Risk Prediction in Cardiovascular Medicine

Cardiovascular Risk Prediction in Patients With Stable and Unstable Coronary Heart Disease

David A. Morrow, MD, MPH

The American Heart Association estimates that 1 in 3 American adults have cardiovascular (CV) disease, including 16.8 million individuals with ischemic heart disease, 8 million individuals with peripheral arterial disease, and 6.5 million individuals with ischemic stroke.1 In 2005, CV disease accounted for 35% of all deaths in the United States. Given the high prevalence of CV disease and its associated morbidity and mortality, prevention of recurrent events in patients with established CV disease is a major public health objective. A fundamental tenet of preventive medicine is to initiate interventions appropriate to the level of risk for the individual. Therefore, risk assessment is an inextricable component of preventive care.

This review is focused on tools for risk assessment in patients with coronary heart disease (CHD). A discussion of risk assessment in patients with atherosclerosis limited to the cerebrovascular or peripheral arterial beds is beyond the scope of this review. However, many of the tools and principles discussed here apply also to patients with atherosclerosis throughout the vascular tree. This review addresses both the early phase of risk after presentation with an acute coronary syndrome (ACS) and the chronic phase in stable CHD. After ACS, the risk of CV death in community-based studies is ~3% to 5% at 30 days and 5% to 8% at 6 months.2 Major CV events occur in 15% to 20% of patients by 6 months.3 In patients with stable CHD, the annual mortality rate is 1% to 3%, and the annual rate of major CV events is 1% to 2%. In a registry of 38 602 patients with stable CHD, the 1-year rate of CV death was 1.9% (95% confidence interval, 1.7 to 2.1) and of CV death, myocardial infarction (MI), or stroke was 4.5% (95% confidence interval, 4.2 to 4.8).4 These data summarize the population average; however, the clinician is able to significantly refine the estimate of risk for the individual using methods described in this review.

Goals of Risk Assessment for Secondary Prevention

The central goal of risk assessment is to guide therapeutic decision making and, in some cases, additional diagnostic evaluation. This goal is shared across the entire clinical spectrum of unstable and stable CHD. Additional objectives are summarized in Figure 1. In patients presenting with ACS, risk assessment may direct triage within the hospital or transfer to tertiary care centers. As such, in the acute setting, an assessment of the risk of death and recurrent ischemia should occur in parallel with the assessment of the probability that the patient’s symptoms are related to atherothrombosis.5 These diagnostic and prognostic assessments, although overlapping, are not identical. The prognostic assessment is valuable because the risk of recurrent events is strongly linked to the potential absolute and relative benefits of specific therapeutic interventions. In patients with stable CHD, an estimate of risk is similarly pivotal in management such as in identifying candidates for coronary angiography and revascularization.6 Although not discussed in this review, evaluation of the risk of complications of therapy (eg, bleeding with antiplatelet agents) is also an important aspect of clinical risk stratification and improves the integrated assessment of potential risks and benefits of therapy.7

Established Tools for Risk Assessment

The History and Physical Examination

The clinical history and physical examination provide valuable information for risk stratification during the course of routine care at no additional cost or risk to the patient. In patients with suspected ACS, features of the presenting history, including multiple risk factors for atherosclerosis, the pace of symptoms (eg, repeated rest angina), or symptoms of heart failure, herald a higher short-term risk of major complications.7 Braunwald’s classification of unstable angina based on provoking conditions and presentation with rest angina, new-onset angina, or increasing angina is associated with angiographic severity of CHD and the risk of death or MI.8 Similarly, in stable CHD, the pattern of angina (unstable or variant, crescendo, or stable), the frequency of symptoms,9 and the presence of dyspnea10 confer prognostic information. In a study of 5712 patients with CHD undergoing stress testing, patients with a history of dyspnea had an annualized mortality rate of 6.4% compared with 2.4% among those with typical angina without dyspnea.10

For patients with CHD, unstable or stable, a history or physical examination findings of atherosclerosis in noncoronary vascular beds indicate high risk.11,12 In an observational study of patients with stable CHD, major CV event rates were...
patients with >0.5- to 1.0-mm ST depression.\textsuperscript{16} In patients with ST-elevation MI, the magnitude of ST-deviation at presentation and the extent of resolution with pharmacological or mechanical reperfusion therapy are associated with mortality rate. Even in patients with normal epicardial arterial flow at angiography, persistent ST-elevation reflects abnormal tissue and microvascular perfusion and predicts poor recovery of wall motion and a higher risk of death and heart failure.\textsuperscript{17} In an analysis of 3 trials, the mortality rate was 2.7%, 4.8%, and 13% in patients with complete (>70%), partial (30% to 70%), or no (<30%) resolution of ST elevation.\textsuperscript{18}

In patients with stable CHD, a normal resting ECG suggests normal ventricular function and is a favorable prognostic indicator.\textsuperscript{19} ST-T-wave abnormalities are associated with higher end-diastolic pressure and ventricular volume, reduced ejection fraction, and lower 5-year survival. Conduction disturbances, most frequently left bundle-branch block and left anterior fascicular block, are also associated with impaired left ventricular function and multivessel disease and indicate a poorer prognosis.\textsuperscript{19}

### Stress Testing

In addition to being diagnostically useful, stress testing provides helpful prognostic data in patients with stable CHD and in patients stabilized after ACS.\textsuperscript{20} Maximal exercise capacity is one of the most consistent predictors of outcome, regardless of whether the test was terminated because of angina, dyspnea, or fatigue. Among 6213 men undergoing exercise testing, each 1–metabolic equivalent (MET) increase in exercise capacity was associated with a 12% improvement in survival.\textsuperscript{21} Individuals with stable CHD who achieved <5 MET of activity were at >4-fold higher risk of death than individuals who exercised to >10.7 MET (Figure 2).\textsuperscript{21} Scoring systems that integrate not only provoked symptoms

---

**Figure 1.** Goals of risk assessment in patients with CV disease.

**Figure 2.** Prognostic value of functional capacity during exercise testing. White labels (right) are the mean heart rate (HR) recovery (HRR; bpm) 1 minute after termination of exercise. Data for exercise capacity and HRR are from References 21 and 24, respectively.
and the presence of ST-deviation but also exercise performance improve risk stratification. The Duke Treadmill Score is calculated using exercise duration (minutes), subtracting 5 times the maximum ST depression (millimeters), and subtracting 4 times an angina index (2 points for limiting angina and 1 point for nonlimiting angina during the test). Five-year mortality rate with a score \( \geq 5 \) is \(< 5\%\) and with a score \(< -10 \) is \(28\%\).22

Other measures obtained from exercise testing such as a fall in blood pressure during exercise, prolonged ST-segment depression (>8 minutes into recovery), and slow heart rate recovery after exercise also indicate increased risk.23 For example, among 2428 patients referred for stress testing, patients with heart rate recovery values \(\geq 12 \text{ bpm} \) had 2-fold higher risk of death after adjustment for risk factors, resting heart rate, nuclear perfusion defects, and achieved workload (Figure 2).24 Concurrent myocardial imaging with nuclear perfusion imaging, echocardiography, or magnetic resonance complements the prognostic data offered by symptoms, exercise performance, and ECG. The following findings from stress nuclear perfusion imaging are indicative of a 3% annual mortality rate: a large stress-induced perfusion defect, multiple moderately sized stress-induced perfusion defects, and a large fixed defect with lung uptake of tracer or ventricular dilatation during stress.20 Normal perfusion imaging indicates an annual risk of death or MI \(1\%\). Analogous to the physical examination, evidence of ventricular dysfunction, regardless of the imaging modality, is one of strongest indicators of reduced survival in patients with CHD.20

**Coronary Angiography**

Coronary angiography is useful for establishing the diagnosis of CHD and for assessing the risk of major CV events. Because the majority of acute coronary events arise from rupture or erosion of atheromatous plaques that are not angiographically critical, the absence of angiographically severe disease does not diminish the indication for preventive therapies in patients with atherosclerosis. Nevertheless, the angiographic extent and severity of epicardial coronary disease are strongly associated with survival.19

In patients with ACS, angiographically visualized thrombus, impaired flow, and greater extent of coronary disease are associated with worse prognosis.25 Similarly, in stable CHD, the severity of disease is associated with prognosis. Indexes that integrate the overall number of lesions, lesion location, severity, and the extent of involvement of branch vessels have been developed; nevertheless, the classification into single-, double-, or triple-vessel disease or left main CAD remains useful (Figure 3).26

**Established Biomarkers**

Biomarkers have become integral to the care of patients with CV disease. In particular, in patients with acute chest discomfort or dyspnea, biomarkers are key to establishing a diagnosis, determining risk, and guiding therapy. In addition, in patients with stable CHD, biochemical testing of modifiable risk factors for progression of atherosclerosis such as hypercholesterolemia is fundamental to directing secondary preventive care. In this section, biomarkers recommended for routine use in patients with established atherosclerosis are discussed.

Measurement of a biomarker of necrosis is recommended for all patients with suspected ACS.27,28 On the basis of tissue-specificity and sensitivity, cardiac troponin (cTn) is the preferred biomarker of necrosis for diagnosis and risk stratification. The detection of cTn in the peripheral circulation is indicative of myocardial injury and in patients with a clinical syndrome consistent with ACS is associated with greater coronary lesion complexity, more frequent visible thrombus, more severely impaired flow in the culprit artery, and diminished microvascular perfusion.29 An elevated cTn is associated with an \(~4\)-fold higher risk of death or MI among patients with ACS.27 Improvements in the analytic performance of available assays, in conjunction with evidence confirming the clinical relevance of low concentrations of cTn, have supported professional recommendations to use a single cut point at the 99th percentile of a reference population as the decision limit for risk stratification.27,28

In patients with stable CHD, biochemical evaluation of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, triglycerides, serum cre-
atinine (estimated glomerular filtration), and fasting blood glucose is important to guide preventive interventions recommended by current professional guidelines.30

Clinical Risk Scores

Focus on individual risk predictors alone does not permit clinicians to use all of the information at their disposal and may lead to misclassification of risk.5 Therefore, approaches that integrate demographic, physiological, and laboratory parameters improve risk prediction. In particular, simple clinical scoring systems that can be calculated at the bedside or via electronic access offer a practical approach to enhance risk assessment.31

Multiple clinical risk scores have been developed and validated for application in ACS. Elements common to the majority of risk scores include age, ST deviation, biomarkers of necrosis, and indicators of heart failure (Figure 4). More complex models that include comorbid medical conditions appear to have superior discriminatory capacity. Nevertheless, computationally simpler scores are practical for bedside application and, in some cases, are well validated for predicting the benefit of therapy.31 As an example, the Thrombolysis in Myocardial Infarction (TIMI) Risk Score for ST-elevation MI stratifies patients across a >30-fold gradient of mortality risk using 8 clinical elements captured during routine care early after presentation (Figure 4).32 Although use of a risk score should not replace experienced clinical judgment, poor correlation between clinicians’ estimates and those from validated risk scores suggests that routine use of a validated risk score may enhance risk stratification and facilitate more appropriate decision making.33

The principle that risk assessment should be updated as new information becomes available is important and has fostered development of instruments for dynamic risk stratification.34 In contrast to the setting of ACS, few integrated risk scores have been reported for patients with stable CHD. A risk stratification instrument developed in a clinical trial of lipid-lowering therapy was based on weighted integer scoring of age, male sex, current tobacco use, prior MI, diabetes mellitus, hypertension, absence of prior revascularization, high total cholesterol, and low high-density lipoprotein cholesterol.35 With this scoring system, patients on statin therapy were stratified between a 5-year risk of death or MI of 5% (score <4) and >15% (score ≥10).35

![Figure 4. Summary of clinical risk scores for ACS.](https://circ.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.109.921355)
Take the case of a hypothetical risk indicator and any treatment “X” that is effective in the overall population ....

A Diminished Effect of “X”
Loss of efficacy in high risk

B Similar Effect of Treatment
Greater absolute benefit in high risk

C Positive Interaction
Greater relative benefit in high risk

D Diabetes Mellitus (DM) as an example

Possible Negative Interaction
Possibly less effect in DM

Similar Effect of Beta-blockers
Greater absolute benefit in DM

Potent Antiplatelet Agent
Greater relative benefit in DM

In patients with ACS, the history, physical examination, and noninvasive testing each aid in predicting the potential for therapeutic benefit. Patients with diabetes mellitus have a higher risk of recurrent CV events and derive greater absolute benefits from effective treatments such as β-blockers. In addition, they appear to have greater relative and absolute benefits with potent antiplatelet therapy than do patients without diabetes mellitus (Figure 5D). Similarly, patients with ST depression at presentation derive greater benefit from potent antiplatelet therapy and an early invasive strategy. In a randomized trial of early invasive compared with conservative management of ACS, patients with ST deviation had an
50% reduction in the primary end point contrasting with no detectable benefit in patients without ST changes. Patients with ACS and elevated cTn also experience greater relative reductions in recurrent events with more aggressive antithrombotic strategies and early invasive therapy than do patients with normal cTn results. For example, administration of a glycoprotein IIb/IIIa inhibitor provided no detectable benefit in patients with normal cTn results undergoing percutaneous coronary intervention after ACS but reduced death or major ischemic events by 28% in patients with a positive result. It is also possible to integrate individual risk predictors through the use of a clinical risk score for therapeutic decision making. Using the TIMI Risk Score for non–ST-elevation ACS to categorize patients establishes a gradient of benefit for the use low-molecular-weight heparins, glycoprotein IIb/IIIa inhibitors, and an early invasive strategy (Figure 6). Similarly, the Global Registry of Acute Coronary Events (GRACE) risk score identifies patients who are optimal candidates for early invasive compared with delayed invasive management.

Among patients with stable CHD, most preventive pharmacotherapy is aimed at modification of specific risk factors such as dyslipidemia or hypertension and therefore is recommended for all patients with established atherosclerosis and modifiable risk factors. However, the profile of overall risk plays a pivotal role in decisions about invasive evaluation and revascularization and may guide the intensity of therapy such as that targeting LDL cholesterol. Both the risk and potential benefits of revascularization are tied to the extent of epicardial coronary disease, the proportion of viable myocardium at risk, and left ventricular function. Patients with left ventricular dysfunction and hibernating myocardium have a high mortality rate with medical therapy and appear to have improved survival with revascularization.

Emerging Candidates for Risk Assessment
In this section, tools with epidemiological evidence for an association with risk in CHD but that are not presently recommended for routine use are reviewed. Some tools discussed here such as continuous ECG (cECG) and several well-studied biomarkers have substantial evidence supporting prognostic value and are recommended for selective use for risk stratification in CHD.

ECG Techniques
The data recorded during performance of a ECG, especially when continuously recorded, are substantially greater than the data available from interpretation of the ST segments alone. Reduced variability in the R-R interval (heart rate variability), diminished deceleration of heart rate (deceleration capacity), and cycle-length perturbations of sinus rhythm after isolated premature ventricular complexes (heart rate turbulence) each reflect a relative decrease in vagal activity and have been associated with higher risk of CV death in patients with CHD. As an example, abnormal heart rate turbulence, studied in 7054 post-MI patients across 7 studies, correlated with a consistent ≥3-fold higher risk of death with a risk relationship that was similar to that for low ejection fraction. Beat-to-beat variability in the timing or shape of T waves on the surface ECG (T-wave alternans) reflects heterogeneity in ventricular repolarization and is associated with higher risk of sudden death. The technique of performing signal-averaged ECG uses computerized averaging of complexes to detect small (microvolt) signals (late potentials) that reflect slow conduction through myocardium disrupted by infarction, inflammation, or edema. Therefore, signal-averaged ECG also may detect underlying substrate for ventricular arrhythmias and predict increased risk for sudden death. Although each of these techniques conveys
prognostic information on sudden death, the therapeutic implications are not established.48

In addition to forecasting the risk of arrhythmias, cECG also detects recurrent ischemia that is associated with a higher mortality rate. In patients with ACS, recurrent ischemia (>1-mm depression lasting ≥1 minute) on cECG during 7 days after presentation was associated with a 2.5-fold higher risk of CV death.49 Improved detection of ischemia in the acute setting may also be accomplished by expanding the number of surface leads such as with ECG body surface mapping.50 In patients with stable CHD, cECG reveals episodes of silent ischemia during normal daily activities. However, outside the setting of recent ACS, the prognostic value of cECG for ischemia has varied between studies with a compelling relationship only in selected patients, generally with exercise testing.51 For these reasons, cECG for ischemia is not recommended for routine use in patients with stable CHD.51

Biomarkers
The investigation of circulating biomarkers in patients with CV disease has generated an expanding list of biomarkers that are associated with CV outcomes in patients with unstable and stable CHD.27 Such investigation has focused on newer biomarkers that may reflect the underlying causes or consequences of atherothrombosis. This research has supported the concept that noninvasive assessment of multiple pathobiologically diverse biomarkers may yield insight into the variety of contributors to atherothrombosis for the individual patient and thereby enhance risk stratification with a multimarker approach.52,53 Emerging biomarkers shown to provide prognostic information include but are not limited to high-sensitivity cTn, neurohormones, inflammatory indicators, coagulation proteins, novel lipid-related parameters, and other metabolic markers. Because there has been insufficient evidence to conclude that these biomarkers can improve treatment, they are not currently recommended for use in all patients. The investigation of biomarker-based strategies for therapeutic decision making is a current priority. Genetic testing is also an emerging technique for risk stratification in CHD and has been reviewed elsewhere.54

Owing to the central role of inflammation in atherothrombosis, candidate biomarkers of inflammation, including acute-phase proteins, cytokines, and cellular adhesion molecules, have been evaluated as prognostic indicators.55 Across >12 clinical studies of ACS, high-sensitivity C-reactive protein (hsCRP) concentration determined either at presentation or in the convalescent phase was associated with short- and long-term CV outcomes.27 In addition, analyses demonstrating a reduction in hsCRP with statins and an association between the achieved concentration of hsCRP and outcome have supported the possible application of hsCRP for monitoring the response to statin therapy.56,57 On the basis of the overall evidence, measurement of hsCRP has been recommended as reasonable (Class IIa) in selected patients with unstable and stable CHD when the clinician desires additional prognostic information.27,58 Other inflammatory biomarkers that provide predictive capacity in patients with CHD include some that are clinically available such as myeloperoxidase59 and many investigational biomarkers that appear promising such as growth differentiation factor 1560 and pregnancy-associated plasma protein-A.55

Biomarkers of hemodynamic stress are among the strongest predictors of death in patients with CHD (Figure 7).27 Across at least 10 studies in ACS, elevated concentrations of B-type natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP) are independently associated with death and heart failure.51–63 In 1 study, a BNP concentration >80 pg/mL was associated with a 5-fold higher risk of new heart failure and a 3-fold higher risk of death after ACS.64 Serial measurement appears to enhance the value of natriuretic peptides for risk stratification after ACS.63,65 Despite the strong prognostic association, data on the interaction of natriuretic peptides with specific therapies such as routine invasive evaluation have been mixed.64,66 Measurement of BNP and NT-proBNP in patients with ACS is recommended as reasonable (Class IIa) to enhance prognostic assessment, along with cTn and other clinical risk indicators.27

Similarly, the natriuretic peptides are predictive of outcome in stable CHD.67,68 In a study of 1034 patients with angiographic CHD, patients with a concentration of NT-proBNP in the fourth quartile were at 2.4-fold higher risk of death during 9 years than patients in the first quartile.67 Moreover, in a comparative analysis of multiple biomarkers in a secondary prevention population, NT-proBNP, in conjunction with traditional risk indicators, provided the best prognostic discrimination for the risk of CV death, MI, or stroke.65 On the basis of these data, measurement of a natriuretic peptide may provide a useful enhancement of risk stratification in selected patients with stable CHD (Class Ib).69 Other biomarkers of hemodynamic stress such as ST270 and copeptin71 have also shown promise and remain under investigation for prognostic application in patients with CHD. As for hsCRP, the natriuretic peptides provide incremental information when used in combination with pathobiologically diverse biomarkers in a multimarker strategy for risk assessment.53 Such approaches continue to show promise for enhanced risk stratification.27

Biochemical markers of lipid-related atherogenic processes are also associated with higher risk in patients with CHD. Measurement of lipoprotein(a), apoprotein B, and small dense LDL appears to add to the determination of total cholesterol and LDL and may be considered a secondary target for treatment in patients who have achieved therapeutic targets for LDL.72 Lipoprotein-associated phospholipase A2 has been associated with the risk of recurrent CV events independently of traditional risk factors and is under study as a specific therapeutic target.73

The application of cTn as an established biomarker for risk stratification in ACS has already been discussed in this review. In addition, emerging assays with improved analytic performance that are able to detect circulating troponin at a concentration 10- to 100-fold lower than present commercial assays may open the door to new clinical applications for risk stratification.74 For example, in a stable community-based elderly population, detectable low concentrations of cTnI were associated a nearly 4-fold higher mortality rate in patients with apparently stable CHD.75 Moreover, in a stable
population undergoing stress testing, an increase in cTn with a highly sensitive research assay was associated with the presence and severity of myocardial ischemia on perfusion imaging.76 These and other potential applications of troponin in patients with stable CHD are in their relative infancy.74

Imaging
Coronary angiography is not a reliable indicator of the functional significance of stenosis, nor does it provide information with respect to the risk of plaque rupture and thrombosis. Two major directions for new coronary imaging have emerged: noninvasive imaging as a method to detect atherosclerosis and invasive and noninvasive methods to characterize the arterial wall and the risk of acute atherothrombosis. The first of these pursuits is aimed primarily at patients without known CHD and is not discussed in this review. The second emerging application is of interest for patients with established CHD and has the potential to improve risk stratification. Invasive characterization of the morphology of coronary atheroma has been described with intravascular ultrasound, optical coherence tomography, and thermal interrogation. Noninvasive techniques for characterization of the atheroma and its propensity for rupture or erosion include magnetic resonance imaging,77 computed tomography,78 positron emission tomography,79 and other novel approaches using molecular imaging that detect specific plaque constituents that are participants in or markers of plaque vulnerability.80

Summary
Risk assessment is essential to effective medical decision making for secondary prevention. A variety of clinical tools, including the most basic elements of the clinical history and the physical examination, provide valuable information on prognosis. In addition, data from the ECG, laboratory testing, and noninvasive and invasive imaging are complementary with respect to prognosis and can aid in informing patients and their families, directing triage, and guiding medical therapy. An integrated approach to risk assessment is optimal, and simple clinical risk scores can assist the clinician in assimilating the diverse sources of data on prognosis. Emerging tools for risk assessment continue to provide new insights into the pathogenesis of atherothrombosis and may advance the extent to which the promise of personalized preventive
medicine can be realized in our routine care of patients with CV disease. Although discussed in the context of CHD, these principles are important to the full spectrum of patients with peripheral and cerebrovascular atherosclerotic disease.

Disclosures
The TIMI Study Group has received research grant support from AstraZeneca, Beckman Coulter, Biocept, Cristol-Myers Squibb, CV Therapeutics, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Merck, Nanosphere, Novartis, Ortho-Clinical Diagnostics, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, Siemens, and Singulex. In the past 2 years, Dr. Morrow has received honoraria from Eli Lilly and Co and Sanofi-Aventis. He has served as a consultant for AstraZeneca, Beckman Coulter, Boeringer Ingelheim, Critical Diagnostics, CV Therapeutics, Genentech, Gilead, Ikaria, Heartscapes, Menarini, OrthoClinical Diagnostics, Roche, Schering-Plough, and Siemens.

References


**Key Words:** angina ■ atherosclerosis ■ myocardial infarction ■ prevention ■ prognosis
Cardiovascular Risk Prediction in Patients With Stable and Unstable Coronary Heart Disease
David A. Morrow

_Circulation_. 2010;121:2681-2691
doi: 10.1161/CIRCULATIONAHA.109.852749
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 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/121/24/2681

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/