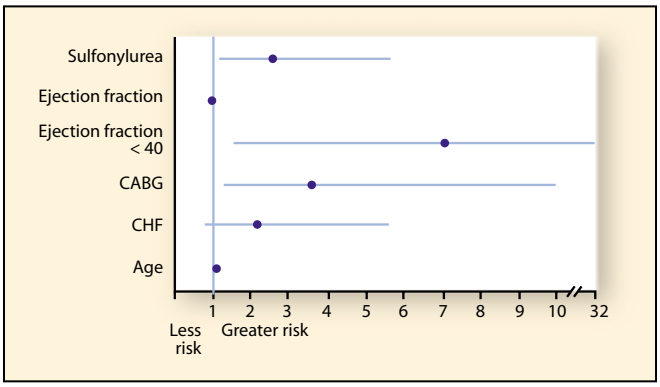

Figure 1. *Multivariate correlates of in-hospital mortality. CABG, coronary artery bypass graft; CHF, congestive heart failure. Adapted with permission from Garratt et al.*

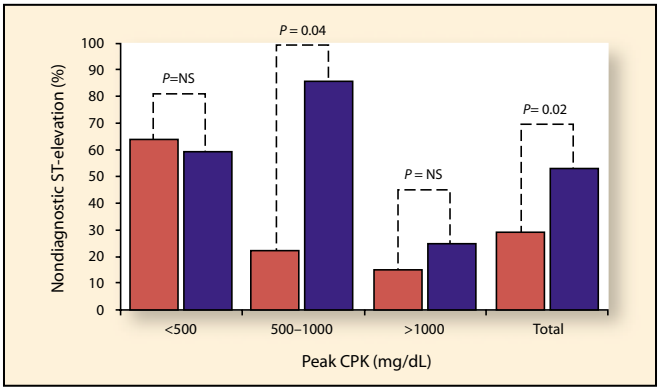

Figure 2. *Nondiagnostic ST-segment elevation during acute myocardial infarction, subdivided by infarct size (total of 88 patients). Red bars = control; purple bars = sulfonylureas. NS, nonsignificant; CPK, creatinine phosphokinase. Adapted with permission from Huizar et al.*

endogenous fibrinolytic system through enhanced production of proinsulin, which is known to stimulate endothelial production of plasminogen activator inhibitor-1.

The study by Huizar and colleagues was a retrospective review of diabetic patients who presented to the Metro West Medical Center with a diagnosis of AMI from October 1996 through August 2000 who met diagnostic criteria for thrombolytic therapy. They were divided into those who were taking SUDs and those who were not. Patients with a left or right bundle-branch block, paced rhythms, and left ventricular hypertrophy were excluded. The first ECG on presentation to the emergency department was evaluated for the presence of ST-elevation. Eighty-eight diabetic patients met the criteria for inclusion. A significantly greater number of nondiagnostic ST-segment elevations was observed in the SUD group than in the non-SUD group (53% vs 29%, $P = .02$) (Figure 2).

The implication of these results, despite the limitations of the trial (outlined in an accompanying editorial by Brady and Jovanovic[2]), is that diabetic patients treated with SUDs who present with an AMI will be less likely to have an ECG meeting criteria for thrombolysis and therefore might not be treated at presentation with either thrombolytic agents or primary percutaneous transluminal coronary angioplasty. This could result in a delay in the patient receiving maximal therapy and thus in worse outcomes. The authors conclude that until the question of whether SUDs have a cardiotoxic effect is resolved their use in patients with cardiovascular disease should "remain a cause for concern to cardiologists…."

Certainly with the variety of agents now available to treat diabetic patients, particularly the thiazolidinediones (Avandia [GlaxoSmithKline, Research Triangle Park, NC] and Actos [Takeda Pharmaceuticals, Lincolnshire, IL]), the biguanide metformin, and the combination agent Avandamet (GlaxoSmithKline), with their positive metabolic effects on lipids and coagulation, we now have first- and second-line options available other than the SUDs for treating diabetic patients, most of whom have occult or clinically significant cardiovascular disease. As we have learned from the treatment of hypertension, it is not only getting to our treatment goal that matters, but also how we get there. ■

References

1. Garratt K, Brady P, Hassinger N, et al. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol.* 1999;33:119–124.
2. Brady P, Jovanovic A. The sulfonylurea controversy: much ado about nothing or cause for concern? *J Am Coll Cardiol.* 2003;42:1022–1025.

Thrombolysis

Long-Term Management of Venous Thromboembolism

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Recently, several important studies have been completed and published that have evaluated the intensity of long-term anticoagulation in patients at risk for recurrent thromboembolism. Two studies specifically looked at the intensity of warfarin therapy to

prevent recurrent venous thromboembolism in patients diagnosed with venous thromboembolism. One study examined the intensity of warfarin therapy for the prevention of recurrent thrombosis in patients with antiphospholipid antibody syndrome.

Long-Term, Low-Intensity Warfarin Therapy for the Prevention of Recurrent Venous Thromboembolism

Ridker PM, Goldhaber SZ, Danielson E, et al.
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The Prevention of Recurrent Venous Thromboembolism (PREVENT) investigation was designed to determine whether low-intensity warfarin therapy (a target international normalized ratio [INR] of 1.5–2.0) would reduce the frequency of recurrent venous thromboembolism in patients who had experienced an episode of idiopathic venous thromboembolism and had received full-dose oral anticoagulation therapy for at least 3 months. The authors reasoned that low-intensity warfarin therapy would be protective against venous thromboembolism without subjecting the patients to a significant risk for bleeding, as had been reported in previous trials that used full-dose (target INR of 2.0–3.0) warfarin therapy. The trial also sought to determine whether individuals with a genetic predisposition for venous thromboembolism (ie, the presence of either factor V Leiden or the prothrombin gene mutation) would be particularly likely to benefit from long-term, low-intensity warfarin therapy.

Patients with idiopathic venous thromboembolism who had already received full-dose warfarin therapy for at least 3 months were randomized to low-intensity warfarin therapy (target INR of 1.5–2.0) or placebo. Patients were followed for an average of 4.3 years. The trial was terminated earlier than intended, after 508 patients had undergone randomization. The reason for the termination was that the data safety monitoring committee deemed that those patients receiving low-intensity warfarin therapy had a significantly reduced risk of recurrent venous thromboembolism compared with patients receiving placebo. Of the 253 patients assigned to placebo, 37 had recurrent venous thromboembolism, whereas of the 255 patients assigned to low-intensity warfarin therapy, 14 had recurrent venous thromboembolism. Thus, low-intensity warfarin therapy was associated with a 64% risk reduction of recurrent venous thromboembolism: 2.6 per 100 person-years in the low-intensity warfarin group versus 7.2 per 100 person-years in the placebo group. A similar benefit was realized in the 77 patients who had either factor V Leiden or the prothrombin gene mutation. In these patients, recurrent venous thromboembolic events were significantly reduced in the low-intensity warfarin group (2.2 per 100 person-years) compared with the placebo group (8.6 per 100 person-years). Major bleeding requiring hospitalization occurred infrequently, affecting two patients (0.4 per 100 person-years) in the placebo group and five patients (0.9 per 100 person-years) in the warfarin treatment group. Minor bleeding or bruising occurred more often in the warfarin than in the placebo group (60 vs 34 patients) and accounted for a hazard ratio of 1.92. Low-dose warfarin therapy reduced the rate of a composite endpoint (recurrent venous thromboembolism, major hemorrhage, or death from any cause) by 48%. Thus, the authors concluded that long-term, low-intensity warfarin therapy was an effective treatment to prevent recurrent venous thromboembolism.

Recent clinical trials in patients with idiopathic venous thromboembolism have found that anticoagulant therapy, when administered for at least 3 to 12 months after the initial event, reduces the risk of recurrent venous thromboembolism compared with placebo.[1–3] Thus, anticoagulant therapy for up to 1 year has become the standard of care for patients after the first episode of idiopathic venous thromboembolism. This trial is the first to extend that notion. It found that patients remained at risk for recurrent venous thromboembolism beyond the 12-month period after the signal event and that long-term therapy with low-intensity warfarin significantly reduces the risk of recurrent venous thromboembolism without substantially increasing the risk of major bleeding. Moreover, the findings were applicable to those with and without a genetic predisposition for venous thromboembolism. These findings should promote a modification in our practice paradigm, such that treatment of patients with idiopathic venous thromboembolism should be continued for at least 4 years and perhaps indefinitely. The results of this trial indicate that low-intensity warfarin, targeting an INR of 1.5 to 2.0, is both safe and effective.

Comparison of Low-Intensity Warfarin Therapy With Conventional-Intensity Warfarin Therapy for Long-Term Prevention of Recurrent Venous Thromboembolism

Kearon C, Ginsberg JS, Kovacs MJ, et al.
N Engl J Med. 2003;349:631–639.

Previous studies have suggested that the annual rate of major hemorrhage with conventional-intensity warfarin (INR of 2.0–3.0) was 4% to 9%.[2,4,5] The Extended Low-Intensity Anticoagulation for Thrombo-Embolism (ELATE) investigators performed a randomized, double-blind study

to assess the efficacy and safety of low-intensity warfarin therapy (target INR of 1.5–1.9) to conventional-intensity warfarin therapy (target INR of 2.0–3.0) in patients who had experienced idiopathic venous thromboembolism. All patients had completed 3 or more months of warfarin therapy. Of 738 patients who were included in this trial, 369 were randomized to low-intensity warfarin therapy, and 369 were assigned to conventional-intensity therapy. Patients were followed for an average of 2.4 years.

Recurrent venous thromboembolism occurred in 16 patients in the low-intensity treatment group, compared with six in the conventional-intensity treatment group. Thus, conventional-intensity warfarin therapy reduced the risk of recurrent venous thromboembolism by 63%, from 1.9 to 0.7 per 100 person-years. There were 16 deaths in the low-intensity group and eight deaths in the conventional-intensity group. Major bleeding occurred in nine patients in the low-intensity group and eight patients in the conventional-intensity group, accounting for 1.1 and 0.9 events per 100 person-years, respectively. Minor bleeding occurred in 30 patients in the low-intensity group and 23 patients in the conventional-intensity group. Thus, the findings refuted the investigators' initial hypothesis: they concluded that conventional-intensity warfarin therapy (targeting an INR of 2.0–3.0) is more effective than low-intensity warfarin therapy (INR of 1.5–1.9) for the prevention of recurrent venous thromboembolism. Moreover, they found that the risk of clinically important bleeding was not reduced by low-intensity compared with high-intensity warfarin.

This study reinforced the need for long-term anticoagulant therapy, extending beyond 12 months after an initial episode of venous thromboembolism, to prevent recurrent venous thromboembolism. In this respect, the study supports the notion put forward in the PREVENT study, that patients with idiopathic venous thromboembolism require prolonged anticoagulant therapy, for at least several years and perhaps indefinitely. It is remarkable that rates of recurrent venous thromboembolism in the low-intensity warfarin groups were so similar between the two studies (2.6 per 100 person-years in PREVENT and 1.9 per 100 person-years in ELATE). However, the ELATE study refutes the notion that low-intensity warfarin therapy is good enough and that higher-intensity warfarin therapy is associated with a greater risk of bleeding. Indeed, in this study, there was a significant reduction in the risk for recurrent venous thromboembolism in patients randomized to conventional-intensity therapy without a significant increase in adverse bleeding events. However, a closer look at the data makes that conclusion more circumspect. Indeed, of the 16 events of recurrent venous thromboembolism in the low-intensity group, five occurred after warfarin therapy had been discontinued; in the conventional-intensity group, three of six recurrent venous thromboembolic events occurred after warfarin therapy had been discontinued. Most notably, of nine patients in the low-intensity therapy group in whom INR values were available at the time of bleeding, five had values in excess of 2.9 (up to 11.3), whereas in the conventional-intensity group the INR ranged from 3.1 to 7.5 in four of eight patients who had major bleeding. Thus, in spite of the treatment assignment, the anticoagulant status of a significant fraction of patients with a major bleeding episode in the low-intensity warfarin group was greater than intended. Nonetheless, that does not negate the fact that high-dose warfarin therapy, with a target INR of 2.0 to 3.0, was more effective in reducing the recurrent venous thromboembolism. Taking the conclusions of these two studies together, it is appropriate to consider long-term use of warfarin therapy in patients who have experienced an episode of idiopathic venous thromboembolism, as long as there is no predisposition to bleeding or other contraindications for other anticoagulant therapy. Although the intensity of therapy seems to be settled, it must be recognized that the ability to maintain a patient's target INR between 2.0 and 3.0 must meet those same standards that occur in clinical trials and requires meticulous follow-up by the patient's health care provider.

Taking the conclusions of these two studies together, it is appropriate to consider long-term use of warfarin therapy in patients who have experienced an episode of idiopathic venous thromboembolism, as long as there is no predisposition to bleeding or other contraindications for other anticoagulant therapy.

A Comparison of Two Intensities of Warfarin for the Prevention of Recurrent Thrombosis in Patients With the Antiphospholipid Antibody Syndrome

Crowther MA, Ginsberg JS, Julian J, et al.
N Engl J Med. 2003;349:1133–1138.

Patients with antiphospholipid antibody syndrome and a history of thrombosis are at increased risk for recurrent thrombosis and require long-term oral anticoagulant therapy. Previous studies have suggested that the risk of recurrent thrombosis in these patients was less if they

received high-intensity warfarin therapy, with a target INR of 3.1 to 4.5, than if they received less-intense therapy.[6,7] Patients with antiphospholipid antibody syndrome were not included in the PREVENT or ELATE trials.

To determine the most effective and safest oral anticoagulant regimen for patients with a history of thrombosis and antiphospholipid antibody, Crowther and colleagues performed a randomized, double-blind study in which patients were randomized to receive moderate-intensity warfarin (target INR of 2.0–3.0) or high-intensity warfarin (target INR of 3.1–4.0). There were 114 patients who participated in this study: 56 randomized to high-intensity warfarin and 58 randomized to moderate-intensity warfarin. They were followed for an average of 2.7 years. The signal event in eligible patients was a confirmed arterial or venous thrombosis in patients who had a positive test for antiphospholipid antibodies on two occasions. The primary outcome was an episode of recurrent thrombosis, defined as stroke or transient ischemic attack, myocardial infarction, peripheral arterial thrombosis, cerebral vein thrombosis, deep vein thrombosis, or pulmonary embolism.

Recurrent thrombosis occurred in six patients receiving high-intensity warfarin and in two patients receiving moderate-intensity warfarin. Thus, patients in the high-intensity group were three times more likely to have recurrent thrombosis than those in the moderate-intensity group. Of the six recurrences in the high-intensity group, one patient had discontinued warfarin, and in three patients the INR values were 0.9, 1.0, and 1.9, respectively. Of the two recurrent thromboses in the moderate-intensity group, the INR values were 1.6 and 2.8. Major bleeding occurred in three patients receiving high-intensity warfarin and in four receiving moderate-intensity warfarin.

The findings of this study refuted the authors' hypothesis that high-intensity warfarin would be more effective than moderate-intensity warfarin therapy. Indeed, moderate-intensity warfarin was as effective—possibly more effective—in reducing recurrent thromboses than high-intensity warfarin therapy. Moreover, there was no difference in major bleeding rates between the two treatment groups. Although there was no placebo group in this study, it stands to reason that patients with antiphospholipid antibody and an episode of thrombosis are at high risk for recurrent thrombosis. Therefore, patients who have had an arterial or venous thrombosis and are found to have antiphospholipid antibodies require long-term therapy with warfarin, sufficient to achieve an INR of 2.0 to 3.0, to prevent recurrent thrombosis. ■

References

1. Schulman S, Rhedin AS, Lindmarker P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. Duration of Anticoagulation Trial Study Group. *N Engl J Med.* 1995;332:1661–1665.
2. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med.* 1999;340:901–907.
3. Agnelli G, Prandoni P, Santamaria MG, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. *N Engl J Med.* 2001;345:165–169.
4. Fihn SD, Callahan CM, Martin DC, et al. The risk for and severity of bleeding complications in elderly patients treated with warfarin. The National Consortium of Anticoagulation Clinics. *Ann Intern Med.* 1996;124:970–979.
5. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med.* 1998;105:91–99.
6. Khamashta MA, Cuadrado MJ, Mujic F, et al. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med.* 1995;332:993–997.
7. Ruiz-Irastorza G, Khamashta MA, Hunt BJ, et al. Bleeding and recurrent thrombosis in definite antiphospholipid syndrome: analysis of a series of 66 patients treated with oral anticoagulation to a target international normalized ratio of 3.5. *Arch Intern Med.* 2002;162:1164–1169.