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EDITORIAL

Combined Therapeutic Strategy to Improve Vascular Endothelial Function After Implantation of Sirolimus-Eluting Stents

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Coronary arteries are readily blocked by atherosclerotic plaques, eventually triggering cardiovascular events (ie, ischemic coronary heart disease and myocardial infarction) in patients. Stent implantation is one strategy often used to attenuate the progression of coronary artery atherosclerosis and decrease cardiovascular-related mortality. Stents significantly reduce the risk rate of restenosis after percutaneous transluminal coronary angioplasty. Furthermore, the use of drug-eluting stents (DES), when compared with bare metal stents (BMS), results in a significantly decreased risk of in-stent restenosis, late stent thrombosis and vascular dysfunction. However, although the clinical effectiveness of diluted sirolimus-eluting stents (SES) is superior when compared with BMS, concerns have been raised regarding impaired vascular function after SES implantation. Although SES reduce vascular restenosis, which is characterized by vascular smooth muscle cell (VSMC) proliferation, migration, and an increased inflammatory response, this particular DES simultaneously impairs vascular endothelial function in humans,[1] which is characterized by increased endothelial cell (EC) inflammation and impaired endothelial-dependent vasomotor function. The occurrence of abnormal endothelial function is problematic because endothelial dysregulation is a major determinant of atherosclerosis in the early pathophysiological stages and has been demonstrated to occur in patients with coronary artery disease, hypertension, and type 2 diabetes. Thus, strategies to improve EC function are being actively investigated in the field.

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Angiotensin II (AngII) is known to be an important vasoactive peptide implicated in the development of in-stent restenosis. AngII type I (AT_1) receptors mediate the effect of AngII on VSMC proliferation and inflammatory signaling. AT_1 receptor blockers (ie, ARBs), widely used as antihypertensive drugs, have been reported to suppress neointimal formation, decrease VSMC proliferation and attenuate vascular inflammation.[2] Candesartan, an ARB, attenuates neointimal formation in human coronary arteries following stent implantation.[3] However, a series of studies identified that candesartan does not reduce neointimal formation or restenosis in patients after stent implantation.[4] Candesartan improves EC function via both antiinflammatory and vasodilatory effects.[5] In hypertensive patients, candesartan therapy significantly reduces plasma levels of monocyte chemotactic protein-1. In addition, candesartan or rosiglitazone therapy significantly lowers plasma levels of tumor necrosis factor (TNF)-α in hypertensive or obese diabetic subjects.[6] Candesartan also decreases TNF-α-induced expression of vascular cell adhesion molecules-1, increases nitric oxide release, and reduces vasoconstriction.[7]

Thiazolidinediones (TZDs) are recognized as ligands for peroxisome proliferator-activated receptor (PPAR)-gamma, a member of the nuclear receptor superfamily.[8] TZDs have potent antiinflammatory and antithrombotic effects, and of major importance, their potent insulin-sensitizing abilities are effective for decreasing blood glucose levels in diabetic patients.[9] In fact, 2 members of the TZD family, rosiglitazone (Avandia) and pioglitazone (Actos) are FDA-approved drugs for treatment of type 2 diabetes. Unfortunately, TZD treatment can often be associated with adverse side effects (ie, weight gain, fluid retention and hepatic steatosis). Moreover, due to the potential for an elevated cardiovascular ischemic risk with rosiglitazone treatment, this particular TZD is currently restricted for use through a Risk Evaluation and Mitigation Strategy (REMS) in the United States and marketing of this drug has been suspended in Europe. On the other hand, clinical trials show that pioglitazone has a favorable effect on cardiovascular outcomes; it improves vascular function through its actions on ECs and VSMCs. Pioglitazone significantly suppresses VSMC proliferation and migration and reduces neointimal volume following coronary stent implantation in nondiabetic patients,[10] as well as neointimal tissue proliferation in patients with type 2 diabetes mellitus,[11] suggesting that TZDs, in addition to their glycemic-lowering activity, exhibit direct antirestenotic effects after stent implantation. In addition, TZDs improve coronary and peripheral endothelial dysfunction and blood pressure.[12]

Mounting evidence suggests that PPAR-γ and AT_1 receptor are 2 critical determinants in the treatment of cardiovascular diseases.[13] In this issue of the Journal, Dohi et al investigate the effects of candesartan or combination therapy (candesartan+pioglitazone) on endothelial function after SES implantation.[14] They investigated the vascular responses to either candesartan (1.5 mg/kg p.o.) alone or a combination of piogli-

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tazone and candesartan (5+1.5 mg/kg, respectively, p.o.) following stent implantation in pigs. No changes were observed in blood pressure in either group. However, combined therapy significantly reduces inflammatory cell adhesion to ECs to a greater extent than the treatment with candesartan alone. When compared with candesartan, the combined therapy significantly attenuated the expression of the inflammatory marker, TNF-α and increased eNOS expression in vascular walls after stent implantation. They also found that stent implantation impairs, but candesartan improves, EC-dependent vascular relaxation at an adjacent segment distal to the SES. Actually, a previous study found that candesartan combined with pioglitazone can improve vascular endothelium-independent relaxation compared with administration of either drug alone.[15] Thus, the major finding of the current study is that the combination of candesartan and pioglitazone, when compared with candesartan treatment alone, improves endothelial function and reduces the inflammatory response to a greater extent. However, the long-term effects of candesartan and pioglitazone, as well as the specific effect of the candesartan and pioglitazone drug combination, in patients with coronary artery atherosclerosis need to be further evaluated after stent implantation.

In conclusion, a combination of an AT_1 receptor blocker (candesartan) and a TZD (pioglitazone) may improve therapeutic efficacy for preserving normal vascular EC function and may be beneficial for the treatment of diabetic or hypertensive patients undergoing stent implantation. There is a growing scientific rationale for investigating the combination of a PPAR-γ agonist and an AT_1 receptor blocker to protect against impaired vascular function following stent implantation.

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