Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate

A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, MD; Pieter W. Kamphuisen, MD; Meertien K. Sijpkens, BSc; Joost C. Meijers, PhD; Harry R. Buller, MD; Marcel Levi, MD

Background—Rivaroxaban and dabigatran are new oral anticoagulants that specifically inhibit factor Xa and thrombin, respectively. Clinical studies on the prevention and treatment of venous and arterial thromboembolism show promising results. A major disadvantage of these anticoagulants is the absence of an antidote in case of serious bleeding or when an emergency intervention needs immediate correction of coagulation. This study evaluated the potential of prothrombin complex concentrate (PCC) to reverse the anticoagulant effect of these drugs.

Methods and Results—In a randomized, double-blind, placebo-controlled study, 12 healthy male volunteers received rivaroxaban 20 mg twice daily (n = 6) or dabigatran 150 mg twice daily (n = 6) for 2½ days, followed by either a single bolus of 50 IU/kg PCC (Cofact) or a similar volume of saline. After a washout period, this procedure was repeated with the other anticoagulant treatment. Rivaroxaban induced a significant prolongation of the prothrombin time (15.8 ± 1.3 versus 12.3 ± 0.7 seconds at baseline; P < 0.001) that was immediately and completely reversed by PCC (12.8 ± 1.0; P < 0.001). The endogenous thrombin potential was inhibited by rivaroxaban (51 ± 22%; baseline, 92 ± 22%; P < 0.002) and normalized with PCC (114 ± 26%; P < 0.001), whereas saline had no effect. Dabigatran increased the activated partial thromboplastin time, ecarin clotting time (ECT), and thrombin time. Administration of PCC did not restore these coagulation tests.

Conclusion—Prothrombin complex concentrate immediately and completely reverses the anticoagulant effect of rivaroxaban in healthy subjects but has no influence on the anticoagulant action of dabigatran at the PCC dose used in this study.

Clinical Trial Registration—URL: http://www.trialregister.nl. Unique identifier: NTR2272. (Circulation. 2011;124:00-00.)

Key Words: anticoagulants ■ coagulation ■ hemorrhage ■ thrombosis ■ trials

Vitamin K antagonists have been the only oral anticoagulants for the treatment of venous thromboembolism for decades despite their unpredictable pharmacology and their slow onset and offset of action. Vitamin K antagonists require frequent monitoring because of a substantial risk of undertreatment or overtreatment. Several new oral anticoagulants with more stable pharmacokinetic and pharmacodynamic profiles have been licensed for clinical practice or are in the final stage of clinical development. At this moment, dabigatran (a direct thrombin inhibitor) and rivaroxaban (a direct factor Xa inhibitor) are the most extensively evaluated novel anticoagulant agents. Both anticoagulants have little interaction with food or drugs and can therefore be prescribed in a fixed dose without the requirement of frequent monitoring. They have been shown to be effective and safe in large trials in the prevention and treatment of venous thromboembolism (VTE) and prevention of stroke in atrial fibrillation. This has led to the registration of both drugs in Europe and Canada for the prevention of VTE in elective orthopedic surgery. Dabigatran has also been licensed recently in Canada and the United States for stroke prevention in atrial fibrillation; registration in Europe will probably follow soon. For rivaroxaban, a submission for stroke prevention in atrial fibrillation treatment was filed in the United States and Europe.

Editorial see p ●●●

Clinical Perspective on p ●●●

In clinical practice, use of these new anticoagulants will facilitate patient care because their properties obviate the need for frequent laboratory testing and dose adjustment. Nevertheless, a drawback is the absence of an antidote.
Regardless of the relative short half-life of these agents, immediate reversal of the anticoagulant effect may be needed in case of major bleeding or emergency surgery. No studies in humans have assessed the ability of prohemostatic drugs to antagonize the anticoagulant effect of either rivaroxaban or dabigatran. Hypothetically, prothrombin complex concentrate (PCC) could overcome the anticoagulant effect induced by thrombin and factor Xa inhibitors because PCC contains the coagulation factors II, VII, IX, and X in a high concentration and in general enhances thrombin generation. In animals, infusion with PCC reversed the effect of rivaroxaban. Unfortunately, results for dabigatran are not as clear-cut. In an animal bleeding model, PCC reversed the effect of dabigatran on hemostatic parameters but had no effect on coagulation assays. Another possible method of reversal is dialysis, although this is an invasive and burdensome procedure, and about one third of dabigatran is bound to plasma proteins and can therefore not be dialyzed. Dialysis is also not suitable for rivaroxaban, which is 95% bound to protein.

This study evaluated the possibility of using PCC to reverse the anticoagulant effect of a randomized, placebo-controlled, crossover trial in healthy volunteers who were treated with dabigatran and rivaroxaban.

Methods

Study Design

Twelve healthy male subjects were included in this randomized, double-blind, placebo-controlled, crossover trial. All gave written informed consent, and the study was approved by the medical ethics committee of the Academic Medical Center of Amsterdam, the Netherlands. The study was registered at the Dutch trial register (http://www.trialregister.nl; identifier, NTR2272). The 12 volunteers in this study first received either dabigatran or rivaroxaban for 2 1/2 days. The last dose of the anticoagulant was taken on the third day with no food consumption. On that third day, subjects were admitted to the hospital for infusion with either PCC or a similar volume of saline. Blood was then collected up to 24 hours after the infusion. After a washout period of 11 days, the healthy subjects received the other anticoagulant drug following the same protocol (Figure 1). All volunteers received financial compensation for the time spent on the study. Subjects were seen at the Clinical Trial Unit, which is an extension of the Cardiac Care Unit of the Academic Medical Center in Amsterdam. Subjects were unblinded to the anticoagulant but blinded to placebo or Cofact. Technicians in the Department of Experimental Vascular Medicine performed the laboratory analyses and were blinded to the treatment administered.

Subjects

Healthy volunteers without a relevant medical history were included. All subjects had normal blood count and normal kidney and liver function. All were tested and found to be negative for hepatitis B and C and HIV.

Study Agents

Dabigatran (Pradaxa, Boehringer Ingelheim, Ingelheim, Germany) and rivaroxaban (Xarelto, Bayer, Leverkusen, Germany) are oral anticoagulants that act rapidly and reach steady-state levels almost immediately after their initiation. Both drugs lose most of their effect within 24 hours; the half-life of dabigatran is 14 to 17 hours and of rivaroxaban is 5 to 9 hours. Dabigatran was provided in capsules of 150 mg twice daily for 2 1/2 days, similar to doses used for the treatment of VTE or atrial fibrillation. Rivaroxaban tablets of 20 mg were given twice daily for 2 1/2 days, a regimen that is higher than the initial dose for the treatment of acute VTE, which is 15 mg twice daily. The dose was chosen for practical reasons: 15-mg and 5-mg tablets are not available yet. Cofact (Sanquin Blood Supply, Amsterdam, the Netherlands) is a nonactivated PCC derived from human plasma. It contains a high concentration of the procoagulation factors II, VII, IX, and X, as well as the natural anticoagulants protein C and S and antithrombin. No heparin is added to Cofact. The specific activity of Cofact is based on the level of factor IX.

In this trial, a fixed dose of 50 U PCC/kg body weight was chosen because the anticoagulant effect of rivaroxaban and dabigatran on bleeding time in animal experiments was reversed most effectively by the same amount (50 U/kg) of another PCC, Beriplex. Prothrombin complex concentrate is administered intravenously, and any anticipated effect is seen immediately after infusion. Cofact 500 IU was reconstituted with 20 mL sterile water before administration.

Blood Collection and Processing

On the day of admission, subjects were given 2 venous catheters: 1 for the infusion of Cofact or placebo and 1 for the collection of blood samples. The catheter for blood samples was flushed with saline, and when blood was collected, the first 5 mL blood was discarded. Citrate tubes were used for blood samples and centrifuged at 15°C for 20 minutes. Platelet-poor plasma was then prepared and frozen at −80°C before processing. Blood was drawn at baseline, on the third day of anticoagulant treatment before infusion, and at 15 minutes, 30 minutes, and 1, 2, 4, 6, and 24 hours after infusion with Cofact or placebo.

Figure 1. Flowchart of the study, a randomized, double-blind, placebo-controlled, crossover trial with healthy male subjects (n=12).
Laboratory Assays
Blood coagulation tests shown to measure the effect of both rivaroxaban and dabigatran most precisely were assessed. For rivaroxaban, the prothrombin time (PT) is affected in a concentration-dependent manner. Thrombin generation as measured by the endogenous thrombin potential (ETP) decreases with rivaroxaban.

For dabigatran, the activated partial thromboplastin time (aPTT) was chosen, although the dose-response curve is not linear and results vary per reagent. The ETP lag time was also used because it is the parameter of the ETP that is influenced most by dabigatran. A much more precise monitoring method for dabigatran than the aPTT is the thrombin clotting time (TT); however, the test can be too sensitive. Although the TT displays a linear dose-response curve for the direct thrombin inhibitor, once steady-state levels are achieved, the assay often becomes immeasurably prolonged. The prolongation of the ECT caused by dabigatran is linear curved and does not exceed measurable quantifications.

The PT, aPTT, and TT were performed on an automated coagulation analyzer (Behring Coagulation System XP) with reagents and protocols from the manufacturer (Siemens Healthcare Diagnostics, Marburg, Germany). The ECT was performed by adding ecarin (1.25 U/mL; Pentapharm LTD, Basel, Switzerland) to plasma and determining the clotting time with the Behring Coagulation System. The Calibrated Automated Thrombogram assays the generation of thrombin in clotting plasma using a microtiter plate–reading fluorometer (Fluoroskan Ascent, ThermoLab Systems, Helsinki, Finland) and Thrombinoscope software (Thrombinoscope BV, Maastricht, the Netherlands). The assay was carried out as described by Hemker et al and the Thrombinoscope manual. Coagulation was triggered by recalcification in the presence of 5 pmol/L recombinant human tissue factor (Innovin, Siemens Healthcare Diagnostics, Marburg, Germany). 4 μmol/L phospholipids, and 417 μmol/L Z-Gly-Gly-Arg-AMC (Bachem, Bubendorf, Switzerland), a fluorogenic substrate. The ETP and related parameters were calculated with the Thrombinoscope software.

Statistical Analysis
SPSS 16.0 was used to perform paired t tests with repeated measures ANOVA for validation. Comparison between groups was analyzed with independent-sample t tests. A value of P < 0.05 was considered statistically significant. Values are presented as mean ± SD.

Results
Twelve healthy male volunteers with an average age of 24 ± 4 year and a body mass index of 23 ± 3 kg/m² were included in this study.

Adverse Events
No major or clinically relevant bleeding complications occurred during treatment, nor were there any other serious adverse events. After removal of the venous catheter, 2 volunteers receiving rivaroxaban and 2 receiving dabigatran developed a small hematoma at the site of infusion. Two other subjects who received dabigatran had gingival bleeds; another subject suffered from a nosebleed, which stopped spontaneously after 1 minute; and 1 subject noticed that a shaving cut bled longer than normal. One subject was diagnosed with diabetes mellitus de novo after his plasma was found to be lipemic on several occasions while the volunteer had fasted for >8 hours. Additional laboratory tests showed persistently high triglycerides and a high serum fasting glucose. His coagulation tests were not influenced by the diabetes mellitus or hypertriglyceridemia; therefore, he was not withdrawn from the study.

Rivaroxaban
Prothrombin Time
The PT was significantly prolonged by rivaroxaban (15.8 ± 1.3 versus 12.3 ± 0.7 seconds at baseline; P < 0.001). Immediately after the infusion of PCC, the PT completely normalized (12.8 ± 1.0 seconds; P < 0.001), which was sustained for 24 hours. As Figure 2A shows, infusion with saline did not reverse the PT prolongation (16.2 ± 0.8 seconds; P = 0.4), and 6 hours after infusion, the PT was still clearly prolonged.

Endogenous Thrombin Potential
Treatment with rivaroxaban decreased the ETP from 92 ± 22% at baseline to 51 ± 21% (P = 0.002). After administration of PCC, the ETP normalized to 114 ± 26% (P < 0.001), whereas saline infusion had no effect (41 ± 6%; P = 0.2; Figure 2B). The effect of PCC persisted for all subsequent measurements, whereas the ETP was still lower after 24 hours compared with baseline in the subjects receiving saline.

Dabigatran
Activated Partial Thromboplastin Time
The aPTT was significantly increased after administration with dabigatran from 33.6 ± 3.3 to 59.4 ± 15.8 seconds (P < 0.001; Figure 3A). Prothrombin complex concentrate had no effect on the aPTT prolongation (70.3 ± 15.1 seconds; P = 0.21), nor did saline (aPTT, 57.9 ± 10.3 seconds; P = 0.64). There was no difference in the aPTT between placebo and PCC (P = 0.13). The aPTT only normalized after 24 hours (Figure 3A).

Endogenous Thrombin Potential Lag Time
The ETP lag time was prolonged by the use of dabigatran from 2.9 ± 0.4 to 7.5 ± 2.5 minutes (mean ± SD; P < 0.001). Prothrombin complex concentrate had no effect on the ETP lag time prolongation (8.7 ± 2.6 minutes; P = 0.20), nor did saline (8.5 ± 2.2 minutes; P = 0.22).

Thrombin Time
The TT was >120 seconds in all subjects with dabigatran, the upper limit for the TT (Figure 3B). The prolongation remained immeasurable both after placebo and PCC infusion (P = 0.36 for both, repeated measures ANOVA; Figure 3B) for at least 6 hours.

Ecarin Clotting Time
Administration of dabigatran significantly prolonged the ECT from 33 ± 1 seconds at baseline to 69 ± 26 seconds after 3 days of dabigatran intake (P = 0.002). This prolongation was not reversed by administration of PCC; it even slightly further increased to 86 ± 20 seconds (P = 0.08). The same pattern was observed for the subjects who received placebo (P = 0.42, PCC versus placebo; Figure 3C).

Discussion
Dabigatran and rivaroxaban are 2 novel oral anticoagulant agents that have been shown to be safe and effective for the treatment and prophylaxis of VTE and for the prevention of stroke in atrial fibrillation. Following these results, both drugs were registered for VTE prevention despite the lack of
information on the proper method to neutralize their anticoagulant activity. Findings from this study, the first conducted in humans, indicate that a nonactivated PCC immediately reverses the effect of full-dose rivaroxaban in healthy individuals but not dabigatran at the PCC dose used in this study.

Prothrombin complex concentrate (Cofact) was chosen as a method of reversal for both rivaroxaban and dabigatran for the following reasons. It contains 4 coagulation factors, namely factors II (prothrombin), VII, IX, and X, that stimulate thrombin formation, thereby potentially bypassing the anticoagulant effect of both drugs. The assessment of the reversal of the anticoagulant effects was based on coagulation assays shown to be sensitive in previous studies.16,22

Indeed, rivaroxaban influenced both the PT and ETP significantly. On the basis of these tests, the anticoagulant effect of rivaroxaban was completely reversed immediately after infusion of 50 U/kg PCC in all subjects, an effect that persisted until the last measurement after 24 hours. Similar results were previously obtained in a rat model with rivaroxaban in which mesenteric bleeding times and coagulation assays (PT) were measured after administration of Beriplex, a PCC. The dose of 25 U Beriplex/kg body weight had no effect on bleeding time, but 50 U Beriplex/kg body weight normalized the bleeding time.14,21 A dose of 50 U/kg was therefore chosen, but we cannot rule out that a lower dose may have been sufficient. Results from the ETP show an increase over time, suggesting perhaps a surplus of thrombin generation. Nevertheless, these results are not seen immediately after the infusion of PCC, and further research is needed to confirm the efficacy of a lower dose of PCC for the reversal of rivaroxaban.

The anticoagulant effect of dabigatran was monitored by the aPTT, lag time of the ETP, TT, and ECT because these assays seemed most sensitive to the direct thrombin inhibitor.
In particular, TT and ECT show linear dose-response curves for dabigatran. Dabigatran treatment clearly prolonged the aPTT, ETP lag time, TT, and ECT in all subjects. Subsequent administration of 50 U/kg PCC had no effect on these assays. In a previous rat-tail bleeding model, Feiba (activated PCC) had no influence on an aPTT prolonged by dabigatran. However, Feiba reversed the bleeding time prolongation caused by dabigatran. Furthermore, in a rabbit kidney injury bleeding model, Beriplex was able to dose-dependently reverse the prolonged bleeding time and the amount of blood loss after dabigatran administration. This discrepancy between the PCC effect on plasma coagulation assays and bleeding time raises the question of whether the coagulation tests adequately monitor the potential of PCC for reversal in cases of bleeding associated with dabigatran. Coagulation assays are obviously only surrogate markers for a bleeding tendency. On the other hand, animal bleeding models may not be representative of major hemorrhagic events in humans.

Figure 3. A, Effect of dabigatran followed by prothrombin complex concentrate (PCC) or placebo on the activated partial thromboplastin time (aPTT; mean ± SD). \( P = 0.21 \) for PCC, repeated measures ANOVA. B, Effect of dabigatran followed by PCC or placebo on the thrombin time (TT; mean ± SD). \( P = 0.36 \) for PCC, repeated measures ANOVA. C, Effect of dabigatran followed by PCC or placebo on the ecarin clotting time (ECT; mean ± SD). \( P = 0.08 \) for PCC, repeated measures ANOVA.

On the basis of the findings in the present study, at the PCC dose used in this study, there is no evidence to support the use of PCC to neutralize the anticoagulant effect of direct thrombin inhibitors. The question of how the effect of dabigatran can be antagonized remains unanswered. A possible candidate may be recombinant factor VIIa; this agent reduced the tail bleeding in the previously mentioned rat model with dabigatran. Recombinant factor VIIa, however, only partially restored the aPTT from 58 ± 8 to 27 ± 2 seconds (baseline aPTT, 7 ± 0.5 seconds). Additionally, a study using a single bolus of recombinant factor VIIa saw no reversal effect on melagatran, another direct thrombin inhibitor, based on aPTT, ETP, and other coagulation markers. A potential limitation of our study is that we used only 1 dose of 1 particular PCC. This does not exclude the potential of an alternative strategy for reversal of dabigatran anticoagulation, eg, by repeatedly administering PCC, by administering recombinant factor VIIa, or by using a combination of PCC and recombinant...
factor VIIa. Studies investigating such reversal strategies for dabigatran have not yet been performed.

Whereas recombinant factor VIIa had no reversal effect on melagatran, it normalized the prolongation of coagulation assays as caused by the factor Xa inhibitors fondaparinux and idraparinux. Although recombinant factor VIIa and PCC are different procoagulants, this result may support our findings, showing that factor Xa inhibition is easier to overcome than thrombin inhibition.28,29

This study was conducted in 12 young healthy male volunteers, and the effect of the PCC was based on surrogate markers, namely coagulation tests. Extrapolating these findings to clinical practice must therefore be done with caution in the absence of a clinical study in which the effect of PCC is assessed in patients who are treated with these new anticoagulant drugs and develop major bleedings or need to undergo invasive interventions. No measurements were performed between 6 and 24 hours after infusion of PCC or placebo. If PCC had any effect of reversal for dabigatran during this time, it may have been missed; similarly, any rebound effect on the anticoagulant activity of rivaroxaban in that same period could not be observed. On the other hand, because both anticoagulants have relative short half-lives (14–17 hours for dabigatran, 5–9 hours for rivaroxaban), an increase in anticoagulant activity is not expected in this specific period. Because PCCs act directly on infusion, any late effect on reversal of dabigatran is unlikely. Finally, as all the figures demonstrate, the measurements at 24 hours after infusion are in line with previous measurements.

Another limitation of this trial may be the small size of the study population, accounting for some variation in the results of a few coagulation tests. The prolongation of the TT and ETP after rivaroxaban treatment was nevertheless significant, as was the reversal with PCC (Cofact). The double-blind, randomized crossover study design may have overcome part of this limitation.

A relatively high dose of PCC of 50 U/kg was used, which may be more than necessary. This dose was based on animal studies in which the influence of rivaroxaban only normalized at 50 U/kg of Beriplex, another PCC.24 Similar doses of Cofact and Beriplex may not lead to the same procoagulant effect, however. Not all PCCs contain similar levels of anticoagulants protein C and S.21 More protein C and S may lead to less thrombin generation; consequently, other PCCs may not produce similar results at a dose of 50 U/kg. Alternative PCCs may therefore be more beneficial in the reversal of dabigatran than the PCC used in this study. Furthermore, a lower or even higher dose may be required for a comparable effect concerning the reversal of rivaroxaban. However, a direct comparative study is required to draw definite conclusions. The increase in thrombin generation beyond baseline after PCC infusion in subjects with rivaroxaban may also indicate that a lower dose is sufficient. Similar doses of PCCs have nevertheless been used for reversal of vitamin K antagonists for a long period, and several studies have shown their safety and efficacy. Side effects such as thrombosis are rare, and transmission of blood-borne infections has not been described with the modern preparation of this PCC.30

Conclusions

This is the first study in humans that investigated the effect of a PCC (Cofact) for reversal of these new anticoagulant agents. Cofact clearly neutralized the anticoagulant effect of rivaroxaban, a factor Xa inhibitor, but had no effect on dabigatran, a direct thrombin inhibitor, at the PCC dose used in this study. Although this trial may have important clinical implications, the effect of PCC has yet to be confirmed in patients with bleeding events who are treated with these anticoagulants.

Acknowledgments

We thank the personnel of the Department of Experimental Vascular Medicine for laboratory analyses.

Sources of Funding

This study was supported by an unrestricted research grant from Sanquin, the Netherlands, which also supplied PCC.

Disclosures

Dr Kamphuisen has served as a consultant for Bayer, Boehringer, CSL Behring, and Ablynx and has received investigator-initiated research grants from Bayer, LeolPharma, Pfizer, and CSL Behring. Dr Buller has served as a consultant to Sanofi-Aventis, Bayer, Pfizer, Glaxo-Smith-Kline, Astellas, Boehringer-Ingehelm, and Daichichi-Sankyo. The other authors report no conflicts.

References

Eerenberg et al

PCC for Reversal of Rivaroxaban and Dabigatran

CLINICAL PERSPECTIVE

Dabigatran and rivaroxaban are new oral anticoagulants that have been evaluated for the prevention and treatment of arterial and venous thrombosis and have subsequently been licensed in the United States, Canada, and Europe for various indications. Both drugs have stable pharmacodynamic profiles, obviating repeated laboratory control and dose adjustments, thereby making them an attractive replacement for vitamin K antagonists such as warfarin. A big disadvantage of these new anticoagulant agents is the lack of a method of reversal in case of major hemorrhage or the need to perform emergency invasive procedures. In the present study, for the first time, the effect of prothrombin complex concentrate was assessed in healthy volunteers who were anticoagulated with either drug. Results from this study show that prothrombin complex concentrate completely and directly reversed the effect of rivaroxaban on the coagulation system, whereas the effect of dabigatran was unaffected. We believe these results are highly relevant for a broad audience such as cardiologists, physicians, and other specialists treating patients with anticoagulant agents. With both drugs on the market, the risk of severe bleeding complications or the need for reversal in case of emergency surgery is clearly present, and the results from this study, when confirmed in the clinical situation, may serve to guide management for these patients.

14. Pezborn E, Trabandt A, Selbach K, Tinel H. Prothrombin complex concentrate completely and directly reversed the effect of rivaroxaban on the coagulation system, whereas the effect of dabigatran was unaffected. We believe these results are highly relevant for a broad audience such as cardiologists, physicians, and other specialists treating patients with anticoagulant agents. With both drugs on the market, the risk of severe bleeding complications or the need for reversal in case of emergency surgery is clearly present, and the results from this study, when confirmed in the clinical situation, may serve to guide management for these patients.
Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate: A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects
Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers, Harry R. Buller and Marcel Levi

Circulation. published online September 6, 2011;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 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/early/2011/09/06/CIRCULATIONAHA.111.029017

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/