Venous Thromboembolism: Mechanisms, Treatment, and Public Awareness

New Anticoagulants for Treatment of Venous Thromboembolism

Peter L. Gross, Jeffrey I. Weitz

Abstract—Anticoagulant therapy is the cornerstone of treatment of venous thromboembolism (VTE). Such treatment is divided into 2 stages: Rapid initial anticoagulation is given to minimize the risk of thrombus extension and fatal pulmonary embolism, whereas extended anticoagulation is aimed at preventing recurrent VTE, thereby reducing the risk of postphlebitic syndrome. With currently available drugs, immediate anticoagulation can only be achieved with parenteral agents, such as heparin, low-molecular-weight heparin, or fondaparinux. Extended treatment usually involves the administration of vitamin K antagonists, such as warfarin. Emerging anticoagulants have the potential to streamline VTE treatment. These agents include idraparinux, a long-acting synthetic pentasaccharide that is given subcutaneously on a once-weekly basis, and new oral anticoagulants that target thrombin or factor Xa. This article (1) reviews the pharmacology of these agents, (2) outlines their potential strengths and weaknesses, (3) describes the results of clinical trials with these new drugs, and (4) identifies the evolving role of new anticoagulants in the management of VTE.

Key Words: venous thromboembolism ■ new anticoagulants ■ factor Xa ■ inhibitors ■ thrombin inhibitors

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity and mortality. In the United States, it is estimated that 2 million people develop DVT each year. DVT progresses to PE in 600 000 of these patients, and the PE is fatal in 200 000.1,2 In addition to PE, DVT can lead to debilitating postphlebitic syndrome in up to one-third of patients.3 The risk of postphlebitic syndrome is highest in patients with extensive DVT and in those with recurrent disease.

Anticoagulant therapy remains the cornerstone of VTE treatment. Such treatment is usually divided into 2 stages. Rapid initial anticoagulation is given to minimize the risk of thrombus extension and subsequent fatal PE, whereas extended anticoagulation is administered to prevent recurrent VTE, thereby reducing the risk of postphlebitic syndrome. With currently available drugs, immediate anticoagulation can only be effected with parenteral anticoagulants, such as heparin, low-molecular-weight heparin (LMWH), or fondaparinux. Extended therapy usually involves the administration of an oral anticoagulant. Currently, the only orally available anticoagulants are the vitamin K antagonists, such as warfarin.

LMWH and fondaparinux have simplified the initial treatment of VTE.4–8 Both agents have better bioavailability after subcutaneous injection and a longer half-life than heparin. In addition, they produce a more predictable anticoagulant response. These features permit once daily subcutaneous dosing without coagulation monitoring. Consequently, the majority of patients with VTE can now be treated with LMWH or fondaparinux as outpatients, an approach that reduces healthcare costs7–9 and enhances patient satisfaction.10

Although LMWH and fondaparinux are important advances in VTE treatment, some difficulties persist. The need for once daily subcutaneous injections renders treatment problematic for some patients. This has prompted the introduction of longer acting parenteral anticoagulants that can be given subcutaneously on a once-weekly basis, and the development of novel oral anticoagulants with a rapid onset of action.

Warfarin also is problematic in the setting of VTE. Its slow onset of action necessitates overlap with a parenteral anticoagulant for at least 5 days.11 The therapeutic dose of warfarin varies from patient to patient reflecting, at least in part, differences in dietary vitamin K intake, genetic polymorphisms in the enzymes involved in warfarin metabolism, and administration of concomitant medications that suppress or potentiate the anticoagulant effects of warfarin.11 Frequent coagulation monitoring is necessary to ensure that a therapeutic anticoagulant response is achieved with warfarin because a subtherapeutic response is associated with an increased risk of thrombosis, whereas excessive anticoagulation increases the risk of hemorrhage.11 The requirement for frequent coagulation monitoring is burdensome for patients and physicians and costly for the healthcare system. The difficulties surrounding warfarin administration have spurred the development of new oral anticoagulants that can be given in fixed doses with little or no coagulation monitoring. The
need for such agents has increased in recent years with emerging evidence that patients with unprovoked VTE require anticoagulation therapy for at least 6 months after their index event, and possibly longer.12

New anticoagulants under investigation for VTE treatment include novel parenteral and orally active agents. Concentrating on drugs that have at least reached phase III clinical testing, this article (1) reviews their pharmacology, (2) highlights the potential advantages of these novel agents over existing anticoagulants, (3) describes the results of the clinical trials evaluating these new agents for VTE treatment, and (4) provides perspective on the opportunities for these drugs and their potential drawbacks.

**Pharmacology of New Anticoagulants**

The new anticoagulants that are under investigation for VTE treatment target factor Xa or thrombin. The factor Xa inhibitors include indirect inhibitors, such as idraparinux and SSR 126517, its biotinylated counterpart, parenteral drugs that target factor Xa in an antithrombin-dependent fashion, and rivaroxaban and apixaban, orally active agents that directly inhibit factor Xa. Dabigatran etexilate is an orally active direct inhibitor of thrombin (Figure).

Inhibitors of factor Xa block thrombin generation, whereas thrombin inhibitors block the activity of thrombin, the enzyme that catalyzes the conversion of fibrinogen to fibrin. Whether thrombin generation is attenuated or thrombin action is suppressed, the net effect is a reduction in thrombin activity and fibrin formation, events that result in inhibition of coagulation. Limiting thrombin generation or activity is critical because, in addition to its role in fibrin formation, thrombin serves as a potent platelet agonist and amplifies its own generation by feedback activation of factors VIII and V, key cofactors involved in factor Xa and thrombin generation, respectively.

Focusing first on the factor Xa inhibitors and then covering the thrombin inhibitors, the pharmacology of these new anticoagulants will be discussed.

**Idraparinux**

A second generation synthetic pentasaccharide, idraparinux, is a hypermethylated derivative of fondaparinux that binds antithrombin with such high affinity that it assumes a plasma half-life of 80 h,13 a half-life similar to that of antithrombin (Table 1). Idraparinux exhibits complete bioavailability after subcutaneous injection, binds only to antithrombin in plasma, and produces a predictable anticoagulant response.13 Consequently, idraparinux can be given by subcutaneous injection once-weekly and does not require coagulation monitoring.

Like fondaparinux, idraparinux is not metabolized and is excreted unchanged via the kidneys. Therefore, the dose of idraparinux must be reduced in patients with renal insufficiency, and idraparinux is contraindicated in those with a creatinine clearance less than 30 mL/min. The safety of idraparinux in pregnancy is uncertain.

There is no antidote for idraparinux. Protamine sulfate, which neutralizes the anticoagulant effects of heparin, does not bind to idraparinux and will not reverse its anticoagulant activity. SSR 126517 was developed to address this problem.

**SSR 126517**

A biotinylated version of idraparinux, SSR 126517 shares the pharmacological features of idraparinux (Table 1).14 The addition of the biotin moiety permits rapid reversal of the anticoagulant effects of SSR 126517 after intravenous injection of avidin. An egg white–derived protein, avidin binds biotin with high affinity to form a stable complex that is cleared within minutes via the kidneys.

**Rivaroxaban**

An oxazolidinone derivative with a molecular weight of 436, rivaroxaban is a potent and selective inhibitor of factor Xa.15 It binds to the active site of factor Xa and inhibits the enzyme in a reversible and competitive fashion regardless of whether factor Xa is free in solution or bound within the prothrombinase complex.16 Rivaroxaban is well absorbed from the gastrointestinal tract with a bioavailability more than 80%, and food has no major effect on its absorption. Plasma levels of the drug peak in about 3 h. The terminal half-life is ≈5 to 9 h in young individuals, and 11 to 13 h in the elderly.17 Rivaroxaban exhibits a dual mechanism of excretion. Approximately 66% is excreted via the kidneys, and the remainder is excreted in the feces. Intestinal excretion of rivaroxaban appears to be mediated, at least in part, by P-glycoprotein, a transport protein, because potent P-glycoprotein inhibitors increase drug levels. Of that found in the urine, ≈30% to 40% reflects unchanged drug that is excreted via a combination of glomerular filtration and tubular secre-
tion, whereas the remainder reflects metabolites. Because of its renal clearance, rivaroxaban must be used with caution in patients with renal insufficiency.

Rivaroxaban is metabolized in the liver via CYP 3A4, CYP 2J2, and CYP-independent mechanisms. The drug is contraindicated in patients with severe liver disease because metabolic inactivation may be impaired. Caution must also be exercised in patients receiving treatment with potent inhibitors of both CYP3A4 and P-glycoprotein, such as ketoconazole or ritonavir. Reduced fecal and renal clearance of rivaroxaban by these drugs can cause an exaggerated anticoagulant effect.

Like other direct factor Xa inhibitors, rivaroxaban prolongs the prothrombin time (PT) and activated partial thromboplastin time (aPTT), with the PT being more sensitive than the aPTT depending on the reagents used for testing. However, the effect of the drug on these tests is short-lived, with prolongation only seen at peak drug levels. Factor Xa inhibition is the best test to monitor drug concentrations in plasma.

Apixaban
A small molecule inhibitor of the active site of factor Xa, apixaban has a molecular weight of 460. Apixaban is a selective and reversible inhibitor of factor Xa and, like rivaroxaban, it inhibits factor Xa bound within the prothrombinase complex as well as the free enzyme. The drug is absorbed from the gastrointestinal tract with a bioavailability of more than 50%, and peak plasma levels are achieved in about 3 h. With repeated doses, the terminal half-life is between 9 and 14 h.

Apixaban is metabolized in the liver via CYP3A4 and CYP-independent mechanisms. Like rivaroxaban, apixaban exhibits a dual mechanism of excretion. Approximately 25% is excreted via the kidneys, whereas the remainder appears in the feces.

Apixaban prolongs the INR and the aPTT in a concentration-dependent fashion. However, its effect on these tests is minimal at therapeutic concentrations. It can be monitored using a factor Xa inhibition assay or a dilute prothrombin time.

Dabigatran Ettexilate
An oral direct thrombin inhibitor, dabigatran etexilate is a double prodrug that is converted by esterases into its active metabolite, dabigatran (BIBR 953), once absorbed from the gastrointestinal tract. The molecular weight of dabigatran etexilate is 628, whereas dabigatran has a molecular weight of 471. Because bioconversion of dabigatran etexilate to dabigatran begins in the gut, the drug enters the portal vein as a combination of prodrug and active compound. Once in the liver, bioconversion of the prodrug is completed and about 20% is conjugated and excreted via the biliary system. The cytochrome P450 system plays no part in the metabolism of dabigatran etexilate. Therefore, the risk of drug-drug interactions is low.

Because the bioavailability of dabigatran etexilate is only approximately 6%, relatively high doses of dabigatran etexilate must be given to ensure that adequate plasma concentrations are achieved. The absorption of dabigatran etexilate in the stomach and small intestine is dependent on an acid environment. To promote such a microenvironment, dabigatran etexilate is provided in tartaric acid-containing capsules. Drug absorption is reduced by 20% to 25% if dabigatran-treated patients are given proton pump inhibitors. Levels of dabigatran peak in the blood about 2 h after dabigatran etexilate administration. The half-life of dabigatran is approximately 8 h after single dose administration and up to 14 to 17 h after multiple doses.

About 80% of circulated dabigatran is excreted unchanged via the kidneys. Consequently, plasma concentrations increase in patients with renal insufficiency. The drug is contraindicated in patients with renal failure.

Dabigatran etexilate prolongs the aPTT, but its effects on this test are not dose-dependent. It has minimal effect on the PT but prolongs the ecarin clotting time in a concentration-dependent fashion.

Clinical Trials With New Anticoagulants
Idraparinux has completed phase III clinical trials for VTE treatment, and trials with SSR 126517 are underway. Phase II trials with rivaroxaban, apixaban, and dabigatran etexilate have been completed, and phase III trials are underway with all 3 agents.

Idraparinux
The phase III Van Gough DVT and PE trials randomized 2904 patients with acute symptomatic DVT and 2215 patients with PE to either a 3- or 6-month course of once-weekly idraparinux (at a dose of 2.5 mg) or to conventional anticoagulant therapy with LMWH or heparin followed by a vitamin K antagonist with the dose adjusted to achieve a target international normalized ratio (INR) between 2 and 3. In the DVT patients, the primary efficacy outcome, the rate of recurrent venous thromboembolism at 3 months, was similar in the idraparinux and conventionally-treated groups (2.9% and 3.0%, respectively). At 3 months, clinically relevant bleeds were less common with idraparinux than with conventional treatment (4.5% and 7.0%, respectively; P=0.004). In the PE patients, idraparinux was less effective than conventional anticoagulant therapy at 3 months. Thus, the rate of recurrent VTE was 3.4% in those treated with idraparinux and 1.6% in those given conventional therapy. Rates of clinically relevant bleeding at 3 months in patients treated with idraparinux or conventional anticoagulant therapy were 5.8% and 8.2%, respectively. The discordant efficacy results in the DVT and PE trials highlight the importance of adequate levels of anticoagulation for initial treatment of PE because the majority of the recurrences occurred early in idraparinux-treated patients. These findings suggest that PE patients require higher initial doses of idraparinux than DVT patients. The safety of higher dose treatment remains to be established.

The efficacy of long-term idraparinux therapy was evaluated in the Van Gough extension trial, which enrolled 1215 patients from the DVT or PE trials who had received 6 months of treatment with either idraparinux or a vitamin K antagonist. Patients were randomized to an additional 6 months of treatment with either idraparinux or a vitamin K antagonist.25 Patients were randomized to an additional 6
months of treatment with either subcutaneous idraparinux (2.5 mg once-weekly) or placebo. Compared with placebo, idraparinux reduced the rate of recurrent VTE from 3.7% to 1.0%, a highly significant 72.9% risk reduction ($P=0.002$). Major bleeding occurred in 3.7% of those given idraparinux and included 3 fatal intracranial bleeds. In contrast, there were no major bleeds in patients randomized to placebo. These findings suggest that although effective compared with placebo, idraparinux causes excessive bleeding. Consequently, further development of idraparinux has been halted and the focus has turned to SSR 126517. It is unclear, however, whether rendering idraparinux reversible through biotinylination will improve the benefit-to-risk profile of the drug.

**SSR 126517**
Phase III trials with SSR 126517 are underway. A bio-equivalent study is comparing anti-Xa levels in 700 DVT patients randomized to once-weekly 2.5 mg dose of SSR 126517 or idraparinux. In a subset of patients, the effect of intravenous avidin on anti-Xa levels will be examined. The Cassiopeia trial is randomizing patients with PE to a 3- or 6-month course of treatment with once-weekly SSR 126517 (at a dose of 3 mg) or to conventional therapy with heparin or LMWH followed by a vitamin K antagonist. The primary efficacy outcome will be recurrent VTE at 3 months.

**Rivaroxaban**
Two phase II trials have been done in patients with DVT. The first trial randomized 613 such patients to a 3-month course of rivaroxaban (at doses of 10, 20, or 30 mg once-daily or 40 mg twice-daily), or to LMWH followed by a vitamin K antagonist. The primary efficacy outcome, a reduction in thrombus burden based on improvement in the results of repeated ultrasound evaluation at 21 days and no evidence of recurrent VTE, was achieved in 43.8% to 59.2% of those given rivaroxaban and in 45.9% of those given conventional anticoagulant therapy. The second trial randomized 543 patients with proximal DVT to a 3-month course of once-daily rivaroxaban (at doses of 20, 30, or 40 mg) or to conventional anticoagulant therapy. The primary efficacy end point, a composite of symptomatic recurrent VTE plus an increase in thrombus burden (as detected by repeated ultrasound and perfusion lung scanning), occurred in 6% of those randomized to rivaroxaban and in 9.9% of those given conventional therapy. There was no apparent dose-response for efficacy with rivaroxaban in either trial. Rates of major bleeding were low both with rivaroxaban and conventional therapy. Based on the results of these trials, phase III trials evaluating rivaroxaban for initial and extended treatment of VTE are using the 20 mg once-daily dose.

**Apixaban**
In a phase II trial, 520 patients with proximal DVT were randomized to a 3-month course of treatment with apixaban (at doses of 5 or 10 mg twice-daily or 20 mg once-daily) or to conventional anticoagulant therapy with LMWH or fondaparinux followed by a vitamin K antagonist. The primary efficacy end point, a composite of recurrent VTE and increased thrombus burden (as detected by repeated ultrasound and perfusion lung scanning), occurred in 6.0%, 5.6%, and 2.6% of patients given apixaban at doses of 5 or 10 mg twice daily or 20 mg once daily, respectively, and in 4.2% of those treated with conventional therapy. Rates of major plus clinically relevant nonmajor bleeding were 8.6%, 4.5%, and 7.3% in the apixaban arms, respectively, and 7.9% in those given conventional treatment. Based on these results, phase III trials will evaluate both a 2.5- and a 5-mg twice-daily regimen of apixaban for initial and extended treatment of VTE.

**Dabigatran Etexilate**
An extensive phase III program is underway with dabigatran etexilate, which includes its evaluation for VTE treatment. No phase II trials have been done with dabigatran etexilate in the VTE setting. Nonetheless, the drug is being studied for initial and extended VTE treatment at a dose of 150 mg twice daily, a dose that has been evaluated in phase II for stroke prevention in atrial fibrillation and has been carried forward into phase III for this indication.

**Opportunities for New Anticoagulants in VTE Treatment**
The introduction of LMWH was a major advance in the initial management of VTE. With once- or twice-daily subcutaneous injection and no need for coagulation management, LMWH shifted initial management of most VTE patients from the hospital to the outpatient setting. The new anticoagulants have the potential to further streamline care and may offer safety advantages over existing agents. Whereas LMWH and fondaparinux must be given by daily subcutaneous injection, idraparinux or its biotinylated counterpart have the advantage of once-weekly dosing. If higher dose SSR 126517 proves as effective and safe as conventional anticoagulation for treatment of PE, the drug could be used as an alternative to LMWH or fondaparinux for initial VTE treatment. Thus, a single subcutaneous injection of SSR 126517 could provide anticoagulation coverage while waiting for a therapeutic response with warfarin, an approach that would simplify management of patients incapable of self injection.

All of the new oral inhibitors of factor Xa or thrombin have a rapid onset of action with peak plasma levels achieved within 2 to 4 h (Table 2). Thus, these agents produce an anticoagulant response in the same timeframe as subcutaneously injected LMWH or fondaparinux. With rapid onset of action, the new oral anticoagulants have the potential to obviate the need for a parenteral anticoagulant for initial VTE management. In addition to eliminating the need for daily injection of LMWH or fondaparinux for initial treatment, new oral anticoagulants also offer advantages over warfarin for extended VTE therapy. With fixed dosing and no need for coagulation monitoring, the new agents will be more convenient than warfarin. If they also cause less bleeding than warfarin, new oral anticoagulants may expand the indications for long-term anticoagulation in patients with unproven VTE.

Ximelagatran, an oral direct thrombin inhibitor that was withdrawn from the world market because of potential hepatic toxicity, exhibited both efficacy and safety for initial
or extended VTE treatment. The findings with ximelagatran validate thrombin as a target. Although the results with fondaparinux suggest that drugs that target factor Xa are effective and safe for initial VTE management, the results with idraparinux in PE patients raise a note of caution. Ongoing studies with high dose SSR 126517 and with rivaroxaban and apixaban will help to clarify the appropriateness of factor Xa as a target for long-term VTE treatment.

With once-weekly subcutaneous injection and no need for coagulation monitoring, SSR 126517 may have a place in the long-term management of VTE provided that its efficacy and safety are confirmed in the phase III trials. However, the availability of shorter-acting oral thrombin or factor Xa inhibitors may limit the need for a long-acting parenteral agent.

**Potential Drawbacks of New Anticoagulants**

The major complication of all anticoagulants is bleeding. When a patient receiving anticoagulant therapy presents with a major bleed, it is desirable to have a safe rapidly-acting antidote to reverse the anticoagulant effects. An antidote also is useful when anticoagulant-treated patients require urgent surgery or suffer from major blunt trauma. Apart from SSR 126517, none of the new agents has a specific antidote. Although not well studied, dialysis is likely to clear the direct factor Xa or thrombin inhibitors, all of which are small molecules.

The experience with ximelagatran has highlighted the challenges of bringing new anticoagulants to the clinic. The unexpected effect of ximelagatran on hepatic enzymes led to its ultimate withdrawal. Because the mechanism responsible for this side effect has yet to be identified, it is difficult to predict whether other oral direct thrombin or factor Xa inhibitors will have the same problem. A phase III trial evaluating the utility of dabigatran etexilate for stroke prevention in patients with atrial fibrillation recently completed enrolment. Of the almost 18 000 patients entered in the trial, two-thirds received dabigatran etexilate. Although follow-up is ongoing, the lack of a safety signal in this trial bodes well for the hepatic safety of this drug.

Although the new anticoagulants have been designed to be given without coagulation monitoring, there are instances where monitoring is helpful. For example, when LMWH is used for VTE treatment, the drug is not routinely monitored. However, anti-Xa levels are often measured to inform LMWH dosing in obese patients or in those with renal impairment. Likewise, anti-Xa levels also may prompt an increase or decrease in LMWH dose if patients present with recurrent thrombosis or bleeding, respectively. What about monitoring the new oral anticoagulants? Monitoring may be needed in patients with hepatic or renal impairment or in those taking concomitant medications that may affect anticoagulant metabolism. Unless the target drug level is known, however, how will appropriate dose adjustments be made with the new agents?

How best to monitor the new anticoagulants is uncertain. SSR 126517 can be monitored using antifactor Xa assays, but the tests must be performed using this drug as a standard. Even if this is done, the therapeutic range for SSR 126517 has yet to be established. Monitoring is more complicated for the oral factor Xa and thrombin inhibitors. These agents have variable effects on routine tests of coagulation, and none of the routine tests provide a good indication of drug levels. Factor Xa inhibition assays may prove useful to monitor oral factor Xa inhibitors. However, these assays have not been standardized and the therapeutic level is likely to vary among the different agents. These issues will need to be addressed as the development of new anticoagulants moves forward. Although the ecarin clotting time can be used to monitor dabigatran etexilate, the test is not available in all laboratories and it has yet to be standardized.

In the absence of routine coagulation monitoring, compliance with new anticoagulants may be difficult to assess. Careful attention to drug packaging and ongoing supervision of patients may help to minimize this problem.

Finally, the cost of new anticoagulants will impact on their uptake, particularly if these drugs prove only to be as safe and effective as existing agents. Although regulatory agencies may approve the new agents on the basis of noninferiority compared with warfarin, payers are unlikely to embrace the higher cost of new anticoagulants in the absence of superior efficacy or safety over warfarin. Warfarin may be difficult to administer in an effective fashion, but it is inexpensive, even
with the added expense of coagulation monitoring. Unless the cost of the new anticoagulants is relatively low, these drugs are likely to be reserved for patients who cannot be adequately controlled on warfarin, or for those without ready access to a laboratory.

Conclusions and Future Directions

New anticoagulants have the potential to further refine VTE treatment. Still unknown is the role of these agents in the management of high-risk VTE patients, such as those with underlying cancer. The safety of these agents in pregnancy also is uncertain.

Recent studies showing an advantage of long-term LMWH over warfarin for patients with VTE in the setting of cancer have prompted some clinicians to use LMWH for such patients. There also has been a suggestion that LMWH improves survival in cancer patients, although this hypothesis requires confirmation. Oral direct thrombin or factor Xa inhibitors may be more convenient than LMWH in cancer patients, a concept that deserves exploration.

Currently, heparin or LMWH is used for VTE treatment during pregnancy. The safety of SSR 126517 in this setting has yet to be established. If safe, SSR 126517 would have the advantage of once-weekly injection. The availability of an oral anticoagulant that is safe in pregnancy would represent an even greater advance.

Never before have we been in a situation where so many anticoagulants are available for study. Emerging data suggest that factor Xa and thrombin are both good targets for new anticoagulants. Whether thrombin generation is attenuated or thrombin activity is suppressed, the relative efficacy and safety appear to be similar. Because head-to-head trials comparing factor Xa inhibitors with thrombin inhibitors are parallel development of these 2 classes of anticoagulants.

Emerging data suggest an even greater advance. An oral anticoagulant that is safe in pregnancy would represent an advance over warfarin for patients with VTE in the setting of cancer.

Acknowledgements

Dr Weitz holds the Canada Research Chair in Thrombosis and the HSFO/J.F. Mustard Chair in Cardiovascular Research. Dr Gross is the recipient of a Hamilton Health Sciences, William E. Noonan Research Career Award.

Disclosures

Dr Weitz has served on Scientific Advisory Boards or acted as a consultant for Sanoﬁ-Aventis, Bayer, Boehringer Ingelheim, and BMS.

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doi: 10.1161/ATVBAHA.108.162677
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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