To the Editor: Intimal hyperplasia surrounding the suture line remains the leading cause of graft failure after coronary artery bypass graft surgery and peripheral vascular bypass surgery. Immunosuppressive drugs, such as tacrolimus, have been shown to inhibit the development of intimal hyperplasia (1,2). We have developed a novel drug-eluting suture coated with tacrolimus (DE-suture). The purpose of the present study performed on a porcine model was to determine the efficacy of the new suture coated with tacrolimus in preventing intimal hyperplasia.

The surface of a 7-0 polyvinylidene difluoride (PVDF) suture was coated with tacrolimus using a bioabsorbable polymer for controlled release of the drug. The porcine models used for the suture experiments were randomized into the following 3 groups: the control group (n = 6), in which noncoated sutures were used; the low-dose DE-suture group (n = 6), in which low-dose (0.13 weight percent) tacrolimus-coated sutures were used; and the high-dose DE-suture group (n = 6), in which high-dose (0.40 weight percent) tacrolimus-coated sutures were used.

The femoral artery was dissected free from the anesthetized animals. After proximal and distal cross-clamping, half-transverse arteriotomy was performed in the femoral artery, followed by interrupted suturing. Four weeks after implantation, femoral arteries were harvested. The paraffin-embedded arterial specimens were stained with hematoxylin-eosin and immunostained using an alpha-smooth muscle actin antibody and a factor VIII antibody to evaluate the degree of intimal hyperplasia and re-endothelialization at the anastomotic site. To characterize neointimal hyperplasia, the ratio of intimal thickness at the suture versus nonsuture sites was calculated.

In regard to the arterial wall morphology, the nonsutured reference site on the arterial wall including the neointimal area showed no intimal hyperplasia. The control group showed significant neointimal hyperplasia at the suture site (the ratio of intimal thickness at the suture/nonsuture sites: 23.0 ± 5.0), whereas the low- and high-dose DE-suture groups showed significant reduction of the neointimal thickness (to 11.0 ± 4.3 and 8.3 ± 3.3; p < 0.05) versus control (Figs. 1A to 1C and 1J). However, there was no difference in the intimal thickness ratio at the suture/nonsuture sites between the low- and high-dose DE-suture groups. The neointima at the suture site contained the smooth muscle cells (SMC) in all groups (Figs. 1D to 1F).

Histological analyses demonstrated a significantly less pronounced medial inflammatory response and adventitial fibrosis in both the DE-suture groups as compared with that in the control group (p < 0.05). In all groups, the arterial lumen was lined by endothelial cells (EC) showing positive immunohistochemical staining for factor VIII, which is an important factor for vascular healing (Figs. 1G to 1I).

Tacrolimus (FK506, Asellas Pharma Inc., Tokyo, Japan) was discovered in 1984 from the fermentation broth of a Japanese soil sample on Mt. Tsukuba that contained the bacterium Streptomyces tsukubaensis. The drug is a macrolide immunosuppressant. It inhibits several steps of the cascade of events leading to neointimal formation and inhibits the proliferation of SMC. Previous experimental data suggest that inhibition of cell cycle progression and neointimal hyperplasia with tacrolimus may be an effective strategy to prevent anastomotic stenosis. We considered that tacrolimus may allow better re-endothelialization (1,2).

Intimal hyperplasia surrounding the suture line remains the leading cause of graft failure. The main cause is invasion and proliferation of SMC. Mechanical artery injury and the foreign body effects of a suture, or viral response to the prosthesis, incite acute and chronic inflammation in the vessel wall, with elaboration of cytokines and growth factors that induce multiple signaling pathways that activate SMC migration and proliferation. While significant neointimal hyperplasia was observed at the suture site in the control group, significant reduction of the neointimal area was observed in the low- and high-dose DE-suture groups. In addition, the arterial lumen was lined in all groups by EC showing positive immunohistochemical staining for factor VIII, an important factor for vascular healing. According to the report by Matter et al. (3), tacrolimus induces less injury of EC proliferation.

Recently, numerous drug-eluting devices have been developed to prevent neointimal hyperplasia (2,4,5). They have been reported to have the effect of preventing neointimal hyperplasia from the adventitial site. Our new device is a simple advance to prevent neointimal hyperplasia at the anastomotic suture site, as it allows slow release of tacrolimus using a bioabsorbable polymer directly into all layers of the blood vessel wall, including the intima, media, and adventitia.

The results of our study in a porcine model demonstrate that the DE-sutures inhibited neointimal hyperplasia at the anastomotic suture site, and also inhibited the inflammatory response and granulation tissue formation in the porcine model. Thus, this novel suture may be useful in both coronary artery bypass graft surgery and peripheral vascular bypass surgery.

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A Critical Reappraisal of Differences in Cardiac Resynchronization Therapy Defibrillator Effectiveness Between Men and Women in the MADIT-CRT Trial

In a recent issue of the Journal, Arshad et al. (1) reported a significantly greater reduction in death and heart failure with cardiac resynchronization therapy defibrillators (CRT-D) in women than in men. In their discussion, they described the characteristics of the patients. We wish to analyze these data more in depth. The study population shows a difference between the overall percentage of men and women, but in our opinion it is worth noting a difference in the etiology of heart failure between sexes. Over the last decades the prevalence of ischemic heart disease has been demonstrated to be similar in both sexes with increasing age (2), whereas in this study the majority of women (72%) had nonischemic heart disease, as compared with only 36% of men with nonischemic heart disease. Baseline functional and structural parameters of left ventricular function are comparable between the 2 groups. In general, patients with ischemic heart disease have a worse prognosis (3,4), and coronary artery disease is a predictor of poor response to cardiac resynchronization therapy.