Efficacy and Safety of a Novel Cholesteryl Ester Transfer Protein Inhibitor, JTT-705, in Humans
A Randomized Phase II Dose-Response Study

Greetje J. de Grooth, MD; Jan Albert Kuivenhoven, PhD; Anton F.H. Stalenhoef, MD, PhD; Jacqueline de Graaf, MD, PhD; Aeilko H. Zwinderman, PhD; Jan L. Posma, MD, PhD; Arie van Tol, PhD; John J.P. Kastelein, MD, PhD

Background—Cholesteryl ester transfer protein (CETP) mediates the transfer of neutral lipids between lipoproteins. High plasma levels of CETP are correlated with low HDL cholesterol levels, a strong risk factor for coronary artery disease. In earlier studies, JTT-705, a novel CETP inhibitor, was shown to increase plasma HDL cholesterol and to inhibit the progression of atherosclerosis in cholesterol-fed rabbits. This study describes the first results using this CETP inhibitor in humans.

Methods and Results—In a randomized, double-blind, and placebo-controlled trial, we evaluated the efficacy and safety of daily treatment with 300, 600, and 900 mg JTT-705 in 198 healthy subjects with mild hyperlipidemia. Treatment with 900 mg JTT-705 for 4 weeks led to a 37% decrease in CETP activity (P < 0.0001), a 34% increase in HDL cholesterol (P < 0.0001), and a 7% decrease in LDL cholesterol (P = 0.017), whereas levels of triglycerides, phospholipid transfer protein, and lecithin-cholesterol acyltransferase were unaffected. In line with the increase of total HDL, a rise of HDL2, HDL3, and apolipoprotein A-I was also noted. JTT-705 showed no toxicity with regard to physical examination and routine laboratory tests.

Conclusions—We show that the use of the CETP inhibitor JTT-705 in humans is an effective means to raise HDL cholesterol levels with minor gastrointestinal side effects (P = 0.06). Although these results hold promise, further studies are needed to investigate whether the observed increase in HDL cholesterol translates into a concomitant reduction in coronary artery disease risk. (Circulation. 2002;105:2159-2165.)

Key Words: cholesterol ■ lipoproteins ■ atherosclerosis ■ cardiovascular diseases

Therapeutic intervention to raise HDL cholesterol (HDL-C) for protection against coronary artery disease has regained significant interest.1 In this quest for novel drugs, cholesteryl ester transfer protein (CETP) represents an important target because this plasma protein plays a key role in HDL metabolism.2 The latter is highlighted by the discovery that genetic CETP deficiency is the main cause of high HDL-C in Asian populations.3 In principle, by raising HDL-C levels, we aim to prevent coronary artery disease; however, the mechanisms by which this may occur are still under discussion.4 HDL mediates the transport of excess cholesterol from the periphery (including the arterial wall) to the liver. This process of reverse cholesterol transport5 is often invoked to explain the atheroprotective effect of HDL. But HDL also is suggested to ameliorate vascular function and to protect against oxidative damage.6 In human lipoprotein metabolism, CETP mediates the transfer of cholesteryl esters from HDL to apolipoprotein (apo) B–containing particles in exchange for triglycerides. Thus, the use of CETP inhibition as a tool to raise HDL-C likely will not only affect reverse cholesterol transport but also influence other functions that are attributed to both HDL and LDL particles.

Despite the above uncertainties, the inverse association between CETP activity and HDL-C levels suggests that pharmacological inhibition of CETP may be warranted and crucial to improve our understanding of the role of this protein in atherogenesis. Various successful strategies already have been developed to inhibit plasma CETP activity.7–9 CETP antibodies can inhibit CETP activity and increase HDL-C in hamsters.10 Also, antisense oligodeoxynucleotides against CETP mRNA, as well as a vaccine that elicits antibodies that block CETP function, lead to significant increases in HDL-C, accompanied by a marked reduction of aortic cholesterol content in rabbits.11,12
Among others, these insights have led to the development of JTT-705, a compound that inhibits CETP activity by forming a disulphide bond with this protein. In cholesterol-fed rabbits, JTT-705 increased plasma HDL-C, decreased non–HDL-C and, importantly, resulted in a 70% decrease of aortic arch lesions. The drug was further tested in 3 phase I studies: In a single-dose study (100 to 1800 mg per day), the drug was well tolerated and did not result in significant toxicity in healthy white men. A 2-period crossover bioavailability study revealed that JTT-705 induced more pronounced CETP inhibition in the postprandial phase compared with the fasted state. In a 14-day multiple-dosing study, daily administration of 600 and 900 mg JTT-705 led to an increase of HDL-C and a decrease of LDL cholesterol (LDL-C) compared with placebo.

In this extended phase II study, we present the results of the safety and efficacy assessment after 4-week treatment with 300, 600, or 900 mg JTT-705 per day in healthy individuals with mild dyslipidemia.

Methods

Patients

The study cohort consisted of healthy individuals (134 men and 64 women), age 18 to 65 years, with HDL-C levels ≤1.6 mmol/L and triglyceride levels ≤4.5 mmol/L (there were no exclusion criteria for LDL-C). The following exclusion criteria were used: genetic hyperlipidemia; recent onset (within 6 months) of vascular disease (eg, unstable angina, myocardial infarction); women capable of child-bearing without adequate birth control; significant comorbid illnesses, such as malignancy, diabetes mellitus, hypothyroidism, hepatic, or renal disease; alcohol abuse; and use of steroids, thiazide-diuretics, antiepileptics, oral contraceptives containing 30 μg estrogen, and cholesterol-lowering agents. Concomitant medication (including β-blockers) was permitted, but only if the dosage was not changed during the study period. All randomized individuals who received ≥1 daily dose of the study medication were included in the analysis.

Trial Design

The study was designed as a 12-week, multicenter, randomized, double-blind, and placebo-controlled trial, evaluating the efficacy and safety of 300, 600, or 900 mg JTT-705 per day. A run-in period of 4 weeks (visits 1 and 2) was followed by 4 weeks of treatment (visits 3, 4, and 5) and 4 weeks of monitoring (visit 6). Participants who used cholesterol-lowering treatment were taken off this medication at visit 1. Participants meeting all criteria at the baseline visit (visit 2) were allocated to placebo or to 300, 600, or 900 mg JTT-705 per day. Blood samples were drawn after an overnight fast. For CETP activity assays, blood was drawn before drug intake and during and after treatment (weeks 2, 3, 4, 5, and 6). Phospholipid transfer protein (PLTP) activity and lecithin-cholesterol acyltransferase (LCAT) activity were determined in 41 individuals (10 per group) before and after 4 weeks of treatment. The counting of returned tablets and empty packages was used to monitor compliance. The ethics committees of all participating centers approved the trial, and all participants gave informed consent.

Laboratory Analyses

Biochemistry, hematometry, lipids, and lipoprotein analyses were performed at the central laboratory of CRL Europe in Belgium. Total cholesterol and triglycerides were measured by established enzymatic methods (Reagents Boehringer Mannheim and Technicon USA). HDL-C was determined with a heparin MnCl₂ precipitation reagent, and LDL-C was calculated by the Friedewald formula. Serum HDL subfractions were determined by serial ultracentrifugation, and apolipoproteins were measured using an established immunonephelometric method (Reagents Dade Behring). CETP activity, CETP concentrations, PLTP activity, and LCAT activity were measured as described elsewhere. For the CETP measurements, plasma from 3 healthy adults was used as control. For PLTP and LCAT activities, human reference pool plasma was obtained by mixing equal amounts of plasma, isolated at 4°C from 250 healthy blood donors.

Safety Parameters

Safety monitoring included physical examination (including vital signs, weight, and waist circumference); ECG; and routine hematometry, biochemistry (including ASAT, ALAT, and creatinin), and urinalysis.

Statistical Analyses

Differences between intervention groups at baseline were evaluated by the χ² test for categorical variables and by the t test for continuous variables. For each treatment group, the absolute changes from baseline lipids, apolipoproteins, and values for lipoprotein-modifying proteins were reported as mean±SD. Analysis was done by fitting an ANOVA model with separate treatment effects for the 4 groups. Safety analyses included all patients who signed the consent form and entered the run-in period. A χ² test was used for statistical analyses of the gastrointestinal adverse events. Statistical analyses were performed with SAS software (SAS Institute Inc).

Results

Patients

The total study cohort consisted of 198 participants who were randomized to placebo or to 300 mg (low dose), 600 mg (medium dose), or 900 mg (high dose) JTT-705 per day for 4 weeks (Figure 1). The majority of the randomized individuals were men, but each treatment group showed a similar male-to-female ratio (ie, 2:1). At baseline, the 4 groups did not show statistically significant differences with respect to demographic characteristics, lipids, lipoproteins, apolipoproteins, CETP activity, CETP concentration, PLTP, and LCAT activities (Table 1).

Effects of JTT-705

Cholesteryl Ester Transfer Protein

A clear dose-dependent decrease in CETP activity was observed after 1 week of treatment, reaching a maximum
de Grooth et al  Efficacy and Safety of JTT-705 in Humans 2161

Table 2 provides the changes in these parameters after 4 weeks of treatment, and the effects of placebo and of 300, 600, and 900 mg JTT-705 on HDL-C, LDL-C, total cholesterol, and triglycerides over time are illustrated in Figure 3.

In the groups on active drug, we observed a dose-dependent increase in HDL-C, reaching a plateau after the first week. The additional effect of 900 mg JTT-705 over 600 mg on HDL-C was only apparent after 4 weeks of treatment at an increase of 33.9% (see Figure 3, top left). The overall rise in HDL-C was caused by significant increases in both HDL₂ and HDL₃ in all treatment groups (in the low-dose group, this did not reach statistical significance for HDL₂; Table 2). The increase in HDL₃ was dose dependent over the explored dose range, whereas the rise in HDL₁ reached a plateau at 300 mg JTT-705 (Table 2). The effect of JTT-705 on HDL-C was not correlated with baseline HDL-C (P=0.75, Figure 4B). The rise in HDL-C also was accompanied by significant increases in both apoA-I and apoA-II levels in all treatment groups.

We also recorded a decrease of LDL-C levels in all treatment groups, reaching statistical significance in the high-dose group (−7.4%, P=0.012). As shown in Figure 4, the cholesterol-lowering effect of JTT-705 was correlated

---

**Figure 2.** Percentage change of CETP activity, CETP mass, HDL-C, and LDL-C according to the dose of JTT-705 after 4 weeks of treatment.

---

**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=50)</th>
<th>JTT-705, 300 mg (n=48)</th>
<th>JTT-705, 600 mg (n=48)</th>
<th>JTT-705, 900 mg (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>50.2±11.3</td>
<td>49.0±9.9</td>
<td>52.4±9.6</td>
<td>50.8±10.0</td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>15/35</td>
<td>13/35</td>
<td>19/29</td>
<td>17/35</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.0±3.5</td>
<td>26.4±2.9</td>
<td>26.8±3.0</td>
<td>26.3±3.3</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>92.0±11.3</td>
<td>95.0±9.6</td>
<td>95.4±12.1</td>
<td>93.1±11.5</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>132.2±15.7</td>
<td>133.1±12.3</td>
<td>131.8±17.1</td>
<td>134.3±13.5</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>82.3±9.3</td>
<td>81.7±7.4</td>
<td>81.8±9.6</td>
<td>83.5±9.1</td>
</tr>
<tr>
<td><strong>Lipoprotein-modifying proteins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CETP activity, % of control</td>
<td>92.0±23.9</td>
<td>90.0±18.6</td>
<td>89.9±17.7</td>
<td>95.2±19.4</td>
</tr>
<tr>
<td>CETP mass, μg/mL</td>
<td>2.0±0.6</td>
<td>2.1±0.5</td>
<td>2.3±0.6</td>
<td>2.3±0.7</td>
</tr>
<tr>
<td>PLTP activity, % of control (n=41)</td>
<td>126±38</td>
<td>120±38</td>
<td>112±28</td>
<td>127±37</td>
</tr>
<tr>
<td>LCAT activity, % of control (n=41)</td>
<td>110±23</td>
<td>116±17</td>
<td>111±18</td>
<td>119±24</td>
</tr>
</tbody>
</table>

**Values are given as mean±SD.**

BMI indicates body mass index; BP, blood pressure; TC, total cholesterol; and TG, triglyceride.

There were no significant differences between any of the groups.

**Lipids, Lipoproteins, and Apolipoproteins**

There were no significant differences between any of the groups.
positively with baseline LDL-C levels (P=0.03, Figure 4A). ApoB, apoE, total cholesterol, and triglyceride levels were not significantly changed by JTT-705 dosages up to 900 mg per day. The atherogenicity index, represented by total cholesterol/HDL-C ratios, was significantly reduced in all 3 active groups compared with the placebo group.

### Safety and Adverse Effects

Dosages up to 900 mg of JTT-705 were well tolerated and exhibited a clean safety profile. During and after the study, we observed no significant changes in vital signs. Also, there were no changes in body mass index, waist circumference, and blood pressure or signs of hepatocellular injury or renal damage. Eight abnormal hematological parameters were found (low hemoglobin, low red/white blood cell counts, and low reticulocyte counts) in 6 individuals: 3 occurred in the placebo group, 3 in the 300-mg group (during treatment), and 2 in the 900-mg group (before treatment started). In the follow-up period, 5 individuals discontinued intervention: 2 complained of migraine (1 was on placebo), 1 had a mild rash, and 2 developed hypertension.

JTT-705 may have mild gastrointestinal side effects, illustrated by the occurrence of diarrhea (5, 4, 3, and 2 individuals in the 900-, 600-, and 300-mg groups and placebo group, respectively), flatulence (2, 2, 3, and 1 individuals in the 900-, 600-, and 300-mg groups and placebo group, respectively), nausea (3, 2, 2, and 0 in the 900-, 600-, and 300-mg groups and placebo group, respectively), and constipation (1 person in each group). Although not statistically significant, the 900-mg dose was associated with a nonsignificant higher frequency of gastrointestinal complaints (P=0.058) after 4 weeks of treatment, as presented in Table 3. There were no withdrawals for gastrointestinal complaints.

### Discussion

Low plasma HDL-C is an independent risk factor for cardiovascular disease.20 In fact, a 1% increase of plasma HDL-C levels is reported to be associated with a 2% to 3% decrease in cardiovascular morbidity and mortality.21 Nevertheless, no good treatment option exists for patients with low HDL-C at this moment. Diet and moderate exercise are ineffective for significantly raising HDL-C,22 whereas the use of HMG-CoA reductase inhibitors and fibrates only confer a 5% to 15% increase in HDL-C.1,23 Nicotinic acid does increase HDL-C by 30% on a 3- to 4-g daily dose, but this drug has side effects that limit its use.24 Conversely, in this study, a novel CETP inhibitor, JTT-705, was shown to effectively raise HDL-C (up to 34%) and apoA-I (up to 16%) with only mild gastrointestinal side effects (P=0.058), although the dosage needed to achieve this effect was rather high (900 mg/d). It is important to note that inhibition of CETP by JTT-705 was accompanied by unchanged PLTP and LCAT activities, underscoring the specificity of this drug. These phase II data are also consistent with the phase I data inasmuch as there were no serious adverse events or clinically relevant changes in safety parameters. Some mild gastrointestinal effects were observed, but no withdrawals occurred for that reason.

The rise in HDL-C levels was caused by significant increases in both HDL$_2$ and HDL$_3$ subfractions, but at higher dosages, HDL$_2$ seemed to reach a plateau, whereas HDL$_3$ still increased. Although CETP inhibition was anticipated to result in a rise in large cholesterol-rich HDL$_2$, the observed rise in HDL$_3$ is

### Table 2: Absolute Changes in CETP Activity, CETP Mass, PLTP Activity, LCAT Activity, Lipids, and Lipoproteins According to the Dose of JTT-705 After 4 Weeks of Treatment

<table>
<thead>
<tr>
<th>Lipoprotein-modifying proteins</th>
<th>Placebo (n=50)</th>
<th>300 mg (n=48)</th>
<th>600 mg (n=47)</th>
<th>900 mg (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CETP activity, % of control</td>
<td>0.9±13.2</td>
<td>−15.4±11.9§</td>
<td>−29.6±19.5§</td>
<td>−37.2±17.6§</td>
</tr>
<tr>
<td>CETP mass, μg/mL</td>
<td>0.0±0.3</td>
<td>0.9±0.6§</td>
<td>1.3±0.5§</td>
<td>1.6±0.8§</td>
</tr>
<tr>
<td>PLTP activity, % of control</td>
<td>9.3±24.5</td>
<td>−4.5±42.5</td>
<td>−6.2±29.5</td>
<td>28.8±31.6</td>
</tr>
<tr>
<td>LCAT, % of control</td>
<td>−0.6±10.0</td>
<td>−0.6±11.0</td>
<td>−4.2±10.3</td>
<td>−2.1±12.2</td>
</tr>
<tr>
<td>Lipids and lipoproteins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>0.0±0.5</td>
<td>−0.1±0.5</td>
<td>0.0±0.6</td>
<td>0.0±0.6</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>0.04±0.15</td>
<td>0.18±0.15†</td>
<td>0.32±0.22§</td>
<td>0.40±0.29§</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>−0.1±0.5</td>
<td>−0.2±0.5</td>
<td>−0.2±0.6</td>
<td>−0.3±0.6†</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>0.0±0.4</td>
<td>0.0±0.6</td>
<td>−0.1±0.5</td>
<td>−0.2±0.6</td>
</tr>
<tr>
<td>TC/HDL ratio</td>
<td>−0.2±0.6</td>
<td>−0.7±0.8‡</td>
<td>−0.9±0.8§</td>
<td>−1.2±0.7§</td>
</tr>
<tr>
<td>HDL$_2$, mmol/L</td>
<td>0.01±0.11</td>
<td>0.09±0.13</td>
<td>0.21±0.22§</td>
<td>0.27±0.28§</td>
</tr>
<tr>
<td>HDL$_3$, mmol/L</td>
<td>0.03±0.13</td>
<td>0.09±0.09†</td>
<td>0.10±0.11§</td>
<td>0.13±0.11§</td>
</tr>
<tr>
<td>ApoA-I, mg/dL</td>
<td>3.2±18.6</td>
<td>11.1±13.2*</td>
<td>19.2±17.4§</td>
<td>21.4±21.8§</td>
</tr>
<tr>
<td>ApoA-II, mg/dL</td>
<td>1.4±3.9</td>
<td>3.5±3.0†</td>
<td>4.5±2.7§</td>
<td>3.8±3.9§</td>
</tr>
<tr>
<td>ApoB, mg/dL</td>
<td>−0.8±14.4</td>
<td>−7.7±16.7</td>
<td>−2.7±14.7</td>
<td>−6.8±18.7</td>
</tr>
<tr>
<td>ApoE, mg/dL</td>
<td>0.1±0.7</td>
<td>0.0±0.7</td>
<td>0.0±1.1</td>
<td>−0.2±1.0</td>
</tr>
</tbody>
</table>

Values are given as mean±SD.

TC indicates total cholesterol, and TG, triglyceride.

*P<0.05; †P<0.01; ‡P<0.001; and §P<0.0001 (each dose group vs placebo).
interesting. The latter may, in part, be explained by processing of HDL₂ through PLTP and hepatic lipase activities, whereby smaller, less cholesterol-rich HDL particles are generated.

The literature on these HDL subfractions is unclear with regard to their biological effects, but most of the evidence indicates that HDL₂ represents the antiatherogenic fraction.²⁵

Our data indicate therefore that JTT-705 has a favorable effect on HDL subfraction composition.

It is of interest to compare human genetic CETP deficiency with pharmacological inhibition of CETP. Absence of plasma CETP in homozygous CETP deficiency has been shown to result in very high HDL-C (2.5 to 3.5 times normal levels) and significant reductions in LDL-C concentrations.³ However, heterozygosity for CETP gene mutations resulting in 35% to 39% CETP concentration reductions, similar to those seen in the highest dose group of the present study, are associated with variable increases in HDL-C (10% to 32%) and LDL-C reductions (1% to 12%).³,²⁶ Most of the variation may be explained through the effects of mild missense mutations such as D442G and severe non-sense mutations (Int14G→A). This is illustrated by the fact that heterozygosity for the latter mutation has largely the same effects on lipids and lipoproteins as observed for the highest dose group of the present analysis.

An effect not seen in genetic CETP deficiency is the profound dose-dependent increase in plasma CETP concen-
The consequences of these increased HDL-C levels are unknown. Studies in rabbits, which develop high CETP plasma levels on a high-cholesterol diet, have shown that CETP inhibition by JTT-705 can protect against atherosclerosis. Studies in mice, which are CETP deficient by nature, however, showed that expression of human CETP can be either atherogenic or antiatherogenic. To date, the precise role of CETP in human atherogenesis and how its activity relates to coronary artery disease risk is still unclear, but JTT-705 is an effective tool to study these relations. End point or surrogate coronary artery disease marker trials have to clarify whether JTT-705 can reduce or prevent cardiovascular disease.

**Acknowledgments**

This CETP inhibitor trial was sponsored by Japan Tobacco Inc, Tokyo, Japan. Orion Clinical Services Ltd, Slough, United Kingdom, managed the project. John J.P. Kastelein is an Established Investigator of the Dutch Heart Foundation (2000D039). Jan Albert Kuivenhoven is a postdoctoral fellow of the Dutch Heart Foundation (D98.001). We thank the following colleagues for recruitment of the participants: D.C.G. Basart, Westfries Hospital, Hoorn; L.H.J. van Kempen, Hospital Rijnstate, Arnhem; D.E. Grobbee, University Medical Center, Utrecht; J.J.C. Jonker, Andro Medical Research BV, Rotterdam; Dr Bulk, Andromed Noord, Groningen; A.J.M. Oude Ophuis, Canisius Hospital, Nijmegen; and I. Stoel, Albert Schweitzer Hospital, Dordrecht, the Netherlands.

**References**


**Figure 4.** A, LDL change according to LDL-C quartiles at baseline in the 900-mg group after 4 weeks treatment. B, HDL change according to HDL-C quartiles at baseline in the 900-mg group after 4 week of treatment.

**TABLE 3. Frequency of Digestive Adverse Events Between Placebo and 3 Dosages of JTT-705**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients With Digestive Complaints (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=50)</td>
<td>6 (12.0)</td>
<td></td>
</tr>
<tr>
<td>JTT-705 300 mg (n=48)</td>
<td>10 (20.8)</td>
<td>0.24</td>
</tr>
<tr>
<td>JTT-705 600 mg (n=48)</td>
<td>12 (25.0)</td>
<td>0.097</td>
</tr>
<tr>
<td>JTT-705 900 mg (n=52)</td>
<td>14 (26.9)</td>
<td>0.058</td>
</tr>
</tbody>
</table>

Values are given as number of patients (%).


Efficacy and Safety of a Novel Cholesteryl Ester Transfer Protein Inhibitor, JTT-705, in Humans: A Randomized Phase II Dose-Response Study

Greetje J. de Grooth, Jan Albert Kuivenhoven, Anton F.H. Stalenhoef, Jacqueline de Graaf, Aeilko H. Zwinderman, Jan L. Posma, Arie van Tol and John J.P. Kastelein

Circulation. 2002;105:2159-2165; originally published online April 15, 2002;
doi: 10.1161/01.CIR.0000015857.31889.7B

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 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/105/18/2159

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/