Effect of a clinical pharmacy service on lipid control in patients with peripheral arterial disease

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Objective: **Our group and others have previously established that patients with peripheral artery disease (PAD) are significantly undertreated with respect to overall cardiovascular risk factor management, despite national guidelines to the contrary. In an effort to maximize risk factor control in our patients with PAD, we established a pharmacist-managed, physician-monitored algorithmic approach to the outpatient management of lipids in patients with PAD. The purpose of this study was to determine the effect of this service on lipid screening and control in patients with PAD.**

Methods: **We analyzed the records of patients treated at a large, group-model, not-for-profit regional managed care system serving approximately 405,000 members. An electronic medical record provided full examination, laboratory, and pharmacy data for all patients. Pharmacy data were analyzed to determine prescriptions for lipid-lowering agents. Lipid control was assessed through fasting lipid data. Patients with validated PAD and the absence of clinical coronary artery disease (CAD) were offered the service between May 2003 and September 2004 and followed up for a minimum of 6 months.**

Results: **We administratively identified 5159 active patients with a diagnosis of PAD. Of these, 1075 could be validated with a noninvasive arterial study. The exclusion of 384 patients with a diagnosis of CAD resulted in a cohort of 691 patients. Of these, 90 patients were enrolled in the lipid service (study group), and 601 received standard care. Mean follow-up was 17.1 months. Screening fasting lipid profiles were found in 95.6% (86/90) of patients in the study group and only 66.9% (402/601) of the standard care patients ($P < .0001$). Low-density lipoprotein cholesterol (LDL-C) control was improved in the pharmacist-managed group, with 79.1% (68/86) achieving an LDL-C of less than 100 mg/dL in comparison to the standard care group (54.8% [219/400]; $P < .0001$). An LDL-C value of more than 130 mg/dL was noted in 1.2% and 14.0% (56/400) in the treatment and control groups, respectively ($P < .001$). Statin use was present in 51.9% (312/601) of the control group patients and 84.4% (76/90) of the pharmacist-managed group ($P < .001$).**

Conclusions: **Despite national consensus of PAD as a CAD equivalent, patients are currently undertreated with regard to atherosclerotic risk factor modification. Initiation of a pharmacist-managed, physician-monitored lipid service provides improved compliance with national guidelines. (J Vasc Surg 2006;43:1205-10.)**

Peripheral artery disease (PAD) is acknowledged to be a relatively common medical condition of the elderly, with an age-adjusted prevalence of 12% to 20%.[1-6] With respect to the limb itself, PAD carries a benign prognosis, with a risk of limb loss of less than 10% for most patients.[7] In stark contrast, the diagnosis of PAD is a surrogate for significant cardiovascular disease, incurring a 3.1-fold increase in all-cause mortality when compared with patients without PAD and a 6.6-fold increased risk of death from coronary artery disease (CAD).[8] Cardiovascular disease is responsible for 75% of all deaths in patients with PAD.[9] The risk of death from a cardiovascular event is equivalent in patients with PAD and no history of CAD and in patients with known CAD.[10] In view of these data, current guidelines[11] have suggested that PAD be treated as a CAD equivalent, with lipid goals identical to those for patients who have had a previous coronary event. Despite these recommendations, atherosclerotic risk factors are less intensively treated in patients with PAD when compared with CAD patients.[4,5,12-15] In a previous study of more than 1700 patients with an isolated diagnosis of PAD, we noted that less than 50% consistently received optimal risk-reduction therapy with regard to use of β-blockade, angiotensin-converting enzyme inhibitors, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), and lipid, blood pressure, and glycemic control.[15] Moreover, 72.5% of PAD patients either had no cholesterol checked or had a value above nationally established goals.

In an effort to maximize risk factor control in our patients with PAD, we established a pharmacist-managed, physician-monitored algorithmic approach to the outpatient management of lipids in patients with PAD. The purpose of this study was to determine the effect of this service on lipid screening and control in patients with PAD.

METHODS

All patients in this study were members of a large, group-model, not-for-profit managed care system serving approximately 405,000 patients. Full outpatient medical,

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pharmacy, laboratory, and radiology data are stored in an electronic medical record, thus allowing for current and comprehensive analysis. All active patients were administratively screened for a diagnosis of PAD, as defined by (1) an International Classification of Diseases, 9th Revision, code for claudication or PAD (443.9 or 440.2*), (2) a history of a peripheral revascularization procedure, (3) a prescription for either pentoxifylline or cilostazol, (4) an ankle-brachial index (ABI) evaluation or full noninvasive arterial study, or (5) confirmation by a vascular surgeon. For the purposes of this study, only cases validated with an ABI less than 0.9 from a full noninvasive arterial study were considered. Patients with CAD (as defined by a history of myocardial infarction, coronary revascularization, coronary catheterization revealing at least 50% stenosis of at least one vessel, or a positive thallium stress test with electrocardiographic changes indicating ischemia or unstable angina) were also excluded. Patients with validated PAD but without clinically evident CAD at 1 (of 16) randomly selected regional medical offices were enrolled in a pharmacist-managed, physician-monitored lipid management service. Patients from the remaining clinics were assigned to standard care through their primary care physicians. Once the feasibility of this pilot program was established, other validated patients were directly referred for treatment. All patients were entered into a shared, intranet tracking data base populated and regularly updated with pertinent administrative, laboratory, and pharmacy data. For patients in the study group, a pharmacist-manager interacted regularly with patients and data, using internally derived protocols approved by an oversight committee to recommend, initiate, and titrate medications; monitor for medication and laboratory compliance; and notify the responsible primary care physician. Patients were enrolled between May 2003 and September 2004 and followed up for a minimum of 6 months. No patient opted out of the study group.

Primary outcome measurements included demographics, screening and absolute fasting lipid levels (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], non–HDL-C, and triglycerides), and all lipid-lowering medications. Baseline and most recent laboratory values were obtained through the closed system's electronic medical record. Achievement of lipid goals was defined as recommended by the National Cholesterol Education Program Adult Treatment Panel III guidelines[16] as follows: LDL-C less than 100 mg/dL, triglyceride level less than 150 mg/dL, HDL-C greater than 40 mg/dL, and non–HDL-C less than 130 mg/dL. Subjects who had at least one pharmacy claim for a statin within 4 months of the baseline and follow-up dates were categorized as currently taking a statin at that time. All patients were members of the managed care system and incurred a significant financial advantage from having their prescriptions filled within the system. Prescriptions were limited to a 60-day supply, thus making it quite likely that we captured all germane pharmacy data.

After an assessment of the distributions of lipid values for each cohort, it was determined that none was normally distributed. Thus, to assess the relationship between the lipid values and groups, individual nonparametric Wilcoxon rank sum tests were performed between cohorts for each value at baseline and follow-up and the change from baseline to follow-up. To assess the relationship between lipid goal achievement and medication use, individual χ^2 tests of association were performed between the cohorts for each lipid goal at baseline, follow-up, and the change from baseline to follow-up.

Table I. Baseline characteristics of patients

Variable	*Control (n = 601)*	*Study (n = 90)*
Age (y)	72.5 ± 10.4	71.2 ± 9.9
% Male	49.8	44.4
% Screened	71.4	78.9
Cholesterol (mg/dL)	195.9 ± 44.1	197.8 ± 37.1
Triglycerides (mg/dL)	205.6 ± 319	206.3 ± 156.2
HDL-C (mg/dL)	51.1 ± 15.3	51.6 ± 14.8
LDL-C (mg/dL)	108.7 ± 35.5	110.6 ± 32.5
Non–HDL-C (mg/dL)	143.7 ± 38.7	146.2 ± 35.5

HDL-C, High-density lipoprotein cholesterol; *LDL-C,* low-density lipoprotein cholesterol.
Nominal data are presented as mean ± SD; a *P* value of $<.05$ was assigned significance.

RESULTS

We administratively identified 5159 active patients with a diagnosis of PAD. Of these, 74.2% were older than 65 years. Because 14.1% of our 405,000 members are older than 65 years, we assume a prevalence of symptomatic PAD of 6.7% in this age group. A mild female predominance was noted in both the PAD and age-over-65 groups. Of the 5159 patients administratively identified with a diagnosis of PAD, 1075 could be validated with an ABI less than 0.9 from the noninvasive arterial laboratory. The exclusion of 384 patients with a diagnosis of CAD resulted in a cohort of 691 patients. Of these, 90 patients were enrolled in the lipid service (study group), and 601 received standard care. In the study group, 64% of patients were from the pilot clinic, and 35% were referred from vascular surgeons. No demographic or outcome differences could be elicited between these groups. The average age in the study group was 71.2 years, and it was 72.5 in the control group. The mean follow-up was 17.1 months.

As depicted in Table I, baseline screening rates and lipid levels were not different between groups. However, after at least 6 months of intervention in the study group, distinct improvements in lipid screening and control were made (Table II). Lesser effects were noted in triglycerides and HDL-C controls. To isolate patient-matched data, mean changes in lipid levels were analyzed (Table III). These "delta" data provide additional insight because each data point ensures preintervention and postintervention values for individual patients. It is interesting to note that significant improvements were made in total cholesterol, LDL-C, and non HDL-C levels in control and study patients, despite no organized intervention.

Table II. Lipid characteristics of patients at follow-up

Variable	*Control (n = 601)*	*Study (n = 90)*	P *value*
% Screened	66.9	95.6	<.0001
Cholesterol (mg/dL)	188.7 ± 42.2	168.8 ± 31.5	<.0001
Triglycerides (mg/dL)	191.0 ± 240.4	164.6 ± 89.1	.04
HDL-C (mg/dL)	53.6 ± 15.3	55.5 ± 17.7	NS
LDL-C (mg/dL)	99.9 ± 31.2	80.8 ± 22.9	<.0001
Non–HDL-C (mg/dL)	135.1 ± 40.2	113.3 ± 25.3	<.0001

HDL-C, High-density lipoprotein cholesterol; *LDL-C,* low-density lipoprotein cholesterol; *NS,* not significant.
Nominal data are presented as mean ± SD; a *P* value of <.05 was assigned significance.

Table III. Mean change in patient lipid levels over the study period

Variable	*Control (n = 310)*	*Study (n = 70)*	P *value*
Δ Cholesterol (mg/dL)	−9.5 ± 39.4	−26.8 ± 41.3	.001
Δ Triglycerides (mg/dL)	−25.9 ± 321.9	−35.6 ± 127.6	NS
Δ HDL-C (mg/dL)	1.2 ± 9.3	3.9 ± 10.9	NS
Δ LDL-C (mg/dL)	−10.2 ± 33.2	−28.6 ± 35.1	<.0001
Δ Non–HDL-C (mg/dL)	−10.4 ± 36.1	−30.6 ± 36.1	<.0001

HDL-C, High-density lipoprotein cholesterol; *LDL-C,* low-density lipoprotein cholesterol; *NS,* not significant.
Nominal data are presented as mean ± SD; a *P* value of <.05 was assigned significance. The mean change in various lipid levels is denoted with Δ.

Achievement of targeted goals for lipid control was improved in the study group. In the pharmacist-managed group, 79.1% (68/86) of patients achieved a LDL-C of less than 100 mg/dL, in comparison to the standard care group (54.8% [219/400]; $P < .0001$). An LDL-C value of more than 130 mg/dL was noted in 1.2% and 14.0% (56/400) in the treatment and control groups, respectively ($P < .001$). Attainment of HDL-C goals was not different between groups, with 79.1% (68/86) of the study group and 82.0% (328/400) of the standard care patients having an HDL-C greater than 40 mg/dL. Triglyceride goal attainment was also similar between groups (57.0% [49/86] of the study group and 49.1% [185/377] of the control group; $P = .65$).

Statin use was present in 51.9% (312/601) of the control group patients and 84.4% (76/90) of the pharmacist-managed group ($P < .0001$). This represents a 28.9% positive change in the study group and a 12.3% increase in the control group.

Side effects were rare in the patients receiving statins. No episodes of rhabdomyolysis or increases of creatine phosphokinase greater than 3 times normal were observed. One patient had an increase of alanine aminotransferase greater than 10 times baseline. This resulted in discontinuation of the statin and subsequent resolution of the laboratory abnormality.

DISCUSSION

In addition to antiplatelet therapy, β-blockade, and angiotensin-converting enzyme inhibition, strict control of lipids is well supported as an adjunct in reducing cardiovascular events after acute myocardial infarction.[11] The correlation between serum cholesterol levels and coronary risk was established through now-legendary epidemiologic studies such as the Framingham study[17] and the Multiple Risk Factor Intervention Trial.[18] Several subsequent large prospective randomized trials[19-22] and meta-analyses[23] have confirmed that statin use results in a 20% to 30% reduction in cardiovascular and all-cause mortality in patients with CAD.

There is broad support for lipid control specific to PAD patients, as well. The Heart Protection Study analyzed the effects of statins on 20,536 patients with vascular disease or diabetes randomly assigned to simvastatin or placebo and followed up for 5 years.[20] The 6748 patients with PAD had the highest event rate of all placebo-receiving groups and showed a significant (19%) relative reduction and a 6.3% absolute reduction in the risk of major vascular events when treated with simvastatin. Furthermore, statins have also been shown to decrease perioperative cardiac complications in patients undergoing noncardiac vascular surgery.[24]

Perhaps even more interesting are the multiple pleiotropic effects of statins in PAD patients. At least three randomized trials have suggested improvements in walking performance in PAD patients receiving statins.[25-27] Mondillo et al[26] performed a prospective, randomized, double-blind trial on the effect of daily simvastatin on walking performance in 86 patients with PAD. The patients randomized to the statin group achieved a significant improvement in pain-free walking distance, maximal walking distance, ABI, and claudication symptoms at 6 months. A larger study prospectively randomized 354 claudicants to placebo or atorvastatin. After 12 months, the patients receiving atorvastatin demonstrated a 63% increase in pain-free walking time.[27] There is also evidence to suggest that lipid control may limit the progression of atherosclerosis in peripheral arteries.[28-31] Moreover, McDermott et al[32] were able to document improvements in leg functioning in patients taking a statin, and this was independent of the change in cholesterol levels or the presence or absence of PAD, thus suggesting some as yet unexplained anti-inflammatory or endothelial effect of these medications.

Despite ample evidence to the contrary, risk factor reduction strategies in patients with PAD are frequently overlooked.[4,5,12-14,33] A previous study from our institution[15] identified 1733 patients with a diagnosis of PAD and the absence of clinical CAD out of a cohort of 92,940 patients. Of these 1733 PAD patients only 31.3% were taking a statin, and 55.7% had a LDL-C level more than 100 mg/dL. Fully 72.5% of PAD patients either had no screening cholesterol level checked or had an LDL-C above national target levels.[16] These data provided the impetus for the current project.

This study demonstrates that improvements in lipid control, statin use, and attainment of national lipid goals are highly achievable in a PAD population when patients are treated in a disease-management fashion. After initiation of a pharmacist-managed, physician-monitored lipid service, screening lipid profiles were obtained in 96% of patients. Of these, 79% of patients achieved an LDL-C of less than 100 mg/dL, and 84% were receiving statin therapy. Because our primary intervention targeted screening, initiation of statins, and targeted LDL-C goals, the effect of the service was most pronounced there, and it showed less dramatic improvements in controlling triglycerides or in increasing HDL-C (Tables II and III). The data also suggest that primary care physicians' awareness of and treatment of PAD may be improving, because the total cholesterol, LDL-C, and statin use seemed to have improved significantly over the study period, although the change was not nearly as remarkable as that in the experimental group (Table III).

It is interesting to note the near-even split in PAD prevalence between sexes. In the unselected population of 5159 patients carrying a diagnosis of PAD, 52.1% are male. After excluding those with CAD and including only patients with an ABI less than 0.9, the number of men decreases further (Table I). Although most atherosclerotic processes are considered to have a male predominance, PAD does not seem to follow this tenet. Most large-scale demographic studies confirm this balanced prevalence between sexes[1,2,5,34,35] or an even slightly increased incidence in women.[36]

Upon initial review, the results of this study may not be surprising. In its most simplified form, this study demonstrates that we can solve a clinical problem by investing time and attention to it. On a larger scale, however, it is clear that risk factor reduction strategies for patients with PAD are not currently met in the community at large and that a systems-based, disease management strategy can maximize their care. This approach to treatment of dyslipidemias has been used previously in CAD populations and seems most effective in closed systems.[37-42] Future studies will certainly need to assess for hard clinical end points (eg, coronary events, death, and utilization) and cost-effectiveness.

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AUTHOR CONTRIBUTIONS

Conception and design: TFR, RSS
Analysis and interpretation: TFR, RSS, HWH
Data collection: RSS
Writing the article: TFR, RSS, HWH
Critical revision of the article: TFR, RSS, HWH
Final approval of the article: TFR, RSS, BGS, JAM, HWH
Statistical analysis: RSS
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DISCUSSION

Unidentified speaker. I can speculate for you as to how my referring men would respond to this but I was wondering if you might differentiate between a not-for-profit setting like yours and a for-profit HMO. More people are dealing with those. Would you comment what you think the, how the for-profit HMO might respond to this sort of approach?

Dr Rehring. Common concerns when disease management strategies are proposed include issues surrounding turf battles, implementation and reimbursement. I believe this approach is profitable in the long run but we currently do not have hard endpoint, long-term data to support that tent. Our primary care physicians have welcomed this approach. It is frequently difficult for primary care physicians to keep up to date with guidelines that change rapidly and they have welcomed some assistance with that.

Dr J. Dennis Baker *(Los Angeles, Calif)*. It often comes as a real shock to people to find out that the best adherence to national guidelines is within the VA. Rather than the personnel-intensive approach you have used, the VA uses the electronic record to create a system of warnings. The computer system identifies those patients who should be on certain types of regimens. If you are a male over a certain age and haven't had a PSA, it warns "PSA highly recommended." A similar notice is generated for a patient with cardiovascular risk factors who is not on statins. This results in having the primary care physicians themselves participate in achieving a very high compliance with prophylactic programs. It is something that I would recommend for people who are working in large systems where this may be easily added to your electronic record systems.

Dr Rehring. I appreciate your comments and I think you are absolutely right. Again, it is a systems approach to solving the problem.

Dr Mark Nehler *(Denver, Colo)*. You didn't design this study for treating triglycerides, but a lot of patients with vascular disease have Syndrome X and hypertriglyceridemia. My understanding is therapy for this condition is more complicated than control of LDL cholesterol. Have you thought about potentially adding that to the regimen? I also believe a lot of organizations, Leap Frog and others, will take note of this data and potentially use it as a benchmark for care. Certainly there are other similar data base systems in diabetes care. This is an outstanding project, and I commend you.

Dr Rehring. Hypertriglyceridemia can be more difficult to control than LDL. We have separate algorithms for isolated hypertriglyceridemia, starting with dietary adjustments and DHA therapy but move on quickly to fibrates.

Dr Steven Merrell *(Salt Lake City, Utah)*. Tom, this was a great presentation and long overdue that we focus more on primary prevention. I think one of the real take-home messages is the profound benefit you have in your integrated health care system with electronic records, terrific data base and patient tracking that isn't really available to many people in private practice. I also would echo that in our private practice primary care acceptance of initiation of what really needs to be done for their patients is very high.

One question. You have terrific improvement in your study patients. You said it should be 100%. I am wondering really how much of the difference between 80-some and 100% is really achievable. Did you look at the incidence of statin intolerance in your patients? I mean how many of the patients really can't do any better and what are the other reasons that may you have less than 100%? Thanks.

Dr Rehring. Thank you, Dr Merrell. With regard to your first comment, this is absolutely a difficult challenge to implement in private practice and I don't have an answer for that, but as Dr Nehler stated it may come for you in some other form down the road.

Clearly 100% statin compliance is not achievable and we believe that 85% is a laudable goal. We will obtain the statin intolerance data and include it in the final manuscript.