



Universiteit
Leiden
The Netherlands

Quality of provided care in vascular surgery : outcome assessment & improvement strategies

Flu, H.C.

Citation

Flu, H. C. (2010, March 24). *Quality of provided care in vascular surgery : outcome assessment & improvement strategies*. Retrieved from <https://hdl.handle.net/1887/15124>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/15124>

Note: To cite this publication please use the final published version (if applicable).

Chapter 3

A Systematic Review of Implementation of Established Recommended Secondary Prevention Measures in Patients with PAOD

Flu HC, Tamsma JT, Lindeman JHN, Hamming JF, Lardenoye JHP

Accepted for publication in the European Journal of Vascular and Endovascular Surgery 2009

ABSTRACT

Objectives: Since patients with peripheral arterial occlusive disease (PAOD) are at high risk for cardiovascular morbidity and mortality, preventive measures aimed to reduce cardiovascular adverse events are advocated in the current guidelines. We conducted a systematic review to assess the implementation of secondary prevention (SP) measures in PAOD patients.

Materials and methods: PubMed, Cochrane Library, EMBASE and Web of Science databases were searched to perform a systematic review of the literature from 1999 till June 2008 on SP for PAOD patients. Assessment of study quality was done following the Cochrane Library review system. The record outcomes were anti-platelet agents, heart rate lowering agents, blood pressure lowering agents, lipid-lowering agents, glucose lowering agents, smoking cessation and walking exercise.

Results: From a total of 2137 identified studies, 83 observational studies met the inclusion criteria of which 24 were included in the systematic review comprising 34157 patients. These patients suffered from coronary artery disease ($n=3516$, 41%), myocardial infarction ($n=2647$, 38%), angina pectoris ($n=1790$, 31%), congestive heart failure ($n=2052$, 14%), diabetes mellitus ($n=10690$, 31%) hypertension ($n=20823$, 73%) and hyperlipidaemia ($n=15067$, 64%). Contrary to what the guidelines prescribe, antiplatelet agents, heart rate lowering agents, blood pressure lowering agents and lipid-lowering agents were prescribed in 63%, 34%, 46% and 45% of the patients respectively. Glucose lowering agents were prescribed in 81% and smoking cessation in 39% of the patients.

Conclusion: The majority of patients suffering from PAOD do not receive the entire approach of secondary preventative measures as suggested by the current guidelines. To our knowledge, the cause of this undertreatment is multifactor: patient-, physician- or health care related.

INTRODUCTION

Peripheral arterial occlusive disease (PAOD) results from the narrowing of blood vessels of the lower limbs, predominantly secondary to atherosclerotic vascular disease. Risk factors (RFs) associated with PAOD include typical cardiovascular RFs, such as older age, smoking, diabetes mellitus, hypercholesterolemia, and hypertension ¹. PAOD is a substantial public health problem and also very common in the western world. The first clinical sign of PAOD is usually intermittent claudication (IC) ² and increases dramatically with advancing age, ranging from 0.6% in individuals aged 45 to 54 years, to 8.8% in patients aged 65 to 74 years ^{3,4}.

The aim of treatment of patients with PAOD is to relieve lower extremity symptoms by interventions such as regular walking exercise, endovascular therapy and/or surgery. However, besides therapeutic strategies aimed at relief of compromised flow to the lower limb, reduction of the risk of future cardiovascular events in this specific high risk patient population is of utmost importance.

Secondary prevention (SP) aims to minimize the risk of vascular morbidity and mortality and requires major changes in lifestyle, such as smoking cessation ⁴ and medical treatment with antiplatelet agents (APA) ⁵⁻⁷, lipid-lowering agents (LLA) ⁷⁻⁹, heart rate lowering agents (HRLA) ^{7, 10-12} and blood pressure lowering agents (BPLA) ^{7, 13-15} that should be continued lifelong. There is substantial evidence that a combination of long-term, tailored medical treatment in combination with life style adjustments is beneficial in reduction of future adverse cardiovascular events in these PAOD patients ¹³⁻¹⁵.

Effective SP is outlined in recent guidelines such as the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC I and II) reporting standards ^{13, 14} and the guidelines for the prevention of cardiovascular events in patients with symptomatic PAOD proposed by the American Heart Association/American College of Cardiology (AHA/ACC) ¹⁵. Although PAOD patients would benefit from aggressive SP, as stated in the TASC and AHA/ACC guidelines, the actual prevalence of these preventative measures in this specific patient population is unknown.

Therefore, we conducted a systematic review to assess the implementation/prevalence of established recommended secondary preventive measures by physicians in patients with intermittent claudication (IC) or critical limb ischaemia (CLI) using recent literature ¹⁶⁻³⁹ concerning implementation established recommended secondary prevention in PAOD patients.

MATERIALS AND METHODS

Search strategy

A systematic search of literature was performed in the medical databases PubMed, Cochrane Library, EMBASE and Web of Science. The search strategy used for each database is described in the Appendix 1-4 respectively. In addition, we manually searched the reference lists of relevant articles to identify articles missed by electronic searches. Language was restricted to English, French, German and Dutch. We did not systematically search abstract books of conference proceedings, did not hand search leading journals, and did not contact leading authors in the field to retrieve potential extra papers.

Inclusion criteria

The inclusion criteria of the studies for the systematic review are listed in Appendix 5.

Types of studies

Any prospective or retrospective study evaluating the evidenced-based medicine guideline-concordance of SP in patients with PAOD was considered. The studies had to be published from 1999 (the year of the TASC I¹³ reporting guidelines) till June 2008. They had to describe an original patient series evaluating the SP in PAOD patients. Studies had to describe a consecutive patient series and had to comprise a minimal number of forty patients to be eligible for inclusion.

Participants, risk factors, comorbidity and secondary prevention

Studies were eligible if they evaluated patients with PAOD: intermittent claudication (IC) or critical lower limb ischaemia (CLI) according to the Society of Vascular Surgery/North American Chapter of the International Society for Cardiovascular surgery (SVS/ISCVS)⁴⁰. As listed in Table 1-3 risk factors (RFs), comorbidity and SP^{5-12, 41-44} were registered of all evaluated studies.

Study selection

Titles and/or abstracts of all selected manuscripts in the initial search were screened by two reviewers (HF and JL) independently to identify potentially relevant articles, using the inclusion criteria and using a standardized form. Discrepancies in judgment were resolved after discussion and, when necessary, after mediation of a third reviewer (JH). Full text of these articles was retrieved for further analysis.

Study quality and data extraction

Studies fulfilling all inclusion criteria were checked on study quality characteristics by two reviewers (HF and JL) independently. Assessment of study quality was done using a form based on a checklist of the Cochrane Library⁴⁵.

Registration and statistical analysis

Statistical analyses were performed with a computerized software package, using Excel (Office XP from Microsoft) and SPSS 16.0 for Windows.

RESULTS

Study selection

The search identified 2137 potentially eligible studies of which 2055 were excluded based on title and abstract. From the remaining 83 studies full articles were collected and evaluated. Twenty four articles met our inclusion criteria and were included in the systematic review. Study flow and reasons for exclusion are presented in Figure 1.

Study descriptions

Characteristics of the included articles are shown in Table 1 and 2. These articles represented 34157 patients diagnosed with PAOD over a period of 10 years. Only 7 studies (29%) were prospective and 17 studies (71%) were retrospective.

Patient characteristics

As listed in Table 1, a total of 20789 men (65%) and 13368 women (35%) were evaluated, with a mean age of 70 years (range 64 - 76). They suffered from coronary artery disease ($n=3516$; 41%), myocardial infarction ($n=2647$; 38%), angina pectoris ($n=1790$; 31%), congestive heart failure ($n=2052$; 14%), diabetes mellitus ($n=10690$; 31%) hypertension ($n=20823$; 73%) and hyperlipidaemia ($n=15067$; 64%). Sixty-seven percent of the patients ($n=14952$) were current smokers.

Table 1. Study characteristics of the evaluated literature 16-39 in this study.

No	Ref	Author	Journal of Publication	Year of Publication	Midpoint of Study	Countryof Origin	Patients	Mean age years	Male Gender	Study Design	PAOD	Type of treatment
1.	16.	Anand	CJC	1999	1997	Canada	195 (1)	71	119 (61)	retrospective	IC and CLI	Revascularization (S), major amputation
2.	17.	Hirsch	JAMA	2001	1999	USA	1865 (5)	70	895 (48)	prospective	IC	Control outpatient clinic
3.	18.	Bismuth	EJVES	2001	1998	Denmark USA	147 (0)	76	82 (56)	retrospective	CLI	Revascularization (S)
4.	19.	Nass	Vasc Med	2001	1997	UK	155 (0)	69	81 (52)	retrospective	IC and CLI	Revascularization (S)
5.	20.	Burns	EJVES	2002	NR	UK	150 (0)	NR	NR	retrospective	IC	Revascularization (E+S)
6.	21.	Cassar	EJVES	2003	2001	UK	104 (0)	70	57 (55)	retrospective	IC	Control outpatient clinic
7.	22.	Torella	Surgeon	2003	1999	USA	89 (0)	68	67 (75)	retrospective	IC	Conservative
8.	23.	Henke	JVS	2004	2000	USA	293 (1)	64	196 (67)	retrospective	IC and CLI	Revascularization (S)
9.	24.	Rehring	JVS	2005	2003	USA	1733 (5)	NR	NR	retrospective	IC	Revascularization (S)
10.	25.	Conte	JVS	2005	2002	USA	1404 (4)	69	899 (64)	retrospective	CLI	Revascularization (S)
11.	26.	Okaa	Vasc Med	2005	2001	USA	101 (0)	73	74 (73)	retrospective	IC	Control outpatient clinic
12.	27.	Ness	JGABSMS	2005	2004	France	209 (1)	72	102 (49)	retrospective	IC	Revascularization (S)
13.	28.	Dedola	AMCV	2005	2000	Sweden	5708 (17)	65	4623 (81)	retrospective	IC and CLI	Control outpatient clinic
14.	29.	Barani	Int Angiol	2005	2001	USA	259 (1)	75	138 (53)	prospective	CLI	Control outpatient clinic
15.	30.	Bhatt	JAMA	2006	2004	UK	8273 (24)	69	5874 (71)	prospective	IC and CLI	Control outpatient clinic
16.	31.	Bradley	EJVES	2006	2004	USA	109 (0)	70	78 (72)	retrospective	CLI	Major amputation
17.	32.	Bianchi	AVS	2007	2006	UK	167 (0)	68	NR	retrospective	IC and CLI	Control outpatient clinic after revasculari-zation (E+S)
18.	33.	Khan	EJVES	2007	2003	UK	473 (1)	68	317 (67)	prospective	IC	Control outpatient clinic
19.	34.	Wilson	EJVES	2007	2005	China	213 (1)	68	138 (65)	prospective	IC	Control outpatient clinic
20.	35.	Hasimu	Circ J	2007	NR	UK	5254 (15)	67	2785 (53)	retrospective	IC and CLI	Revascularization (E+S), major amputation

21.	36.	Dunkley	PMJ	2007	2005	Denmark	103 (0)	73	64 (62)	retrospective	IC and CLI	Control outpatient clinic
22.	37.	Gasse	EJVES	2008	2000	Canada	4592 (13)	72	2362 (51)	retrospective	IC and CLI	Revascularization (S)
23.	38.	Makowsky	AHJ	2008	2002	UK	2509 (7)	69	1806 (72)	prospective	IC and CLI	Revascularization (E+S), major amputation
24.	39.	Janes	BJC	2008	2003		52 (0)	73	31 (60)	prospective	IC and CLI	Revascularization (S)
							34157	67	20789 (65)			

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

No=number; Ref=reference; CJC=The Canadian Journal of Cardiology; JAMA=The Journal of the American Medical Association; EJVES=European Journal of Vascular and Endovascular Surgery; Vasc Med= Vascular Medicine; JVS=Journal of Vascular Surgery; JGABMS=The Journals of Gerontology: Biological Sciences and Medical Sciences; AMCV= Arch Mal Coeur Vaiss; Int Angiol=Internal Angiology; AVS=Annals of Vascular Surgery; Circ J=Circulation Journal; PMJ=Postgrad Medical Journal; AHJ=American Heart Journal; BJC=British Journal of Cardiology; NR=not reported/not possible to retrieve data; S=surgical; E=endovascular.

Secondary prevention

As listed in Table 2 and 3 and Figure 2a-e, a vast minority of the PAOD patients received proper SP. Contrary to what the guidelines prescribe, about 45% ($n=15227$ range 5-70%) of the patients were treated with LLA, 63% ($n=21657$; range 5-88%) of all patients were treated with APA, 34% ($n=8750$; range 12-69%) of the PAOD patients (treated with revascularization or major amputation) were treated with HRLA and 46% ($n=6340$; range 29-71%) of all patients with hypertension were treated with BPLA. Eighty-one percent of the patients with diabetes mellitus with indication for treatment ($n=4213$; range 33-100%) were treated with glucose lowering agents (GLA), 39% of the current smokers ($n=762$; range 1-96%) were advised on smoking cessation and 23% of the IC patients ($n=155$, range 2-56%) were prescribed with walking exercise.

DISCUSSION

In this study we describe a high prevalence of modifiable risk factors for cardiovascular disease in patients suffering from PAOD (IC and CLI) and a disappointing level of implementation of secondary preventive measures to reduce cardiovascular events in this specific high risk patient group. These conclusions are the results of a systematic review of recent literature concerning SP in PAOD patients in vascular surgery because of IC or CLI.

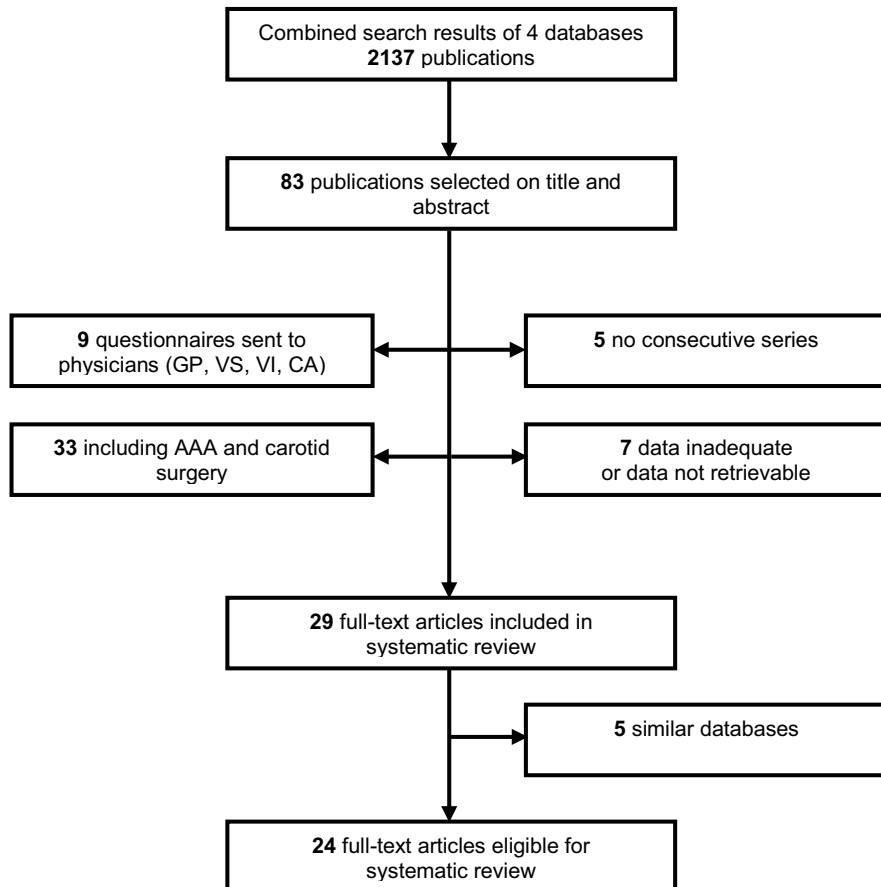
PAOD is not only a manifestation of extensive atherosclerosis but also a marker of increased risk for coronary and cerebrovascular complications including death. Given the high baseline risk of this population and the effectiveness of the SP^{14, 15, 46}, a combination of multiple drug therapies, in

Table 2. Cardiovascular/atherosclerosis risk factors in PAOD patients of the evaluated literature¹⁶⁻³⁹ in this study.

Ref	Author	DM	HT	HL	CAD	MI	AP	AR	CHF	CABG	PCI	SMO	CVD
16.	Anand	74 (38)	97 (50)	35 (18)	106 (54)	66 (34)	58 (30)	NR	NR	18 (9)	NR	134 (69)	38 (19)
17.	Hirsch	770 (41)	628 (87)	1214 (65)	NR	456 (24)	530 (28)	NR	290 (16)	380 (20)	244 (13)	1173 (63)	365 (20)
18.	Bismuth	38 (26)	96 (65)	NR	NR	25 (17)	21 (14)	37 (25)	18 (12)	3 (2)	NR	112 (76)	25 (17)
19.	Nass	72 (46)	86 (55)	NR	NR	63 (41)	NR	NR	95 (61)	NR	NR	123 (79)	NR
20.	Burns	80 (53)	NR	33 (22)	16 (24)	NR	NR	NR	NR	NR	NR	105 (70)	NR
21.	Cassar	30 (29)	NR	NR	NR	NR	NR	NR	NR	NR	NR	40 (38)	NR
22.	Torella	16 (18)	52 (58)	47 (53)	NR	44 (49)	41 (46)	NR	NR	NR	NR	NR	NR
23.	Henke	155 (53)	205 (70)	142 (48)	149 (51)	NR	NR	NR	41 (14)	53 (18)	29 (10)	88 (30)	38 (13)
24.	Rehring	414 (24)	970 (56)	1085 (63)	NR	NR	NR	NR	NR	NR	NR	NR	NR
25.	Conte	899 (64)	1151 (82)	772 (55)	646 (46)	421 (30)	NR	NR	NR	351 (25)	239 (17)	1039 (74)	281 (20)
26.	Oka	27 (27)	55 (54)	57 (56)	49 (49)	NR	38 (38)	NR	13 (13)	NR	NR	77 (76)	13 (13)
27.	Ness	94 (45)	188 (90)	184 (88)	132 (63)	NR	NR	NR	NR	NR	NR	148 (71)	75 (36)
28.	Dedola	1313 (23)	3596 (63)	3539 (62)	2226 (39)	NR	NR	NR	NR	NR	NR	4053 (71)	514 (9)
29.	Barani	123 (47)	181 (70)	165 (64)	NR	NR	122 (47)	NR	NR	NR	NR	156 (60)	NR
30.	Bhatt	3640 (44)	6701 (81)	5543 (67)	NR	NR	NR	NR	NR	NR	NR	6205 (75)	NR
31.	Bradley	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
32.	Bianchi	92 (55)	135 (81)	110 (66)	NR	NR	NR	NR	NR	NR	NR	73 (44)	NR
33.	Khan	96 (20)	265 (56)	206 (44)	141 (30)	69 (15)	87 (18)	NR	NR	44 (9)	17 (4)	406 (86)	35 (7)
34.	Wilson	48 (23)	138 (65)	89 (42)	NR	NR	NR	NR	NR	NR	NR	81 (38)	NR
35.	Hasimu	716 (14)	NR	NR	NR	NR	NR	NR	408 (8)	NR	NR	NR	661 (13)
36.	Dunkley	30 (29)	71 (69)	NR	51 (50)	19 (18)	32 (31)	12 (12)	NR	NR	NR	81 (79)	23 (22)
37.	Gasse	1090 (24)	3283 (71)	NR	NR	NR	NR	NR	507 (11)	NR	NR	NR	757 (16)
38.	Makowsky	855 (34)	1895 (76)	1845 (74)	NR	1484 (59)	861 (34)	NR	680 (27)	242 (10)	205 (8)	858 (34)	677 (27)
39.	Janes	19 (37)	28 (54)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Total evaluated		34048 (99)	28540 (84)	23641 (69)	8636 (25)	6940 (20)	5741 (17)	250 (1)	14916 (44)	6886 (20)	6544 (19)	22328 (65)	22853 (67)
Diagnosed with		10690 (31)	20823 (73)	15067 (64)	3516 (41)	2647 (38)	1790 (31)	49 (20)	2052 (14)	1190 (16)	734 (11)	14952 (67)	3502 (15)

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

PAOD=peripheral arterial occlusive disease; Ref=reference; DM=diabetes mellitus; HT=hypertension; HL=hyperlipidaemia; CAD=coronary arterial disease; MI=myocardial infarction; AP=angina pectoris; AR=arrhythmia; CHF=congestive heart failure; CABG=coronary artery bypass graft; PCI=percutaneous coronary intervention; SMO=smoking; CVD=cerebrovascular disease; NR=not reported/not possible to retrieve data.

Figure 1. Study flow and exclusion criteria.

GP=general practitioner; VS=vascular surgeon; VI=vascular internist; CA=cardiologist.

combination with aggressive lifestyle change and revascularization, can substantially reduce the burden of morbidity and mortality in patients with PAOD. Most patients with PAOD substantially benefit from aggressive medical therapy⁴⁷. Optimal SP reduces the risk of revascularization; it can improve functional status and quality of life in the long term and is cost effective. These approaches are expected to produce a cumulative relative risk reduction of approximately 75%⁴⁸.

SP is recommended in evidence based guidelines for the prevention of cardiovascular events in patients with PAOD as proposed in the AHA/ACC - and TASC I and - II reporting guidelines and several other evidence-based recommendations. However, the implementation of the updated and revised AHA/ACC or TASC I and II reporting guidelines is unknown. In this systematic review of predefined specific studies evaluating SP, a substantial gap between recommendations in guidelines and actual clinical practice in

Table 3. Review of implementation of established recommended secondary prevention measures in patients with PAOD of the evaluated literature¹⁶⁻³⁹ in this study.

Ref	Author	Walking exercise	Smoking cessation	Glucose lowering agent	Lipid lowering agent	Anti platelet agent	Heart rate lowering agent	Blood pressure lowering agent
16.	Anand	NR	NR	68 (92)	31 (16)	73 (37)	39 (20)	NR
17.	Hirsch	NR	532 (45)	644 (84)	773 (41)	1223 (60)	NR	NR
18.	Bismuth	NR	NR	NR	8 (5)	70 (48)	17 (12)	38 (40)
19.	Nass	NR	NR	NR	47 (30)	69 (45)	40 (26)	58 (67)
20.	Burns	24 (16)	23 (15)	38 (48)	57 (38)	105 (70)	NR	NR
21.	Cassar	15 (14)	34 (85)	18 (60)	39 (38)	75 (72)	NR	NR
22.	Torella	NR	NR	NR	29 (33)	61 (69)	NI	NR
23.	Henke	NR	NR	NR	164 (56)	272 (93)	202 (69)	137 (67)
24.	Rehring	NR	NR	166 (40)	543 (31)	87 (5)	574 (33)	281 (29)
25.	Conte	NR	NR	NR	646 (46)	941 (67)	674 (48)	NR
26.	Oka	55 (54)	1 (1)	9 (33)	39 (39)	63 (62)	NI	NR
27.	Ness	NR	NR	NR	140 (67)	178 (85)	130 (62)	NR
28.	Dedola	NR	NR	NR	2569 (45)	4509 (79)	1256 (22)	NR
29.	Barani	NR	NR	NR	61 (24)	180 (69)	NR+NI	97 (54)
30.	Bhatt	NR	NR	3094 (85)	5791 (70)	6784 (82)	3557 (43)	3150 (47)
31.	Bradley	NR	NR	NR	51 (47)	65 (60)	NR	NR
32.	Bianchi	NR	NR	92 (100)	88 (53)	115 (69)	70 (42)	96 (71)
33.	Khan	NR	37 (9)	84 (88)	212 (45)	335 (71)	NI	123 (46)
34.	Wilson	4 (2)	65 (80)	NR	132 (62)	34 (16)	NR+NI	NR
35.	Hasimu	NR	NR	NR	1891 (36)	3047 (58)	NR	NR
36.	Dunkley	58 (56)	78 (96)	NR	70 (68)	91 (88)	NI	NR
37.	Gasse	NR	NR	NR	489 (11)	1248 (27)	622 (14)	1027 (31)
38.	Makowsky	NR	NR	NR	1340 (53)	2085 (83)	1569 (63)	1321 (70)
39.	Janes	NR	NR	NR	17 (33)	25 (48)	NR	12 (43)

†	Total evaluated	671 (2)	1963 (6)	5223 (15)	34157 (100)	34157 (100)	25385 (74)	13846 (66)
††	Diagnosed with	155 (23)	762 (39)	4213 (81)	15227 (45)	12635 (63)	8750 (34)	6340 (46)

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

PAOD=peripheral arterial occlusive disease. Ref=reference; NR=not reported/not possible to retrieve data; NI=not included because of non-invasive treatment;

TASC=Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease reporting standards; AHA/ACC=American Heart Association/American College of Cardiology.

Smoking cessation=all smoking PAOD patients who were prescribed/advised with smoking cessation.

Glucose lowering agents=only the PAOD patients diagnosed with diabetes mellitus and indicated for glucose lowering treatment were included.

Lipid lowering agents and antiplatelet agents=according to the TASC I and II^{13,14} and AHA/ACC reporting guidelines¹⁵, all PAOD should be treated with both of these agents.

Heart rate lowering agent=only the PAOD patients after invasive treatment by revascularization (endovascular, surgical) or with a major amputation (below knee - or above knee) were included.

Blood pressure lowering agent=only the PAOD patients diagnosed with hypertension indicated for prescription of antihypertensive medications were included.

† Total of patients actual evaluated in the literature.

†† Total of patients prescribed with the concerning SP of the actual evaluated total patients in the literature.

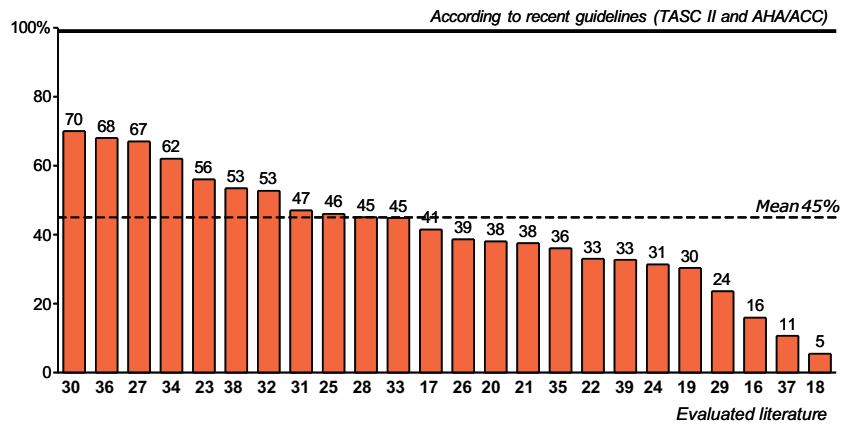
the care of PAOD patients is demonstrated. Only a minority of patients were at AHA/ACC or TASC I and II guideline target goals for SP.

Lifestyle adjustments concerning SP

Although detailed analysis of prevalence of smoking was not described in all evaluated studies; only 39% of registered smokers entered a smoking cessation program. Smoking is associated with PAOD severity, an increased risk of amputation, peripheral graft occlusion and mortality in PAOD patients⁴⁹. All patients who smoke should strongly and repeatedly be advised to stop smoking, and should receive a program of physician advice, group counselling sessions and nicotine replacement. Although detailed analysis of prevalence of walking exercise was not described in all evaluated studies; only 23% of the patients entered a walking exercise program. These programs improve functional performance and alter cardiovascular risk^{50, 51}. Important to stress is that supervised exercise therapy has statistically significant benefits on treadmill walking distance compared with non-supervised regimens, which is currently the main prescribed exercise therapy for people with intermittent claudication

⁵².

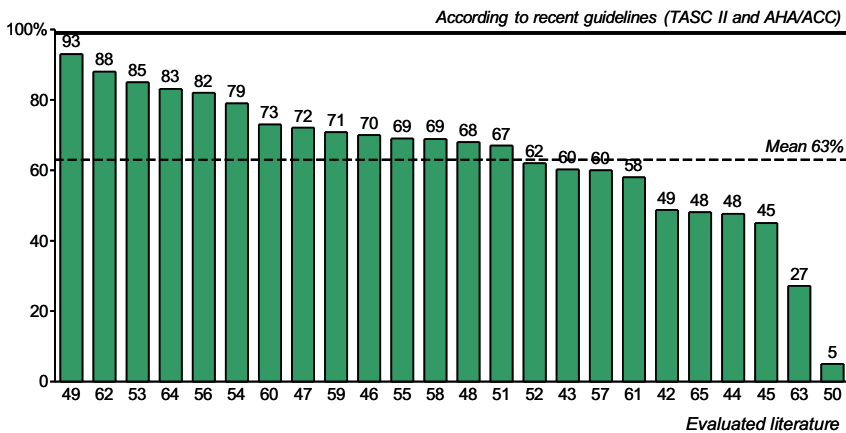
Figure 2a. Percentage of patients actually treated with lipid lowering agents in the evaluated in the literature ¹⁶⁻³⁹.



Data are presented as %.

The bottom numbers of the bar graph are the corresponding reference numbers (30, 36, 27, 34, 23, 38, 32, 31, 25, 28, 33, 17, 26, 20, 21, 35, 22, 39, 24, 19, 29, 16, 37 and 18)

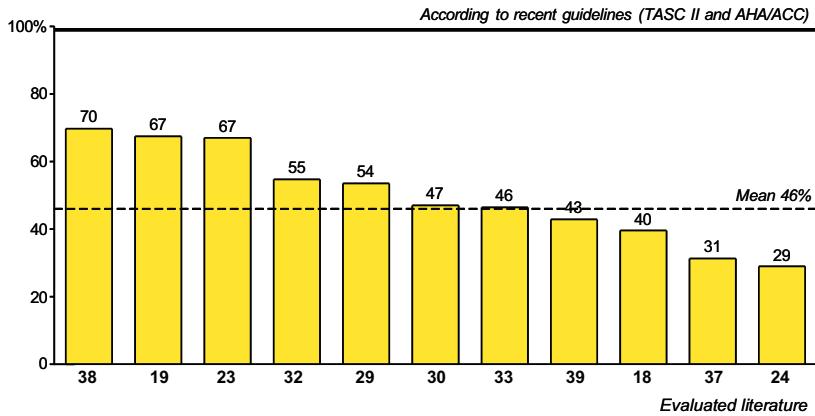
Figure 2b. Percentage of patients actually treated with anti-platelet agents in the evaluated in the literature ¹⁶⁻³⁹.



Data are presented as %.

The bottom numbers of the bar graph are the corresponding reference numbers (20, 36, 27, 38, 30, 28, 34, 21, 33, 20, 29, 32, 22, 25, 26, 17, 31, 35, 16, 39, 18, 19, 37 and 24).

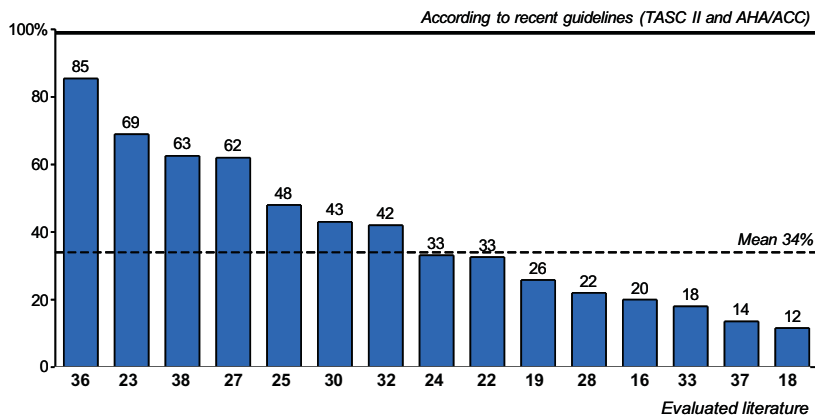
Figure 2c. Percentage of patients actually treated with blood pressure lowering agents in the evaluated in the literature ¹⁶⁻³⁹.



Data are presented as %.

The bottom numbers of the bar graph are the corresponding reference numbers (38, 19, 23, 32, 29, 30, 33, 39, 18, 37, 24).

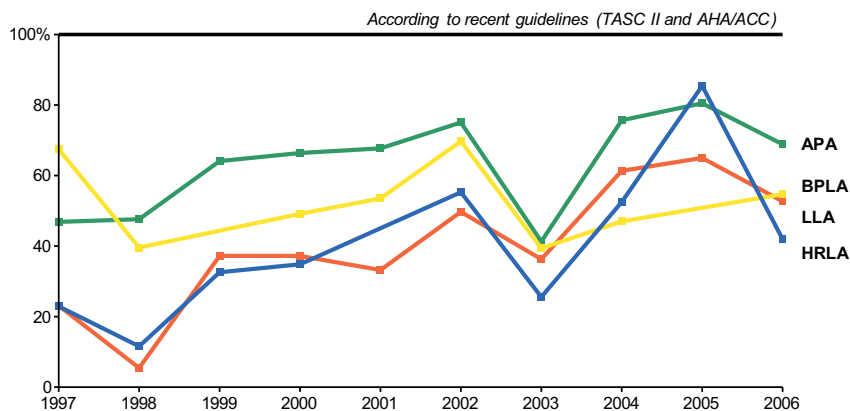
Figure 2d. Percentage of patients actually treated with heart rate lowering agents in the evaluated in the literature ¹⁶⁻³⁹.



Data are presented as %.

The bottom numbers of the bar graph are the corresponding reference numbers (36, 23, 38, 27, 25, 30, 32, 24, 22, 19, 28, 16, 33, 37 and 18).

Figure 2e. Percentage of patients actually treated with anti-platelet agents, blood pressure lowering agents, lipid lowering agent and heart rate lowering agents in the evaluated in the literature ¹⁶⁻³⁹ from 1997 till 2007.



Data are presented as %.

APA=anti-platelet agents; BPLA=blood pressure lowering agents; LLA=lipid lowering agent; HRLA=heart rate lowering agent.

Medical treatment concerning SP

Antiplatelet agents

Detailed analysis of prevalence of prescribed APA was described in all evaluated studies; only 63 % of all PAOD patients were prescribed with an APA. The use of APA is indicated as secondary cardiovascular prevention in patients presenting with PAOD. All symptomatic PAOD patients with or without a history of other cardiovascular disease should be prescribed APA long term to reduce the risk of cardiovascular morbidity and mortality. Patients who withdraw APA prior to the event have worse outcomes than those who either continued on APA or those who have never received APA ^{5-7, 46}.

Blood pressure - and heart rate regulation

Although detailed analysis of prevalence of prescribed antihypertensive medication is not described in all evaluated studies; only 34% of all PAOD patients were prescribed with HRLA and 46% of the patients were treated with BPLA. The interpretation of this intensity of medical treatment with these agents is not straightforward. First, control of hypertension is essential for the prevention of stroke, myocardial infarction and congestive heart failure in hypertensive patients and in patients at increased cardiovascular risk including presence of PAOD (HOPE-trial) ⁵³. In this systematic review, 73% of the patients were found to have hypertension. Most of these patients will need medical therapy in addition to lifestyle treatment. However, these subjects are not uncomplicated hy-

pertensive patients but patients with hypertension and clinical evident PAOD making defining them as high to very high risk patients for recurrent cardiovascular events and death due to those events.

Blood pressure lowering agents

In this setting, it is important to recall studies such as the HOPE-trial⁵³, it makes the case for the beneficial effect of ACEi (ramipril) in PAOD patients, and the ABCD-trial⁵⁴ (enalapril) illustrating these effects for diabetic patients. In the latest guidelines⁵⁵ for the management of patients with PAOD, ACEi may be considered for cardiovascular risk reduction. They are recommended for treatment of left ventricular dysfunction and patient well-being by reducing in-hospital stay and increasing patient survival⁵⁶. Patients with asymptomatic systolic left ventricular dysfunction (left ventricular ejection fraction <40%) should receive ACEi treatment. Patients with asymptomatic systolic left ventricular dysfunction (left ventricular ejection fraction <40%) and myocardial infarction in past history should receive β -blocker as well, for improvement of left ventricular function and heart rate control.

Heart rate regulation lowering agents

In the DECREASE-I trial⁵⁷, treatment with the highly β -1 selective β -blocker bisoprolol was initiated at least 30-day prior to surgery and, to maximize beneficial effects, patients were titrated according to tolerance to achieve heart rate control between 65-70 beats per minutes⁵⁷. In literature it is suggested that the long-term beneficial effects of β -blocker therapy might be explained by a decrease of progress of coronary atherosclerosis⁵⁸. In contrast to the instant effect on heart rate control as demonstrated in the DECREASE-1 trial, the effect of β -blockers on plaque stabilization may therefore be achieved only after prolonged treatment. The latest AHA/ACC guidelines on perioperative heart regulation initiate β -blocker treatment in patients with 1 or more cardiovascular clinical risk factors to achieve perioperative heart rate between 65-70⁵⁹.

Lipid-lowering agents

LLA, especially using statins, has been shown to dramatically improve outcome of subjects with proven atherosclerotic cardiovascular disease (HPS-trial)⁶⁰. This was observed for many primary and secondary outcome measures including cardiovascular mortality. Subgroup analysis showed PAOD patients benefited from statin treatment like all other secondary and primary prevention patients studied. Accordingly, most if not all guidelines recommend treatment with statins in all SP patients including PAOD patients. In our review we found detailed analysis of prevalence of prescribed LLA in all evaluated studies; only 53% of all PAOD patients were prescribed statins or other LLA clearly making the point for further improvement. Of note, the specific impact of LLA on PAOD

related vessel changes and improvement of clinical presentations is less well studied. However, favourable influences on leg functioning, walking performance and positive effects on the arterial wall structure and function has been described ⁶¹. Nevertheless, in our opinion, the major proven consideration to prescribe LLA to PAOD patients is the prevention of cardiovascular death and (recurrent) major cardiovascular events such a myocardial infarction.

Glucose lowering agents

Detailed analysis of prevalence of diabetes mellitus was described in almost all evaluated studies; almost 81% of registered diabetic patients were prescribed with GLA. Although, a substantial part of diabetics will improve blood glucose levels by alteration of life style including weight loss, exercise and nutrition, intensive glucose monitoring and oral or IM medication is frequently indicated. Aggressive diabetes mellitus control decreases microangiopathy and its related complications and may decrease vascular mortality and morbidity rates ⁶².

Related factors of suboptimal implementation of established recommended SP

In this systematic review, several factors were identified causing the suboptimal SP prevalence. These factors can be divided in patient related -, physician related and health care related factors. Important to mention is that we summed the opinion of the authors of the articles included in this systematic review.

Patient related factors

First, it is relevant that patients understand the threat of the disease, which depends on their perception of its seriousness and their own susceptibility ^{24, 26, 32, 35}. The patient should clearly understand the dose, frequency, timing and duration of SP. Patients want to be regarded as sophisticated and sceptical clients and need proper information so that they can be involved in healthcare decisions ⁶³.

Second, another potential cause that contributes to the lower rates of SP for PAOD patients could be the lack of patient compliance to prescription medication ³². Patient-related factors for non-compliance appear to be younger age, smoking, lack of low fat diet and exercise ⁶⁴. To improve compliance, physicians should discuss compliance with their patients at every visit in a non-judgemental manner and should also communicate their respect for the patient's perspective on his/her condition ⁶⁵. To increase patient behaviour, regular and frequent scheduled out patient visits, contacts via telephone, and follow-up by mail using an automatically prescription generated reminder chart result in a practical and cost effective aid to compliance ^{66 67}.

Third, polypharmacy because of coexisting cardiovascular RFs results in the patients' non-compliance with newly prescribed medications³². Increased numbers of cardiovascular drugs per patient brings about a decreased perception for a specific drug⁶⁴ and improper use⁶⁸.

Physician related factors

First, inadequate recognition and underdiagnosis of PAOD due to deficiencies in physician knowledge contribute to a lower rate of atherosclerotic risk factor reduction in patients with PAOD^{16, 17, 19-30, 33-35, 37-39}. Primary care physicians usually not conduct a full vascular RF profile with subsequent SP⁶⁵.

Second, in this systematic review the main cause of suboptimal SP in PAOD patients is the lack of physicians' knowledge of risk factor modification in this specific patient population^{16, 20, 21, 23-30, 33-35, 37}. This finding is in accordance with several reports described in literature⁶⁹⁻⁷² concluding that deficiencies in physician knowledge contribute to lower rates of RF reduction and SP for PAOD patients. These studies reveal that physicians' perceptions toward risk reduction in PAOD identify glaring knowledge and action gaps, despite the overwhelming recognition that recommending and instituting therapy should be the responsibility of the physician. With the suboptimal utilization rate of SP, only one-fourth of the participants rated their knowledge about risk reduction as above average.

Third, important to realize is that most of the physicians lack time for a structured and repetitive SP for each PAOD patient in the outpatient clinic and/or during admission for PAOD treatment^{20, 24, 32}. Time is simply too scarce for a structured history evaluation, complete physical examination, laboratory and duplex ultrasound evaluation. Furthermore, evaluation of implemented SP during follow-up is often too time consuming.

Fourth, the lack of reimbursement for risk factor assessment in PAOD patients may be an important barrier to effective SP in PAOD²⁶. Risk factor evaluation in the outpatient clinic is time consuming and without direct reimbursement for this process most easily disregarded. Without direct reimbursement for these preventative strategies, a decreased interest or responsibility for the actual SP in these high risk patients can be expected.

Health care related factors

The responsibility for SP of patients with PAOD is spread out across a number of specialties. Many of the PAOD patients with extensive co-morbidity have been treated by a variety of specialists such as cardiologists, diabetologists, internal medicine, stroke physicians and vascular surgeons depending on their co-morbidities^{19, 20, 31, 32, 36, 37, 39}. Although all these physicians have an important role in the treatment of specific signs and symptoms of the PAOD patient, a coordination of SP is frequently lacking.

Suggestions for optimising the implementation of established recommended SP

The message is evident, clear and alarming; therefore it becomes even more important to find ways to improve SP.

Computer analysis database system

We composed a user-friendly computer analysis database system for vascular patients in daily practice. Such an integrated health care system with electronic medical records and communication could represent a viable model of comprehensive care whereby vascular specialists could initiate changes and interactively communicate to primary physicians and pharmacists during follow-up (Appendix 6).

Multidisciplinary meeting

We advice the implementation of a standardized multidisciplinary approach with all specialists surrounding the PAOD patient; this can result in improvement of quality of care ⁷³. The aim of this meeting is reducing patient morbidity and mortality and to strive for the highest possible quality of care by optimizing the implementation of established recommended SP in patients with PAOD.

Limitations of the study

Some limitations of our study should be mentioned. First, publication bias for studies reporting on evaluation of SP limits conclusions from this outcome. All studies included, reporting prevalence of SP in patients suffering from PAOD, are considered to be centres with specific focus on this topic. Therefore, SP in these centres is more likely to implement recent guidelines than centres without this preventative aim. So, actual SP in today's medicine is probably less implemented compared to evaluated literature. Second, the literature search resulted in a large number of case series containing small numbers of patients. We excluded series with less than forty patients, and as a result some data may have been lost from the systematic review. Third, in some of these reports clear definitions of SP concerning APA, LLA, HRLA and BPLA is lacking, which may have confounded our review. Fourth, the number of prospective studies was relatively low, which makes interpretation of these results difficult. We tried to reduce the large degree of clinical heterogeneity by defining strict inclusion criteria.

CONCLUSION

Our study provides current evidence that the SP of patients with PAOD still needs improvement. This is disappointing given international efforts to increase the awareness and profile of this condition. We have found that despite clear guidelines for the medical community regarding cardiovascular prevention, a large percentage of patients with PAOD are not receiving appropriate SP for their comorbidities or are not meeting the established goals with only a minority of patients at target goals. In our opinion, reasons for this disparity may include patient related factors, physician related factors and health care related factors. We are of the opinion that to rectify this suboptimal SP, there is a need for increased physician awareness of PAOD, reimbursement and implementation of screening programs and more aggressive treatment of RFs.

REFERENCES

1. Meijer WT, Grobbee DE, Hunink MG, Hofman A, Hoes AW. Determinants of peripheral arterial disease in the elderly: The rotterdam study. *Arch Intern Med* 2000; 160(19): 2934-8.
2. Baumgartner I, Schainfeld R, Graziani L. Management of peripheral vascular disease. *Annu Rev Med* 2005; 56: 249-72.
3. Ouriel K. Peripheral arterial disease. *Lancet* 2001; 358(9289): 1257-64.
4. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: A systematic review. *Jama* 2003; 290(1): 86-97.
5. Clagett GP, Sobel M, Jackson MR, Lip GY, Tangelder M, Verhaeghe R. Antithrombotic therapy in peripheral arterial occlusive disease: The seventh accp conference on antithrombotic and thrombolytic therapy. *Chest* 2004; 126(3 Suppl): 609S-626S.
6. Collet JP, Montalescot G, Blanchet B, Tanguy ML, Golmard JL, Choussat R, Beygui F, Payot L, Vignolles N, Metzger JP, Thomas D. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. *Circulation* 2004; 110(16): 2361-7.
7. Flu WJ, Hoeks SE, van Kuijk JP, Bax JJ, Poldermans D. Treatment recommendations to prevent myocardial ischemia and infarction in patients undergoing vascular surgery. *Curr Treat Options Cardiovasc Med* 2009; 11(1): 33-44.
8. Grundy SM, Cleeman JI, Merz CN, Brewer HB, Jr., Clark LT, Hunninghake DB, Pasternak RC, Smith SC, Jr., Stone NJ. Implications of recent clinical trials for the national cholesterol education program adult treatment panel iii guidelines. *Circulation* 2004; 110(2): 227-39.
9. Schanzer A, Hevelone N, Owens CD, Beckman JA, Belkin M, Conte MS. Statins are independently associated with reduced mortality in patients undergoing infrainguinal bypass graft surgery for critical limb ischemia. *J Vasc Surg* 2008; 47(4): 774-781.
10. Schouten O, Bax JJ, Dunkelgrun M, Feringa HH, Poldermans D. Pro: Beta-blockers are indicated for patients at risk for cardiac complications undergoing noncardiac surgery. *Anesth Analg* 2007; 104(1): 8-10.
11. Fleisher LA, Poldermans D. Perioperative beta blockade: Where do we go from here? *Lancet* 2008; 371(9627): 1813-4.

12. Hoeks SE, Scholte Op Reimer WJ, van Urk H, Jorning PJ, Boersma E, Simoons ML, Bax JJ, Poldermans D. Increase of 1-year mortality after perioperative beta-blocker withdrawal in endovascular and vascular surgery patients. *Eur J Vasc Endovasc Surg* 2007; 33(1): 13-9.
13. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (pad). Tasc working group. Transatlantic inter-society consensus (tasc). *J Vasc Surg* 2000; 31(1 Pt 2): S1-S296.
14. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, Bell K, Caporusso J, Durand-Zaleski I, Komori K, Lammer J, Liapis C, Novo S, Razavi M, Robbs J, Schaper N, Shigematsu H, Sapoval M, White C, White J, Clement D, Creager M, Jaff M, Mohler E, 3rd, Rutherford RB, Sheehan P, Sillesen H, Rosenfield K. Inter-society consensus for the management of peripheral arterial disease (tasc ii). *Eur J Vasc Endovasc Surg* 2007; 33 Suppl 1: S1-75.
15. Smith SC, Jr., Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, Grundy SM, Hiratzka L, Jones D, Krumholz HM, Mosca L, Pasternak RC, Pearson T, Pfeffer MA, Taubert KA. Aha/acc guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: Endorsed by the national heart, lung, and blood institute. *Circulation* 2006; 113(19): 2363-72.
16. Anand SS, Kundi A, Eikelboom J, Yusuf S. Low rates of preventive practices in patients with peripheral vascular disease. *Can J Cardiol* 1999; 15(11): 1259-63.
17. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR. Peripheral arterial disease detection, awareness, and treatment in primary care. *Jama* 2001; 286(11): 1317-24.
18. Bismuth J, Klitfod L, Sillesen H. The lack of cardiovascular risk factor management in patients with critical limb ischaemia. *Eur J Vasc Endovasc Surg* 2001; 21(2): 143-6.
19. Nass CM, Allen JK, Jermyn RM, Fleisher LA. Secondary prevention of coronary artery disease in patients undergoing elective surgery for peripheral arterial disease. *Vasc Med* 2001; 6(1): 35-41.
20. Burns P, Lima E, Bradbury AW. Second best medical therapy. *Eur J Vasc Endovasc Surg* 2002; 24(5): 400-4.
21. Cassar K, Coull R, Bachoo P, Macaulay E, Brittenden J. Management of secondary risk factors in patients with intermittent claudication. *Eur J Vasc Endovasc Surg* 2003; 26(3): 262-6.
22. Torella F, Washington S, Cooper A, Parry AD, McCollum CN. Pharmacological prevention of cardiac risk in claudicants with ischaemic heart disease. *Surgeon* 2003; 1(5): 296-8.
23. Henke PK, Blackburn S, Proctor MC, Stevens J, Mukherjee D, Rajagopalan S, Upchurch GR, Jr., Stanley JC, Eagle KA. Patients undergoing infrainguinal bypass to treat atherosclerotic vascular disease are underprescribed cardioprotective medications: Effect on graft patency, limb salvage, and mortality. *J Vasc Surg* 2004; 39(2): 357-65.
24. Rehring TF, Sandhoff BG, Stolcpart RS, Merenich JA, Hollis HW, Jr. Atherosclerotic risk factor control in patients with peripheral arterial disease. *J Vasc Surg* 2005; 41(5): 816-22.
25. Conte MS, Bandyk DF, Clowes AW, Moneta GL, Namini H, Seely L. Risk factors, medical therapies and perioperative events in limb salvage surgery: Observations from the prevent iii multicenter trial. *J Vasc Surg* 2005; 42(3): 456-64; discussion 464-5.
26. Okaa RK, Umoh E, Szuba A, Giacomini JC, Cooke JP. Suboptimal intensity of risk factor modification in pad. *Vasc Med* 2005; 10(2): 91-6.
27. Ness J, Aronow WS, Newkirk E, McDanel D. Prevalence of symptomatic peripheral arterial disease, modifiable risk factors, and appropriate use of drugs in the treatment of peripheral arterial disease in older persons seen in a university general medicine clinic. *J Gerontol A Biol Sci Med Sci* 2005; 60(2): 255-7.

28. Dedola M, Godoi E, Coppe G, Cambou JP, Cantet C, Mas JL, Guerillot M, Vahanian A, Herrman MA, Jullien G, Leizorovicz A, Boccalon H. [risk factors management in 5708 ambulatory patients suffering from peripheral vascular disease followed in urban practices]. *Arch Mal Coeur Vaiss* 2005; 98(12): 1179-86.
29. Barani J, Mattiasson I, Lindblad B, Gottsater A. Suboptimal treatment of risk factor for atherosclerosis in critical limb ischemia. *Int Angiol* 2005; 24(1): 59-63.
30. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, Goto S, Liao CS, Richard AJ, Rother J, Wilson PW. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *Jama* 2006; 295(2): 180-9.
31. Bradley L, Kirker SG. Secondary prevention of arteriosclerosis in lower limb vascular amputees: A missed opportunity. *Eur J Vasc Endovasc Surg* 2006; 32(5): 491-3.
32. Bianchi C, Montalvo V, Ou HW, Bishop V, Abou-Zamzam AM, Jr. Pharmacologic risk factor treatment of peripheral arterial disease is lacking and requires vascular surgeon participation. *Ann Vasc Surg* 2007; 21(2): 163-6.
33. Khan S, Flather M, Mister R, Delahunty N, Fowkes G, Bradbury A, Stansby G. Characteristics and treatments of patients with peripheral arterial disease referred to uk vascular clinics: Results of a prospective registry. *Eur J Vasc Endovasc Surg* 2007; 33(4): 442-50.
34. Wilson AM, Bachoo P, Mackay IA, Cassar K, Brittenden J. Completing the audit cycle: Comparison of cardiac risk factor management in patients with intermittent claudication in two time periods. *Eur J Vasc Endovasc Surg* 2007; 33(6): 710-4.
35. Hasimu B, Li J, Yu J, Ma Y, Zhao M, Nakayama T, Ma W, Yang J, Zheng L, Li X, Luo Y, Xu Y, Zhang L, Zou L, Xiao W, Han Y, Hu D. Evaluation of medical treatment for peripheral arterial disease in chinese high-risk patients. *Circ J* 2007; 71(1): 95-9.
36. Dunkley A, Stone M, Sayers R, Farooqi A, Khunti K. A cross sectional survey of secondary prevention measures in patients with peripheral arterial disease in primary care. *Postgrad Med J* 2007; 83(983): 602-5.
37. Gasse C, Jacobsen J, Larsen AC, Schmidt EB, Johannesen NL, Videbaek J, Sorensen HT, Johnsen SP. Secondary medical prevention among danish patients hospitalised with either peripheral arterial disease or myocardial infarction. *Eur J Vasc Endovasc Surg* 2008; 35(1): 51-8.
38. Makowsky MJ, McAlister FA, Galbraith PD, Southern DA, Ghali WA, Knudtson ML, Tsuyuki RT. Lower extremity peripheral arterial disease in individuals with coronary artery disease: Prognostic importance, care gaps, and impact of therapy. *Am Heart J* 2008; 155(2): 348-55.
39. Janes SEJ WJ, Hopkinson BR, Walsh JT. Pharmacological secondary prevention in people with peripheral arterial disease compared to those with coronary artery disease: A missed opportunity. *Br J Cardiol* 2008; 15(1): 48-50.
40. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, Jones DN. Recommended standards for reports dealing with lower extremity ischemia: Revised version. *J Vasc Surg* 1997; 26(3): 517-38.
41. Third report of the national cholesterol education program (ncep) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel iii) final report. *Circulation* 2002; 106(25): 3143-421.
42. American diabetes association: Clinical practice recommendations 1999. *Diabetes Care* 1999; 22 Suppl 1: S1-114.
43. The sixth report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997; 157(21): 2413-46.

44. Chalmers J. The 1999 who-ish guidelines for the management of hypertension. *Med J Aust* 1999; 171(9): 458-9.
45. <http://WWW.cochrane.nl/nl/newPage1.html>.
46. Kinikini D, Sarfati MR, Mueller MT, Kraiss LW. Meeting aha/acc secondary prevention goals in a vascular surgery practice: An opportunity we cannot afford to miss. *J Vasc Surg* 2006; 43(4): 781-7.
47. Hackam DG, Goodman SG, Anand SS. Management of risk in peripheral artery disease: Recent therapeutic advances. *Am Heart J* 2005; 150(1): 35-40.
48. Mukherjee D, Lingam P, Chetcuti S, Grossman PM, Moscucci M, Luciano AE, Eagle KA. Missed opportunities to treat atherosclerosis in patients undergoing peripheral vascular interventions: Insights from the university of michigan peripheral vascular disease quality improvement initiative (pvd-qiz). *Circulation* 2002; 106(15): 1909-12.
49. Hirsch AT, Treat-Jacobson D, Lando HA, Hatsukami DK. The role of tobacco cessation, antiplatelet and lipid-lowering therapies in the treatment of peripheral arterial disease. *Vasc Med* 1997; 2(3): 243-51.
50. Izquierdo-Porrera AM, Gardner AW, Powell CC, Katzel LI. Effects of exercise rehabilitation on cardiovascular risk factors in older patients with peripheral arterial occlusive disease. *J Vasc Surg* 2000; 31(4): 670-7.
51. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. *Jama* 1995; 274(12): 975-80.
52. Bendermacher BLW, Willigendael EM, Teijink JAW, PrinsMH. Supervised exercise therapy versus nonsupervised exercise therapy for intermittent claudication. *Cochrane Database of Systematic Reviews* 2006(2): Art. No.: CD005263. DOI: 10.1002/14651858.CD005263.pub2.
53. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The heart outcomes prevention evaluation study investigators. *N Engl J Med* 2000; 342(3): 145-53.
54. Villarosa IP, Bakris GL. The appropriate blood pressure control in diabetes (abcd) trial. *J Hum Hypertens* 1998; 12(9): 653-5.
55. Hirsch AT, Haskal ZJ, Hertzner NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WR, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor LM, Jr., White CJ, White J, White RA, Antman EM, Smith SC, Jr., Adams CD, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. Acc/aha 2005 practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): A collaborative report from the american association for vascular surgery/ society for vascular surgery, society for cardiovascular angiography and interventions, society for vascular medicine and biology, society of interventional radiology, and the acc/aha task force on practice guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease): Endorsed by the american association of cardiovascular and pulmonary rehabilitation; national heart, lung, and blood institute; society for vascular nursing; transatlantic inter-society consensus; and vascular disease foundation. *Circulation* 2006; 113(11): e463-654.
56. Dickstein. Esc guidelines for the diagnosing and treatment of acute and chronic heart failure 2008. *Eur Heart J* 2008; 10: 1093.
57. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, Baars HF, Yo TI, Trocino G, Vigna C, Roelandt JR, van Urk H. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. *Dutch echocardi-*

- graphic cardiac risk evaluation applying stress echocardiography study group. *N Engl J Med* 1999; 341(24): 1789-94.
58. Sipahi I, Tuzcu EM, Wolski KE, Nicholls SJ, Schoenhagen P, Hu B, Balog C, Shishehbor M, Magyar WA, Crowe TD, Kapadia S, Nissen SE. Beta-blockers and progression of coronary atherosclerosis: Pooled analysis of 4 intravascular ultrasonography trials. *Ann Intern Med* 2007; 147(1): 10-8.
 59. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 2002 guidelines on perioperative cardiovascular evaluation for noncardiac surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol* 2007; 50(17): e159-241.
 60. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. *Lancet* 2002; 360(9326): 7-22.
 61. Schillinger M, Exner M, Mlekusch W, Amighi J, Sabeti S, Muellner M, Rumpold H, Wagner O, Minar E. Statin therapy improves cardiovascular outcome of patients with peripheral artery disease. *Eur Heart J* 2004; 25(9): 742-8.
 62. Adler AI, Stevens RJ, Neil A, Stratton IM, Boulton AJ, Holman RR. UKPDS 59: Hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. *Diabetes Care* 2002; 25(5): 894-9.
 63. Mosca L, Linfante AH, Benjamin EJ, Berra K, Hayes SN, Walsh BW, Fabunmi RP, Kwan J, Mills T, Simpson SL. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. *Circulation* 2005; 111(4): 499-510.
 64. Kim YS, Sunwoo S, Lee HR, Lee KM, Park YW, Shin HC, Kim CH, Kim DH, Kim BS, Cha HS, Huh BY. Determinants of non-compliance with lipid-lowering therapy in hyperlipidemic patients. *Pharmacoepidemiol Drug Saf* 2002; 11(7): 593-600.
 65. Roter DL, Hall JA, Kern DE, Barker LR, Cole KA, Roca RP. Improving physicians' interviewing skills and reducing patients' emotional distress. A randomized clinical trial. *Arch Intern Med* 1995; 155(17): 1877-84.
 66. Raynor DK, Booth TG, Blenkinsopp A. Effects of computer generated reminder charts on patients' compliance with drug regimens. *Bmj* 1993; 306(6886): 1158-61.
 67. Yilmaz MB, Biyikoglu SF, Guray Y, Karabal O, Caldir V, Cay S, Sahin O, Sasmaz H, Korkmaz S. Level of awareness of on-treatment patients about prescribed statins. *Cardiovasc Drugs Ther* 2004; 18(5): 399-404.
 68. Davis DA, Thomson MA, Oxman AD, Haynes RB. Changing physician performance. A systematic review of the effect of continuing medical education strategies. *Jama* 1995; 274(9): 700-5.
 69. McDermott MM, Hahn EA, Greenland P, Cella D, Ockene JK, Brogan D, Pearce WH, Hirsch AT, Hanley K, Odom L, Khan S, Criqui MH, Lipsky MS, Hudgens S. Atherosclerotic risk factor reduction in peripheral arterial disease: Results of a national physician survey. *J Gen Intern Med* 2002; 17(12): 895-904.
 70. Cassar K, Belch JJ, Brittenden J. Are national cardiac guidelines being applied by vascular surgeons? *Eur J Vasc Endovasc Surg* 2003; 26(6): 623-8.

71. Al-Omran M, Lindsay TF, Major J, Jawas A, Leiter LA, Verma S. Perceptions of canadian vascular surgeons toward pharmacological risk reduction in patients with peripheral arterial disease. *Ann Vasc Surg* 2006; 20(5): 555-63.
72. Badger SA, Soong CV, Lee B, Swain GR, McGuigan KE. Prescribing practice of general practitioners in northern ireland for peripheral arterial disease. *Angiology* 2008; 59(1): 57-63.
73. Flu H, Breslau PJ, Krol-van Straaten JM, Hamming JF, Lardenoye JW. The effect of implementation of an optimized care protocol on the outcome of arteriovenous hemodialysis access surgery. *J Vasc Surg* 2008; 48(3): 659-68.

Appendix 1. The PubMed search strategy.

("secondary prevention" OR "secondary medical prevention" OR "risk factors"[majr] OR "risk factors"[ti] OR "risk factor"[ti] OR "risk factor management" OR "risk factor modification" OR "risk factors management" OR "risk factor treatment" OR "risk factors treatment" OR "risk factors modification" OR "risk factor control" OR "risk factors control" OR "risk factor profile" OR "risk factor profiles" OR "risk factors profile" OR "risk factors profiles" OR "modifiable risk factors" OR "modifiable risk factor" OR "secondary risk factor" OR "secondary risk factors" OR "medical management" OR cardioprotect*[ti] OR "Angiotensin-Converting Enzyme Inhibitors"[majr] OR "Angiotensin-Converting Enzyme Inhibitors"[ti] OR "Receptors, Angiotensin"[majr] OR "Angiotensin Receptors"[ti] OR "antiplatelet agents"[ti] OR "Platelet Aggregation Inhibitors"[majr] OR "antihypertensive agents"[majr] OR antihypertensive[ti] OR "Antilipemic Agents"[majr] OR "lipid-lowering"[ti] OR beta-blocker[ti] OR beta-blockers[ti] OR "Adrenergic beta-Antagonists"[majr] OR "calcium channel blockers"[mesh] OR "calcium channel blockers"[ti] OR "Cardiovascular Agents"[majr] OR "Physician's Practice Patterns"[majr] OR "medical treatment"[ti] OR "medical therapy"[ti] OR "medical therapies"[ti] OR "tobacco use"[ti] OR smoking[ti] OR "smoking"[majr] OR "smoking cessation"[majr] OR "Tobacco Use Cessation"[majr] OR "exercise treatment"[ti] OR "exercise therapy"[majr] OR "exercise therapy"[ti] AND ("Peripheral Vascular Diseases"[Majr:NoExp] OR "peripheral vascular"[ti] OR ("Arteriosclerosis"[Majr:NoExp] OR arteriosclerosis[ti] OR Arteriolosclerosis[ti] OR "Arteriolosclerosis"[majr] OR Atherosclerosis[ti] OR "Atherosclerosis"[majr] OR "Intermittent Claudication"[majr] OR "Intermittent Claudication"[ti] OR atherosclerotic[ti]) AND ("lower extremity"[tw] OR "lower extremities"[tw] OR "lower limb"[tw] OR "lower limbs"[tw] OR "Lower Extremity"[mesh:NoExp] OR foot OR feet OR leg OR legs)) OR "peripheral arterial occlusive"[tiab] OR "peripheral arterial disease"[tiab] OR "peripheral arterial diseases"[tiab] OR "critical lower limb ischaemia" OR "critical lower limb ischemia" OR critical lower limb ischaemic OR critical lower limb ischemic OR (ischemia AND lower extremity))

Appendix 2. The Cochrane Library search strategy.

#1 "secondary prevention" OR "secondary medical prevention" OR "risk factor management" OR "risk factor modification" OR "risk factors management" OR "risk factor treatment" OR "risk factors treatment" OR "risk factors modification" OR "risk factor control" OR "risk factors control" OR "risk factor profile" OR "risk factor profiles" OR "risk factors profile" OR "risk factors profiles" OR "modifiable risk factors" OR "modifiable risk factor" OR "secondary risk factor" OR "secondary risk factors" OR "medical management" :ti,ab,kw
 #2 "risk factors" OR "risk factor" OR cardioprotect* OR "Angiotensin-Converting Enzyme Inhibitor" OR "Angiotensin-Converting Enzyme Inhibitors" OR "ace-inhibitor" OR "ace-inhibitors" OR "angiotensin receptor" OR "Angiotensin Receptors" OR "antiplatelet agents" OR "Platelet Aggregation Inhibitors" OR "Platelet Aggregation Inhibitor" OR antihypertensive OR Antilipemic OR "lipid-lowering" OR beta-blocker OR beta-blockers OR "Adrenergic beta-Antagonists" OR "Adrenergic beta-Antagonist" OR "calcium channel blocker" OR "calcium channel blockers" OR "Cardiovascular Agent" OR "cardiovascular agents" OR "medical treatment" OR "medical therapy" OR "medical therapies" OR tobacco OR smoking OR "exercise treatment" OR "exercise therapy":ti
 #3 MeSH descriptor Physician's Practice Patterns explode all trees
 #4 (#1 OR #2 OR #3)
 #5 "peripheral vascular":ti
 #6 ((Arteriosclero* OR Arteriolosclero* OR Atherosclero* OR "Intermittent Claudication") AND ("lower extremity" OR "lower extremities" OR "lower limb" OR "lower limbs" OR foot OR feet OR leg OR legs)) :ti,ab,kw
 #7 "peripheral arterial occlusive" OR "peripheral arterial disease" OR "peripheral arterial diseases" OR "critical lower limb ischaemia" OR "critical lower limb ischemia" OR "critical lower limb ischaemic" OR "critical lower limb ischemic" OR (ischemia AND lower extremity):ti,ab,kw
 #8 (#5 OR #6 OR #7)
 #9 (#8 AND #4)

Appendix 3. The EMBASE search strategy.

secondary prevention/ OR secondary prevention.mp OR secondary medical prevention.mp OR *risk factor/ OR risk factor.ti OR risk factors.ti OR risk factor management.mp OR risk factor modification.mp OR risk factor treatment.mp OR risk factors treatment.mp OR risk factors modification.mp OR risk factor control.mp OR risk factors control OR risk factor profile.mp OR risk factor profiles.mp OR risk factors profile.mp OR risk factors profiles.mp OR modifiable risk factors.mp OR modifiable risk factor.mp OR secondary risk factor.mp OR secondary risk factors.mp OR medical management.mp OR cardioprotect\$.ti OR *Dipeptidyl Carboxypeptidase Inhibitor/ OR Angiotensin-Converting Enzyme Inhibitors.ti OR *angiotensin receptor/ OR angiotensin receptor.ti OR angiotensin receptors.ti OR *Antithrombocytic Agent/ OR antiplatelet agent.ti OR antiplatelet agents.ti OR Antithrombocytic agent.ti OR Antithrombocytic agents.ti OR platelet aggregation inhibitors.ti OR *antihypertensive agent/ OR antihypertensive.ti OR *Antilipemic Agents/ OR lipid lowering.ti OR *Beta Adrenergic Receptor Blocking Agent/ OR beta blocker.ti OR beta blockers.ti OR beta-blocker.ti OR beta-blockers.ti OR *calcium channel blocking agent/ OR calcium channel blocker\$.ti OR *cardiovascular agent/ OR *tobacco dependence/ OR tobacco abuse.ti OR *smoking/ OR *smoking cessation/ OR *kinesiotherapy/ OR exercise treatment.ti OR exercise therapy.ti OR exercise therapies.ti OR medical treatment.ti OR medical therapy.ti OR medical therapies.ti) AND (*Peripheral Vascular Disease/ OR peripheral vascular.ti OR (*Arteriosclerosis/ OR arteriosclerosis.ti OR Arteriolosclerosis.ti OR *Arteriolosclerosis/ OR Atherosclerosis.ti OR *Atherosclerosis/ OR *Intermittent Claudication/ OR Intermittent Claudication.ti. OR atherosclerotic.ti) AND (*leg/ OR lower extremity.ti OR lower extremities.ti OR lower limb.ti OR lower limbs.ti OR Lower Extremity.ti OR *foot/ OR foot.ti OR feet.ti OR leg.ti OR legs.ti)) OR exp *peripheral occlusive artery disease/ OR peripheral occlusive artery.ti OR peripheral occlusive arteries.ti OR peripheral arterial disease.ti OR peripheral arterial diseases.ti OR (*limb ischemia/ AND (leg/ OR lower extremity.mp OR lower extremities.mp OR lower limb.mp OR lower limbs.mp OR Lower Extremity.mp OR foot/ OR foot.mp OR feet.mp OR leg.mp OR legs.mp)) OR lower limb ischaemia.ti OR lower limb ischemia.ti OR *leg ischemia/ OR leg ischemia.ti OR leg ischaemia.ti)

Appendix 4. The Web of Science search strategy.

(ts=("secondary prevention" OR "secondary medical prevention" OR "risk factor management" OR "risk factor modification" OR "risk factors management" OR "risk factor treatment" OR "risk factors treatment" OR "risk factors modification" OR "risk factor control" OR "risk factors control" OR "risk factor profile" OR "risk factor profiles" OR "risk factors profile" OR "risk factors profiles" OR "modifiable risk factors" OR "modifiable risk factor" OR "secondary risk factor" OR "secondary risk factors" OR "medical management") OR TI=("risk factor*" OR cardioprotect* OR "Angiotensin-Converting Enzyme Inhibitor*" OR "ACE-inhibitor*" OR "Angiotensin Receptor*" OR antiplatelet OR "Platelet Aggregation Inhibitor*" [ti] OR antihypertensive OR antilipemic OR "lipid-lowering" OR "beta-blocker*" OR "Adrenergic beta-Antagonist*" OR "calcium channel blocker*" OR "Cardiovascular Agent*" OR "medical treatment" OR "medical therapy" OR "medical therapies" OR "tobacco use" OR smoking OR "exercise treatment" OR "exercise therapy"))

AND

((TI=("peripheral vascular") OR (ti=(arteriosclero* OR Arteriolosclero* OR atherosclero* OR "Intermittent Claudication") AND ts=("lower extremit*" OR "lower limb*" OR foot OR feet OR leg OR legs)) OR ts=("peripheral arterial occlusive" OR "peripheral arterial disease*" OR "critical lower limb isch*"))

Appendix 5. Inclusion criteria

• Symptomatic PAOD according to the SVS/ISCVS guidelines⁴⁰

- Intermittent claudication
- Critical limb ischaemia

• Secondary prevention measures

- Antiplatelet agents (APA) defined as the prescription of antiplatelet agents (acetylsalicylic acid, dipyridamole or clopidogrel)
- Lipid-lowering agents (LLA) defined as the prescription of agents used to treat lipid abnormalities (statins)
- Heart rate lowering agents (HRLA) defined as the prescription of heart rate lowering agents (β -blockers)
- Blood pressure lowering agents (BPLA) defined as the prescription of antihypertensive medications (angiotensin converting enzyme inhibitors, and/or calcium channel blockers, angiotensin II receptor blockers and/or diuretics)
- Glucose lowering agents (GLA) defined as the current use of diabetes medications (insulin and oral hypoglycemic agents)

• Treatment

- Conservative
- Revascularization (endovascular / surgical)
- Major amputation (below knee amputation / above knee amputation)
- Control after invasive treatment

• Period

- After initiation of the TASC-I guidelines¹³

• Patient series

- Original
- Consecutive

• Evaluating

- Implementation of established recommended secondary prevention in patients with PAOD

• Language

- English
- French
- Dutch
- German

• Total patients

- Comprise a minimal number of forty patients
-

PAOD=Peripheral Arterial Occlusive Disease; *SVS/ISCVS*=Society of Vascular Surgery / North American Chapter of the International Society for Cardiovascular surgery; *TASC*=Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease.

Appendix 6a. Example of the ‘medication screen’ of the recommended computer analysis database system to be used in a real time electronic file for patients diagnosed with PAOD. Important to stress is that the registered information in this appendix does not contain actual patient information, it is all made-up.

Registration, policy and guidelines of PAOD patients

Search

Contact

Service

Logoff

REGISTRATION

Lower extremity arterial (occlusive)

Medication

Laboratory

Comorbidity

Clinical risk evaluation

GUIDELINES

WEBSITES

JOURNALS

Name patient: Bond, James
Gender: Male
Date of birth: 1946-12-15
Age: 63 years

Anti platelet - and coagulation agents

☒ Acetylsalicylic acid
☒ Clopidogrel
☐ Dipyridamole
☐ Coumarin

Lipid lowering agents

☒ statin

Glucose lowering agents

☐ Oral
☒ Insuline

Heart rate lowering agents

☒ β -blocker

Blood pressure lowering agents

☒ Angiotensin converting enzyme inhibitor
☐ Angiotensin II receptor blockers
☐ Calcium channel blockers
☐ Diuretics

Arythmia

☒ Digoxine

save

Appendix 6b. Example of the ‘laboratory screen’ of the recommended computer analysis database system to be used in a real time electronic file for patients diagnosed with PAOD. Important to stress is that the registered information in this appendix does not contain actual patient information, it is all made-up.

Registration, policy and guidelines of PAOD patients

Search

Contact

Service

Logoff

REGISTRATION

Lower extremity arterial (occlusive)

Medication

Laboratory

Comorbidity

Clinical risk evaluation

GUIDELINES

WEBSITES

JOURNALS

Name patient: Bond, James
Gender: Male
Date of birth: 1946-12-15
Age: 63 years

Hyperlipidaemia

Cholesterol: 6 <5 mmol/L
HDL: 5 <4,5 mmol/L
LDL: 7 <4,5 mmol/L

Diabetes mellitus

HbA1c: 7 4,0-6,0%
Glucose: 13 4-6,4 mmol/L

Cardiac

Troponine-T: 0,00 <0,05 micro g/L

Renal

Urea: 7 2,5-6,4 mmol/L
V-POSSUM: 2
Creatinine: 50 μ : 40-80 mmol/L
 μ : 50-100 mmol/L
Clearance: 25 2,5-6,4 mmol/L

Electrolytes

Sodium: 137 135-145 mmol/L
V-POSSUM: 2
Potassium: 6 3,5-5 mmol/L
V-POSSUM: 8

Infection

Leucocytes: 13 135-145 mmol/L
V-POSSUM: 2
CRP: 6 3,5-5 mmol/L

Coagulation and viscosity

Hgb: 9 μ : 7,5-10 mmol/L
 μ : 8,5-11 mmol/L
V-POSSUM: 8

Ht:

0,41 0,38-0,49 L/L

Trombocytes:

354 150-400 x10⁹/L

aPTT:

60 22-29 sec

PT:

12 11-14 sec

INR:

3,2 <0,05 micro g/L

Nutrition

Serum albumine: 31 35-55 g/L

save

Appendix 6d. Example of the 'clinical risk evaluation screen' of the recommended computer analysis database system to be used in a real time electronic file for patients diagnosed with PAOD. Important to stress is that the registered information in this appendix does not contain actual patient information, it is all made-up.

Vascular Patient Registration

Registration, policy and guidelines of PAOD patients									
REGISTRATION Lower extremity arterial (occlusive)		Name patient:		Gender:	Date of birth:	Age:			
		Bond, James		Male	1946-12-15	63 years			
Medication Laboratory Comorbidity Clinical risk evaluation GUIDELINES WEBSITES JOURNALS		Comorbidity Coronary: Yes Smoking: Yes Valvular: Yes Hypertension: Yes Myocardial infarction: Yes Hyperlipidaemia: Yes Arythmia: Yes Diabetes mellitus: Yes Cardiac: Yes Pulmonary: No Carotid: Yes Renal: Yes				Secondary prevention APA: Yes LLA: Yes GLA: Yes HRLA: No BPLA: Yes		BMI: 25 SVS/ISCVS 2,6 ASA: 4 V-POSSUM: 36 physiological score:	<input type="button" value="save"/>
Advice: secondary prevention <i>Lifestyle:</i> Smoking cessation: Yes Dietary: Yes DM foot inspection: Yes Walking exerce: Yes <i>Medication:</i> APA: No LLA: No GLA: No HRLA: Yes BPLA: No		Advice: peri-operative <i>Extra:</i> Laboratory: Yes ECG en X-thorax: Yes Anaesthesiology: Yes Vascular internal medicine: Yes Cardiology: Yes Pulmonary medicine: No Nephrology: Yes <i>Postoperative location:</i> ICU		<input type="button" value="print"/>					

APA=anti platelet agent; LLA=lipid lowering agent; GLA=glucose lowering agent; HRLA=heart rate lowering agent; BPLA=blood pressure lowering agent; BMI=body mass index; SVS/ISCVS=Society of Vascular Surgery / North American Chapter of the International Society for Cardiovascular surgery; ASA=American Society of Anaesthesiologists; POSSUM=Physiological and Operative Severity Score for the enumeration of Mortality and morbidity; ECG=electrocardiogram; ICU=intensive care unit.