The effect of supervised exercise and cilostazol on coagulation and fibrinolysis in intermittent claudication: A randomized controlled trial

Simon D. Hobbs, MBChB,[a] Tim Marshall, MSc,[b] Chris Fegan, MD,[c] Donald J. Adam, MD,[a] and **Andrew W. Bradbury, MD,[a]** *Birmingham, United Kingdom*

Background: **The prothrombotic, hypofibrinolytic state that develops in patients with intermittent claudication (IC) upon walking due to ischemia-reperfusion injury (IRI) of the leg muscles may contribute to the high incidence of life- and limb-threatening thrombotic events observed in this patient group. Treatments, such as angioplasty, that obtund the IRI also ameliorate the procoagulant diathesis. The effect on this diathesis of supervised exercise and cilostazol, both of which provide symptomatic benefit in IC, but without significantly obtunding IRI, is unknown.**

Methods: **Thirty-four patients (27 men and 7 women; median age, 67 years; range, 63-72 years) were randomized to receive best medical therapy (BMT) plus supervised exercise (n = 9), BMT plus cilostazol (n = 9), BMT plus supervised exercise plus cilostazol (n = 7), or BMT alone (n = 9) in a 2 × 2 factorial design. Thrombin-antithrombin complex and prothrombin fragments 1 and 2, both markers of thrombin generation; plasminogen activator inhibitor antigen and tissue plasminogen activator antigen, both markers of fibrinolysis; ankle-brachial pressure index (ABPI); and initial and absolute claudication distance (ACD) were measured at baseline and then 3 and 6 months after randomization.**

Results: **At 6 months, when compared with receiving BMT only, supervised exercise and cilostazol resulted in improvements in ABPI of 18% and 13% and in ACD of 40% and 64%, respectively. The effects on ABPI and ACD of combining supervised exercise and cilostazol were additive. Supervised exercise, cilostazol, and supervised exercise combined with cilostazol had no significant effect on any of the four hemostatic markers.**

Conclusions: **Treatment of IC by supervised exercise or cilostazol results in significant improvements in ABPI and ACD but has no demonstrable effect on the prothrombotic diathesis. This suggests that supervised exercise and cilostazol, unlike angioplasty, are unlikely to have a long-term beneficial effect on the thrombotic risks faced by these patients. (J Vasc Surg 2007;45:65-70.)**

Intermittent claudication (IC) affects up to 5% of the middle-aged white population.[1] Although only a small minority of affected individuals will develop limb-threatening ischemia,[2] when compared with an age- and sex-matched population, claudicants exhibit a threefold to fourfold increase (approximately 5%-10% per year) in thrombotic cardiovascular events such acute coronary syndrome and ischemic stroke.[3,4] Previous work from our group has demonstrated that individuals with IC exhibit a procoagulant diathesis characterized by excessive thrombin generation and relative hypofibrinolysis and that this diathesis is acutely exacerbated by exercise.[5] We have hypothesized that this procoagulant diathesis results from ischemia-reperfusion injury (IRI) of the leg muscles upon walking and that it contributes to the high incidence of thrombotic morbidity and mortality observed in this condition. This hypothesis is supported by our recent observation that lower limb revascularization by percutaneous balloon angioplasty results in a medium-term improvement in the resting procoagulant and hypofibrinolytic state.[6]

Supervised exercise therapy and cilostazol have both previously been shown to result in significant improvements in initial (ICD) and absolute (ACD) claudication distance in subjects with IC.[7-9] However, there is continuing uncertainty with regard to the possible mechanisms underlying these benefits, and there are only limited data on their effects on hemostasis. The aim of this study was to compare the effects of supervised exercise and cilostazol on ICD and ACD; ankle-brachial pressure index (ABPI); and thrombin generation and fibrinolysis in patients randomized within the INtermittent Claudication, EXercise, and Cilostazol Trial (INEXACT).

METHODS

Local ethics committee approval was obtained, and all patients provided written, fully informed consent. All patients referred to our unit from primary care or other hospital specialties with a suspected diagnosis of IC were reviewed in a dedicated, one-stop IC clinic. Subjects with clinically confirmed IC (diagnosed by using the Edinburgh Claudication Questionnaire[10] and the finding of a reduced ABPI [<0.9] in the affected leg) were commenced on best medical therapy (BMT) as previously described[11] and

From the University Departments of Vascular Surgery[a] and Haematology,[c] Heart of England NHS Foundation Trust, and Department of Public Health and Epidemiology, University of Birmingham.[b]

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Reprint requests: Simon D. Hobbs, MBChB, Glaslyn, 17 High House Dr, Lickey, Birmingham, Worcestershire, UK B45 8ET (e-mail: simon@hobbsy.fsworld.co.uk).

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Table I. INEXACT trial inclusion and exclusion criteria

Inclusion criteria	*Exclusion criteria*
Intermittent claudication*	Significant aortoiliac disease
Maximum walking distance 20-500 m	Unable to complete treadmill assessment to ACD
Willing to participate	MI, TIA, CVA, or PTCA in past 3 mo
	GFR <20 mL/min†
	Congestive heart failure
	Known predisposition for bleeding
	CYP3A4 or CYP2C19 inhibitor use‡

INEXACT, INtermittent Claudication, EXercise, and Cilostazol Trial; *ACD,* absolute claudication distance; *MI,* myocardial Infarction; *TIA,* transient ischemic attack; *CVA,* cerebrovascular accident; *PTCA,* percutaneous transluminal coronary angioplasty.

*Positive Edinburgh claudication questionnaire[10] and ankle-brachial pressure index less than 0.9 in the affected limb.

†Glomerular filtration rate (GFR) estimated by the modification of diet in renal disease equation 7 (MDRD7).

‡For example, cimetidine, diltiazem, erythromycin, ketoconazole, lansoprazole, omeprazole, and human immunodeficiency virus 1 protease inhibitors.

reviewed again after 3 to 6 months. At this stage, subjects were evaluated for eligibility for randomization into INEXACT according to the inclusion and exclusion criteria detailed in Table I. Eligible subjects were randomized in a 2 × 2 factorial design to continue BMT only or to receive BMT + supervised exercise, BMT + cilostazol, or BMT + supervised exercise + cilostazol. The 2 × 2 factorial design is well recognized as one of the most robust study designs and allows for greater interrogation of the data, as well as allowing the interaction of different treatments to be assessed.

The supervised exercise comprised a 3-month, twice-weekly, 1-hour physiotherapist-led exercise program, as previously described.[6] In addition to the supervised sessions, subjects were provided with a videotape of the exercise program and encouraged to undertake the exercises at home and complete an exercise log on the days that they did not attend the classes. Cilostazol was prescribed at a dose of 100 mg twice daily. If side effects were encountered (most commonly headache and diarrhea), the dosing regimen was halved for 1 week.

Subjects were assessed immediately after randomization and at 3 and 6 months after randomization. Before each visit, subjects were asked to refrain from smoking or eating a heavy meal and to avoid unaccustomed exercise in the preceding 24 hours. All visits took place between 8:30 AM and 9:00 AM, and subjects were transported to the hospital by taxi and then transferred to the Vascular Investigation Unit by wheelchair to avoid walking. Subjects rested for 60 minutes before undergoing venipuncture from an antecubital fossa vein without tourniquet. Blood was collected into sodium citrate tubes and was immediately centrifuged at 4°C for 15 minutes at 2000*g*. The resultant plasma was stored at −80°C for later batch analysis. ABPI was measured in both legs by using a Mini Dopplex with an 8-MHz probe (Huntleigh Diagnostics, Cardiff, UK). For each leg, the highest recorded pressure from the three ankle vessels (anterior tibial, posterior tibial, and perforating peroneal) was used to determine the ABPI. Subjects then exercised by a standard treadmill exercise test (3 km/h at a 10% incline) to their ACD or 1000 m (at follow-up visits), whichever was soonest. The distance when claudication pain was first perceived was recorded as the ICD.

Studies of coagulation and fibrinolysis. Thrombin generation cannot be directly measured because, under pathologic conditions, less than 1% of circulating prothrombin is transformed to thrombin, and it is rapidly inactivated by antithrombin III. Thrombin generation can, however, be measured indirectly by measuring the amount of inactivated thrombin, namely, thrombin-antithrombin (TAT) complex, and by measuring the cleavage products of prothrombin as it is converted to thrombin, namely, prothrombin fragments 1 and 2 (PF1+2).[12] Plasma levels of TAT and PF1+2 (both Dade-Behring, Marburg, Germany) were determined by enzyme-linked immunosorbent assay (ELISA). The analysis was manual except for the reading, which was performed on an ELISA workstation (Triturus, Grifols, Cambridge, UK).

Fibrinolytic function was examined by measuring plasminogen activator inhibitor (PAI)-1 antigen levels and tissue plasminogen activator (t-PA) antigen and t-PA activity levels. A hypofibrinolytic state is associated with increased PAI-1 and t-PA antigen levels and reduced t-PA activity. PAI, t-PA antigen, and t-PA activity levels (all Technoclone, Vienna, Austria) were determined by ELISA. PAI activity was not measured, because we were unable to find an activity assay that produced reproducible results. All assays were performed by an accredited laboratory. Samples were analyzed as one batch, and the intra-assay coefficient of variation for all assays was less than 5%.

Sample size and statistical analysis. Statistical analysis was performed by using SPSS 11.0 (SPSS Inc, Chicago, Ill) on an intention-to-treat basis. Groups were compared at baseline by using the analysis of variance (ANOVA) test for continuous data and the Fisher exact test for categorical data. Changes over time within groups were analyzed by using the Wilcoxon signed rank test. The effect of treatment among the four groups was examined by ANOVA by using an additive General Linear Model. The combined effect of supervised exercise and cilostazol was explored by using a multiplicative General Linear Model. A P value ≤.05 was considered statistically significant. On the basis of pilot data, 32 subjects were required to detect a 50% reduction in TAT in the treatment groups with 80% power and a P value of <.05.

RESULTS

Overall, 38 subjects were randomized into this substudy of the INEXACT trial. Of these, four subjects withdrew after randomization (three no longer wished to continue to participate in the trial, and one subject sustained a fractured ankle unrelated to trial participation). The remaining 34 subjects (27 men and 7 women) were studied up to 6 months after randomization (Table II). In total, 9

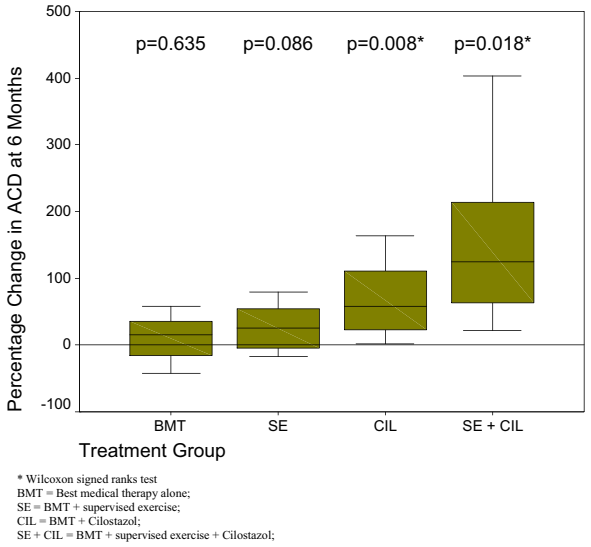

Fig. Change in absolute claudication distance over 6 months by treatment group. *****Wilcoxon signed rank test. *BMT,* best medical therapy alone; *SE,* BMT + supervised exercise; *CIL,* BMT + cilostazol; *SE + CIL,* BMT + supervised exercise + cilostazol; *ACD,* absolute claudication distance.

were randomized to remain on BMT, 16 to receive supervised exercise, and 16 to receive cilostazol in the 2 × 2 factorial design.

Six subjects encountered side effects with cilostazol; three reported diarrhea and two headaches, all of which responded to halving the treatment dose (100 mg daily) for 1 week before returning to 100 mg twice daily. These side effects have been previously described.

ABPI and claudication distance. The proportional changes in ABPI, ICD, and ACD between baseline and 6 months and the overall effect of treatment compared with receiving BMT alone are shown in Table III.

In subjects randomized to remain solely on BMT, there was no significant change in ABPI (median [interquartile range; IQR] ABPI at baseline, 3 months, and 6 months: 0.74 [0.68-0.92], 0.76 [0.60-0.90], and 0.74 [0.59-0.84]; $P = .138$); however, those randomized to supervised exercise (median [IQR] ABPI at baseline, 3 months, and 6 months: 0.67 [0.58-0.77], 0.79 [0.67-0.91], and 076 [0.67-0.92]; $P = .005$) and cilostazol (median [IQR] ABPI at baseline, 3 months, and 6 months: 0.68 [0.56-0.82], 0.80 [0.69-0.98], and 0.81 [0.66-0.93]; $P = .048$) both showed small but significant improvements in ABPI. ANOVA demonstrated that supervised exercise ($P < .001$) and cilostazol ($P = .003$) both resulted in significant improvements in ABPI when compared with no adjuvant treatment (BMT only). The effects of supervised exercise and cilostazol combined did not fit into a multiplicative model ($P = .383$), thus indicating that the beneficial effects of combined adjuvant therapy are likely to be only additive.

With regard to claudication distance, no significant improvement was observed in ICD or ACD in subjects remaining solely on BMT (median [IQR] ICD at baseline, 3 months, and 6 months: 59 m [48-72 m], 73 m [46-80 m], and 64 m [47-77 m]; $P = .678$; ACD: 94 m [79-162 m], 137 m [94-175 m], and 120 m [91-160 m]; $P = .635$); however, significant improvements were observed in ICD and ACD with both supervised exercise (median [IQR] ICD at baseline, 3 months, and 6 months: 60 m [45-95 m], 110 m [66-194 m], and 127 m [62-180 m]; $P = .01$; ACD: 99 m [81-241 m], 218 m [122-339 m], and 206 m [122-369 m]; $P = .002$) and cilostazol (median [IQR] ICD at baseline, 3 months, and 6 months: 68 m [48-76 m], 126 m [74-194 m], and 149 m [95-213 m]; $P < .001$; ACD: 116 m [76-229 m], 226 m [105-335 m], and 204 m [118-405 m]; $P = .001$). ANOVA indicates that neither exercise ($P = .488$) nor cilostazol ($P = .090$) affords any significant improvement in terms of ICD when compared with BMT alone. However, there were significant benefits in terms of ACD with both supervised exercise ($P = .037$) and cilostazol ($P = .005$) (Fig). As with ABPI, the effect on ACD of supervised exercise and cilostazol combined is likely to be additive, because it did not fit into a multiplicative model ($P = .362$).

Thrombin generation. None of the treatment groups demonstrated any significant change in resting TAT levels over the 6-month study period (median [IQR] TAT levels at baseline, 3 months, and 6 months—BMT alone: 1.2 μg/L [0.6-3.2 μg/L], 1.5 μg/L [1.2-3.9 μg/L], and 2.4 μg/L [1.5-4.3 μg/L]; $P = .123$; supervised exercise: 1.2 μg/L [0.1-2.5 μg/L], 0.75 μg/L [0.3-2.6 μg/L], and 1.1 μg/L [0.1-3.3 μg/L]; $P = .929$; cilostazol: 1.1 μg/L [0.1-2.1 μg/L], 0.8 μg/L [0.4-2.1 μg/L], and 1.0 μg/L [0.1-1.7 μg/L]; $P = .65$; Wilcoxon test).

Subjects randomized to receive cilostazol demonstrated a significant increase in resting PF1+2 levels at 6 months (median [IQR] PF1+2 levels at baseline, 3 months, and 6 months: BMT alone: 0.7 nmol/L [0.6-1.0 nmol/L], 0.7 nmol/L [0.6-1.0 nmol/L], and 0.7 nmol/L [0.6-1.1 nmol/L]; $P = .916$; supervised exercise: 0.8 nmol/L [0.6-1.0 nmol/L], 0.8 nmol/L [0.7-1.3 nmol/L], and 0.9 nmol/L [0.7-1.3 nmol/L]; $P = .083$; cilostazol: 0.6 nmol/L [0.6-0.7 nmol/L], 0.8 nmol/L [0.6-1.3 nmol/L], and 1.0 nmol/L [0.6-1.3 nmol/L]; $P = .002$; Wilcoxon test). However, subjects taking cilostazol had significantly lower resting baseline PF1+2 levels than subjects who did not receive cilostazol ($P = .004$; Mann-Whitney *U* test). TAT and PF1+2 showed no correlation with ABPI, ICD, or ACD at baseline or at 6 months.

Fibrinolysis. There were no significant differences in baseline values or changes over 6 months in measured t-PA antigen (median [IQR] t-PA antigen levels at baseline, 3 months, and 6 months—BMT alone: 6.4 ng/L [3.5-10.5 ng/L], 6.2 ng/L [2.9-8.8 ng/L], and 6.7 ng/L [4.0-9.0 ng/L]; $P = .779$; supervised exercise: 4.5 ng/L [2.9-6.5 ng/L], 4.9 ng/L [3.2-6.0 ng/L], and 5.3 ng/L [3.4-7.5 ng/L]; $P = .084$; cilostazol: 4.5 ng/L [2.9-5.6 ng/L], 3.8 ng/L [1.9-5.6 ng/L], and 3.8 ng/L [2.6-5.8 ng/L]; $P = .717$; Wilcoxon test), t-PA activity (virtually all 0.1 U/mL), or PAI-1 antigen

Table II. Demographic details, medication, and disease severity of subjects enrolled onto the INEXACT trial

Variable	*BMT*	*Supervised exercise*	*Cilostazol*	*Supervised exercise + cilostazol*	P *value*
No. subjects	9	9	9	7	
Age (y)	67 (63.5-74)	66 (63-71)	58 (52-71)	72 (63-74)	.196*
Sex (M:F)	7:2	7:2	8:1	5:2	
Smoking status					
Current smoker	3	4	3	2	NS†
Ex-smoker	5	4	6	4	NS†
Never smoker	1	1	0	1	NS†
Diabetes	2	1	3	1	NS†
Medication					
Antiplatelet agent	9	9	9	7	NS†
Statin	8	9	9	7	NS†
Antihypertensive	8	8	6	6	NS†
ACE inhibitor	5	5	3	4	NS†
Baseline treated lipid profile					
Total cholesterol (mmol/L)	6.0 (4.5-6.7)	4.1 (3.7-4.7)	4.5 (3.4-4.9)	4.3 (4.0-6.0)	0.059*
Triglycerides (mmol/L)	1.6 (1.0-2.0)	2.6 (1.7-3.0)	2.0 (1.7-3.4)	1.5 (1.2-2.0)	0.311*

INEXACT, INtermittent Claudication, EXercise, and Cilostazol Trial; *BMT,* best medical therapy; *NS,* not significant; *ACE,* angiotensin-converting enzyme.
Figures represent numbers of subjects or median (interquartile range) where appropriate.
*Analysis of variance.
†Fisher exact test.

(median [IQR] PAI antigen levels at baseline, 3 months, and 6 months—BMT alone: 24.5 ng/L [15.3-44.8 ng/L], 19.5 ng/L [12.3-42.0 ng/L], and 28.0 ng/L [14.3-42.0 ng/L]; $P = .889$; supervised exercise: 18.0 ng/L [1.0-34.8 ng/L], 17.0 ng/L [1.8-30.3 ng/L], and 22.0 ng/L [1.0-33.0 ng/L]; $P = .553$; cilostazol: 21.5 ng/L [3.3-32.5 ng/L], 13.5 ng/L [2.0-33.5 ng/L], and 20.0 ng/L [1.5-32.8 ng/L]; $P = .55$; Wilcoxon test). Furthermore, there was no correlation between these markers and ABPI, ICD, or ACD.

DISCUSSION

These data confirm that, after 6 months, BMT + supervised exercise and BMT + cilostazol are superior to BMT alone in terms of improving ACD. There was no statistical difference between BMT + supervised exercise and BMT + cilostazol in terms of ACD, and the effect of combined treatment seems to be additive rather than multiplicative. The 64% improvement in ACD observed after 6 months of BMT + cilostazol is comparable to that reported in previous randomized controlled trials (35% and 109%).[9] In contrast, the 40% improvement in ACD after 6 months of BMT + supervised exercise is rather lower than improvements previously reported in meta-analyses of randomized controlled trials.[7,8] Although this discrepancy may be a consequence of the design of the exercise program, in pilot and other clinical studies, our exercise program has been validated for use in subjects with IC. Monitoring of maximal heart rates and repetitions performed at each exercise station in the circuit demonstrated a significant training effect over the 12-week program. We therefore believe that the intensity of the exercise in the program was adequate. We assume that the sample size is the reason why significant improvements were not observed after supervised exercise. It is important to note, however, that the treatment effects of supervised exercise in our study were calculated over and above the effect observed with remaining solely on BMT (most claudication exercise trials do not do this). Because 6 months of medical therapy improved ACD by 9% in our study, this therefore further reduces the treatment effect of supervised exercise.

In addition to improvements in ACD, subjects receiving 6 months of BMT + supervised exercise or BMT + cilostazol, but not BMT only, also enjoyed significant increases in their ICD on paired statistical analysis. When compared with BMT only, supervised exercise and cilostazol both resulted in significant improvements in ABPI of 18% and 13%, respectively. Again, these results are consistent with previous studies of cilostazol[13] and exercise therapy.[14] Overall, the evidence for exercise-induced increases in blood flow in claudicants is limited and inconsistent, and it is likely that mechanisms other than increases in collateral blood flow account for most symptomatic and functional improvements seen with exercise programs (such as improvements in microcirculation, muscle metabolism, walking economy, and blood viscosity). Although our study showed significant (albeit small) improvements in ABPI with exercise and cilostazol when compared with BMT only, much of this improvement became apparent only because of the deterioration of ABPI in subjects randomized to BMT only, presumably as a result of disease progression. Thus, although not powered to look at ICD, ACD, and ABPI as end points, this substudy has produced some clinical and hemodynamic results that are consistent, qualitatively and quantitatively, with those that have been reported in previous trials and might be expected from the full INEXACT trial.

This substudy of INEXACT has demonstrated that, unlike balloon angioplasty, which has previously been shown to ameliorate the procoagulant diathesis in patients with IC,[6] treatment with supervised exercise or cilostazol, either singly or in combination, despite resulting in symp-

Table III. Mean ratios (standard deviation) of ankle-brachial pressure index, initial and absolute claudication distance compared with baseline and at 6 months for each treatment group, and the overall effect at 6 months compared with receiving no adjuvant treatment

Treatment group	*Change from baseline to 6 mo*	*Overall effect by 6 mo**	P *value*†
ABPI			
BMT	0.93 (0.11)		
BMT + exercise	1.09 (0.11)	1.17	
BMT + cilostazol	1.05 (0.13)	1.13	
BMT + cilostazol + exercise	1.30 (0.24)	1.40	
No exercise	0.99 (0.13)		
All exercise	1.17 (0.19)	1.18	<.001
No cilostazol	1.01 (0.14)		
All cilostazol	1.14 (0.21)	1.13	.003
ICD			
BMT	1.23 (0.73)		
BMT + exercise	2.22 (2.71)	1.80	
BMT + cilostazol	3.34 (4.23)	2.72	
BMT + cilostazol + exercise	3.84 (3.62)	3.12	
No exercise	2.28 (3.14)		
All exercise	2.93 (3.14)	1.29	.488
No cilostazol	1.72 (1.99)		
All cilostazol	3.56 (3.86)	2.07	.090
ACD			
BMT	1.09 (0.34)		
BMT + exercise	1.45 (0.80)	1.33	
BMT + cilostazol	1.69 (0.59)	1.55	
BMT + cilostazol + exercise	2.58 (1.39)	2.37	
No exercise	1.39 (0.56)		
All exercise	1.94 (1.20)	1.40	.037
No cilostazol	1.27 (0.62)		
All cilostazol	2.08 (1.68)	1.64	.005

ABPI, Ankle-brachial pressure index; *BMT,* best medical therapy alone; *No exercise,* BMT alone and BMT + cilostazol; *All exercise,* BMT + supervised exercise and BMT + supervised exercise + cilostazol; *No cilostazol,* BMT alone and BMT + supervised exercise; *All cilostazol,* BMT + cilostazol and BMT + supervised exercise + cilostazol.

*Compared with receiving no treatment.

†General Linear Model.

tomatic improvement, had no significant or consistent effect on the subjects' resting prothrombotic and hypofibrinolytic state. We hypothesize that this finding is because neither obtunds the IRI associated with walking. It is possible, of course, that as supervised exercise and cilostazol both resulted in a small improvement in ABPI, this also could have resulted in a small improvement in the procoagulant diathesis, but because of a type II error, this was not detected in this study. Therefore, the results need to be interpreted with some degree of caution. Regardless of this, it is clear that these treatments do not produce the previously published hemostatic improvements observed with angioplasty.

To our knowledge, this is the first study to examine the effects of cilostazol and the second to examine the effect of supervised exercise on coagulation in subjects with IC. Although evidence exists for training-induced adaptations for some markers of coagulation potential in healthy individuals, the effect of exercise training on thrombin production in subjects with peripheral arterial disease has not been fully evaluated, and in subjects with coronary heart disease, the data are equivocal.[15] With regard to fibrinolysis and exercise training, only one nonrandomized study in peripheral arterial disease has assessed the effect of training on fibrinolysis, and it found that a 6-month training program improved the resting fibrinolytic state.[16] Our study did not show an improvement in fibrinolysis as a result of exercise training. To our knowledge, this study is also the first to examine the clinical, hemodynamic, and coagulation effects of combined adjuvant therapy with BMT + supervised exercise + cilostazol.

What is the longer-term clinical significance of symptomatic improvement, but without the amelioration of IRI and the procoagulant diathesis seen after supervised exercise and/or cilostazol adjuvant treatment, when compared with the effects of balloon angioplasty and, presumably, surgery?[6,17] It is possible that by obtunding IRI and, thus, attenuating the resting and postexercise prothrombotic state, balloon angioplasty and, presumably, surgery, but not supervised exercise and/or cilostazol, have the potential to improve morbidity and mortality from thrombotic events in this group of patients in the longer term. If so, there would be a strong argument for attempting, where possible, to revascularize the ischemic limbs of patients with IC either by surgical or endovascular means.

AUTHOR CONTRIBUTIONS

Conception and design: SDH, CF, DJA, AWB
Analysis and interpretation: SDH, TM, AWB
Data collection: SDH
Writing the article: SDH
Critical revision of the article: TM, CF, DJA, AWB
Final approval of the article: SDH, TM, CF, DJA, AWB
Statistical analysis: SDH, TM
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Overall responsibility: SDH

REFERENCES

1. Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol 1991;20:384-92.
2. TransAtlantic Inter-Society Consensus (TASC). Epidemiology, natural history, risk factors. Eur J Vasc Endovasc Surg 2001;19(Suppl A):S4-30.
3. Kannel WB. The demographics of claudication and the aging of the American population. Vasc Med 1996;1:60-4.
4. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381-6.
5. Burns PJ, Wilmink ABM, Fegan C, Bradbury AW. Exercise in claudicants is associated with excessive thrombin generation. Eur J Vasc Endovasc Surg 2003;26:150-5.
6. Hobbs SD, Marshall T, Fegan C, Adam DJ, Bradbury AW. The constitutive procoagulant and hypofibrinolytic state in patients with intermittent claudication due to infra-inguinal disease significantly improves with percutaneous transluminal balloon angioplasty. J Vasc Surg 2006; 43:40-6.
7. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. JAMA 1995;274:975-80.

8. Leng GC, Fowler B, Ernst E. Exercise for intermittent claudication. Cochrane Database Syst Rev 2000;2:CD000990.
9. Bradbury AW. The role of cilostazol (Pletal) in the management of intermittent claudication. Int J Clin Pract 2003;57:405-9.
10. Leng GC, Fowkes FGR. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. J Clin Epidemiol 1992;45:1101-9.
11. Burns P, Gough S, Bradbury AW. Management of peripheral arterial disease in primary care. BMJ 2003;326:584-8.
12. Baglin T. The measurement and application of thrombin generation. Br J Haematol 2005;130:653-61.
13. Mohler ER III, Beebe HG, Salles-Cuhna S, Zimet R, Zhang P, Heckman J, et al. Effects of cilostazol on resting ankle pressures and exercise-induced ischemia in patients with intermittent claudication. Vasc Med 2001;6:151-6.
14. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. N Engl J Med 2002;347:1941-51.
15. Womack CJ, Nagelkirk PR, Coughlin AM. Exercise-induced changes in coagulation and fibrinolysis in healthy populations and patients with cardiovascular disease. Sports Med 2003;33:795-807.
16. Killewich LA, Macko RF, Montgomery PS, Wiley LA, Gardner AW. Exercise training enhances endogenous fibrinolysis in peripheral arterial disease. J Vasc Surg 2004;40:741-5.
17. Oldridge NB, Guyatt GH, Fischer ME, Rimm AA. Cardiac rehabilitation after myocardial infarction. Combined experience of randomized clinical trials. JAMA 1988;260:945-50.

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INVITED COMMENTARY

Lois A. Killewich, MD, PhD, *Galveston, Tex*

Based on the findings of this study and a previous one,[1] Hobbs et al have proposed a novel idea: that angioplasty or surgery for infrainguinal arterial occlusive disease might reduce cardiovascular morbidity and mortality to a greater degree than exercise rehabilitation or the pharmacologic agent cilostazol, or both. In fact, they suggest that exercise may actively increase the risk of events such as myocardial infarction because the ischemia–reperfusion injury in leg muscle associated with walking contributes to atherothrombotic morbidity and mortality.

These conclusions are based on observations in their current study that neither exercise rehabilitation nor cilostazol had any beneficial effects on thrombin generation or fibrinolysis, as well as observations from the previous study that patients treated with angioplasty experienced significantly increased fibrinolysis and reduced thrombin generation.[1] Indeed, there is also literature showing that walking, by promoting ischemia–reperfusion in leg muscles, is associated with increased inflammation and that this in turn may promote progression of atherosclerotic disease.[2,3]

Taking these findings together, should we conclude that walking is bad for patients with claudication? Should we encourage more invasive treatments on the supposition that they are better, that they protect our patients from myocardial infarction and stroke? Some caution is in order.

Numerous trials and studies have shown that pain-free and maximal walking distances in patients with claudication can be increased by exercise rehabilitation.[4] Population studies such as the Honolulu Heart Study showed that individuals who walk more have a lower incidence of myocardial infarction compared with those who walk less.[5] The studies by Hobbs et al, although randomized, are small, with <50 patients in each. It is possible that the lack of effects of exercise therapy on thrombin generation and fibrinolytic activity are related to a type II error from the small sample size. Our group completed two studies on patients with peripheral arterial disease showing that fibrinolytic activity in patients with claudication was directly correlated with physical activity level, and that a 6-month exercise regimen improved fibrinolysis in these patients.[6,7]

Nonetheless, the ideas of Hobbs et al deserve serious consideration, and further study is clearly warranted. Perhaps the vascular community should embrace invasive therapy for claudication not only to improve walking ability and functional status but also to reduce cardiovascular morbidity and mortality.

REFERENCES

1. Hobbs SD, Marshall AT, Fegan C, Adam DJ, Bradbury AW. The constitutive procoagulant and hypofibrinolytic state in patients with intermittent claudication due to infrainguinal disease significantly improves with percutaneous transluminal balloon angioplasty. J Vasc Surg 2006;43:40-6.
2. Mika P, Spodaryk K, Cencora A, Unnithan VB, Mika A. Experimental model of pain-free treadmill training in patients with claudication. Am J Phys Med Rehabil 2005;84:756-62.
3. Tisi PV, Shearman CP. The evidence for the exercise-induced inflammation in intermittent claudication: should we encourage patients to stop walking? Eur J Endovasc Surg 1998;15:7-17.
4. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. N Engl J Med 2002;347:1941-51.
5. Hakim AA, Petrovitch H, Burchfiel CM, Ross GW, Rodriguez BL, White LR, et al. Effects of walking on mortality among nonsmoking retired men. N Engl J Med 1998;338:94-9.
6. Gardner AW, Killewich LA. Association between physical activity and endogenous fibrinolysis in peripheral arterial disease: a cross-sectional study. Angiology 2002;53:367-74.
7. Killewich LA, Macko RF, Montgomery PS, Wiley LA, Gardner AW. Exercise training enhances endogenous fibrinolysis in peripheral arterial disease. J Vasc Surg 2004;40:741-5.