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Medication Underuse During Long-Term Follow-Up in Patients With Peripheral Arterial Disease

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Background—Patients with peripheral arterial disease constitute a high-risk population. Guideline-recommended medical therapy use is therefore of utmost importance. The aims of our study were to establish the patterns of guideline-recommended medication use in patients with PAD at the time of vascular surgery and after 3 years of follow up, and to evaluate the effect of these therapies on long-term mortality in this patient group.

Methods and Results—Data on 711 consecutive patients with peripheral arterial disease undergoing vascular surgery were collected from 11 hospitals in the Netherlands (enrollment between May and December 2004). After 3.1±0.1 years of follow-up, information on medication use was obtained by a questionnaire (n=465; 84% response rate among survivors). Guideline-recommended medical therapy use for the combination of aspirin and statins in all patients and β-blockers in patients with ischemic heart disease was 41% in the perioperative period. The use of perioperative evidence-based medication was associated with a reduction of 3-year mortality after adjustment for clinical characteristics (hazard ratio, 0.65; 95% CI, 0.45 to 0.94). After 3 years of follow-up, aspirin was used in 74%, statins in 69%, and β-blockers in 54% of the patients respectively. Guideline-recommended medical therapy use for the combination of aspirin, statins, and β-blockers was 50%.

Conclusions—The use of guideline recommended therapies in the perioperative period was associated with reduction in long-term mortality in patients with peripheral arterial disease. However, the proportion of patients receiving these evidence-based treatments—both at baseline and 3 years after vascular surgery—was lower than expected based on the current guidelines. These data highlight a clear opportunity to improve the quality of care in this high-risk group of patients. **(*Circ Cardiovasc Qual Outcomes*. 2009;2:338-343.)**

Key Words: peripheral arterial disease ■ surgery ■ medication ■ prognosis ■ guideline adherence

Peripheral arterial disease (PAD) is a common condition, and its prevalence is expected to increase because of the aging population.[1] Importantly, only 1 of 9 patients with PAD are symptomatic, but vascular morbidity and mortality is estimated to be similar in patients with symptomatic or asymptomatic PAD.[2,3] This poses PAD to be a major health burden. Patients with PAD undergoing vascular surgery are known to be at risk for both early and late cardiovascular events.[4,5] Hertzer's landmark study in 1000 consecutive patients undergoing surgery for PAD who underwent preoperative cardiac catheterizations reported that only 8% had normal coronary arteries, and approximately one third had severe-correctable or severe-inoperable ischemic heart disease (IHD).[6] The estimated cardiovascular risk in PAD is as high as in IHD.[5,7] Adequate risk reduction management is clearly of utmost importance in these patients.

The international prospective Reduction of Atherothrombosis for Continued Health (REACH) Registry demonstrated a substantial gap between guideline recommendation and clinical practice throughout the atherothrombotic spectrum.[8] In addition, the REACH registry demonstrated that optimal risk factor control was associated with fewer cardiovascular events. Patients with PAD scheduled for surgery are an even higher-risk population. Data are limited in this specific population about the application of risk factor control. Earlier studies have shown that the implementation of guidelines in the perioperative period is rather poor, but data are lacking about medication use in vascular surgery patients at late follow-up.[9,10] From observational studies it is known that these patients benefit from long-term medical treatment.[11,12] However, the composite effect of perioperative guideline recommended medication in vascular surgery patients long-term outcome, is however, not well established in daily clinical practice.

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The aims of our study were to establish the patterns of guideline-recommended medication use in patients with PAD at the time of vascular surgery and after 3 years of follow up, and to evaluate the effect of these therapies on long-term mortality in this patient group.

Methods

Study Population

Between May and December 2004, a survey of clinical practice in vascular surgery patients was conducted in 11 hospitals in the Netherlands.[9,13] The total study population consisted of 711 consecutively enrolled patients undergoing peripheral vascular surgery. Five hospitals were located in the central part of the country, 3 were located in the northern region, and 3 were located in the southern region. Two centers were university hospitals, which act as tertiary referral centers. This survey was an integral part of the infrastructure of the survey program supported by the Netherlands Heart Foundation in the context of the Euro Heart Survey Programme. All patients who were admitted to the vascular surgery department of the participating hospitals were screened. Endovascular surgery procedures included aortic endografts or peripheral angioplasties with or without stenting. The open procedures comprised abdominal aortic surgery, carotid endarterectomy, or infrainguinal arterial bypass grafting. All patients provided informed consent before participation. The 11 participating hospitals met the requirements for ethical approval based on local standards. After 3 years, follow-up information on vital status was obtained through the Civil Registries. Patient status could be determined in 701 patients (99%), of whom 149 patients (21%) died during 3-year period. All 552 survivors were contacted to complete questionnaires including medical treatment and the occurrence of cardiovascular events during the 3-year period. Of these, 87 (16%) patients did not respond, leaving 465 (84%) patients for further analysis at 3-year follow-up. The median follow-up time of these patients was 3.1 years (interquartile range, 3.07 to 3.19).

Data Collection

Baseline measurements, patient characteristics, and risk factors were collected by trained research assistants. The hospital charts were searched for information on the relevant clinical characteristics, such as cardiovascular history, diabetes, and renal insufficiency. Furthermore, the following medication use was noted: aspirin, statins, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, antithrombotics, calcium-channel blockers, and diuretics. Clinical data including the presence of IHD and cerebrovascular disease (CVD) were updated at 3 years after surgery. Polyvascular disease was defined as coexistent arterial disease in 1 or 2 other territories (coronary or cerebral) within each patient with PAD. Ischemic heart disease was defined as history of myocardial infarction, angina, or previous coronary revascularization. Cerebrovascular disease (CVD) was defined as a previous ischemic cerebrovascular accident.

Guideline-Recommended Medical Therapy Use

All patients with PAD were considered candidates for aspirin and statins in this study. β-blockers were indicated in patients with known IHD. These indications are based on national and international guidelines for patients with PAD.[14–17] Guideline-recommended medical therapy for the combination of aspirin, statins, and β-blockers was considered to be present when (1) aspirin, statins, as well as β-blockers were used in patients with IHD, or (2) aspirin and statins were used in patients without IHD, irrespective of β-blockers. The extent of guideline recommended medical treatment was quantified by the absolute number of used drugs, ie, 0 to 1, 2, or all 3 drugs per individual patient (aspirin, statins, β-blockers).

Outcome

The main outcome measure of this study was all-cause mortality within 3 years after vascular surgery.

Statistical Analyses

Clinical characteristics are described as numbers and percentages for dichotomous variables, and the continuous variable age was reported as mean with standard deviation. Comparisons between categorical variables were performed using Pearson χ^2 tests. Trend tests were used to calculate the probability value for trend across the number of vascular beds. The relation between guideline-recommended medical therapy use in the perioperative period and 3-year mortality was evaluated by multivariable Cox proportional hazard regression analysis with adjustment for confounders. All potential confounders (age, gender, IHD, heart failure, CVD, diabetes, renal insufficiency, and type of surgery) were entered in the multivariable model to ensure giving an as unbiased as possible estimate for the relation between medical therapy use and long-term mortality. Sensitivity analyses were performed using a hierarchical model with hospital as random effect. Kaplan–Meier survival curves were calculated to assess the relation between the extent of guideline compliant medical treatment and long-term survival and compared with a log-rank test. For all tests, a probability value <0.05 (2-sided) was considered significant. All statistical analyses were performed using SPSS 15.0 statistical software.

Results

Of the 711 included patients, 149 (21%) died during the 3-year follow up period. Baseline characteristics are presented in Table 1. Half of patients underwent an endovascular procedure (n=354), 328 patients (46%) had open surgery, and 29 patients (4%) underwent carotid endarterectomy. Three-year mortality rates increased from 18% in PAD only to 28% in patients with 3 affected vascular beds (trend $P=0.014$). Nonresponder data analysis showed that responders did not differ significantly from nonresponders with regard to age, sex, and other cardiovascular risk factors.

Baseline Medication

Of the initial 711 patients, 28% had IHD and 17% had CVD at baseline. Polyvascular disease was present in 41%. Aspirin was used in 534 patients (75%), 398 (56%) used statins, and 340 (48%) used β-blockers in the perioperative period (Table 2). β-blocker use in patients with IHD (n=201) was 69%. Overall, guideline-recommended medical therapy use for the combination of aspirin and statins in all patients and β-blockers in patients with IHD was 41%. Patients with guideline-recommended medical therapy use were younger (66 versus 68 years, $P=0.019$) and more often had a history of CVD (21% versus 15%, $P=0.040$) and polyvascular disease (46% versus 37%, $P=0.014$) compared to patients without this treatment (Table 3). Three-year mortality in patients with or without guideline compliant medical treatment was 15% and 26%, respectively ($P<0.001$). The use of evidence-based medication was associated with a significant reduction in long-term mortality after adjustment for clinical characteristics (hazard ratio, 0.65; 95% CI, 0.45 to 0.94). Sensitivity analyses using a hierarchical model with hospital as random effect revealed comparable results. Furthermore, there was a clear relationship between the increasing number of guideline-recommended therapies and long-term mortality (Figure 1).

Table 1. Baseline Characteristics

	All Patients	3-Year Follow-Up		
		Deceased	Nonresponders*	Responders
No.	711	149	97	465
Demographics				
Age (mean±SD), y	66.9±10.4	73.9±8.9	64.9±11.0	65.1±9.9
Male gender, n (%)	496 (69.8)	108 (72.5)	65 (67.0)	323 (69.5)
Cardiovascular history, n (%)				
IHD	201 (28.3)	46 (30.9)	20 (20.6)	135 (29.0)
Myocardial infarction	106 (14.9)	30 (20.1)	9 (9.3)	67 (14.4)
Angina	99 (13.9)	16 (10.7)	10 (10.3)	73 (15.7)
Previous revascularization	116 (16.3)	27 (18.1)	12 (12.4)	77 (16.6)
Heart failure	38 (5.4)	18 (12.1)	2 (2.1)	18 (3.9)
CVD	123 (17.3)	38 (25.5)	16 (16.5)	69 (14.8)
Risk factors, n (%)				
Diabetes	149 (21.0)	41 (27.5)	12 (12.4)	96 (20.6)
Renal insufficiency	51 (7.2)	24 (16.1)	3 (3.1)	24 (5.2)
Affected vascular beds, n (%)				
PAD only	423 (59.5)	75 (50.3)	64 (66.0)	284 (61.1)
PAD+(IHD or CVD)	252 (35.4)	64 (43.0)	30 (30.9)	158 (34.0)
PAD+IHD+CVD	36 (5.1)	10 (6.7)	3 (3.1)	23 (4.9)

*Nonresponders include 10 patients with missing survival status and 87 patients who did not respond to the questionnaire.

Follow-Up Medication Use

Of the 465 patients at 3-year follow-up, mean age was 68 years with 70% male. A history of IHD at 3-year follow-up was present in 163 patients (35%) and CVD in 82 (18%). In total, 251 (54%) patients had "PAD only," 183 (39%) had PAD in combination with 1 other affected vascular bed (IHD or CVD), and 31 (7%) had 3 affected vascular beds. The percentage of medication use at long-term follow-up was still low (Table 2). Aspirin was used in 74% of patients, statins in 69%, and β-blockers in 54% of patients after 3 years. In patients with PAD only, statin use increased from 48% to 65% in the 3-year period. This increase was also observed in CVD patients. Guideline-recommended medical therapy use for the combination of aspirin and statins in all patients and β-blockers in patients with IHD was only 50%. A clear relationship between medication use and number of vascular beds was observed (Figure 2). Patients with PAD only were treated less intensively with statins (trend $P=0.016$) and β-blockers (trend $P<0.001$), compared to patients with more affected vascular beds.

Discussion

Perioperative and long-term use of guideline-recommended medications in vascular surgery patients proved to be lower than expected based on the current guidelines. However, we noted a clear relationship between greater evidence-based medication use and increasing number of affected vascular beds. Importantly, we also observed a significantly lower 3-year mortality in patients who where treated according to the guidelines. These data clearly indicate the need for both initiating optimal medical treatment during perioperative assessment and improving the rates of long-term evidence-based medication use.

Risk factors for atherosclerotic disease are common in patients with PAD. The prognosis of patients with PAD is predominantly determined by the presence and extent of the underlying IHD.[5] Consequently, IHD is the most common cause of death in patients with PAD. Thus, atherosclerotic risk factor control and optimal pharmacological treatment are key elements of perioperative and long-term management of patients with PAD. Importantly, our survey demonstrated a graded relationship between greater use of evidence-based therapies in the perioperative period and lower mortality after 3 years of follow-up in consecutive PAD patients seen in daily clinical practice. Our data are in accordance with studies in IHD patients, which also showed significant associations between guideline adherence and better outcomes.[18,19] Our findings suggest that adherence to guideline-recommended therapies during hospitalization for vascular surgery might serve as a marker of quality of care.

Adherence to evidence-based guidelines appears to be an important component in improving cardiovascular outcomes in PAD patients. Data from observational studies and registries, however, show that the use of evidence-based medical therapy in the perioperative period remains suboptimal in this high-risk population.[10,13,20,21] Our results are in line with previous findings regarding disparities in risk factor management among patients with atherothrombotic disease. McDermott and colleagues previously reported that PAD patients received less intensive drug treatment compared to IHD patients, irrespective of comparable risk.[22] Additionally, in a large risk factor–matched population, patients with IHD

Table 2. Medical Treatment at Baseline and at 3-Year Follow-Up

	Baseline	3-Year Follow-Up
No.	711	465
Aspirin, n (%)	534 (75.1)	344 (74.0)
PAD only	308/423 (72.8)	187/251 (74.5)
IHD	162/201 (80.6)	116/163 (71.2)
CVD	92/123 (74.8)	62/82 (75.6)
Statins, n (%)	398 (56.0)	321 (69.0)
PAD only	204/423 (48.2)	163/251 (64.9)
IHD	143/201 (71.1)	115/163 (70.6)
CVD	80/123 (65.0)	69/82 (84.1)
β-blockers, n (%)	340 (47.8)	251 (54.0)
PAD only	160/423 (37.8)	111/251 (44.2)
IHD	138/201 (68.7)	112/163 (68.7)
CVD	68/123 (55.3)	51/82 (62.2)
Any antithrombotic therapy, n (%)	618 (86.9)	413 (88.8)
PAD only	347/423 (82.0)	221/251 (88.0)
IHD	194/201 (96.5)	145/163 (89.0)
CVD	111/123 (90.2)	76/82 (92.7)
ACE inhibitors, n (%)	219 (30.8)	143 (30.8)
Calcium channel blockers, n (%)	168 (23.6)	102 (21.9)
Diuretics, n (%)	211 (29.7)	144 (31.0)

ACE indicates angiotensin-converting enzyme.

Numbers are presented in total population and in patients with PAD only, IHD, and CVD, respectively.

Presence of IHD/CVD at time of baseline or 3-year follow-up, respectively.

Table 3. Patient Characteristics Stratified by the Use of Guideline Recommended Perioperative Medication Use

	Guideline Recommended Perioperative Medication Use		
	Yes	No	*P*
No.	288	423	
Demographics			
Age (mean±SD), y	65.8±9.5	67.7±11.0	0.019
Male gender, n (%)	198 (68.8)	298 (70.4)	0.628
Cardiovascular history, n (%)			
IHD	92 (31.9)	109 (25.8)	0.073
Myocardial infarction	51 (17.7)	55 (13.0)	0.084
Angina	45 (15.6)	54 (12.8)	0.280
Previous revascularization	56 (19.4)	60 (14.2)	0.062
Heart failure	9 (3.1)	29 (6.9)	0.030
CVD	60 (20.8)	63 (14.9)	0.040
Risk factors, n (%)			
Diabetes	65 (22.6)	84 (19.9)	0.383
Renal insufficiency	19 (6.6)	32 (7.6)	0.623
Affected vascular beds, n (%)			0.027
PAD only	155 (53.8)	268 (63.4)	
PAD+(IHD or CVD)	114 (39.6)	138 (32.6)	
PAD+IHD+CVD	19 (6.6)	17 (4.0)	

received more cardiovascular medications, compared with PAD patients.[5] The observed poor medical control of PAD patients may explain the worse outcome of PAD patients compared with IHD patients as observed by the study of Welten et al.[5,23] The reason for this poor medical control seems to be multifactorial. First, national physician surveys have reported deficiencies in physician knowledge and attitudes regarding the importance of atherosclerotic risk factor reduction in PAD patients.[22,24,25] Furthermore, data from the REACH registry demonstrated substantial variation in patients' medication use by physician specialty.[26] For example, statin prescription was 79% among cardiologists and 49% among vascular surgeons, and the same differences were observed for β-blockers (70 versus 34, respectively). In addition, patients themselves are also known to underestimate the cardiovascular risks associated with PAD. A population-based survey showed major knowledge gaps regarding PAD.[27] Only 1 of 4 PAD patients were aware of the fact that PAD is associated with increased risk of myocardial infarction and stroke. These data highlight a significant opportunity to improve the use of preventive therapies in these high-risk patients and improve patient compliance.

The discrepancy between daily clinical practice and guideline recommendation demonstrates the need for improving perioperative and long-term care of patients of patients with PAD. In cardiac patients it has been demonstrated that in-hospital initiation of medication has an impressive effect on long-term treatment rates and patients compliance.[28] The preoperative visits to the hospital related to the intended vascular procedure in patients with PAD can be considered as an ideal opportunity to initiate medical therapy and lifestyle changes with achievement of treatment targets according to the guidelines. Furthermore, long-term care should be provided by all involved cardiovascular principles. Increased efforts should be focused on implementing guideline recommendations in both the perioperative and long-term period. This can potentially be achieved by implementing disease management programs including critical pathways, patient education, and multidisciplinary hospital teams.[29] Programs such as American College of Cardiology Guidelines Applied in Practice (GAP) and the American Heart Association Get With The Guidelines (GWTG) program are examples of successful quality improvement programs that are designed to

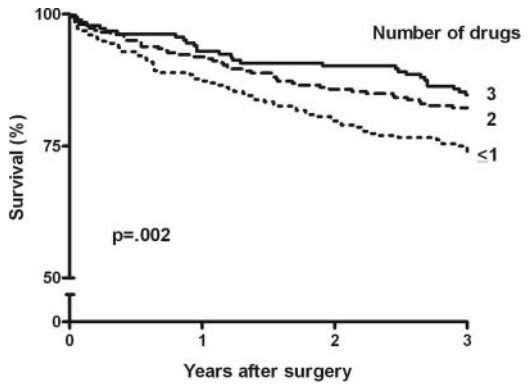

Figure 1. Survival according to the number of evidence-based medications (ie, aspirin, statins, and β-blockers).

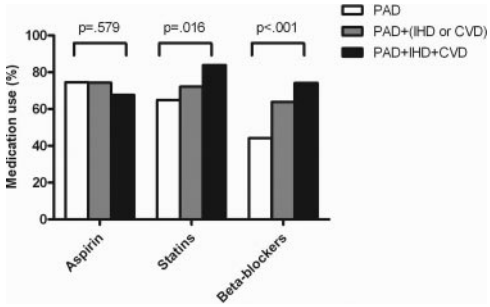

Figure 2. Medication use at 3 years of follow-up according to the number of affected vascular beds.

improve guideline adherence through tools and system redesign strategies. The GAP project resulted in increased adherence to key treatments in the administration of aspirin and β-blockers on admission and the use of aspirin and smoking cessation counseling at discharge.[30] The GWTG coronary artery disease program was also associated with improved guideline adherence.[31] The use of β-blockers, ACE inhibitors, statins, aspirin, and smoking cessation counseling were significantly increased.[32] Our findings highlight the need to implement similar programs in patients with PAD and study their impact on adherence to guideline-recommended therapies and subsequent patient outcomes.

Our study needs to be considered in the context of several potential limitations. First, although adjustments were made for known covariates, there is the possibility of residual confounding by unmeasured factors. Second, we relied on patient report for assessment of long-term medication use. Third, we did not have the data regarding potential contraindications to guideline-recommended therapies. Therefore, we could not determine the rates of medication use among "ideal candidates." Another potential limitation of our work is that the response rate of our study was not 100%. A response rate of 84%, however, is regarded as quite good and importantly, nonresponder analyses revealed no differences between the patients who responded and those who did not.

In conclusion, we showed that perioperative guideline-recommended medical treatment is associated with improved survival in patients with PAD. However, the rates of evidence-based medication use remain low in these high-risk patients—both at baseline and during long-term follow-up. These results highlight an important potential opportunity to improve the quality of care in patients with PAD.

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Disclosures

None.

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