ORIGINAL INVESTIGATION

Factors Predicting Improvements in Lipid Values Following Cardiac Rehabilitation and Exercise Training

Carl J. Lavie, MD, Richard V. Milani, MD

Background: Cardiac rehabilitation and exercise training improve prognosis following major cardiac events, partly by improving coronary risk factors, including plasma lipids. Only limited data are available to define predictors of lipid improvements following aggressive non-pharmacologic therapy with cardiac rehabilitation.

Methods: We studied 237 consecutive patients from two institutions who were enrolled in outpatient phase 2 cardiac rehabilitation and exercise programs. By univariable and multivariable analyses, we assessed the impact of numerous clinical variables, including indexes of obesity, age, gender, lipid concentrations, exercise capacity, and psychological factors, on improvements in plasma lipid values with cardiac rehabilitation.

Results: Coronary risk factors improved following cardiac rehabilitation, including levels of low-density lipoprotein cholesterol (-4%; $P<.05$), high-density lipoprotein cholesterol (7%; $P<.0001$), and triglycerides (-13%; $P<.0001$); body mass index (-2%; $P<.0001$); percentage of body fat (-5%; $P<.0001$); and exercise capacity (26%; $P<.0001$). By both univariable and multivariable analyses, corresponding dyslipidemic baseline values were the strongest predictors of improvements in levels of low-density lipoprotein cholesterol (univariable: $r=.51$, $P<.0001$;

multivariable: $t=8.5$, $P<.0001$), high-density lipoprotein cholesterol (univariable: $r=.37$, $P<.0001$; multivariable: $t=6.6$, $P<.0001$), and triglycerides (univariable: $r=.36$, $P<.0001$; multivariable: $t=6.8$, $P<.0001$). By multivariable analyses, reductions in body mass index ($t=4.6$, $P<.0001$) and older age ($t=4.0$, $P<.0001$) were strong independent predictors of reduction in triglyceride values following cardiac rehabilitation. However, low baseline triglyceride values were independently associated with improvements in both low-density and high-density lipoprotein cholesterol levels. Using a model incorporating 13 clinical variables, improvements in lipid values with cardiac rehabilitation were only modestly predictable with the variables assessed, accounting for only 30% to 40% of the improvements in lipid values.

Conclusions: (1) Coronary risk factors markedly improved following cardiac rehabilitation and exercise training. (2) Improvements in lipid values are modestly predictable. (3) Those patients with the worst baseline lipid values had the most improvements in lipid values following cardiac rehabilitation. However, patients with combined hyperlipidemia and low levels of high-density lipoprotein cholesterol are likely to require drug treatment.

(Arch Intern Med. 1993;153:982-988)

From the Department of Internal Medicine, Section on Cardiology, Cardiovascular Health Center, Ochsner Clinic and Alton Ochsner Medical Foundation, New Orleans, La. Dr Milani was previously with the Department of Preventive Medicine, Cardiovascular Health Center, Massachusetts General Hospital, Boston.

CARDIAC REHABILITATION and exercise training have now been proven to reduce the risk of coronary heart disease (CHD) and improve quality of life following major cardiac events.[1-5] These well-proven benefits of cardiac rehabilitation include improvements in exercise capacity, weight, glucose tolerance, lipid values, and psychosocial factors.[1-4] Although individual randomized studies of cardiac rehabilitation and exercise training after myocardial infarction were not large enough to demonstrate signifi-

cant improvements in survival, recent pooled data from these trials demonstrate significant reductions in major cardiac events, cardiac mortality, and all-cause mortality.[2,4]

Substantial and irrefutable data now support the role of lipids in the pathogenesis of coronary atherosclerosis and the im-

See Subjects and Methods on next page

SUBJECTS AND METHODS

We reviewed data at baseline and after an outpatient phase 2 cardiac rehabilitation and exercise program in 237 consecutive patients (160 from Massachusetts General Hospital, Boston, and 77 from Ochsner Medical Institutions, New Orleans, La; the mean age was 58 years; range, 32 to 82 years; 85% were men). All patients were referred after a major cardiac event, such as acute myocardial infarction, coronary artery bypass grafting, or percutaneous balloon angioplasty for an acute ischemic syndrome. None of these patients were treated with lipid-lowering medications, and dosages of other medications known to affect lipid values (eg, estrogens, β-adrenergic blockers, diuretics, α-adrenergic blockers, and calcium antagonists) were stable for at least 4 weeks before study entry and were not altered during the program.

PROTOCOL

Patients participated in an outpatient phase 2 cardiac rehabilitation program that usually lasted 12 weeks (36 exercise and educational sessions). The duration of the program, however, was occasionally altered according to the patient's ability to progress in improving coronary risk factors and developing independence in performing and monitoring the individually prescribed exercise program. Each session consisted of approximately 10 minutes of warm-up stretching and calisthenics, 30 to 40 minutes of continuous upright aerobic and dynamic exercise (various combinations of walking, bicycling, jogging, rowing, etc), along with light isometric exercises (eg, hand weights) and approximately a 10-minute cool-down period of stretching and calisthenics. Exercise intensity was prescribed on an individual basis so that the patient's exercise heart rate was approximately 75% to 85% of the maximal heart rate, or 10 to 15 beats per minute below the level of any exercise-induced myocardial ischemia. In addition to the supervised exercise sessions, all patients were encouraged to exercise one to three times per week outside the program. Each patient's exercise prescription was periodically adjusted to encourage gradual increases in exercise performance. All patients were instructed while hospitalized and again at the beginning of the phase 2 program and were frequently encouraged by physicians, dieticians, nurses, and exercise physiologists to comply with both the dietary (phase 1 diet of the American Heart Association and the National Cholesterol Education Program) and the exercise portions of the program.

DATA COLLECTION

Height, weight, body mass index (BMI), percentage of body fat, age, gender, fasting plasma lipid values, and estimated metabolic equivalents (METs) were assessed at baseline (4 to 8 weeks after a major cardiac event; average, 6 weeks) and again within 1 week of completing the cardiac rehabilitation and exercise program. Baseline psychological factors, including symptoms of hostility and depression, were assessed in the patients at Massachusetts General Hospital according to a previously described protocol.[16]

Before entering the program, patients at both institutions underwent symptom-limited exercise testing, usually using a standard Bruce treadmill protocol, although about one third underwent an alternative treadmill protocol or an upright bicycle ergometric protocol. Following the outpatient cardiac rehabilitation program, each patient underwent a protocol similar to the preprogram assessment. Exercise capacity was estimated in METs using standard methods.[17]

STATISTICAL METHODS

Continuous variables were compared before and after cardiac rehabilitation using Student's paired t test. Factors predicting improvements in lipid values (eg, percentage reduction in LDL-C, percentage increase in HDL-C, and percentage reduction in triglyceride values) were assessed by univariable and multivariable analyses with STAT-View II software on a Macintosh II computer system. Simple linear regression used a one X one Y and multiple regression of many X one Y statistic to compute r (Pearson's Correlation Coefficient), R^2, adjusted R^2, root mean square residual, analysis of variance table residual statistics, beta coefficient table, and confidence interval tables. The following variables were assessed: age, gender, baseline BMI, baseline LDL-C, baseline HDL-C, and baseline triglyceride values, baseline METs, percentage reduction in BMI, percentage reduction in LDL-C levels, percentage increase in HDL-C levels, percentage reduction in triglyceride values, and percentage increase in METs. In addition, baseline hostility score and depression indexes were also included in the model for the subgroup of patients at Massachusetts General Hospital.

---

portance of lipid intervention, directed at both low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), for both primary and secondary prevention of major cardiac events, as well as for preventing progression of coronary atherosclerosis.[6-12] Although the independent role of triglycerides in the risk of CHD remains controversial, several studies suggest that triglycerides are independently associated with CHD events and progression of coronary atherosclerosis,[13,14] and re-cent data suggest that elevated triglyceride values are extremely important, particularly in patients with an elevated LDL-C/HDL-C ratio.[15] It seems likely, therefore, that improvements in lipid values following cardiac rehabilitation and exercise training could account for much of the reduction in subsequent cardiac events. Only limited data are available to define predictors of lipid value improvements following aggressive nonpharmacological therapy with cardiac rehabilitation. Therefore, we reviewed

baseline and postprogram data in 237 consecutive patients entering cardiac rehabilitation and exercise training to determine those factors predicting improvements in lipid values following cardiac rehabilitation.

RESULTS

Following cardiac rehabilitation and exercise training, significant improvements occurred in coronary risk factors (**Table 1**), including significant reductions in levels of total cholesterol (−2%, $P<.03$), triglycerides (−13%, $P<.0001$), and LDL-C (−4%, $P<.05$); LDL-C/HDL-C ratio (−10%, $P<.0001$), BMI (−2%, $P<.0001$), and percentage of body fat (−5%, $P<.0001$); and increases in HDL-C levels (7%, $P<.0001$) and exercise capacity (26%, $P<.0001$). The improvements in coronary risk factors were similar in both genders and in younger vs older patients. Although reduction in BMI was greater in obese patients ($P<.01$), improvements in other risk factors were similar in obese and nonobese patients. In patients with low baseline capacity (<6 METs), improvement in exercise capacity was significantly greater compared with those with higher baseline exercise capacity (39% vs 19%; $P<.0001$). However, those patients with higher baseline exercise capacity (≥6 METs) had a slightly greater reduction in LDL-C levels (6% vs no change; $P<.02$) and LDL-C/HDL-C ratio (−13% vs −6%; $P=.05$). Improvement in other coronary risk factors was similar in those patients with low or high baseline functional capacity.

Reduction in LDL-C levels following cardiac rehabilitation was only strongly associated with high baseline LDL-C levels ($r=.51$, $P<.0001$) by univariable analysis (**Table 2**). Male sex, low baseline triglyceride values, and improvement in exercise capacity were weakly associated with re-

duction in LDL-C levels, but none of these variables reached statistical significance. In a multivariable analysis incorporating 11 variables, only high baseline LDL-C levels were strongly and independently associated with improvement in LDL-C levels after cardiac rehabilitation ($t=8.5$, $P<.0001$). Male sex, improvement in exercise capacity, and low baseline triglyceride values were weakly, but independently, associated with reduction in LDL-C levels. In a model incorporating all of these variables, 34% of the reduction in LDL-C levels was predicted ($F=8.4$, $P<.0001$).

An increase in HDL-C levels following cardiac rehabilitation was associated with low baseline HDL-C levels ($r=.37$, $P<.0001$), reduction in triglyceride values ($r=.27$, $P<.0001$), and reduction in BMI ($r=.19$, $P<.01$) by univariable analysis (**Table 3**). By multivariable analysis, low baseline HDL-C levels were the strongest independent predictor of increasing HDL-C levels with rehabilitation ($t=6.6$, $P<.0001$). Reduction in triglyceride values, low baseline

Cardiac rehabilitation and exercise training reduce coronary artery disease risk factors, improve quality of life, and reduce subsequent CHD morbidity and mortality

triglyceride values, and female sex were all weakly, but independently, associated with increases in HDL-C levels. High baseline exercise capacity, older age, and improvement in exercise capacity were all associated with increases in HDL-C levels by multivariable analysis, but these did not reach statistical significance. Using a model incorporating 11 variables, 29% of the increase in HDL-C levels with cardiac rehabilitation was predicted ($F=6.5$, $P<.0001$).

Reduction in triglyceride values following cardiac rehabilitation was most strongly associated with high baseline triglyceride values ($r=.36$, $P<.0001$) by univariable analyses (**Table 4**). Reduction in BMI, increases in HDL-C levels, older age, and low baseline HDL-C levels were all associated with a reduction in triglyceride values. By multivariable analysis, high baseline triglyceride values ($t=6.8$, $P<.0001$), reduction in BMI ($t=4.6$, $P<.0001$), and older age ($t=4.0$, $P<.0001$) were all strongly and independently associated with a reduction in triglyceride values. Increases in HDL-C levels, low baseline BMI, and improvement in exercise capacity were also associated with a reduction in triglyceride values by multivariable analysis, although the latter two variables did not reach statistical significance. The model incorporating 11 variables accounted for 37% of the triglyceride value reduction ($F=9.7$, $P<.0001$).

In the patients at Massachusetts General Hospital, baseline psychological variables, including hostility scores and depression indexes, were not associated with reduction in levels of LDL-C or triglycerides or increases in lev-

Table 1. Improvements in Coronary Risk Factors Following Cardiac Rehabilitation (N=237)

Variable*	Cardiac Rehabilitation			
	Before, Mean±SD	After, Mean±SD	% Change	P
Total cholesterol, mmol/L (mg/dL)	5.40±1.06 (209±41)	5.28±0.96 (204±37)	−2	<.03
Triglycerides, mmol/L (mg/dL)	1.89±1.02 (167±90)	1.64±0.81 (145±72)	−13	<.0001
HDL-C, mmol/L (mg/dL)	0.98±0.28 (37.9±10.9)	1.05±0.29 (40.7±11.1)	7	<.0001
LDL-C, mmol/L (mg/dL)	3.6±0.96 (139±37)	3.47±0.83 (134±32)	−4	<.05
LDL-C/HDL-C	3.9±1.3	3.5±1.2	−10	<.0001
Body mass index, kg/m²	27.3±4.2	26.8±4.1	−2	<.0001
Body fat, %	24.2±6.3	22.9±6.2	−5	<.0001
Exercise capacity, METs	7.2±2.9	9.1±3.4	26	<.0001

*HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and, METs, metabolic equivalents.

Table 2. Factors That Predict Percentage Reductions in Low-Density Lipoprotein Cholesterol (LDL-C) Levels Following Cardiac Rehabilitation and Exercise Training (N=237)

Variable	r	t	P
Univariable Predictors			
High baseline LDL-C	.51	8.4	<.0001
Male sex	.13	1.9	.06
Low baseline TG	.12	1.7	.09
Low Δ METs	.12	1.7	.09
Multivariable Predictors*			
High baseline LDL-C	...	8.5	<.0001
Male sex	...	2.5	.01
Low Δ METs	...	2.3	.02
Low baseline TG	...	2.0	.04

*Model incorporating 11 variables: $F=8.4$; $r=.58$; $R^2=.34$; $P<.0001$. TG indicates triglycerides; Δ, percentage of change following cardiac rehabilitation; and METs, metabolic equivalents.

els of HDL-C by either univariable or multivariable analysis, and incorporation of these two variables did not improve the overall model for any of these lipid variables.

COMMENT

The current data support the role of cardiac rehabilitation and exercise training in improving cardiac risk factors, including plasma lipids, indexes of obesity, and exercise capacity. The improvements in plasma lipid levels, however, were only modestly predictable and were mostly related to baseline values. For the three lipid factors studied, which were reductions in levels of LDL-C and triglycerides and increases in HDL-C, the strongest independent predictors of lipid improvements were abnormal baseline values. Patients with the worst baseline lipid values seemed to have the most improvements following cardiac rehabilitation and exercise training.

AGE

Although there seems to be a strong age bias in the approach to treating elderly patients with heart disease,[18] recent data from our institution suggest that improvements in exercise capacity, obesity indexes, and lipids are similar in older and younger patients enrolled in cardiac rehabilitation and exercise training.[19] In fact, the current data indicate that older age is independently associated with greater increases in HDL-C levels ($P=.06$) and reductions in triglyceride values ($P<.0001$) following cardiac rehabilitation and exercise training. We believe that these data further support the idea that elderly patients should not be denied the psychosocial, physical, and risk factor benefits of formal cardiac rehabilitation and supervised exercise training and that the elderly should be rou-
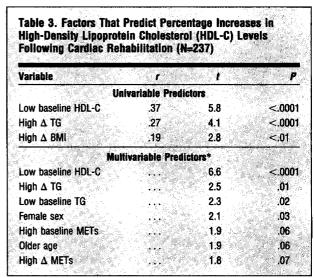
tinely referred and vigorously encouraged to participate in these programs.[4,19]

GENDER

Data have increasingly focused on an apparent gender bias to treating women with heart disease.[20,21] However, we recently demonstrated that coronary risk factors improved markedly following cardiac rehabilitation and exercise training in female coronary patients.[22] In the current study by using multivariable analysis, we demonstrated that male sex was independently associated with a reduction in LDL-C levels following cardiac rehabilitation, whereas female gender was independently associated with an increase in HDL-C levels. Based on these data, it seems warranted to focus greater attention on dietary reduction in LDL-C levels in female coronary patients, with greater emphasis on increasing HDL-C levels in male patients.

OBESITY

We have been interested in the impact of obesity on cardiovascular diseases, including whether levels of arterial pressure are increased,[23-25] eccentric left ventricular hypertrophy is increased,[23,24,26] and insulin resistance and plasma lipid levels are worsened,[27] and, in particular, whether HDL-C levels are reduced and triglyceride values are raised, the prevalence and complexity of ventricular dysrhythmias are increased,[23,24,26,28] and the risk of CHD is independently increased.[29,30] Previous data have indicated the importance of weight reduction in improving lipid values, particularly HDL-C and triglycerides.[31,32] In our study, cardiac rehabilitation and exercise training were associated with only modest, although strongly statistically significant, reductions in BMI and percentage of body fat.

Table 3. Factors That Predict Percentage Increases in High-Density Lipoprotein Cholesterol (HDL-C) Levels Following Cardiac Rehabilitation (N=237)

Variable	r	t	P
Univariable Predictors			
Low baseline HDL-C	.37	5.8	<.0001
High Δ TG	.27	4.1	<.0001
High Δ BMI	.19	2.8	<.01
Multivariable Predictors*			
Low baseline HDL-C	...	6.6	<.0001
High Δ TG	...	2.5	.01
Low baseline TG	...	2.3	.02
Female sex	...	2.1	.03
High baseline METs	...	1.9	.06
Older age	...	1.9	.06
High Δ METs	...	1.8	.07

*Model incorporating 11 variables: $F=6.5$; $r=.54$; $R^2=.29$; $P<.0001$. Δ indicates percentage of change with cardiac rehabilitation; TG, triglycerides; BMI, body mass index; and METs, metabolic equivalents.

Reductions in indexes of obesity, however, were not associated with improvement in LDL-C levels by either univariable or multivariable analysis. Though not an independent factor, reduction in BMI was associated with increases in HDL-C levels; however, it was strongly and independently related to reduction in triglyceride values. Although these improvements in lipid values are significant clinically, the benefits of weight reduction not related to lipid values may be even more important for reducing CHD risks.[23,30]

EXERCISE CAPACITY

Substantial data now indicate that regular exercise is associated with the primary and secondary prevention of CHD.[4,31,32] Increased exercise capacity has also been associated with low risk of CHD,[4,33,34] although limited data are available regarding the impact of a change in exercise capacity on reducing CHD. However, the 26% increase in exercise capacity noted in the current study seems promising and should improve quality of life as well as overall prognosis.

Although exercise is known to raise HDL-C and reduce triglyceride values,[4,35,36] in our study, an increase in exercise capacity following cardiac rehabilitation and exercise training was only a weak independent factor associated with improving these lipid fractions that did not quite obtain statistical significance. However, because all patients participated in exercise training and nearly all had at least modest (>10%) improvement in exercise capacity, the relative impact of an increase in exercise capacity on CHD risk factors noted is probably lessened. Although patients with a low baseline exercise capacity

Improvements in most CHD risk factors following cardiac rehabilitation were not affected by baseline age, gender, obesity indexes, or exercise capacity

usually gain the most from cardiac rehabilitation and exercise training, at least with regard to improvement of functional capacity and quality of life, a high baseline exercise capacity was actually a weak, independent factor associated with an increase in HDL-C levels with cardiac rehabilitation.

PSYCHOLOGICAL FACTORS

In the current study, baseline psychological factors were not associated with improvements in plasma lipid values following cardiac rehabilitation and exercise training. A limitation of our study is that it did not assess the impact of cardiac rehabilitation on psychological factors (eg, re-

Table 4. Factors That Predict Percentage Reductions in Triglyceride (TG) Levels Following Cardiac Rehabilitation (N=237)

Variable	r	t	P
Univariable Predictors			
High baseline TG	.36	5.7	<.0001
High Δ BMI	.28	4.2	<.0001
High Δ HDL-C	.27	4.1	<.0001
Older age	.2	3.0	<.01
Low baseline HDL-C	.13	1.9	.05
Multivariable Predictors*			
High baseline TG	...	6.8	<.0001
High Δ BMI	...	4.6	<.0001
Older age	...	4.0	<.0001
High Δ HDL-C	...	2.5	.01
Low baseline BMI	...	1.8	.07
High Δ METs	...	1.7	.09

*Model incorporating 11 variables: F=9.7; r=.61; R²=.37; P<.0001. BMI indicates body mass index; Δ, percentage of change following cardiac rehabilitation; HDL-C, high-density lipoprotein cholesterol; and METs, metabolic equivalents.

ducing hostility and depressive symptoms) and CHD risk factors. Preliminary data from our institution suggest that psychological factors strongly predict improvements in exercise capacity following cardiac rehabilitation, as well as improvements in quality of life in these patients.[3-5,37,38]

TRIGLYCERIDES

A common belief is that improvements in lipid values with vigorous nonpharmacological therapy are greater in patients with elevated levels of triglycerides; however, data supporting this belief are lacking. In our study, reductions in triglyceride values were strongly and independently associated with high baseline triglyceride levels and were independently associated with increases in HDL-C levels. However, reductions in LDL-C and increases in HDL-C levels actually were both independently associated with low baseline levels of triglycerides. Although vigorous nonpharmacological therapy is certainly indicated in patients with hypertriglyceridemia, the current data support both our clinical impression and the Helsinki Heart Study, suggesting that patients with combined hyperlipidemia and low HDL-C levels will often require drug treatment to improve lipid values.[15,39]

LIMITATIONS

Several limitations of the current study should be emphasized. First, some selection bias may be present since the patients studied were referred for and decided to participate in cardiac rehabilitation and exercise training. Second, no control group was included, which would be more essential if the main purpose of this study was to demonstrate the marked benefits of cardiac rehabilitation and

exercise training; however, this study assessed factors predicting improvements in lipid values in patients participating in cardiac rehabilitation and exercise training. Third, it is known that lipid values often change soon after an acute cardiac event, and only limited data are available regarding the exact time required for these values to return to baseline. However, we studied our patients 6 weeks

Patients with combined hyperlipidemia and low HDL-C levels will often require drug treatment to improve lipid values

after their cardiac event, and substantial data suggest that by this time, lipid values were likely to have returned to their pre-event levels.[40-43] It should be noted, however, that nearly all of our patients received phase 1 cardiac rehabilitation during their hospitalization and had already received dietary recommendations. In fact, in a subgroup of 50 cardiac rehabilitation patients who had a complete fasting lipid profile performed within 6 months of their cardiac event, their prephase 2 cardiac rehabilitation values for LDL-C and triglycerides were reduced by 3% and 8%, respectively, without any significant change in HDL-C levels. Finally, we do not have data regarding dietary or exercise recall, so we cannot determine the relative impact of these two aspects of the cardiac rehabilitation program on lipid improvements.

CONCLUSION

Despite these limitations, we believe that our results strongly support the beneficial effects of cardiac rehabilitation and exercise training on plasma lipid values, indexes of obesity, and exercise capacity. Improvements in lipid values are modestly predictable; in general, those patients with the worst baseline lipid values had the most improvement in lipid values following cardiac rehabilitation. Although patients with the highest baseline triglyceride values had the greatest reductions in triglyceride values following cardiac rehabilitation, low baseline triglyceride levels were independently associated with improvements in LDL-C and HDL-C levels. These data may be useful for predicting which patients may benefit the most from vigorous, nonpharmacological therapy as opposed to which patients may be more likely to require drug treatment, particularly in those with combined hyperlipidemia and low HDL-C levels.

REFERENCES

1. Squires RW, Gau GT, Miller TD, Allison TG, Lavie CJ. Cardiovascular rehabilitation: status, 1990. Mayo Clin Proc. 1990;65:731-755.
2. O'Connor GT, Buring JE, Yusuf S, et al. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. Circulation. 1989;80: 234-244.
3. Milani RV, Littman AB, Lavie CJ. Psychological adaptation to cardiovascular disease. In: Messerli FH, ed. Cardiovascular Diseases in the Elderly. 3rd ed. Norwell, Mass: Kluwer Academic Publishers; 1992:401-412.
4. Lavie CJ, Milani RV, Squires RW, Boykin C. Exercise and the heart: good, benign, or evil? Postgrad Med. 1992;91:130-150.
5. Milani RV, Lavie CJ, Boykin JC, Speirer D, Robichaux R. Quality of life is enhanced in elderly patients following cardiac rehabilitation. Clin Res. 1992;40: 227A. Abstract.
6. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med. 1987;317:1237-1245.
7. Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med. 1990;323:1289-1298.
8. Blankenhorn DH, Nessim SA, Johnson RL, et al. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA. 1987;257:3233-3240. Erratum: JAMA. 1988;259:2698.
9. Lavie CJ, Gau GT, Squires RW, Kottke BA. Management of lipids in primary and secondary prevention of cardiovascular diseases. Mayo Clin Proc. 1988; 63:605-621.
10. Lavie CJ, O'Keefe JH, Blonde L, Gau GT. High-density lipoprotein cholesterol: recommendations for routine testing and treatment. Postgrad Med. 1990;87: 36-51.
11. Lavie CJ, Milani RV. National Cholesterol Education Program's recommendations, and implications of 'missing' high-density lipoprotein cholesterol in cardiac rehabilitation programs. Am J Cardiol. 1991;68:1087-1088.
12. Mailander L, Lavie CJ, Milani RV, Gaudin D. High-density lipoprotein cholesterol is the most important lipid risk factor in coronary patients. South Med J. In press.
13. Carlson LA, Rosenhamer G. Reduction of mortality in the Stockholm Ischaemic Heart Disease Prevention Study by combined treatment with clofibrate and nicotinic acid. Acta Med Scand. 1988;223:405-418.
14. Campeau L, Enjalbert M, Lesperance J, et al. The relation of risk factors to the development of atherosclerosis in saphenous-vein bypass grafts and the progression of disease in the native circulation: a study 10 years after aortocoronary bypass surgery. N Engl J Med. 1984;311:1329-1332.
15. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. Circulation. 1992;85:37-45.
16. Ruberman W, Weinblatt E, Goldberg JD, Chaudhary BS. Psychosocial influences on mortality after myocardial infarction. N Engl J Med. 1984;311:552-559.
17. Bardsley WT, Mavkin HT. Exercise testing. In: Brandenburg RD, Fuster V, Giuliani ER, McGoon CD, eds. Cardiology Fundamentals and Practice. St Louis, Mo: Mosby-Year Book; 1987:369-402.
18. Yusuf S, Furberg CD. Are we biased in our approach to treating elderly patients with heart disease? Am J Cardiol. 1991;68:54-56.
19. Lavie CJ, Milani RV. Benefits of cardiac rehabilitation and exercise training in

the elderly. *J Am Coll Cardiol.* 1991;19(3):377. Abstract.

20. Wenger NK. Gender, coronary artery disease, and coronary bypass surgery. *Ann Intern Med.* 1990:112:557-558.

21. Healy B. The Yentl syndrome. *N Engl J Med.* 1991;325:274-275.

22. Lavie CJ, Milani RV, Boykin JC, Malbrough SJ, Santos MA. Gender differences in patients referred for cardiac rehabilitation and exercise training. *J Cardiopulmonary Rehabil.* 1992;12:348. Abstract.

23. Lavie CJ, Messerli FH. Cardiovascular adaptation to obesity and hypertension. *Chest.* 1986;90:275-279.

24. Lavie CJ, Ventura HO, Messerli FH. Left ventricular hypertrophy: its relationship to obesity and hypertension. *Postgrad Med.* 1992;91:131-143.

25. Messerli FH. Cardiovascular effects of obesity and hypertension. *Lancet.* 1982; 1:1165-1168.

26. Lavie CJ, Ventura HO, Messerli FH. Regression of increased left ventricular mass by antihypertensives. *Drugs.* 1991;42:945-961.

27. Laws A, Reaven G. Insulin resistance, hyperinsulinemia, dyslipidemia and cardiovascular disease. In: Braunwald E, ed. *Heart Disease: Update.* 4th ed. Philadelphia, Pa: WB Saunders Co; 1991:1-9.

28. Messerli FH, Nunez BD, Ventura HO, Snyder DW. Overweight and sudden death: increased ventricular ectopy in cardiopathy of obesity. *Arch Intern Med.* 1987; 147:1725-1728.

29. Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of obesity and risk of coronary heart disease in women. *N Engl J Med.* 1990;322:882-889.

30. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation.* 1983;67:968-977.

31. Paffenbarger RS Jr, Hyde RT, Wing AL, et al. Physical activity, all-cause mortality, and longevity of college alumni. *N Engl J Med.* 1986;314:605-613.

32. Paffenbarger RS Jr, Hyde RT. Exercise in the prevention of coronary heart disease. *Prev Med.* 1984;13:3-22.

33. Blair SN, Kohl HW III, Paffenbarger RS Jr, et al. Physical fitness and all-cause mortality: a prospective study of healthy men and women. *JAMA.* 1989;262: 2395-2401.

34. Morris K, Ueshima K, Kawaguchi T, Froelicher VF. A prognostic value of exercise capacity: a review of the literature. *Am Heart J.* 1991:122:1423-1431.

35. Wood PD, Stefanick ML, Williams PT, Haskell WL. The effects of plasma lipoproteins of a prudent weight-reducing diet, with or without exercise, in overweight men and women. *N Engl J Med.* 1991;325:461-466.

36. Wood PD, Stefanick ML, Dreon DM, et al. Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared with exercise. *N Engl J Med.* 1988;319:1173-1179.

37. Milani RV, Lavie CJ. Factors predicting improvement in exercise capacity following cardiac rehabilitation and exercise program. *Circulation.* 1991;84:II-220. Abstract.

38. Milani RV, Lavie CJ, Littman AB. Hostility and depression indices predict functional improvement following cardiac rehabilitation and exercise. *Clin Res.* 1992; 40:348A. Abstract.

39. Lavie CJ. Mailander L, Milani RV. Marked benefit with sustained-release niacin therapy in patients with 'isolated' very low levels of high-density lipoprotein cholesterol and coronary artery disease. *Am J Cardiol.* 1992;69:1083-1085.

40. Watson WC, Buchanan KD, Dickson C. Serum cholesterol levels after myocardial infarction. *BMJ.* 1963;2:709-712.

41. Cunningham MJ, Boucher TM, McCabe CH, Horowitz GL, Pasternak RC. Changes in total cholesterol and high-density lipoprotein cholesterol in men after coronary artery bypass grafting. *Am J Cardiol.* 1987;60:1393-1394.

42. Rönnemaa T, Viikari J, Irjala K, Peltola O. Marked decrease in serum HDL cholesterol level during acute myocardial infarction. *Acta Med Scand.* 1980;207:161-166.

43. Ryder REJ, Hayes TM, Mulligan IP, Kingswood JC, Williams S, Owens DR. How soon after myocardial infarction should plasma lipid values be assessed? *BMJ.* 1984;289:1651-1653.