Efficacy and Safety of Edifoligide

To the Editor: In the PREVENT (Project of Ex-vivo Vein Graft Engineering via Transfection) IV study, the PREVENT IV investigators[1] found a high proportion of saphenous vein graft failure (VGF) (>25% of grafts) occurring within the first 12 to 18 months after coronary artery bypass graft (CABG) surgery, with more than 40% of the patients who underwent CABG surgery having at least 1 graft occluded within this period. Moreover, pretreatment of harvested saphenous veins with the E2F transcription factor decoy edifoligide with the aim of preventing neointimal hyperplasia and accelerated atherosclerosis did not reduce the failure rate of the venous conduits. The PREVENT IV investigators suggest that a substantial proportion of venous graft failures takes place early in the perioperative period as major adverse cardiac events occur soon after surgery, more frequently in association with graft failure, but they do not provide an explanation for this phenomenon.

Early occlusion of venous conduits is concomitant with significant perturbations of the hemostatic and fibrinolytic system. During the intraoperative period, the prothrombotic burst occurs mainly in patients undergoing CABG surgery with the use of cardiopulmonary bypass (on-pump), but an increase in thrombin generation is detectable both in on-pump and off-pump CABG surgery up to at least 2 months after surgery.[2-4] This suggests that patients undergoing CABG surgery are at risk of developing thrombosis irrespective of the use of cardiopulmonary bypass.

Thus, the prothrombotic postoperative status is likely responsible for the consistent VGF rate observed by the PREVENT IV investigators. This supports the concept that currently recommended postoperative antithrombotic therapy for these patients (low-dose aspirin)[5] is not sufficient for the prevention of VGF. The use of antithrombotic strategies specifically targeted against the generation of thrombin should be considered in future trials in patients undergoing CABG surgery.

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To the Editor: In the PREVENT IV study,[1] edifoligide did not affect the rate of VGF, and on the basis of angiographic data the PREVENT IV investigators concluded that edifoligide did not have an appreciable effect on neointimal hyperplasia. We believe it may be premature to conclude that the lack of clinical benefit is due to a failure to inhibit neointimal proliferation and suggest 3 alternative explanations.

First, remodeling of vein grafts in the early postoperative period is substantial[2,3] and may confound the determination of intimal thickness by luminal angiography. Minor differences in the degree of remodeling of vein grafts could obscure effects on neointimal thickening.

Second, if neointimal proliferation was inhibited, as might be expected from preclinical studies of edifoligide,[4] neointimal proliferation may be more relevant to later causes of VGF (such as providing a substrate for later atherodegenerative change in the vein graft) than to failure in the first 18 months. This is consistent with data presented in Figure 4 of the article,[1] where the progressive but nonsignificant divergence of curves suggests possible later outcome benefits.

Finally, as indicated in the accompanying Editorial by Drs Conti and Hunter,[5] the vein graft preparative technique used for transfection may have promoted VGF above the expected rate, obscuring potential benefits of edifoligide-mediated inhibition of neointimal hyperplasia.

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To the Editor: In the PREVENT IV study[1] comparing vein graft patency between patients receiving gene therapy with edifoligide vs placebo, the PREVENT IV investigators report a 1-year incidence of vein graft occlusion of 26.1% in the edifoligide group and 26.5% in the placebo group. Other contemporary multicenter angiographic studies in patients with a similar burden of coronary disease have found an incidence of 1-year vein graft occlusion of less than 15%,[2,3] substantially lower than that observed by the PREVENT IV investigators. In noting this difference, the authors suggest that the higher occlusion rate they observed may be due to more extensive and diffuse anatomic disease. To fully understand the role of target vessel characteristics on VGF, it would be helpful for the patency results to be stratified by quality and size of the target vessel.

An alternative explanation for the poor graft patency seen in this study may be that exposure of saphenous veins in both the edifoligide group and the placebo group to the pressure-mediated gene-therapy delivery system may have caused damage to the saphenous vein endothelium leading to the high rates of early graft attrition observed in both groups. A third group of control vein grafts that were not exposed to the pressure-mediated gene-therapy delivery system would have provided important information about the validity of the high vein graft occlusion rates.

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In Reply: Dr Parolari and colleagues propose that early VGF may result from coagulation perturbations following cardiopulmonary bypass or cardiac surgery itself. Early VGF has largely been attributed to technical and flow-related factors; however, the systemic and perhaps local perturbations of platelet hemostasis and coagulation that occur with cardiac surgery also may be important.[1] Despite limited randomized clinical trial data supporting efficacy (or safety), dual antiplatelet therapy was used postoperatively in almost 20% of the PREVENT IV participants and was associated with a modestly higher unadjusted rate of VGF than aspirin alone (51% vs 42%; χ^2 P=.002). We support the need for additional research and adequately powered clinical trials on safer, more effective antithrombotic regimens before, during, and after CABG surgery to improve graft patency and more importantly to reduce ischemic and hemorrhagic clinical events.

Mr Lau and Dr Kritharides speculate that edifoligide may affect neointimal proliferation despite neutral angiographic and 12-month clinical findings from the PREVENT IV study. Coronary angiography is an insensitive measure of neointimal hyperplasia, and a small effect of edifoligide on neointimal proliferation cannot be excluded from our study results. Given the absence of an effect on VGF, however, we believe that the nonsignificant trend toward benefit on major adverse cardiac events at 12 months most likely represents a chance effect. Irrespective of the effect of edifoligide, longer-term (5-year) clinical follow-up of the PREVENT IV population is warranted and is ongoing.

Drs Desai and Fremes comment on the relatively high rate of VGF in the PREVENT IV trial. As we discussed, comparisons between studies are challenging. For example, the studies that they cite[2,3] were designed to answer different questions and thus included different patient populations; were substantially smaller than PREVENT IV; were performed at 1 and 13 institutions, respectively, compared with PREVENT IV's 104 centers; and used different definitions of VGF, including only occlusions and not early deaths. We speculated that more extensive disease may partly explain the observed VGF rates and, although not reported in the article, target artery quality was one of the strongest predictors of VGF.[4] An analysis of predictors of VGF is in preparation. Notably, other recent studies also report comparably higher rates of VGF.[5]

Finally, both Lau and Kritharides and Desai and Fremes question whether the pressure-mediated delivery system could have contributed to VGF. This could not be assessed in the PREVENT IV trial. However, in the PREVENT II trial,[6] treatment with edifoligide, including the pressure-mediated delivery system, was associated with a 42% reduction in VGF compared with a control treatment, which involved just placing the grafts into the chamber without pressurization. Based on this experience, we believe it highly unlikely that the delivery system contributed to what likely represents the true contemporary rate of VGF. Research should focus on novel technical, antithrombotic, and alternative antineointimal

hyperplastic approaches to improving vein graft patency and outcomes following CABG surgery.

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Strategies to Prevent Suicide

To the Editor: In their Review article on suicide prevention strategies, Dr Mann and colleagues[1] conclude that recognition of depression and restricted access to lethal methods can reduce suicide rates. Less information is provided about suicidal patients with disorders other than major depression and treatments other than antidepressants. Notably, in bipolar disorder, the risk of suicide is at least as high as in unipolar depression.[2] Evidence for reduced risk of suicide and suicide attempts in bipolar and other mood disorders during long-term treatment with lithium is abundant, consistent, and compelling, including data from randomized, controlled trials.[3-5] Moreover, such efficacy of lithium may exceed that of anticonvulsants with antimanic or proposed mood-stabilizing effects.[3,4]

Given the strong association between clinical depression and suicide, it is puzzling that information pertaining to reduction of suicidal risk with antidepressant treatment remains inconsistent and inconclusive.[5] Ecological analyses have found correlations between reductions in suicide rates and increases in prescription rates of antidepressants in some countries or regions.[1] However, controlled trials do not indicate decreased risk of suicide or attempts with antidepressants compared with placebo.[5] The efficacy and safety of antidepressant treatment for bipolar depression remain particularly uncertain, and such treatment risks inducing agitated, psychotic, or mixed manic depressive states in which suicide is especially prevalent.[3,5]

Serious interest in scientific study of the experimental therapeutics of suicide has emerged only very recently, and only clozapine for patients with schizophrenia (since 2003) has US Food and Drug Administration approval for reducing risk of suicidal behaviors. Scientifically sound research on treatment effects on suicidal risk is ethically and practically feasible, and much more is required to clarify optimal clinical management of patients at increased risk for suicide.

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To the Editor: Dr Mann and colleagues[1] provide a comprehensive review of specific strategies that may be effective for reducing the public health burden and personal loss due to suicide. However, their categorization of the Air Force Suicide Prevention Program (AFSPP) as a "gatekeeper" strategy for preventing suicide (in Table 1 of their article) is an oversimplification of a multifaceted suicide prevention program that has demonstrated sustainability in reducing suicide events.[2-5]

The AFSPP comprises 11 initiatives that use a comprehensive approach that integrates different strategies, one of which is the gatekeeper programs. These additional strategies include public educational campaigns, curriculum-based programs, community preventive and clinical services, and policy changes. The AFSPP is distinctive because of its adoption of the integrated framework to prevent sui-