Platelet/Endothelial Biomarkers in Depressed Patients Treated With the Selective Serotonin Reuptake Inhibitor Sertraline After Acute Coronary Events

The Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) Platelet Substudy

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Background—Depression after acute coronary syndromes (ACSs) has been identified as an independent risk factor for subsequent cardiac death. Enhanced platelet activation has been hypothesized to represent 1 of the mechanisms underlying this association. Selective serotonin reuptake inhibitors (SSRIs) are known to inhibit platelet activity. Whether treatment of depressed post-ACS patients with SSRIs alters platelet function was not known. Accordingly, we serially assessed the release of established platelet/endothelial biomarkers in patients treated with sertraline vs placebo in the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART).

Methods and Results—Plasma samples (baseline, week 6, and week 16) were collected from patients randomized to sertraline (n=28) or placebo (n=36). Anticoagulants, aspirin, and ADP-receptor inhibitors were permitted in this study. Platelet factor 4, \( \beta \)-thromboglobulin (\( \beta \)TG), platelet/endothelial cell adhesion molecule-1, P-selectin, thromboxane B\( _2 \), 6-ketoprostaglandin \( \mathrm{F}_{1\alpha} \), vascular cell adhesion molecule-1, and E-selectin were measured by ELISA. Treatment with sertraline was associated with substantially less release of platelet/endothelial biomarkers than was treatment with placebo. These differences attained statistical significance for \( \beta \)TG (\( P=0.03 \)) at weeks 6 and 16 and for P-selectin (\( P=0.04 \)) at week 16. Repeated-measures ANOVA revealed a significant advantage for sertraline vs placebo for diminishing E-selectin and \( \beta \)TG concentrations across the entire treatment period.

Conclusions—Treatment with sertraline in depressed post-ACS patients is associated with reductions in platelet/endothelial activation despite coadministration of widespread antplatelet regimens including aspirin and clopidogrel. The antplatelet and endothelium-protective properties of SSRIs might represent an attractive additional advantage in patients with depression and comorbid coronary artery and/or cerebrovascular disease. (Circulation. 2003;108:939-944.)

Key Words: depression ■ coronary disease ■ platelets ■ antidepressants ■ trials

During the last decade, a number of studies, largely epidemiologic, have provided evidence that depression is associated with an increased risk of cardiovascular morbidity and mortality.\(^1\)\(^2\) Indeed, individuals who suffer from depression are at an increased risk for myocardial infarction and cardiovascular death. Moreover, patients hospitalized with either unstable angina\(^3\) or myocardial infarction\(^4\) and who subsequently develop depression are at an increased risk of subsequent cardiac death. Multiple biologic substrates contribute to an increased risk. One factor that likely under-
lies this increased vulnerability of heart disease is increased platelet activation.3 The question that remains is whether treatment of depression reduces the risk for cardiovascular events.

The older tricyclic antidepressants are well known to possess serious cardiovascular side effects and are contraindicated in many patients with an acute coronary syndrome (ACS).6 The selective serotonin reuptake inhibitors (SSRIs) are well-established antidepressant drugs that have shown little evidence of cardiac toxicity, even in patients with stable heart disease.7–9 However, no data on the safety or efficacy of SSRIs in either post–acute myocardial infarction (AMI) or unstable angina patients were available until the recent Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) of 364 depressed patients with ACSs.10 The results of SADHART documented no evidence of harm with sertraline treatment. Moreover, a trend toward a reduction in morbidity and mortality among the sertraline-treated patients was observed.10 Although this reduction did not attain statistical significance, the study was not powered to demonstrate such a difference. However, the results are consistent with the finding of lower cardiovascular morbidity and mortality in SSRI-treated patients reported in recent epidemiologic studies11–13 and a study of 137 poststroke patients treated with sertraline who were followed up for 1 year.14 Taken together, these results suggest that SSRIs might reduce cardiovascular and cerebrovascular morbidity and mortality. These findings need to be replicated in adequately powered, randomized trials. Nevertheless, the available data do raise the question of which mechanism(s) might be involved.

Because data have accumulated indicating that depression is associated with platelet activation, it also became apparent that the SSRIs in general and sertraline in particular affect platelet function.15,16 SSRIs block reuptake of serotonin not only in nerve cells but also in platelets as well. One study, for example, has demonstrated that paroxetine reduces the abnormality in platelet hyperreactivity observed in depressed patients.17 In the SADHART trial, 89% of the patients received aspirin, 17% received clopidogrel or ticlopidine, and 29% received either warfarin or Coumadin. We therefore assessed the release of 8 platelet/endothelial biomarkers in serial blood samples from a subset of the SADHART patients to determine whether sertraline treatment provided additional antiplatelet effects in depressed ACS patients concurrently receiving conventional antithrombotic treatment.

### Methods

**Patients**

Platelet/endothelial biomarkers were measured in a subset of 64 patients in the multicenter SADHART study (5 outpatient cardiology and psychiatry clinics in the United States and Canada). Depressed patients, identified during hospitalization for ACSs (unstable angina or AMI), were randomized to 24 weeks of double-blind treatment with either sertraline or placebo. The details of the SADHART are described in detail elsewhere.10 Patients who fulfilled preliminary screening for conventional ACS criteria provided written, informed consent before undergoing evaluation with the structured Diagnostic Interview Schedule for major depression and completion of the self-rated Beck Depression Inventory and Clinical Global Impression Improvement scale for evaluation of clinical depression. All patients enrolled in the study met DSM-IV criteria for major depression. The diagnosis of major depressive disorder was confirmed by a site psychiatrist, and the diagnosis of ACS was confirmed by an attending cardiologist. Patients were excluded from the platelet substudy when they had a history of bleeding diathesis, stroke within 3 months, prothrombin time >1.5 times control, platelet count <100,000/mm³, or hematocrit <25%. Enrolled patients received sertraline (50 to 200 mg/d) or matching placebo.

**Samples**

Platelet/endothelial biomarkers were measured serially at baseline, week 6, and week 16 after sertraline/placebo randomization. Blood samples were obtained with a 19-gauge needle by direct venipuncture from the antecubital vein directly into two 7-mL evacuated tubes (Vacutainer, Becton Dickinson) containing 3.8% trisodium citrate at room temperature. The tube was filled to capacity and gently inverted 3 to 5 times to ensure complete mixing of the anticoagulant. The blood-citrate mixture was centrifuged at 3000 rpm for 10 minutes. The resulting platelet-poor plasma was frozen at −80°C for platelet/endothelial marker assays. All participating sites underwent extensive training on uniform and accurate blood collection, sampling, processing, and storage. Only those sites where research nurses had experience in similar studies were involved. Identical laboratory supplies and instructions were provided, and the substudy was coordinated by the core facility at the Sinai Thrombosis Center of Johns Hopkins University.

**Biomarkers**

Platelet factor 4 (PF4), β-thromboglobulin (βTG; Diagnostica Stago), platelet/endothelial cell adhesion molecule-1 (PECAM-1), P-selectin, vascular cell adhesion molecule-1 (VCAM-1), E-selectin, (R&D Systems), thromboxane B2 (TXB2), and prostacyclin (6-keto-prostaglandin [PG] F1α; Cayman Chemical) were measured by ELISAs. Each sample was measured in duplicate, and the overall intra-assay coefficient of variation was between 2.8 ± 0.3% and 7.9 ± 1.2%, with a plasma recovery rate between 87.6% and 98.9%. Twenty-four samples were submitted but not usable from a technical standpoint.

**Statistical Analysis**

Biomarker measures were obtained in blood samples taken at baseline and at weeks 6 and 16 of the double-blind treatment period. The changes from baseline to week 6 and week 16 were analyzed by a mixed-model, repeated-measures ANOVA. The model included the effects of treatment, week, and treatment-by-week interaction. The baseline value was used as a covariate in the model.18 The changes from baseline to weeks 6 and 16 were obtained from the model and compared by a 2-sample t test.19

**Results**

Major clinical characteristics of the SADHART trial participants (n = 369) and the subset of post-ACS patients enrolled into the platelet substudy (n = 64) are listed in Table 1. The demographic and clinical characteristics, depression severity scores, and use of antiplatelet agents did not differ significantly between the groups, except for a relatively greater proportion of patients with unstable angina and heart failure in the platelet substudy compared with the general SADHART participant population. Also, the number of prior coronary interventions and of heart surgery was lower (P = 0.03) for the sertraline compared with the placebo group for the patients enrolled in the substudy. There was a trend toward higher index AMIs and lower prior AMIs in the sertraline-treated patients compared with the placebo group.

Finally, use of oral anticoagulants was less frequent in the sertraline group; however, this difference did not reach significance.
The measures of platelet/endothelial cell function are listed in Table 2. Measurements are displayed for 8 different measures at 3 different time points. Initial baseline measures obtained after hospitalization for ACSs diminished at the 6- and 16-week observation points in every instance. The changes from baseline were statistically significant in 12 of 16 observations in the sertraline treatment group compared with only 8 of 16 observations in the placebo treatment group. Because the 16 observations consisted of 8 different measures made at 2 different points during the trial, the comparison between sertraline and placebo can be made at either the 6- or 16-week observation or for the entire 16-week period by using a repeated-measures ANOVA. At individual time points, sertraline was superior to placebo at 6 and 16 weeks for $\beta$-TG and at 16 weeks for P-selectin. The biomarker changes were numerically greater on drug than placebo in 14 of the 16 observations, and this difference was statistically significant in 4 of the 14 instances. However, in 1 instance (PECAM-1) at 6 weeks, the change was statistically greater on placebo. Across the entire treatment period, there was a statistically greater reduction in $\beta$-TG and E-selectin in patients treated with sertraline compared with placebo, and in no measure was placebo treatment superior to the SSRI.

### Discussion

The results of the present prospective study support previous in vitro and retrospective observations and demonstrate that treatment with sertraline in depressed post-ACS patients is associated with reductions in platelet/endothelial activation, despite the coadministration of widespread antiplatelet regimens including aspirin and clopidogrel. These findings might, at least in part, explain why SSRIs are apparently beneficial for the survival of depressed patients after vascular ischemic events, as suggested in the SADHART study. Platelet inhibition by SSRIs might represent an independent therapeutic modality for these drugs in patients with depression and perhaps even for nondepressed patients with ischemic vascular disease. Indeed, SSRIs might represent an attractive class of dual agents for treating depression as well as protecting patients from secondary vascular events by simultaneously inhibiting platelet activation.
Depression is common in ACS patients and is associated with increased mortality.\textsuperscript{3,4} Indeed, \textasciitilde{}40\% of patients with AMI report experiencing symptoms of depression,\textsuperscript{20} and \textasciitilde{}20\% to 25\% of these patients actually develop major depression.\textsuperscript{21} In the Cardiac Arrhythmia Pilot Study composed of 502 post-AMI patients with significant ventricular arrhythmias, patients who reported a high incidence of depressive symptoms between 6 and 60 days after their AMI exhibited a 20-fold 1-year risk of mortality or cardiac arrest.\textsuperscript{22} Prospective studies subsequently showed that the diagnosis of major depression before discharge from hospitalization for an AMI conferred a substantial \textasciitilde{}4-fold increased independent risk of subsequent cardiac death.\textsuperscript{23} Recent data in almost 900 ACS patients revealed an increased mortality rate associated with depression over 5 years of follow-up.\textsuperscript{4} Enhanced platelet activation has been suggested as a possible mechanism contributing to the increased cardiac risk associated with the diagnosis of major depression.\textsuperscript{15,16} Patients with major depression have consistently been shown to exhibit alterations of multiple platelet parameters, including reduction of serotonin transporter platelet binding sites by imipramine,\textsuperscript{24,25} as well as increases in serotonin 5HT\textsubscript{2} receptor binding sites on the platelet surface compared with controls.\textsuperscript{26} Platelet monoamine oxidase activity has been previously reported in depressed patients without heart disease.\textsuperscript{30} This observation was supported by an earlier report of enhanced platelet activity reflected in markedly

<table>
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<th>Variable</th>
<th>Sertraline</th>
<th>Time of Treatment vs Baseline (t Test)*</th>
<th>Placebo</th>
<th>Placebo vs Baseline (t Test)†</th>
<th>Sertraline vs Placebo at Single Time Point (t Test)</th>
<th>Sertraline vs Placebo Across All Weeks (ANOVA)</th>
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<td>57.4±24.3 . . .</td>
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<td>38.1±26.0 .015</td>
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<td>43.6±20.1 .032</td>
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<td>44.6±16.5 .001</td>
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<td>48.0±22.0 .001</td>
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<td>Baseline</td>
<td>113.1±32.2</td>
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<td>119.7±31.2 . . .</td>
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<td>43.7±25.7 NS</td>
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<td>16 weeks</td>
<td>42.7±15.2</td>
<td>.005</td>
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<td>6-Keto-PGF1α, pg/mL</td>
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<td>Baseline</td>
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<td>256.8±120.3 . . .</td>
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<td>186.4±106.6</td>
<td>.042</td>
<td>210.5±111.1 NS</td>
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<td>146.3±95.3</td>
<td>.002</td>
<td>179.6±121.3 .042</td>
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<tr>
<td>Baseline</td>
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<td>84.5±20.1 . . .</td>
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<td>VCAM-1, ng/mL</td>
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<tr>
<td>Baseline</td>
<td>898.2±312.9</td>
<td>. . .</td>
<td>838.0±306.4 . . .</td>
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<td>6 Weeks</td>
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<td>NS</td>
<td>789.1±316.9 NS</td>
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<td>718.1±272.5</td>
<td>.044</td>
<td>813.0±247.3 NS</td>
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NS indicates not significant.
elevated β-TG and PF4 levels in patients with both depression and chronic ischemic heart disease.31 Reduced platelet serotonin uptake,32 enhanced serotonin 5HT2 receptor expression,33 and increased platelet calcium mobilization in response to serotonin stimulation have also been reported.34,35
Sertraline is a potent SSRI that acts primarily by a selective, dose-related inhibition of the serotonin transporter, thereby downregulating serotonin 5-HT2a autoreceptors and other serotonin receptors in the brain.36 Administration of the drug causes a selective, dose-related inhibition of serotonin uptake into platelets as well.37 Eight weeks of sertraline therapy resulted in decreased [1H]paroxetine platelet binding in patients with major depression.38 Interestingly, collagen-induced platelet secretion, an integral component of the clotting cascade, is significantly reduced after treatment with sertraline.39
The present data are in agreement with earlier in vitro observations,14 suggesting that long-term therapy with sertraline is associated with inhibition of platelets and possibly other steps in the clotting cascade. Indeed, at 6 weeks after randomization, patients treated with sertraline exhibited a significant decrease in βTG, the well-defined platelet α-granule constituent. This decrease persisted at the 16-week measurement. Also at week 16 in addition to βTG, other adhesion molecules and selectins, namely P-selectin and E-selectin, which can be released from both platelets and vascular endothelium, decreased significantly in the sertraline-treated patients. Levels of the selectively endothelial products (6-keto-PGF1α, VCAM-1), did not change significantly. These results suggest a relatively selective platelet effect of sertraline, rather than a vessel wall effect.
This study of biomarkers was conducted in a population of patients after ACSs, which explains the decrease in plasma levels over time in both treatment arms. The exposure to a variety of medications, including aspirin and thienopyridines, also diminished the degree of platelet activation. The present data are in agreement with the earlier report that elevations of plasma Tx concentrations in post-ACS patients decrease significantly after 3 weeks after the acute event.40 Moreover, an initial increased release into plasma, followed by a gradual decrease to normal rates of production, is known for PF4, BTG, and P-selectin, the established markers of platelet activation in post-ACS patients.41–44 Elevated plasma concentrations of PECAM-1, VECAM-1, and E-selectin are also well established in patients with ACSs, although the changes in these markers over the long term are unclear.45,46 Based on our data, it will be very difficult if not impossible to identify a single biomarker affected by sertraline. Most likely, sertraline initially targets platelet serotonin receptors and then indirectly affects major platelet functions, such as adhesion, aggregation, secretion, or receptor expression. Thus, antiplatelet properties of sertraline differ from those of aspirin, dipyridamole, clopidogrel, and glycoprotein IIb/IIIa inhibitors, the pathways of which are well identified.
Whether the favorable effects of sertraline as observed in this study are readily observable in patients with stable coronary artery disease remains to be determined. The clinical relevance of these findings is also unknown. SADHART was not powered to correlate the effects of SSRIs, platelet function, and incidence of future coronary events. However, evidence is accumulating that implicates serotonin as a key contributor in the pathogenesis of coronary disease and a role for serotonin antagonism in cardiovascular therapeutics.47,48 Excessive transcardiac accumulation of serotonin appears to play a role in the conversion of chronic stable angina to an unstable coronary syndrome.49 Moreover, serotonin along with other substances has been reported to mediate the intermittent coronary obstruction caused by platelet aggregation and dynamic vasoconstriction. Activation of platelets leads to local coronary release of serotonin, which stimulates sympathetic afferents. This event causes vasoconstriction and recurrent aggregation of platelets with cyclic flow reductions.50 Serotonin might also act as a growth factor that stimulates mitogenesis and migration of arterial smooth muscle cells, both of which are unfavorable events after percutaneous interventions. Furthermore, in animal models of coronary artery stenosis and endothelial injury, serotonin receptor antagonists exhibited potent protection against repetitive platelet aggregation, even when systemic catecholamine levels were markedly elevated.47,48
There are several limitations of this study. First, the sample size was relatively small. We were limited to only 5 sites in North America that met certain additional criteria for participation in the biomarker substudy (high enrolment, experienced personnel, presence of a −70°C refrigerator, etc.). Expecting that the differences in biomarker changes between sertraline and placebo groups could be relatively small, we decided that the quality of the analyzed samples was critical, thereby jeopardizing our ability to expand the sample size. Moreover, a majority of the nurses were experienced in psychiatric rather than cardiovascular trials, with limited knowledge of biomarker studies requiring uniform blood-drawing techniques, sample preparation, and storage. Therefore, we deliberately limited the sample size to ensure the quality of the data. Second, other established tests for assessing platelet function, such as aggregometry and whole-blood flow cytometry after treatment with SSRIs, would have been informative. We were not enrolling SADHART patients locally and therefore, were unable to perform conventional platelet tests, which require immediate blood processing and are not appropriate when there are shipment delays. In addition, the incidence of heart failure was different between the 2 groups. Furthermore, broad use of antecedent aspirin and ADP-receptor blockers, though equally distributed between the 2 groups, might have influenced the results of this study. Finally, broad use of other medications besides aspirin and thienopyridines might have affected the biomarkers.
In conclusion, despite concomitant antiplatelet regimens including aspirin and ADP-receptor blockers, treatment with sertraline in depressed post-ACS patients was associated with diminished activation of platelets. Antiplatelet properties of SSRIs might represent an attractive additional advantage for patients with depression and comorbid coronary artery disease and ischemic stroke.

Acknowledgments
This study was supported by Pfizer, Inc (New York, NY). We are grateful for the dedication of the staff of all participant sites whose
commitment made this study possible. Our special thanks go to James J. Ferguson III, MD, for critical review of the manuscript.

References
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for the SADHART Study Group

Circulation. 2003;108:939-944; originally published online August 11, 2003;
doi: 10.1161/01.CIR.000085163.21752.0A
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/108/8/939

An erratum has been published regarding this article. Please see the attached page for:
/content/108/25/3165.1.full.pdf

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In the article, “Platelet/Endothelial Biomarkers in Depressed Patients Treated With the Selective Serotonin Reuptake Inhibitor Sertraline After Acute Coronary Events: The Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) Platelet Substudy” by Serebruany et al, which appeared in the August 26, 2003, issue of the journal (Circulation. 2003;108:939–944), some information was inadvertently omitted from the conflict-of-interest disclosure footnote. The following disclosures are added:

Dr Califf has received research support from and served as a consultant for Pfizer (all proceeds donated to Duke University). Dr O’Connor has received research support from and has consulted for Pfizer, GlaxoSmithKline, Eli Lilly, and Forest Pharmaceuticals, and holds patents for selective serotonin reuptake inhibitor research.

DOI: 10.1161/01.CIR.0000112316.97283.9D

In the article, “Physiology and Pathophysiology of Vascular Signaling Controlled by Cyclic Guanosine 3',5'-Cyclic Monophosphate–Dependent Protein Kinase” by Münzel et al, which appeared in the November 4, 2003, issue of the journal (Circulation. 2003;108:2172–2183), the word “cyclic” was mistakenly duplicated in the title. The title should have read as follows:

Physiology and Pathophysiology of Vascular Signaling Controlled by Guanosine 3',5'-Cyclic Monophosphate–Dependent Protein Kinase

DOI: 10.1161/01.CIR.0000112319.29689.0C

In the article, “Novel Index for Invasively Assessing the Coronary Microcirculation” by Fearon et al, which appeared in the July 1, 2003, issue of the journal (Circulation. 2003;107:3129–3132), an author (Anthony D. Caffarelli) was inadvertently omitted from the byline. The byline should have read as follows:

William F. Fearon, MD; Leora B. Balsam, MD; H.M. Omar Farouque, MB, BS, PhD; Anthony D. Caffarelli, MD; Robert C. Robbins, MD; Peter J. Fitzgerald, MD, PhD; Paul G. Yock, MD; Alan C. Yeung, MD

DOI: 10.1161/01.CIR.0000112321.37196.64

In the article, “Comparison of Coronary Thermodilution and Doppler Velocity for Assessing Coronary Flow Reserve” by Fearon et al, which appeared in the November 4, 2003, issue of the journal (Circulation. 2003;108:2198-2200), an author (Anthony D. Caffarelli) was inadvertently omitted from the byline. The byline should have read as follows:

William F. Fearon, MD; H.M. Omar Farouque, MB, BS, PhD; Leora B. Balsam, MD; Anthony D. Caffarelli, MD; David T. Cooke, MD; Robert C. Robbins, MD; Peter J. Fitzgerald, MD, PhD; Alan C. Yeung, MD; Paul G. Yock, MD

DOI: 10.1161/01.CIR.0000112324.93632.9C