Influence of Lovastatin Plus Gemfibrozil on Plasma Lipids and Lipoproteins in Patients With Heterozygous Familial Hypercholesterolemia

D. Roger Illingworth, MD, PhD, and Sandra Bacon, RN

We investigated the hypocholesterolemic effects of lovastatin alone and in combination with gemfibrozil on plasma lipids and lipoproteins in 12 adult patients with well-characterized heterozygous familial hypercholesterolemia. Plasma concentrations of low density lipoprotein (LDL) cholesterol decreased from 321±14 mg/dl on diet only to 207±8 mg/dl (−35.5%) on single-drug therapy with lovastatin at a dose of 40 mg twice daily, whereas triglyceride concentrations fell by 27.6% (from 145±20 to 105±20 mg/dl). Subsequent addition of gemfibrozil at a dose of 600 mg twice daily resulted in a nonsignificant further reduction in LDL cholesterol to 194±7 mg/dl (−39.6% change from baseline), whereas triglycerides decreased to 80 mg/dl (−44.8%, p < 0.05 vs. single-drug therapy with lovastatin). Plasma concentrations of high density lipoprotein (HDL) increased slightly during lovastatin and combined drug therapy (from 45±4 mg/dl at baseline to 46±4 mg/dl on lovastatin to 48±4 mg/dl on lovastatin plus gemfibrozil). The response to combined drug therapy in individual patients was heterogeneous and clinically significant decreases in LDL cholesterol concentrations were noted in two of the 12 patients, whereas in three patients LDL cholesterol concentrations increased on the combined drug regimen. One patient developed an asymptomatic increase in creatine kinase on monotherapy with lovastatin and a more pronounced and symptomatic increase during combination drug therapy with lovastatin plus gemfibrozil. We conclude that the combination of lovastatin plus gemfibrozil does not provide significant further LDL lowering as compared with monotherapy with lovastatin alone in patients with heterozygous familial hypercholesterolemia and that this combined drug regimen may be associated with an increased risk of myopathy. (Circulation 1989;79:590–596)

Familial hypercholesterolemia (FH) is an autosomal dominantly inherited disorder characterized by high plasma concentrations of total and low density lipoprotein (LDL) cholesterol, tendon xanthomas, and, in untreated patients, the development of premature coronary artery disease.1–5 Plasma concentrations of LDL cholesterol are increased from twofold to threefold in heterozygous patients and usually exceed 250 mg/dl in adults. As a group, patients with heterozygous FH constitute a population in whom long-term hypolipidemic drug therapy aimed at substantially reducing plasma concentrations of total and LDL cholesterol is most clearly indicated.6 However, because of the severe hypercholesterolemia commonly seen in patients with heterozygous FH, monotherapy with cholestyramine or colestipol, nicotinic acid, or lovastatin often fail to achieve optimal reductions in plasma LDL cholesterol concentrations, and the use of combined drug regimens is frequently necessary to further reduce plasma lipid concentrations.7

Lovastatin is one of a new class of clinically effective hypocholesterolemic drugs that are structural analogs of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG CoA) and competitively inhibit HMG CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis.8–11 The hypocholesterolemic effects of lovastatin and its dose-response relations with plasma LDL cholesterol have been reported in patients with heterozygous FH12,13 and, at dosages of 40 mg twice daily, this drug reduces plasma concentrations of LDL cholesterol by 35–40%.

Gemfibrozil is an effective hypotriglyceridemic drug whose mechanism of action appears to be mediated in part by a reduction in very low density lipoprotein (VLDL) triglycerides, but its effect on plasma LDL cholesterol is not substantial.14

From the Division of Endocrinology, Metabolism, and Clinical Nutrition, Department of Medicine, The Oregon Health Sciences University, Portland, Oregon.

Supported in part by National Institutes of Health Research Grants HL-32271 and HL-37940 and by the General Clinical Research Center’s Program (RR334).

Address for correspondence: D. Roger Illingworth, MD, PhD, Department of Medicine, L465, The Oregon Health Sciences University, Portland, OR 97201.
lipoprotein synthesis,\textsuperscript{14} which, in patients with primary hypercholesterolemia, may lead to a reduction in LDL cholesterol concentrations.\textsuperscript{15} Gemfibrozil is one of three drugs that have been demonstrated to reduce the incidence of coronary artery disease in prospective clinical trials; the beneficial effects of gemfibrozil therapy have been proposed to be due to both a reduction in the plasma concentrations of LDL cholesterol and an increase in the plasma concentrations of HDL.\textsuperscript{16,17}

In a recent study, East et al.\textsuperscript{18} reported on the efficacy of combined drug therapy with lovastatin plus gemfibrozil in patients with familial combined hyperlipidemia but to our knowledge the efficacy of this combination in patients with primary hypercholesterolemia due to heterozygous FH has not previously been examined. In the present study, we have examined the hypolipidemic effects of lovastatin alone and in combination with gemfibrozil in patients with heterozygous FH.

### Methods

**Subjects**

Twelve adult patients with well characterized heterozygous FH\textsuperscript{12,19} participated in this study. Pertinent clinical characteristics as well as baseline lipid and lipoprotein concentrations are described in Table 1. None of the patients had diabetes and all had normal thyroid, renal, and hepatic function tests. Although several of the patients were receiving drugs known to influence lipid metabolism (e.g., estrogens, \(\beta\)-blockers), therapy with these agents remained constant during the period of drug treatment. All patients were seen as outpatients in the Clinical Research Center of The Oregon Health Sciences University. Informed consent was obtained from each patient, and the protocol was approved by the Human Research Committee of our institution and by the US Food and Drug Administration.

### All hypolipidemic drugs were withdrawn for a minimum period of 4 weeks before blood samples were collected for initial baseline values. No patient was previously being treated with probucol.

**Study Protocol**

Before entry into the study, all patients underwent a comprehensive physical examination, and blood samples were obtained to exclude secondary causes of hyperlipidemia. An ophthalmologic examination was also conducted, which included a slit lamp examination and detailed examination of the lens. All patients had received prior dietary instruction and were on a low-cholesterol, low-fat diet conforming to at least phase one of the American Heart Association’s diet\textsuperscript{20} or, in some cases, a more rigorous lipid-lowering diet. Further dietary instruction was given before entry into the study, and patients were seen by a registered dietitian periodically during the study for reinforcement of dietary advice. After satisfying eligibility criteria, all patients were instructed to take one capsule twice daily with breakfast and dinner (the capsules were a placebo) for a 4-week baseline period in a single-blind fashion and were seen on three occasions during this time period. The placebo capsules appeared identical to lovastatin, and patients received two bottles of capsules (one for use in the morning and one for the evening). Compliance, estimated by pill counts, was 92.4\% during this 4-week placebo baseline period. Patients were then begun on lovastatin in a nonblinded period of drug treatment and were seen at 4, 6, and 10 weeks after commencing lovastatin therapy. At each visit, patients were questioned concerning side effects; vital signs were obtained; and brief physical examinations performed if clinically indicated. Blood samples were obtained at each visit for lipid and lipoprotein studies and for clinical chemistry determinations and hematology.

### Table 1. Characteristics of the Patients With Familial Hypercholesterolemia

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>Weight (kg)</th>
<th>Tendon xanthoma</th>
<th>Plasma cholesterol (mg/dl)</th>
<th>Plasma TG (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>LDL</td>
</tr>
<tr>
<td>1</td>
<td>42 F</td>
<td>68</td>
<td>+</td>
<td>418</td>
<td>337</td>
</tr>
<tr>
<td>2</td>
<td>55 M</td>
<td>84</td>
<td>+</td>
<td>433</td>
<td>369</td>
</tr>
<tr>
<td>3</td>
<td>40 M</td>
<td>82</td>
<td>+</td>
<td>369</td>
<td>306</td>
</tr>
<tr>
<td>4</td>
<td>34 M</td>
<td>88</td>
<td>+</td>
<td>319</td>
<td>263</td>
</tr>
<tr>
<td>5</td>
<td>49 F</td>
<td>70</td>
<td>+</td>
<td>456</td>
<td>397</td>
</tr>
<tr>
<td>6</td>
<td>49 F</td>
<td>81</td>
<td>+</td>
<td>459</td>
<td>359</td>
</tr>
<tr>
<td>7</td>
<td>53 F</td>
<td>83</td>
<td>+</td>
<td>433</td>
<td>348</td>
</tr>
<tr>
<td>8</td>
<td>30 M</td>
<td>112</td>
<td>+</td>
<td>426</td>
<td>336</td>
</tr>
<tr>
<td>9</td>
<td>45 M</td>
<td>78</td>
<td>+</td>
<td>315</td>
<td>256</td>
</tr>
<tr>
<td>10</td>
<td>50 M</td>
<td>89</td>
<td>+</td>
<td>390</td>
<td>313</td>
</tr>
<tr>
<td>11</td>
<td>30 M</td>
<td>74</td>
<td>+</td>
<td>350</td>
<td>273</td>
</tr>
<tr>
<td>12</td>
<td>62 M</td>
<td>79</td>
<td>+</td>
<td>343</td>
<td>291</td>
</tr>
<tr>
<td>Mean</td>
<td>44.9</td>
<td>82.3</td>
<td></td>
<td>392.6</td>
<td>320.7</td>
</tr>
<tr>
<td>±SEM</td>
<td>2.9</td>
<td>3.3</td>
<td></td>
<td>±15.0</td>
<td>12.9</td>
</tr>
</tbody>
</table>

Abbreviations: LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglyceride.
Compliance to medication was assessed by verbal questionnaires and by return of unused medications. Compliance was more than 90% in this selected and highly motivated patient population. The 12 patients described in this report all showed LDL cholesterol concentrations of more than 160 mg/dl on single drug therapy with lovastatin at a dose of 40 mg twice daily; after 10 weeks on treatment with this maximal dosage of lovastatin, they were begun on additional therapy with gemfibrozil at a dose of 600 mg twice daily. Patients were advised to take both drugs concurrently with breakfast and their evening meal. Patients were seen at monthly intervals after the addition of gemfibrozil for a period of 3 months (three outpatient visits), and at each visit blood samples were obtained as previously described.

The patients were seen in the morning after having fasted for at least 12 hours and had not taken the study medications before being seen in the clinic. Blood samples for lipid and lipoprotein analysis were obtained in tubes containing 1 mg/dl EDTA as anticoagulant, and plasma was separated at 4°C in a refrigerated centrifuge. Total plasma cholesterol and triglyceride levels were measured on an autoanalyzer. Concentrations of HDL cholesterol were determined on the supernatant obtained after heparin manganese precipitation of plasma. The cholesterol content of the HDL fraction was determined directly, and the LDL concentration was calculated. Lipid determinations were standardized with samples of known composition obtained from the Centers for Disease Control, Atlanta, Georgia. In addition to the lipid and lipoprotein studies, at each visit a complete blood count and urine analysis were performed. Biochemical assessments included total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, creatinine, total serum protein, uric acid, fasting serum glucose, electrolytes, and creatine kinase. In addition, platelet count, prothrombin time, and partial thromboplastin times were performed at each visit.

Statistical Analysis

Statistical analysis was performed by one-way analysis of variance with repeated measures followed by the Neuman-Keuls post hoc test.

Results

All 12 patients completed the placebo baseline and lovastatin study periods, whereas one patient was withdrawn after 8 weeks on combined drug therapy with lovastatin plus gemfibrozil due to symptoms of muscle tenderness and a markedly increased creatine kinase concentration.

The stability of lipid and lipoprotein concentrations during the three treatment periods is illustrated in Figure 1. Analysis of variance with repeated measures of this data showed no significant differences between the concentrations of total and LDL cholesterol obtained during the three baseline visits, during the three visits on single drug therapy with lovastatin (40 mg twice daily), and during three visits while the patients were receiving combined drug therapy with lovastatin plus gemfibrozil. These results are consistent with previous studies, which have indicated that stable lipid values are achieved after 4 weeks on monotherapy with lovastatin and after a similar period on combination drug therapy.

Changes in the plasma concentrations of total cholesterol, LDL cholesterol, and HDL cholesterol and plasma triglycerides are shown in Table 2. Total cholesterol concentrations decreased from 395 ± 15 mg/dl (mean ± SEM) at baseline to 274 ± 10 mg/dl on monotherapy with lovastatin (p < 0.01) and fell to 259 ± 9 mg/dl on combination therapy with lovastatin plus gemfibrozil (not statistically significant). Plasma concentrations of LDL cholesterol decreased in parallel with total cholesterol concentrations and fell from 321 ± 14 mg/dl (mean ± SEM) at baseline to 207 ± 8 mg/dl on monotherapy with lovastatin (p < 0.01) and decreased to 194 ± 7 mg/dl on lovastatin plus gemfibrozil (NS). Concentrations of HDL cholesterol fell from
Table 2. The Influence of Lovastatin Alone or in Combination With Gemfibrozil on Plasma Lipids and Lipoproteins in Patients With Familial Hypercholesterolemia

<table>
<thead>
<tr>
<th></th>
<th>Plasma cholesterol (mg/dl)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>LDL</td>
<td>HDL</td>
<td>Plasma TG (mg dl)</td>
</tr>
<tr>
<td>Baseline</td>
<td>395 ± 15</td>
<td>321 ± 14</td>
<td>45 ± 4</td>
<td>145 ± 20</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>274 ± 10*</td>
<td>207 ± 8*</td>
<td>46 ± 4</td>
<td>105 ± 20</td>
</tr>
<tr>
<td>(Percent change)</td>
<td>(-30.6)</td>
<td>(-35.5)</td>
<td>(+2.21)</td>
<td>(-27.6)</td>
</tr>
<tr>
<td>Lovastatin + gemfibrozil</td>
<td>259 ± 9†</td>
<td>194 ± 7†</td>
<td>48 ± 4</td>
<td>80 ± 10†</td>
</tr>
<tr>
<td>(Percent change from baseline)</td>
<td>(-34.4)</td>
<td>(-39.6)</td>
<td>(+6.7)</td>
<td>(-44.8)</td>
</tr>
</tbody>
</table>

Data represent the mean ± SEM from three separate values on each regimen in 12 patients except patient 5 in which data on lovastatin + gemfibrozil is from two determinations.

LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglyceride.

*p < 0.01 Baseline vs. lovastatin.
†p < 0.01 Baseline vs. lovastatin + gemfibrozil.
‡p < 0.05 Lovastatin vs. lovastatin + gemfibrozil.

Cholesterol rose slightly on single drug therapy with lovastatin (from 45 ± 4 to 46 ± 4 mg/dl) and increased to 48 ± 4 mg/dl on combined drug therapy with lovastatin plus gemfibrozil. These changes are not statistically significant from baseline. Plasma triglyceride concentrations fell 27.6% (from 145 ± 20 mg/dl at baseline to 105 ± 20 mg/dl) on single drug therapy with lovastatin and decreased by a total of 44.8% to 80 ± 10 mg/dl on combined drug therapy with lovastatin plus gemfibrozil.

Mean concentrations of LDL cholesterol at baseline, on single drug therapy with lovastatin, and on combined drug therapy withLovastatin plus gemfibrozil in the 12 patients are presented graphically in Figure 2. Concentrations of LDL decreased in all 12 patients during therapy with Lovastatin. Upon addition of gemfibrozil, nine patients showed an additional decrease in LDL cholesterol, whereas in three patients LDL cholesterol concentrations increased slightly. Two patients (patients 1 and 2 in Table 1) showed decreases in LDL cholesterol concentrations of more than 35 mg/dl on addition of gemfibrozil. Both of these patients have subsequently been treated with Lovastatin plus colestipol and have achieved greater reductions in LDL cholesterol than was achieved on combined drug therapy with Lovastatin plus gemfibrozil.

The following side effects were reported during the period of study. During the placebo baseline period, one patient complained of an increase in arthritis and dry eyes, and a second patient noted an increase in gastric acidity. Neither of these patients reported side effects during treatment with Lovastatin. One patient noted an increase in gastric irritation with Lovastatin, and a second patient commented that his scalp was drier; neither of these side effects necessitated discontinuation of drug therapy. Side effects were reported by five patients during combined drug therapy with Lovastatin plus gemfibrozil and necessitated discontinuation of both drugs in one patient (patient 5). In four patients, the addition of gemfibrozil was associated with symptoms of more frequent bowel movements, increased gas, and occasional abdominal cramps. Bilateral popliteal muscle pain developed in one patient (patient 5) after 6–7 weeks of therapy with Lovastatin plus gemfibrozil. These symptoms were associated with a marked increase in creatine kinase (discussed below), and both drugs were discontinued.

No changes were observed in hematologic parameters, prothrombin times, partial thromboplastin times, or serum glucose or electrolytes. An asymptomatic rise in creatine kinase occurred in patient 5 at the second visit on Lovastatin (creatine kinase was 966 units/l compared with 48 units/l at baseline), but the value had decreased to 65 units/l 1 month later.

Figure 2. Plot of concentrations of low density lipoprotein (LDL) cholesterol in 12 patients with heterozygous familial hypercholesterolemia during the placebo baseline period and during treatment with Lovastatin (40 mg twice daily) and Lovastatin plus gemfibrozil (600 mg twice daily). The values in each panel represent the means of three separate determinations obtained under steady-state conditions except for data from patient 5 on combined drug therapy with Lovastatin plus gemfibrozil in which the data are the mean from two outpatient visits. The numbers at the bottom represent the mean ± SEM for all 12 patients.
and the patient remained asymptomatic. During combined lovastatin plus gemfibrozil therapy this patient developed symptomatic myopathy; when seen after 8 weeks on combined drug therapy, the creatine kinase concentration was 7,840 units/L. Subsequently, this patient has been treated with lovastatin alone and in combination with colestipol without recurrence of her symptoms, and it seems likely that the myopathy that occurred in this patient was linked to combined drug therapy with lovastatin plus gemfibrozil. None of the other 11 patients experienced significant rises in creatine kinase, transaminases, or alkaline phosphatase; mean values for these biochemical parameters were not significantly different at baseline, on single drug therapy with lovastatin, or on the combination of lovastatin plus gemfibrozil in the remaining 11 patients.

Discussion

The bile acid sequestrants cholestyramine and colestipol, nicotinic acid, and lovastatin are the most effective hypocholesterolemic agents available for the therapy of patients with primary hypercholesterolemia; when used as monotherapy, reductions in the plasma concentrations of LDL cholesterol of 20–40% can be achieved in patients with heterozygous FH.24 However, because single drug therapy of adult patients with heterozygous FH often fails to achieve optimal reductions in the plasma concentrations of LDL cholesterol, combination drug therapy has often been used to achieve greater lipid lowering. The bile acid sequestrants, cholestyramine and colestipol, have figured prominently in these drug combinations; before the availability of HMG CoA reductase inhibitors such as lovastatin, the most effective drug combinations have utilized a bile acid sequestrant plus nicotinic acid. Reductions of 32–55% in the plasma concentrations of LDL cholesterol have been reported in adult patients with heterozygous FH treated with this combination.25–29 Combined drug therapy with a bile acid sequestrant and either fenofibrate,30,31 bezafibrate,32 probucol,33,34 or gemfibrozil35 has also been reported to enhance the hypolipidemic effects seen with single drug therapy on bile acid sequestrants.

Several investigators have used HMG CoA reductase inhibitors in combination drug therapy for patients with heterozygous FH (reviewed in Reference 24). Combined drug therapy with lovastatin or mevastatin and a bile acid sequestrant has been reported to reduce LDL cholesterol concentrations by 52–55%,19,36,37 whereas reductions of 49% and 55% have been reported with the combination of lovastatin plus nicotinic acid.38,39 In contrast to the additive effect noted when either bile acid sequestrants or nicotinic acid have been used in combination with lovastatin, no significant additional LDL lowering effect has been observed with combinations involving lovastatin plus neomycin40 or lovastatin plus probucol.38

Gemfibrozil is a well-tolerated drug that has been shown to reduce plasma concentrations of total and LDL cholesterol in patients with primary hypercholesterolemia and to concurrently increase plasma concentrations of HDL cholesterol.15,16 In the Helsinki Heart Study, therapy with gemfibrozil was associated with a significant reduction in cardiovascular morbidity and mortality.16,17 In the present study, we have evaluated the potential therapeutic efficacy of combination drug therapy with lovastatin plus gemfibrozil in 12 patients with heterozygous FH who remained hypercholesterolemic on single drug therapy with lovastatin. The rationale behind evaluating this combination was that not all patients are able to take bile acid sequestrants or nicotinic acid and that in single drug use gemfibrozil is generally well tolerated.

Despite the limitation that a placebo baseline period may be inferior in design to a study involving concurrent random assignment to either placebo or active drug, our results confirm the hypocholesterolemic effects of lovastatin in patients with heterozygous FH.24 The addition of gemfibrozil as a second drug, however, results in a small and variable effect on plasma lipids and lipoproteins (mean concentrations of LDL cholesterol were reduced by 6.3%, a change that was not statistically significant). The response among individual patients was heterogeneous, and two patients showed decreases of more than 35 mg/dl in LDL cholesterol on addition of gemfibrozil to monotherapy with lovastatin. This heterogeneity in response is similar to that previously noted with the combinations of lovastatin plus either bile acid sequestrants, nicotinic acid, or probucol.24

The development of a myopathy has been reported in patients treated with lovastatin, but in patients on monotherapy with this drug, the incidence is low and has been estimated at less than 0.2%.41 In contrast, the risk of this side effect has been shown to be much higher in patients on concurrent therapy with cyclosporine42,43 (30% incidence), nicotinic acid,41,42 or gemfibrozil41,43 (5% incidence). In the present study, one patient developed an asymptomatic rise in creatine kinase on monotherapy with lovastatin but a marked and symptomatic increase on combination drug therapy with lovastatin plus gemfibrozil. Although no clinical or biochemical signs of myopathy occurred in the other 11 patients, our results support the view41,43 that combined drug therapy with lovastatin plus gemfibrozil may be associated with an increased risk of myopathy; if patients are to be treated with this combination, it should be used with caution and with appropriate warnings to the patient concerning symptoms of muscle tenderness.

Although combined drug therapy with lovastatin plus gemfibrozil may be useful in the therapy of patients with familial combined hyperlipidemia,18 our results do not support the use of this drug combination in the therapy of patients with hetero-
zygous FH who remain hypercholesterolemic on monotherapy with lovastatin.

Acknowledgments

We are grateful to Dr. J.A. Tobert (Merck, Sharp & Dohme, Rahway, New Jersey) for supplies of lovastatin, to the nursing staff of the Clinical Research Center for assistance, to Dr. G.J. Sexton for help with the statistical analysis of the data, and to Marcia Hindman for careful preparation of this manuscript. We are also indebted to the patients involved in this study for their interest and cooperation.

References

37. Grundy SM, Vega GL, Bilheimer DW: Influence of combined therapy with mevinolin and interruption of bile acid reabsorption on low density lipoproteins in heterozygous

Ilungworth and Bacon

Lovastatin Plus Gemfibrozil in Hypercholesterolemia
38. Lees AM, Stein SW, Lees RS: Therapy of hypercholesterolemia with mevinolin and other lipid lowering drugs (abstract). Arteriosclerosis 1986;6:544A

KEY WORDS • hypolipidemic agents • low density lipoproteins • high density lipoproteins • lovastatin • gemfibrozil • familial hypercholesterolemia
Influence of lovastatin plus gemfibrozil on plasma lipids and lipoproteins in patients with heterozygous familial hypercholesterolemia.

D R Illingworth and S Bacon

_Circulation_. 1989;79:590-596
doi: 10.1161/01.CIR.79.3.590

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/79/3/590

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/