties in de lies.

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Deutsche Zusammenfassung

Immer mehr Patienten leiden an chronischer arterieller Verschlusskrankheit der unteren Extremitäten bis hin zur kritischen Ischämie (CLTI) mit hohem Risiko einer Amputation und hohem Mortalitätsrisiko und einige entscheidende Aspekte für eine optimale Behandlung dieser Patienten sind bisher unklar. In den letzten Jahrzehnten wurden zahlreiche interventionelle und operative Revaskularisationstechniken entwickelt. In der Literatur findet sich eine beeindruckende Variabilität, wenn es um die Wahl einer Behandlung für Patienten mit CLTI geht. Die mangelnde Einheitlichkeit der Behandlung unterstreicht, dass noch keine bestmögliche Versorgung der betroffenen Patienten festgelegt wurde.[1-4] Um zwei der Diskussionspunkte zu adressieren, konzentriert sich diese Arbeit auf die Effektivität der Revaskularisation bei über-80-Jährigen mit CLTI (**Teil I**) und auf die Behandlung von postoperativen Wundinfektionen der Leiste als Komplikation nach Revaskularisation (**Teil II**).

Revaskularisation bei über-80-Jährigen (Teil I)

Die Revaskularisation ist der Eckpfeiler der Behandlung von Patienten mit CLTI. Bei über-80-Jährigen kann der klinische Nutzen eines Revaskularisationansatzes jedoch begrenzt sein. Das fortgeschrittene Alter ist ein bekannter Risikofaktor für Herz-Kreislauf-Erkrankungen, und die allgemeine Erwartung ist, dass die Ergebnisse der Revaskularisation durch Begleiterkrankungen negativ beeinflusst wird. Angesichts der Tatsache, dass randomisierte klinische Studien zu diesem Thema niemals ethisch vertretbar sein werden, haben wir durch eine Metaanalyse mit großer Stichprobengröße eine validierte Überprüfung der bereits allgemein akzeptierten Erwartung durchgeführt. **Kapitel 2** beschreibt die Ergebnisse dieser systematischen Review und Metaanalyse zur Effektivität der Revaskularisation bei über-80-Jährigen. Mehr als 17000 Patienten mit CLTI konnten einbezogen werden und wir fanden bei über-80-Jährigen eine 1-Jahres-Mortalitätsrate von 32% nach Revaskularisation, die signifikant höher war als bei unter-80-Jährigen (17%).

Diese Ergebnisse wurden in unserer retrospektiven Kohorten Studie mit 329 Patienten mit CLTI bestätigt, wie in **Kapitel 3** beschrieben. Es wurde eine 1-Jahres-Mortalitätsrate von 44% bei über-80-Jährigen und 18% bei Patienten unter 80 Jahren gefunden, während die Amputationsraten vergleichbar waren. In dieser Studie waren Alter ≥ 80 Jahre, Dialyse,

Rutherford-Kategorie 5/6 und Herzinsuffizienz Prädiktoren für die Mortalität in der Cox-Regressionsanalyse, was zu einer Mortalitätsrate von 58% führte, wenn alle Risikofaktoren vorhanden waren. Diese Ergebnisse sind für die klinische Praxis von großer Bedeutung, um Patienten und Kollegen während des Therapieentscheidungsprozesses angemessen über eine Intervention in dieser fragilen Patientengruppe informieren zu können. Eine adäquate Patientenauswahl ist von großer Bedeutung, und unsere Prädiktoren können bei der Entscheidung helfen, ob Patienten von einer Revaskularisation profitieren oder nicht. Eine konservative Behandlung kann auch bei ausgewählten Patienten in Betracht gezogen werden, da es zunehmend Studien gibt, die zeigen, dass ausgewählte Patienten auch mit primärer Amputation oder konservativer Behandlung angemessen behandelt werden können.[5,6] In unserer begrenzten Analyse war die Sterblichkeitsrate konservativ behandelter Oktogenarier so hoch wie gut, aber es wurden keine größeren Amputationen durchgeführt.

Postoperative Wundinfektionen nach Revaskularisation (Teil II)

Wundkomplikationen in der Leistengegend sind ein häufiger Grund für post-operative Morbidität und auch Letalität nach gefäßchirurgischen Eingriffen. Eine postoperative Infektion kann zu einer tiefen Gefäßprotheseninfektion mit erhöhtem Risiko für eine nachfolgende Amputation und Mortalität führen. In dieser Arbeit wurden sowohl Behandlungs- als auch Präventionsstrategien untersucht. Die Behandlung schwerer Wundkomplikationen in der Leistengegend bleibt für Gefäßchirurgen eine Herausforderung. Die Bedeckung der Leistengegend mit einem Oberschenkelmuskellappen ist ein mögliches vielversprechendes Therapieverfahren. **Kapitel 4** beschreibt die Ergebnisse unserer systematischen Review zur Effektivität der Muskellappenplastiken bei postoperativen tiefen Leisteninfektionen (Rectus-femoris-Muskellappen (RFF) im Vergleich zum Sartorius-Muskellappen (SMF)). Beide Muskellappen zeigten sich gleichwertig gut bezüglich der Amputations- und Mortalitätsrate und es konnte demonstriert werden, dass eine Muskellappenplastik ein effektives Verfahren ist, um tiefe Defekte nach Infektionen der Leistenwunde zu behandeln und zu bedecken.
Diese Ergebnisse wurden in zwei retrospektiven Kohorten Studien bestätigt. Wie in **Kapitel 5** beschrieben, wurden in einer Kohorte von 88 Patienten mit 96 RFF niedrige Raten von

Amputationen, Transplantatverlust und Mortalität gefunden. Diese Studie präsentiert die bisher größte Kohorte von RFFs und die Ergebnisse zeigen, dass die RFF-Technik ein wirksamer Weg ist, um tiefe Leistendefekte zu behandeln, die aus einem Wunddebridement nach Infektionen resultieren. **Kapitel 6** vergleicht unsere Ergebnisse von RFFs und SMFs und es wurden gleichwertig gute Ergebnisse mit beiden Techniken gefunden. Daher kann der Schluss gezogen werden, dass beide Techniken einer lokalen Muskellappenplastik effektive Verfahren sind zur Behandlung von infizierten Leistenwunden und mit beiden Techniken gute Ergebnisse hinsichtlich des Erhaltes von Gliedmaßen und Gefäßprothesen erzielt werden in einer herausfordernden Patientenpopulation mit schlechter Prognose. Wir empfehlen, die Art der Muskellappenplastik entsprechend den spezifischen Vorlieben und Erfahrungen des Operationsteams sowie den anatomischen und Patientenmerkmalen durchzuführen, welche in dieser Arbeit nicht berücksichtigt wurden. Der Rectus-femoris-Muskellappen könnte bevorzugt verwendet werden, um große Weichteildefekte zu bedecken, während der Sartorius-Muskellappen bevorzugt verwendet werden könnte, um kleinere Defekte in der Leiste zu bedecken.

Schließlich beschreibt **Kapitel 7** unsere prospektive randomisierte Studie, die darauf abzielte, diese Art von postoperativen Wundinfektionen zu verhindern, indem Gentamicin-Implantate nach einer Gefäßoperation in die Leistenwunde eingesetzt wurden. In dieser multizentrischen Studie wurden 288 Patienten randomisiert entweder ein Gentamicin-Implantat zu erhalten oder nicht. Interessanterweise zeigte sich die Wirkung von Gentamicin-Implantaten auf die Infektion-Rate signifikant unterschiedlich zwischen den Kliniken. Gentamicin-Implantate reduzierten die Inzidenz von Infektionen in Hochrisikozentren signifikant (> 10% Infektionen in der Kontrollgruppe), hatten jedoch in Niedrigrisikozentren keine Wirkung. Daher kann die prophylaktische Verwendung von Gentamicin-Implantaten nach aktuellen Erkenntnissen nicht routinemäßig empfohlen werden. Die Verwendung von Gentamicin-Implantaten kann jedoch eine wertvolle Ergänzung zur Verbesserung der Ergebnisse in Gefäßzentren mit hoher Wundinfektionsrate sein.

Fazit

Die in dieser Arbeit durchgeführten Forschungsarbeiten haben ergänzende Erkenntnisse in der Debatte um die optimale Behandlung von Patienten mit CLTI geliefert; ein wichtiger Schritt, um CLTI und seine Behandlungsstrategien besser zu verstehen und aktuelle Herausforderungen und Unsicherheiten zu adressieren. Drei Hauptschlussfolgerungen konnten gezogen werden:

1. Die Revaskularisation bei über-80-Jährigen ist mit einer beträchtlich hohen Letalitätsrate verbunden. Eine angemessene Patientenauswahl ist von großer Bedeutung und es sollte ein individueller therapeutischer Ansatz eingeleitet werden, der sich auf die Lebensqualität dieser Patienten konzentriert.
2. Postoperative Infektionen der Leistengegend nach der Revaskularisation können in Kombination mit einem chirurgischen Wunddebridement mithilfe einer Muskellappenplastik wirksam behandelt werden. Anatomische und Patientenmerkmale sind entscheidend für die Entscheidung, welcher Muskellappen die beste Behandlungsoption für einen einzelnen Patienten darstellt.
3. Die prophylaktische Anwendung von Gentamicin-Implantaten nach gefäßchirurgischen Eingriffen kann nicht routinemäßig empfohlen werden, sollte jedoch in Gefäßzentren mit einer hohen Inzidenz von Wundinfektionen in der Leiste in Betracht gezogen werden.

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Impact paragraph

Nowadays, awareness of the impact of performed academic research not only within science, but also on the society, is of increasing importance. This addendum is intended to address the societal and economical relevance of the research performed during this PhD-project.

This thesis addresses two important challenges in the treatment of patients suffering from Chronic Limb Threatening Ischaemia (CLTI): revascularization of octogenarians and surgical site infection as complication after revascularization. Research on both topics is relevant for our society for various reasons.

As already highlighted in the introduction of this thesis, there is an increasing number of octogenarians suffering from CLTI. Due to the overall aging of our society and increased life expectancies, the financial load on our health care system is constantly increasing. Treatment of CLTI is known to be an expensive therapy and especially in a frail patient group as octogenarians with potentially limited benefit from revascularisation, cost-effectiveness becomes a topic of discussion.[1, 2] The results of this thesis showed that the 1-year mortality rate after revascularization is extremely high in octogenarians, making this question even more important. Should we revascularize all octogenarians? The predictive risk factors described in this thesis can facilitate the decision-making in vascular surgery, resulting in safer and more efficient treatment and adequate patient selection. Avoiding costly inefficient operations can not only reduce health care costs with positive impact on the economy. It also saves patients from inefficient and therefore unnecessary operations with positive impact on the well-being of the patient itself. All patients with CLTI should be afforded best medical care, but in octogenarians surgery might not lead automatically to the best clinical outcome, especially when talking about quality of life.

Reducing health care costs is also a major benefit from prevention and optimal treatment of surgical site infections after revascularization. Avoiding costly re-operations, re-admissions and longer hospital stays due to deep groin infections should be aimed and the results of the studies presented in this thesis contribute to this aim.

As already implied, the results of this thesis are not only of interest for medical specialists and the economic health care sector, but for the patient and its well-being as well. We aim to avoid

inefficient operations in a frail group of elderly patients. The results of most recent studies, including ours, focus on objective outcome measurements such as mortality and limb salvage. We support however the increasing awareness to the fact that quality of life and pain relief should be the major therapeutic goals in this group of patients. Available data on these outcomes are very scarce and should be the focus of further research. Until results of this future research are available, we showed that an individual decision-making with every single patient, especially octogenarian, is needed. Patients have to be informed adequately as part of shared-decision-making and they have to decide what is important for their own quality of life.

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Curriculum vitae

Lina Franziska Wübbeke was born on January 23rd 1994 in Lich, Germany. She grew up in Olpe and after finishing high school at the St. Franziskus Gymnasium in Olpe in 2012, she started her study in the Netherlands. After graduating the bachelor Medical Biology at the Radboud University in Nijmegen in 2015, she continued with the study Medicine at the Maastricht University. During this Master Physician-Clinical Investigator, she started her research projects in the Maastricht University Medical Center under supervision of dr. BME Mees. The results of this research are presented in this thesis. After graduation in 2019, she started the surgical specialisation in Orthopaedic and Trauma Surgery at the University Medical Center Göttingen, Germany.

Lina Franziska Wübbeke wurde am 23. Januar 1994 in Lich geboren. Sie wuchs in Olpe auf und begann nach dem Abitur am St. Franziskus Gymnasium in Olpe im Jahr 2012 ihr Studium in den Niederlanden. Nach ihrem Bachelorabschluss in Medizinischer Biologie an der Radboud Universität in Nijmegen im Jahr 2015, setzte sie das Medizinstudium an der Maastricht University fort. Während des Masters Arzt-Klinischer Forscher startete sie ihre Forschungsprojekte im Maastricht University Medical Center unter der Aufsicht von Dr. BME Mees. Die Ergebnisse dieser Forschung werden in dieser Arbeit vorgestellt. Nach ihrem Abschluss im Jahr 2019 begann sie mit der chirurgischen Spezialisierung in Orthopädie und Unfallchirurgie am Universitätsklinikum Göttingen.