Downloadable Software Algorithm Reduces Inappropriate Shocks Caused by Implantable Cardioverter-Defibrillator Lead Fractures

A Prospective Study

Charles D. Swerdlow, MD; Bruce D. Gunderson, MS; Kevin T. Ousdigian, MS; Athula Abeyratne, PhD; Haresh Sachanandani, MS; Kenneth A. Ellenbogen, MD

Background—Downloadable software upgrades are common in consumer electronics but not in implantable medical devices. Fractures of implantable cardioverter-defibrillator (ICD) leads present commonly as inappropriate shocks. A lead-integrity alert (LIA) designed to reduce inappropriate shocks is the first software download approved to enhance nominally functioning, previously implanted ICDs.

Methods and Results—We performed a prospective study to determine whether an LIA could reduce inappropriate shocks. Patients were included if they had ICD lead fractures confirmed by analysis of explanted leads. The LIA group included the first 213 patients who met the inclusion criteria after the LIA was approved who had the LIA downloaded. The LIA is triggered either by high impedance or rapid oversensing. It responds by delaying detection of ventricular fibrillation and initiating a patient alert every 4 hours. The control group included the first 213 patients who did not have the LIA downloaded. They were monitored by conventional daily impedance measurements that respond with a daily alert. The LIA group had a 46% relative reduction (95% confidence interval 34% to 55%) in the percentage of patients with inappropriate shock (LIA 38% versus control 70%, \( P < 0.001 \)) and a 50% relative reduction (95% confidence interval 33% to 61%) in the percentage with 5 shocks (25% versus 50%, \( P < 0.001 \)). The LIA group also had a higher percentage of patients who either did not receive a shock or had ≥3 days of warning before the shock (72% versus 50%, \( P < 0.001 \)).

Conclusions—A software download that upgrades previously implanted ICDs without surgical revision reduces inappropriate shocks caused by lead fractures. (Circulation. 2010;122:1449-1455.)

Key Words: implantable cardioverter-defibrillators ■ device safety ■ software

Failures of implantable cardioverter-defibrillator (ICD) leads remain an important limitation of ICD therapy. Fractures of pace-sense conductors in defibrillation leads may cause an oversensing of nonphysiological potentials that results in inappropriate detection of ventricular fibrillation (VF) and shocks. Despite alerts based on high impedance, fractures commonly present with clusters of inappropriate shocks. Fractures have been reported to cause loss of pacing, failure of defibrillation, or fatal proarrrhythmia. To reduce inappropriate shocks, we developed a lead-integrity alert (LIA) triggered by either oversensing or high impedance that can be downloaded into previously implanted ICDs.

On August 28, 2008, LIA software was released for 17 models of previously implanted ICDs, constituting 98% of Medtronic ICDs connected to Fidelis leads. The present prospective study was designed to determine whether the LIA reduces inappropriate shocks in patients with Fidelis lead fractures.

Methods

Study Design

Hypothosis and Inclusion Criteria

We hypothesized that the LIA would reduce the percentage of patients who received inappropriate shocks compared with a concurrent control group monitored by impedance only. We tested this hypothesis prospectively using data from patients with Fidelis leads who met 3 criteria: (1) The lead was explanted and returned to the manufacturer for returned product analysis (RPA). (2) ICD diagnos-
Table 1. Comparison of Lead-Failure Alert Features in the Control and LIA Groups

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>LIA Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-impedance trigger</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Oversensing trigger</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Notifications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Audible—patient</td>
<td>1×/d</td>
<td>6×/d</td>
</tr>
<tr>
<td>Wireless—clinician</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(wireless-telemetry ICDs only)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Automatic change in ICD detection to reduce shocks from transient oversensing</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Electrogram diagnostics to determine cause of oversensing</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

+ Indicates present; 0, absent.

Alert Operation in the Control and LIA Groups

The lead-failure alert features in the 2 groups are shown in Table 1. The control group was monitored by automated daily impedance measurements performed at night. An alert was triggered if the measured impedance exceeded the threshold between 1000 and 2500 Ω that was programmed by the physician. If an alert was triggered, the ICD would sound an audible tone once daily at a prespecified time.

The LIA has been described in detail. With the LIA, an alert is triggered by either abnormally high impedance relative to the patient’s baseline impedance or rapid oversensing that is unlikely to represent a physiological event. Impedance is measured once daily, but oversensing is measured continuously.

The LIA impedance trigger is designed for chronic leads. It uses a threshold based on the average of the most recent measurements: 1000 Ω if the average is <700 Ω, 1500 Ω if the average is 700 to 1100 Ω, and 2000 Ω if the average is ≥1100 Ω. The LIA oversensing trigger detects nonphysiologically short R-R intervals caused by pace-sense conductor fracture on the basis of 2 existing diagnostics, the sensing-integrity counter and the nonsustained tachycardia log. The sensing-integrity counter stores the cumulative number of nonphysiologically short R-R ≤130 ms. The LIA’s sensing-integrity counter criterion is satisfied by a count ≥30 within 3 days. The nonsustained tachycardia log stores 5 or more consecutive sensed events with cycle length less than the ventricular tachycardia detection interval. Most true nonsustained ventricular tachycardias have a cycle length ≥220 ms. The LIA’s nonsustained tachycardia criterion is satisfied by 2 episodes with average cycle length <220 ms in 60 days. The LIA’s oversensing trigger is activated if both the sensing-integrity counter and nonsustained tachycardia criteria are fulfilled.

Once an LIA warning is triggered, an audible tone sounds immediately and every 4 hours thereafter. Thus, the alert sounds whenever the oversensing trigger is met or when daily impedance is measured. The LIAs also reprogram the number of intervals to detect VF (NID) from the value programmed at the physician’s discretion (nominally 18/24) to 30/40 and stores electrograms for any interval shorter than 200 ms. The purpose of the high NID is to reduce inappropriate shocks caused by transient fracture-induced oversensing. The stored electrograms provide a diagnostic to determine the cause of rapid oversensing based on electrogram characteristics. In newer ICDs with wireless telemetry, alerts in both groups initiate Internet notifications if this feature is enabled.

End Points

End points were defined prospectively. The primary end point was the percentage of patients who received at least 1 inappropriate shock caused by lead-related oversensing before in-person ICD interrogation. Lead-related oversensing was diagnosed by electrograms that showed high-frequency "noise," characteristic of lead fracture. We defined 3 secondary end points prospectively. The first was the percentage of patients who received ≥5 inappropriate shocks. Multiple studies report that ICD patients who receive ≥5 shocks have reduced quality of life compared with those who receive fewer shocks. The second was a composite end point designed to estimate the impact of LIA warnings if patients received care promptly, within a realistic time frame. We defined this as the percentage of patients who either did not receive any shocks or had ≥3 days of warning alerts before shock. The third end point was the time from an alert to in-person ICD interrogation for patients who were not shocked. Its purpose was to determine the time course over which patients received medical care as a result of alerts. We determined the same primary and secondary end points for the prospectively defined subgroup of the control group in whom ICDs were programmed according to Medtronic’s recommended values (impedance threshold of either 1000 or 1500 Ω and NID ≥18/24).

To estimate the benefit of automatically increasing the NID after an LIA warning on preventing inappropriate shocks, we used both the number of aborted inappropriate shocks with NID at 30/40 that would have been delivered with NID at 18/24 and the number of oversensing episodes that resulted in >18 sensed VF intervals. The latter would have resulted in either delivered or aborted shocks for programmed NID ≤18/24.

Adoption of LIA

LIA software was downloaded at the discretion of treating physicians using standard programmers during routine clinic visits, which occur every 3 to 12 months. The present study’s primary data set of patients with Fidelis fractures does not permit calculation of the percentage of all Fidelis patients whose ICDs had LIA as a function of time. To provide this estimate, we reviewed data from the CareLink Internet-based remote-monitoring network in the United States because transmissions indicate whether LIA software has been downloaded. The denominator was the number of eligible patients who made transmissions in each quarter after LIA release, starting December 1, 2008; the numerator was the number of patients in whom LIA software was downloaded at the time of the most recent transmission for each period multiplied by 100.

LIA Predictive Value

The study’s primary data set also does not provide a measure of the predictive value of the LIA, because it includes only patients with confirmed fractures. We conducted prospective follow-up of 2770 Fidelis patients who participated in remote monitoring and whose lead performance was being tracked for product-performance reporting. Patients were included in the present analysis if they had LIA software installed by July 29, 2009.

We cross-checked these patients against Medtronic’s device registration and RPA database to determine the status of each lead. The physician was contacted to determine whether the lead had been replaced and the indication for replacement. We reviewed stored data...
for all patients, focusing on impedance trends and electrogram characteristics of lead fracture and other types of oversensing.\textsuperscript{5,13} Lead fracture was diagnosed clinically if the lead was replaced for the diagnosis of lead failure and diagnostics showed either an abrupt change in impedance >350 $\Omega$ between successive measurements or electrograms characteristic of lead fracture.\textsuperscript{5,12,13} as judged by warnings.

Positive LIA warnings due to lead fractures divided by all LIA positive predictive value was computed as the number of true-positive LIA warnings due to lead fractures divided by all LIA warnings.

Statistical Analysis

We used the Fisher exact test to compare proportions, including the percentages between the 2 groups for the primary and first 2 secondary end points. We used the exact binomial method to compute confidence intervals (CIs) for proportions and the Wald method to compute CIs for relative risks. To determine whether LIA reduced the time from an alert to ICD interrogation without a shock, we performed a Kaplan-Meier survival analysis on all patients who received an alert. We compared the curves for LIA and control groups using the Wilcoxon test. The $P$ values have not been adjusted for multiple comparisons. Only the $P$ value for the primary end point was interpreted at face value. Data are presented as mean±SD.

Results

LIA Download

Overall, 59 123 (46%) of the 128 174 patients with Fidelis leads and eligible ICDs in service on December 1, 2009, were followed up by remote monitoring during the previous 12 months. Of these, 69% (40 825 of 59 123 patients) had LIA software downloaded. The percentage of eligible ICDs into which LIA software was downloaded increased over time on the remote-monitoring network. During successive 3-month periods after LIA release, the percentages were 41%, 59%, 69%, and 73%, respectively. The corresponding numbers of patients who made remote transmissions in each period were 39 633, 40 926, 41 320, and 37 962.

Control and LIA Groups

The control and LIA groups did not differ significantly with respect to age; gender; percentages of single-, dual-, and triple-chamber ICDs; or percentage of patients with remote monitoring (Table 2). Overall, only 12% of patients made remote-monitoring transmissions using wireless-telemetry ICDs. The percentage of control group patients programmed with Medtronic’s recommended values was 87% for NID, 80% for impedance-alert threshold, and 72% for both.

Effect of LIA on Inappropriate Shocks

Figure 1 shows that the LIA group had a 46% reduction in inappropriate shocks relative to the control group (95% CI 34% to 55%) among those patients who received 1 or more shocks (LIA 38% versus control 70%, $P<0.001$). The LIA group also had a 50% relative reduction (95% CI 33% to 61%) in the percentage of patients with ≥5 inappropriate shocks (LIA 25% versus control 50%, $P<0.001$).

Compared with the subgroup of control group patients whose ICDs were programmed to recommended values (153 patients), the LIA group had a 44% relative reduction (95% CI 31% to 54%) in the percentage of patients who received 1 or more shocks (38% for the LIA group versus 68% for the control group with recommended programming, $P<0.001$) and a 50% relative reduction (95% CI 33% to 62%) in the percentage with ≥5 shocks (25% versus 50%, respectively; $P<0.001$). A higher percentage of the LIA group reached the composite end point, defined as the percentage of patients who either did not receive a shock or had ≥3 days of warning before shock (72%), than either the entire control group (50%, $P<0.001$) or the subgroup whose ICDs were programmed with recommended values (56%, $P=0.002$).

ICD Alert Triggers and Patient Response to Alerts

Figure 2 shows that alerts were triggered without shocks or before shocks in a significantly higher percentage of patients in the LIA group than in the control group (LIA 86% versus control 58%, $P<0.001$). Overall, a similar percentage of LIA and control group patients met conditions for impedance alerts (LIA 53% versus control 58%, $P=0.329$); however, in the LIA group, the oversensing trigger was the only trigger activated in 33% of patients and was the first or only trigger in 46%.

Figure 3 shows that patients received medical attention sooner after alerts in the LIA group than in the control group ($P<0.001$). At 3 and 15 days, the fractions of interrogated ICDs were 42% (95% CI 35% to 51%) and 83% (95% CI 75% to 89%) in the LIA group versus 11% (95% CI 6% to 19%) and 40% (95% CI 30% to 51%), respectively, in the control group. Although a majority of shocked patients in both groups had no warning or less than 1 day of warning (LIA 54% versus control 64%), more than one-fourth of

Table 2. Patient Characteristics of Control and LIA Groups

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>LIA Group</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y, mean±SD</strong></td>
<td>61.3±15.9</td>
<td>60.7±15.4</td>
<td>0.674</td>
</tr>
<tr>
<td>Gender, % male (95% CI)</td>
<td>75 (69, 81)</td>
<td>70 (63, 76)</td>
<td>0.278</td>
</tr>
<tr>
<td>ICD type, VR/DR/CRT, %</td>
<td>23/43/34</td>
<td>24/38/38</td>
<td>0.599</td>
</tr>
<tr>
<td>Remote monitoring, % (95% CI)</td>
<td>67 (60, 73)</td>
<td>68 (61, 74)</td>
<td>0.918</td>
</tr>
</tbody>
</table>

VR indicates single chamber; DR, dual chamber; and CRT, cardiac resynchronization.

Figure 1. Histogram shows percentages of patients who received any inappropriate shocks or ≥5 inappropriate shocks in each study group. Error bars denote 95% CIs. RR indicates relative reduction.
shocked patients in both groups had ≥3 days of warning (27% versus 29%).

ICD Response to Alerts

Shocks Prevented by NID Increase in the LIA Group

After LIA warnings, there were 38 aborted shocks in 25 patients (1 aborted shock in 14 patients, 2 aborted shocks in 9 patients, and 3 aborted shocks in 2 patients) that would have been delivered with the nominal NID. Additionally, there were 31 oversensing episodes in 22 patients that were not detected inappropriately as VF but would have been detected inappropriately at the nominal NID. Figure 4 shows examples of stored electrograms.

Electrogram Diagnostics

Among patients who did not receive shocks, electrograms of oversensing events were stored in a higher percentage of LIA patients than control patients (LIA group 78% [102/131] versus control 17% [11/63], P<0.001).

Predictive Value of LIA Warnings

LIA was installed in 1144 of the 2770 Fidelis patients with intact leads whose lead performance was being tracked prospectively. We conducted follow-up of these patients for 442 patient-years after LIA software was downloaded. There were 18 LIA warnings, 1 each in 18 patients. Of these, 15 were caused by lead fractures. Eight fractures were confirmed by RPA; 7 fractures were diagnosed clinically. Of the remaining 3 alerts, 1 each was caused by a header-connector problem that required surgical revision, gradually increasing impedance that did not require intervention, and true VF storm. The false-positive alert during VF storm occurred because a sufficient number of intervals between true ventricular activations were short enough to be classified as nonphysiological. Thus, the positive predictive value was 83% (15/18, 95% CI 59% to 96%) for a lead fracture and 89% (16/18, 95% CI 65% to 99%) for a problem that required surgical correction. The rate of false-positive triggers for events other than lead fracture was 0.0068 per patient-year.

Discussion

This prospective study demonstrates that the LIA reduces inappropriate shocks due to lead fractures compared with a concurrent control group monitored by conventional alerts based on impedance. LIA software was downloaded during follow-up visits into many models of clinically approved ICDs by use of a standard programmer. It is the first downloadable software designed to enhance the performance of nominally functioning ICDs and the first ICD monitoring feature that triggers real-time changes in ICD programming.

Early and Accurate Diagnosis of Lead Failure

Defibrillation leads are the weakest link in ICD systems. Despite alerts based on impedance, inappropriate shocks are the most common presentation of lead failures. The rationale for a lead failure diagnostic that incorporates oversensing in addition to impedance is that oversensing is the causal antecedent of inappropriate shocks. A fracture may generate sufficient oversensing to cause inappropriate shocks either without an impedance increase or with an impedance increase in the interval between daily impedance measurements. A high sensing-integrity count of nonphysiological short intervals ≤130 ms has been proposed as a single sensitive oversensing criterion to diagnose lead fracture but is nonspecific.

In a retrospective simulation, LIA was a more sensitive indicator of Fidelis fractures than impedance monitoring alone. On the basis of this simulation, the LIA software was released, recommended by professional societies, and downloaded into many thousands of ICDs. The present prospective study validates the clinical value of LIA in patients with Fidelis fractures: The percentage who had either no inappropriate shock or ≥3 days of warning was 72% in patients monitored by LIA, higher than the percentage in those monitored by impedance only (50%) and comparable to the previously reported percentage for LIA in a retrospective simulation (76%). Preliminary reports of 2 single-center retrospective studies also support the benefit of LIA.
However, most diagnoses of lead fracture in these studies were based only on ICD diagnostics, which have limited specificity for lead fracture and cannot distinguish header-connector problems from fractures. The present study provides the largest reported series of fractured leads confirmed by structural analysis of explanted leads.

**Preventing Inappropriate Shocks**

Several components of LIA are designed to work together to reduce inappropriate shocks: Addition of the oversensing trigger to the impedance trigger; immediate activation of audible tones and Internet-based alerts; frequent audible tones; and an increase in the VF NID. The present data indicate that each component contributed to reducing shocks: Oversensing was the first or only LIA trigger in 46% of patients; patients received medical attention more rapidly after LIA warnings than after standard impedance alerts; and some shocks that would have been delivered at lower programmed values of NID were aborted after LIA automatically increased NID.

**Clinical Approach After LIA Warning**

We found that patients responded faster to alerts that sounded every 4 hours than those that sounded daily. Our prospective data confirmed prior retrospective simulation, individual cases, and a preliminary report that indicated that the interval between LIA warning and inappropriate shock may be short. Thus, the value of the LIA depends on timely response by both patient and physician. Because 27% of shocked LIA patients had delays of 3 days or more, prompt response may further reduce inappropriate shocks. We had insufficient data to determine the reasons for delay in each case; however, we are aware of individual cases in which either patients or physicians misinterpreted audible alerts or patients did not hear the alert tone. Use of remote monitoring with wireless-telemetry ICDs permits automatic transmission of LIA notifications and might reduce delays if physicians respond promptly. In the present study, too few patients had automated LIA notifications transmitted by remote monitoring to determine whether automatic alerts reduce shocks caused by lead fractures.
Once a patient presents with an alert, physicians should disable detection of VF to prevent patients from receiving inappropriate shocks during evaluation.\textsuperscript{21} In a retrospective simulation, the positive predictive value of LIA was 72\% for lead fracture and 81\% for problems that required surgical revision.\textsuperscript{5} The corresponding prospectively determined values in the present study were 83\% and 89\%, respectively. The LIA in newer ICDs was modified to require an abrupt increase for activation of the impedance trigger, which reduced the number of false-positive alerts.\textsuperscript{22} Nevertheless, diagnostic steps\textsuperscript{5,12,13} should be performed before surgery to exclude a false-positive alert. These include review of electrograms with single, short intervals after LIA triggers (Figure 4B and 4C) that provide previously unavailable recordings of transient oversensing.

**Downloadable Software in ICDs**

Although downloadable software has been used to test investigational features in limited numbers of ICDs,\textsuperscript{28} LIA is the first downloadable algorithm developed to enhance nominally functioning ICDs, and it can be downloaded into almost all of the manufacturer’s presently implanted ICDs. Within a year of its release, LIA was downloaded into 73\% of Fidelis patients who use remote monitoring. Thus, many thousands of previously implanted ICD systems were upgraded to reduce the risk of inappropriate shocks without surgical revision.

Downloadable software upgrades are common in consumer electronics and computers. Given the increasing memory of ICDs, increasing pulse-generator longevity, risks associated with generator replacement, and rapid software innovation, LIA may set a precedent for upgrading software in nominally functioning ICDs to improve patient care.

**Study Limitations**

First, we assumed that inappropriate shocks would have been equally likely in the LIA group and control group if LIA had not been downloaded. In support of this assumption, the 2 groups did not differ significantly in the percentage of patients who had impedance alerts. Thus, a similar percentage in each group would have had warnings if LIA had not been downloaded. Second, we assumed that the benefit of LIA applied to all Fidelis fractures, not just to fractures analyzed by RPA. We studied only fractures confirmed by RPA to remove diagnostic uncertainty inherent in the clinical diagnosis of lead fracture.\textsuperscript{5,20} Third, because of the consecutive method of patient selection, we assumed that our patients were representative of patients whose fractures are analyzed by RPA, but we lack complete clinical data. Fourth, LIA software cannot be downloaded into ICDs from other manufacturers.

**Conclusions**

LIA reduces inappropriate shocks caused by lead fractures compared with conventional impedance monitoring. It is most valuable when patients and physicians respond rapidly to alerts. LIA is the first downloadable software developed to upgrade almost all presently implanted, nominally functioning ICDs from 1 manufacturer. It may set a precedent for downloadable upgrades of implanted electronic devices to improve patient care.

**Acknowledgments**

We thank Ron Behrendt, David Griffon, Ryan Keillor, Mike Lenarz, Shelby Li, James Payne, Taryn Randall, Kathy Schultz, Jay Wilcox, and Julia Yang for data analysis and Linda Chaman for manuscript preparation.

**Sources of Funding**

This study was funded by Medtronic Inc.

**Disclosures**

Drs Swerdlow and Ellenbogen are consultants to Medtronic and have received speaking honoraria from Medtronic. Messrs Gunderson, Ousdigian, Abeyratne, and Sachanandani are employees of Medtronic.

**References**

15. Herrmann C, von zur Muhlen F, Schumann A, Buss U, Kemper S, Wantzen C, Gonska BD. Standardized assessment of psychological...


**CLINICAL PERSPECTIVE**

Fractures of pace-sense electrodes in implantable cardioverter-defibrillator patients are a common cause of inappropriate shocks. To reduce inappropriate shocks, we developed a lead-integrity alert (LIA) triggered by either oversensing or high impedance that can be downloaded into previously implanted implantable cardioverter-defibrillators. This prospective study tested the hypothesis that the LIA would reduce the percentage of patients who receive inappropriate shocks compared with a concurrent control group monitored by impedance only. Each group included a prospectively determined sample size of 213 consecutive patients with fractures confirmed by structural analysis of explanted leads. The LIA group had a 46% relative reduction (95% confidence interval 34% to 55%) in the percentage of patients with ≥1 inappropriate shock (LIA 38% versus control 70%, *P*<0.001) and a 50% relative reduction (95% confidence interval 33% to 61%) in the percentage with ≥5 shocks (25% versus 50%, *P*<0.001). These data show that a software download that upgrades previously implanted implantable cardioverter-defibrillators without surgical revision reduces inappropriate shocks caused by lead fractures.
Downloadable Software Algorithm Reduces Inappropriate Shocks Caused by Implantable Cardioverter-Defibrillator Lead Fractures: A Prospective Study
Charles D. Swerdlow, Bruce D. Gunderson, Kevin T. Ousdigian, Athula Abeyratne, Haresh Sachanandani and Kenneth A. Ellenbogen

_Circulation_. 2010;122:1449-1455; originally published online September 27, 2010; doi: 10.1161/CIRCULATIONAHA.110.962407
_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/122/15/1449

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/