Effect of Atorvastatin on Risk of Recurrent Cardiovascular Events After an Acute Coronary Syndrome Associated With High Soluble CD40 Ligand in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study

Scott Kinlay, MBBS, PhD; Gregory G. Schwartz, MD, PhD; Anders G. Olsson, MD, PhD; Nader Rifai, MD; William J. Sasiela, PhD; Michael Szarek, SM; Peter Ganz, MD; Peter Libby, MD; for the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators

Background—Patients with acute coronary syndromes have elevated plasma levels of the proinflammatory, prothrombotic cytokine CD40 ligand (sCD40L). Statins inhibit CD40L signaling in vitro, but there are no prospective studies of statins and sCD40L in acute coronary syndromes.

Methods and Results—We measured sCD40L in subjects with an acute coronary syndrome enrolled in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study. Subjects were randomized in this double-blind trial to atorvastatin 80 mg/d or placebo for 16 weeks. Plasma CD40L was measured from 2908 (94%) of 3086 subjects at baseline and 2352 (76%) at 16 weeks. Odds ratios (ORs) and 95% CIs from logistic regression models assessed the risk of recurrent cardiovascular events over 16 weeks (death, nonfatal myocardial infarction, cardiac arrest, and worsening angina requiring rehospitalization) in the placebo group from baseline sCD40L and the effect of atorvastatin on the risk associated with CD40L in all subjects. The effects of atorvastatin on plasma concentrations of CD40L were assessed by Wilcoxon tests. There was a threshold effect, with only high sCD40L (≥90th centile) being a risk factor for a recurrent cardiovascular event (OR 1.86, 95% CI 1.25 to 2.77). This risk was abolished by atorvastatin (OR 1.09, 95% CI 0.69 to 1.76), which reduced the risk by 48%. Atorvastatin had only a modest effect on sCD40L (P=0.08).

Conclusions—In patients with acute coronary syndromes, atorvastatin abrogated the risk of recurrent cardiovascular events associated with high sCD40L. Early statin therapy after acute coronary syndromes counters the risk associated with elevated sCD40L. (Circulation. 2004;110:386-391.)

Key Words: inflammation • thrombosis • statins • risk • trials

Inflammation promotes rupture of atherosclerotic plaques and acute coronary syndromes.1 Soluble inflammatory mediators produced in acute coronary syndromes provide a window on pathophysiology and the mechanisms of preventive therapies. The proinflammatory mediator CD40 ligand (CD40L) has particular interest because it plays a proximal role in a cascade of proatherothrombotic functions thought to be important in the pathogenesis of acute coronary syndromes.2-4 These include augmented production of metalloproteinases, prothrombotic tissue factor, proinflammatory chemokines, cytokines, and cellular adhesion molecules5-10 and impaired regeneration of endothelial cells that may be particularly important after acute coronary syndromes.11 A variety of cells associated with disrupted atheroma can express CD40L when activated, among them endothelial cells, smooth muscle cells, macrophages, T lymphocytes, and platelets.2-4 CD40L can be cleaved from cell membranes to form a soluble fragment termed sCD40L, which retains biological activity12,13 and can be measured in plasma. Activated platelets release abundant sCD40L.5,14 Plasma levels of sCD40L correlate with LDL levels and platelet activation,15 increase after arterial injury from percutaneous coronary interventions,12 and are higher in patients with unstable compared with stable coronary syndromes.12,16

In patients with acute coronary syndromes treated with percutaneous coronary intervention, CD40L concentrations
are related to the future risk of recurrent cardiovascular events, and the Ib/IIa receptor antagonist abciximab ameliorates this risk.17 However, the relationship of CD40L concentrations to the natural history of acute coronary syndromes (ie, in those not treated by early revascularization) has not been studied in a prospective cohort. HMG-CoA reductase inhibitors (statins) reduce cardiovascular risk in broad patient categories and could affect CD40L and its relationship to recurrent cardiovascular events. Recent studies show that oxidized LDL increases activation of the CD40/CD40L dyad and that statins inhibit this effect in vitro in cells involved in atherosclerosis.15,18 Two studies in patients with stable coronary syndromes also indicate that statins may reduce sCD40L.18,19 However, the impact of statins on sCD40L in patients with acute coronary syndromes has not been studied prospectively in a large randomized, controlled trial.

In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study, high-dose atorvastatin (80 mg/d) started within 24 to 96 hours of admission for unstable angina or non–Q-wave myocardial infarction decreased recurrent ischemic events over 16 weeks of treatment compared with placebo.20 The present analysis examined the relationship between sCD40L and the risk of recurrent cardiovascular events soon after an acute coronary syndrome in the MIRACL Study and tested whether the clinical benefit from statin therapy was related to a reduction in proinflammatory and prothrombotic stimuli as indicated by sCD40L.

Methods

Study Population

The design and main results of the MIRACL Study have been described.20 MIRACL was a multicenter study conducted in 122 centers in 19 countries in patients admitted to the hospital with a diagnosis of unstable angina or non–Q-wave acute myocardial infarction. These diagnoses required chest discomfort that lasted at least 15 minutes within the 24 hours before hospitalization and that represented a change in the usual pattern of angina. The diagnosis of unstable angina required new or dynamic ST-wave or T-wave changes in at least 2 contiguous standard ECG leads, a new wall-motion abnormality by echocardiography, a new and reversible myocardial perfusion defect by radionuclide scintigraphy, or elevation of cardiac troponin to a level not exceeding 2 times the upper limit of normal. The diagnosis of non–Q-wave myocardial infarction required elevation of serum creatine kinase or its MB fraction or of troponin to a level exceeding 2 times the upper limit of normal.20

Exclusion criteria included serum cholesterol >7.0 mmol/L (270 mg/dL), anticipated coronary revascularization, Q-wave myocardial infarction within the previous month, CABG within 3 months, percutaneous coronary intervention within 6 months of enrollment, or treatment with other lipid-lowering drugs. All patients provided informed consent, and the protocol was approved by each local institutional review board.

Study Design

Between 24 and 96 hours after hospital admission, patients were randomly assigned to double-blind treatment with atorvastatin 80 mg/d or matching placebo for 16 weeks. Total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were measured at randomization and at 16 weeks. The primary efficacy measure (cardiac event) was the time to first occurrence of death, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, or worsening angina with new objective evidence of ischemia and that required emergency hospitalization. A committee of 6 cardiologists blinded to treatment assignment adjudicated all clinical end points.20

Measurement of sCD40L

For this report, patients had blood collected into a tube with EDTA anticoagulant at baseline and at 16 weeks as previously recommended.21 The tubes were centrifuged on site, and the plasma was separated and shipped to a central laboratory, where it was stored at −70°C. The paired baseline and 16-week samples were shipped to the inflammatory markers core laboratory and measured in batches.22 sCD40L was measured with an ELISA (R&D Systems). There was excellent reproducibility of the assay over the study period, with coefficients of variation of 7.9% at 636 pg/mL and 4.9% at 1929 pg/mL. Troponin I was measured at baseline with the ACS:180 Chemiluminescence cTnl Immunoassay (Bayer Diagnostics).

Statistical Analysis

In this report, the relationship of baseline sCD40L to outcome at 16 weeks was assessed in 1463 (93%) of the 1548 subjects in the MIRACL Study who were randomly allocated to placebo and had baseline sCD40L measured. As expected, the distribution of sCD40L was highly positively skewed (Figure 1). On the basis of a nested case-control study of apparently healthy middle-aged women that suggested only high sCD40L was associated with increased cardiovascular risk,23 we used logistic regression to examine the relationship of median baseline sCD40L and high concentrations (75th to 90th centile, or greater than the 90th centile, compared with less than 75th centile) to prognosis with and without adjustment for baseline LDL and log-troponin. We evaluated whether statin therapy modified the risk of recurrent events using interaction effects in separate models that included 2908 (94%) of all subjects in the MIRACL trial allocated to statin or placebo. The effect of statin therapy on sCD40L over 16 weeks was assessed in the 2352 subjects (76%) who had baseline and 16-week samples available for sCD40L measurement. Medians and interquartile ranges (25% to 75%) were used to describe the baseline and 16-week data. To improve the distributional assumptions of the statistical models, we transformed the sCD40L data to log (sCD40L + 1), and a Wilcoxon test was used to compare the change in sCD40L between the treatment groups. We also measured the Pearson correlation coefficient between baseline log(CD40L + 1) and LDL cholesterol and high-sensitivity C-reactive protein (hsCRP).22 Statistical significance was defined as P<0.05. Because the major source of sCD40L may differ between patients with unstable angina (activated platelets and vascular inflammation) and those with non–Q-wave myocardial infarction (activated platelets, vascular and myocardial inflammation), we expected differences in the relationship to risk and the response to statins in these 2 groups of patients. Therefore, these analyses were repeated for these 2 subgroups.

Results

Risk of a Recurrent Cardiovascular Event

The baseline characteristics of all 2908 subjects in the MIRACL Study with sCD40L measured are shown in Table 1 and Figure 1. The frequency distribution of sCD40L is right-skewed, with a large proportion of the distribution lying above 600 pg/mL. The 75th and 90th centiles of sCD40L were 699 and 791 pg/mL, respectively. The distribution of sCD40L differed between the 2 subgroups.
Of the 1463 subjects allocated to placebo with baseline sCD40L measured, 256 (17%) reached a primary cardiovascular end point over the 16-week follow-up. In the placebo group, subjects with sCD40L above the median (50th centile, 205 pg/mL) were not at increased risk of a recurrent event compared with subjects below the median sCD40L (OR 1.13, 95% CI 0.86 to 1.48, \( P = 0.31 \)). Compared with subjects with sCD40L below the 75th centile (<955 pg/mL), those with sCD40L from the 75th to 90th centiles were not at increased risk of a recurrent event (Table 2). The risk was elevated only for subjects with sCD40L above the 90th centile (>4369 pg/mL, OR 1.86, 95% CI 1.25 to 2.77, \( P < 0.01 \)), which supports a threshold effect of sCD40L and risk of recurrent cardiovascular events (Table 2).

Similar results occurred in the subgroups of unstable angina and non–Q-wave myocardial infarction. Only high sCD40L (>90th centile) was associated with an increased risk of a recurrent event (Table 2). The addition of plasma troponin to the models actually strengthened the relationships of high sCD40L to cardiovascular risk (Table 2). Thus, the increased risk associated with high sCD40L was independent of the degree of myocardial necrosis. There were no significant correlations between baseline sCD40L and LDL cholesterol (\( r = 0.01 \)) or baseline sCD40L and hsCRP (\( r = 0.01 \)).

### Modification of High Risk Associated With High CD40L With Statin Therapy

Statin therapy abrogated the increased incidence of recurrent cardiovascular events with high sCD40L (>90th centile) in all subjects (Figure 2) and had a consistent effect in both major subgroups (unstable angina and non–Q-wave myocardial infarction; Figure 3). Compared with placebo, the relative risk of an event with high sCD40L (above the 90th centile) was 48% lower (OR 0.52, 95% CI 0.29 to 0.92) with atorvastatin therapy in all subjects, 44% lower (OR 0.56, 95% CI 0.26 to 1.18) in those with non–Q-wave myocardial infarction, and 55% lower (OR 0.45, 95% CI 0.24 to 0.86) in those with unstable angina.

### Table 1. Baseline Characteristics of the 2908 Patients Who Did and Did Not Develop a Recurrent Cardiovascular Event Over the 16 Weeks of the Trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Recurrent Event (n=470)</th>
<th>Event Free (n=2438)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>69 (11)</td>
<td>64 (12)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>313 (67)</td>
<td>1579 (65)</td>
</tr>
<tr>
<td>Presenting syndrome, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>217 (46)</td>
<td>1119 (46)</td>
</tr>
<tr>
<td>Non–Q-wave myocardial infarction</td>
<td>253 (54)</td>
<td>1319 (54)</td>
</tr>
<tr>
<td>Past myocardial infarction, n (%)</td>
<td>165 (35)</td>
<td>550 (23)</td>
</tr>
<tr>
<td>Prior coronary revascularization, n (%)</td>
<td>62 (13)</td>
<td>232 (10)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>164 (35)</td>
<td>866 (36)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>255 (54)</td>
<td>1315 (54)</td>
</tr>
<tr>
<td>Diabetes mellitus type II, n (%)</td>
<td>131 (28)</td>
<td>528 (22)</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD), mg/dL</td>
<td>203 (42)</td>
<td>206 (37)</td>
</tr>
<tr>
<td>LDL cholesterol, mean (SD), mg/dL</td>
<td>123 (36)</td>
<td>124 (33)</td>
</tr>
<tr>
<td>HDL cholesterol, mean (SD), mg/dL</td>
<td>45 (12)</td>
<td>47 (12)</td>
</tr>
<tr>
<td>Triglycerides, mean (SD), mg/dL</td>
<td>180 (79)</td>
<td>183 (94)</td>
</tr>
<tr>
<td>sCD40L, median, pg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50th centile</td>
<td>222</td>
<td>203</td>
</tr>
<tr>
<td>75th centile</td>
<td>1370</td>
<td>904</td>
</tr>
<tr>
<td>90th centile</td>
<td>7679</td>
<td>3850</td>
</tr>
<tr>
<td>Troponin I, median (25%, 75%), ng/mL</td>
<td>0.85 (0.11, 3.79)</td>
<td>0.66 (0.04, 3.60)</td>
</tr>
</tbody>
</table>

1. Of the 1463 subjects allocated to placebo with baseline sCD40L measured, 256 (17%) reached a primary cardiovascular end point over the 16-week follow-up. In the placebo group, subjects with sCD40L above the median (50th centile, 205 pg/mL) were not at increased risk of a recurrent event compared with subjects below the median sCD40L (OR 1.13, 95% CI 0.86 to 1.48, \( P = 0.31 \)). Compared with subjects with sCD40L below the 75th centile (<955 pg/mL), those with sCD40L from the 75th to 90th centiles were not at increased risk of a recurrent event (Table 2). The risk was elevated only for subjects with sCD40L above the 90th centile (>4369 pg/mL, OR 1.86, 95% CI 1.25 to 2.77, \( P < 0.01 \)), which supports a threshold effect of sCD40L and risk of recurrent cardiovascular events (Table 2).

### Table 2. Risk of a Recurrent Cardiovascular Event for Different Cutpoints of Baseline sCD40L in 1463 Placebo-Treated Subjects and in the Subgroups of Unstable Angina and Non–Q-wave Myocardial Infarction at Baseline

<table>
<thead>
<tr>
<th>Baseline Event</th>
<th>≤75th Centile (≤955 pg/mL)</th>
<th>75th to &lt;90th Centile (&gt;955–4369 pg/mL)</th>
<th>&gt; 90th Centile (&gt;4369 pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>181/1104 (16%)</td>
<td>36/213 (17%)</td>
<td>39/146 (27%)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00</td>
<td>1.04 (0.70–1.54)</td>
<td>1.86 (1.25–2.77)</td>
</tr>
<tr>
<td>P value</td>
<td>...</td>
<td>0.86</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>P value adjusted for baseline troponin</td>
<td>...</td>
<td>0.72</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Non–Q-wave myocardial infarction</td>
<td>101/601 (17%)</td>
<td>18/118 (15%)</td>
<td>22/87 (25%)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00</td>
<td>0.89 (0.52–1.54)</td>
<td>1.68 (0.99–2.84)</td>
</tr>
<tr>
<td>P value</td>
<td>...</td>
<td>0.68</td>
<td>0.06</td>
</tr>
<tr>
<td>P value adjusted for baseline troponin</td>
<td>...</td>
<td>0.72</td>
<td>0.04</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>80/503 (16%)</td>
<td>18/95 (19%)</td>
<td>17/59 (29%)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00</td>
<td>1.24 (0.70–2.18)</td>
<td>2.14 (1.16–3.95)</td>
</tr>
<tr>
<td>P value</td>
<td>...</td>
<td>0.46</td>
<td>0.01</td>
</tr>
<tr>
<td>P value adjusted for baseline troponin</td>
<td>...</td>
<td>0.40</td>
<td>0.01</td>
</tr>
</tbody>
</table>

ORs and \( P \) values from models including randomized treatment assignment and interaction terms. ORs compared with ≤75th centile.
Effect of High-Dose Atorvastatin on sCD40L Concentrations

The baseline characteristics of the 2352 subjects with sCD40L measured at baseline and week 16 did not differ significantly between the treatment groups or with those who did not have week 16 blood measurements (Table 3). Overall, sCD40L tended to increase over the 16-week study (Table 4). The changes in sCD40L in both groups were modest. There was no significant change in the median values of both groups, but the interquartile range suggested a small shift in the distributions that favored an increase in sCD40L in the placebo group that was not apparent with atorvastatin (sCD40L change with atorvastatin versus placebo, P = 0.08). There was no difference in the number of subjects changing from high sCD40L to ≤90th centile of sCD40L (placebo 13/120 [11%], atorvastatin 14/116 [12%]) or the number of subjects changing from ≥90th centile sCD40L to high sCD40L (placebo 20/1072 [2%], atorvastatin 14/1044 [1%]). Analysis by the prespecified subgroups showed similar relationships between atorvastatin therapy and sCD40L (Table 4).

Discussion

Increasing evidence implicates the CD40/CD40L dyad as a central signaling mechanism that stimulates an array of proatherothrombotic processes. Moreover, CD40 ligation leads to activation of inflammatory cells, endothelium, and platelets—cells integral in the development of plaque disruption, acute coronary syndromes, and recurrent cardiovascular events. In the present study of patients with acute coronary syndromes, high sCD40L was related to the risk of recurrent cardiovascular events. The excess risk associated with sCD40L was eliminated by atorvastatin. These data provide further evidence that proinflammatory and prothrombotic pathways contribute to recurrent cardiovascular events and that statins counteract these mechanisms.

High sCD40L, Not Average sCD40L, Is Associated With Elevated Risk

Although patients with unstable coronary syndromes have elevated sCD40L, the present study showed that particularly high levels of sCD40L are associated with an increased risk of recurrent events. The highly skewed distribution of sCD40L is not unusual, and a relationship of high sCD40L, but not average sCD40L with cardiovascular events was also evident in a case-control study of apparently healthy middle-aged women. In the present study, the relationship was independent of the level of plasma troponin, a known predictor of the risk of recurrent events. A recent nested case-control analysis of 390 patients in the OPUS-TIMI16 trial also suggested that the risk of recurrent events associated with high sCD40L was independent of troponin. This suggests that high sCD40L that is associated with increased risk is derived from vascular inflammation or thrombosis rather than sites of downstream myocardial necrosis.

Activated platelets release sCD40L. High levels of sCD40L may reflect ongoing platelet activation at active culprit lesions that may lead to recurrent events. In fact, a recent study of patients undergoing percutaneous coronary intervention for the management of acute coronary syn-
dromes suggested that platelet glycoprotein IIb/IIIa receptor antagonists reduce the risk associated with elevated sCD40L.17 However, the use of glycoprotein IIb/IIIa receptor antagonists or the use of percutaneous coronary intervention did not appreciably influence the results of the present study, because only 1% and 9% of patients received these forms of treatment, respectively, in the MIRACL Study.

Effect of Statin Therapy

Risk factor modification, and statins in particular, can reduce inflammation and diminish platelet activation, the 2 principal sources of sCD40L. Nonetheless, in this acute coronary syndrome setting, atorvastatin had little effect on plasma levels of sCD40L over 16 weeks. In a study of patients with stable coronary syndromes or strong family history of cardiovascular disease, both conventional and more aggressive statin therapy decreased sCD40L over 2 years, with greater lowering at 2 years than at 1 year.19 In addition to the fact that different patients were studied (those with stable coronary syndromes), in that study, sCD40L was measured from serum after the blood samples were allowed to clot.19 sCD40L concentrations tend to be higher in serum (reflecting greater release from platelets activated by clot formation) than in EDTA plasma such as was used in the present study.21 The different results of the studies may reflect the higher inflammatory state of patients with acute coronary syndromes in the present study, the different assays, or a follow-up interval in the present study that was insufficient to observe a significant effect of statins on sCD40L concentrations.

Although atorvastatin did not affect sCD40L in the present study, it eliminated the risk of a recurrent event associated with high sCD40L. This apparent paradox may be explained if atorvastatin, by lipid or nonlipid mechanisms, targets downstream effects related to high sCD40L or aspects of inflammation or thrombosis marked by elevated sCD40L. The CD40/CD40L dyad can activate multiple pathways important in atherosclerosis progression and destabilization. These include the expression of proinflammatory cellular adhesion molecules, the platelet IIb/IIIa receptor, and receptors on vascular cells that activate transcription factors, cytokines, chemokines, metalloproteinases, and the procoagulant tissue factor.6,14 Statins and LDL lowering have favorable effects on many of these functions that are downstream of CD40 ligation,27 which may explain how atorvastatin counteracted the risk associated with high CD40L without appreciably altering its plasma concentration.

In conclusion, patients presenting with acute coronary syndromes with highly elevated sCD40L had a higher risk of recurrent coronary events. In this setting, intensive statin therapy reduced the risk of recurrent events associated with high sCD40L levels without affecting plasma concentrations of this cytokine. The present study points to anti-inflammatory and antithrombotic actions of lipid lowering with statins as a mechanism of benefit after acute coronary syndromes.

Disclosure
Dr Sasiela and M. Szarek are employees of Pfizer, Inc. Drs Kinlay, Schwartz, Olsson, Ganz, and Libby have served as consultants to all of the manufacturers of lipid-lowering pharmaceuticals.

Acknowledgments
This study was supported by an unrestricted research grant from Pfizer, Inc; program project grant NHLBI HL-48743; and a grant from the Foundation Leducq.

References


Effect of Atorvastatin on Risk of Recurrent Cardiovascular Events After an Acute Coronary Syndrome Associated With High Soluble CD40 Ligand in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study
Scott Kinlay, Gregory G. Schwartz, Anders G. Olsson, Nader Rifai, William J. Sasiela, Michael Szarek, Peter Ganz and Peter Libby
for the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators

_Circulation_. 2004;110:386-391; originally published online July 19, 2004;
doi: 10.1161/01.CIR.0000136588.62638.5E
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 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/110/4/386

**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/