

Coronary Restenosis after Drug-Eluting Stent Implantation in Diabetic Patients

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ABSTRACT

In the era of drug-eluting stents (DESs), the angiographic rates of restenosis at later months have been dramatically reduced, but these rates have been less prominently reduced in diabetic patients. The rate of coronary restenosis is still higher in diabetic patients, when compared with non-diabetic patients, and even after DES implantation. Diabetes remains a significant predictor of coronary restenosis even in the era of DES, and especially in cases having a small baseline vessel size, a small post-PCI vessel size and a longer stent length. The use of the sirolimus-eluting stent in diabetic patients has been associated with a decreased rate of restenosis, and this suggests a reduced risk of target lesion revascularization. Diabetes still remains a major risk factor for coronary restenosis after DES implantation, and so aggressive risk factor management with the concomitant pharmacotherapy should be done to reduce the risk of coronary restenosis. (*Korean Circulation J* 2006;36:1-7)

KEY WORDS : Diabetes ; Coronary restenosis.

Introduction

People with diabetes mellitus are more prone to coronary heart disease, stroke and peripheral vascular disease than people without diabetes,¹⁾ and diabetes mellitus is regarded as an independent risk factor for the progression of coronary artery disease.^{2,3)} Several studies have reported that diabetes increased the risk of cardiovascular mortality in both men and women.^{4,5)} Moreover, diabetes has been considered to be a predictor of a poor prognosis after the performance of coronary artery bypass surgery⁶⁾ and percutaneous transluminal coronary angioplasty (PTCA).⁷⁻⁹⁾ The long-term clinical and angiographic outcomes after percutaneous coronary intervention (PCI) with BMSs have been demonstrated to be worse in diabetic patients as compared with that of nondiabetic patients.¹⁰⁻¹²⁾ Restenosis is a main clinical and angiographic concern after BMS implantation, and this is especially true in diabetic patients. Diabetes is known to be a major risk factor for in-stent restenosis after bare-metal stenting.¹³⁾

As noted by several studies, with the introduction of drug-eluting stents (DESs), the angiographically-deter-

mined rates of restenosis at the later months after implantation have been dramatically reduced.¹⁴⁻¹⁶⁾ The RAVEL study group demonstrated a significant reduction in restenosis with using sirolimus-eluting stents (SESs), as compared with BMSs, among 238 patients suffering with coronary artery disease.¹⁷⁾ The result of a subgroup analysis of the diabetic patients in the RAVEL trial is even more surprising: among the 19 patients who received SESs, the coronary restenosis rate was 0% compared with 42% for the 25 patients who received BMSs. Since the RAVEL trial included diabetic patients with relatively simple coronary lesions, the following SIRIUS trial enrolled patients who had more complex lesions compared with the RAVEL trial.¹⁸⁾ Among the diabetic patients in the SIRIUS trial, the coronary restenosis rates were 18% for 131 patients with SESs and 51% for 148 patients with BMSs. In the TAXUS-IV trial, 1314 patients were prospectively randomized either to the slow rate-of-release paclitaxel-eluting stent (PES) group or to the BMSs group, and 318 diabetic patients were included in the study. When the TAXUS-IV investigators analyzed the 318 diabetic patients, the PESs were also highly effective in reducing clinical and angiographic restenosis in the patients with diabetes.¹⁹⁾ The PES substantially reduced the late lumen loss, the late loss index and the coronary restenosis compared with the control BMS.¹⁹⁾ The PES implantation demonstrated significantly lower rates of

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target lesion revascularization (TLR) and target vessel revascularization (TVR) in diabetics, and so it reduced the need for repeat percutaneous coronary intervention and bypass surgery. The meta-analysis of four major trials that compared BMSs with DESs, 2 trials with SESs (RAVEL, SIRIUS) and 2 trials with PESs (TAXUS II, TAXUS IV), revealed that the diabetic patients, as compared with the nondiabetic patients, had a 94% higher risk of coronary restenosis in the group that received BMSs (Fig. 1).²⁰ The diabetic patients had a 124% higher risk of coronary restenosis compared with the nondiabetic patients in the group that received DESs (Fig. 2).²⁰ Even with DESs, the diabetic patients showed increased rates of restenosis and a higher late loss index compared with the nondiabetic patients included in this meta-analysis. One may presume that the angiographic rates of restenosis after DES implantation have dramatically decreased compared with BMS implantation, but this is less prominent in diabetic patients.

Pathophysiologic Mechanisms of Coronary Restenosis

In-stent restenosis in diabetic patients is associated with complex pathophysiological processes that are not yet completely understood. Hyperplasia of smooth muscle cells in the intimal layer of the vessel wall, the so called neointimal hyperplasia, plays a major role in the process of in-stent restenosis.²¹ The process of coronary restenosis starts with the initial insult to coronary vessels; this is caused by both intracoronary balloon inflation and stent implantation, and the response to this initial insult is more prominent in diabetic patients. Several studies have suggested that the pathophysiological mechanisms of coronary restenosis in diabetic patients are related to a greater degree of underlying vascular inflammation and endothelial dysfunction, the elevated fractions of activated platelets with thrombus formation, the dysregulation of the growth factor expression and the elevated levels of advanced glycosylation end products.²²⁾²³ Impaired insulin sensi-

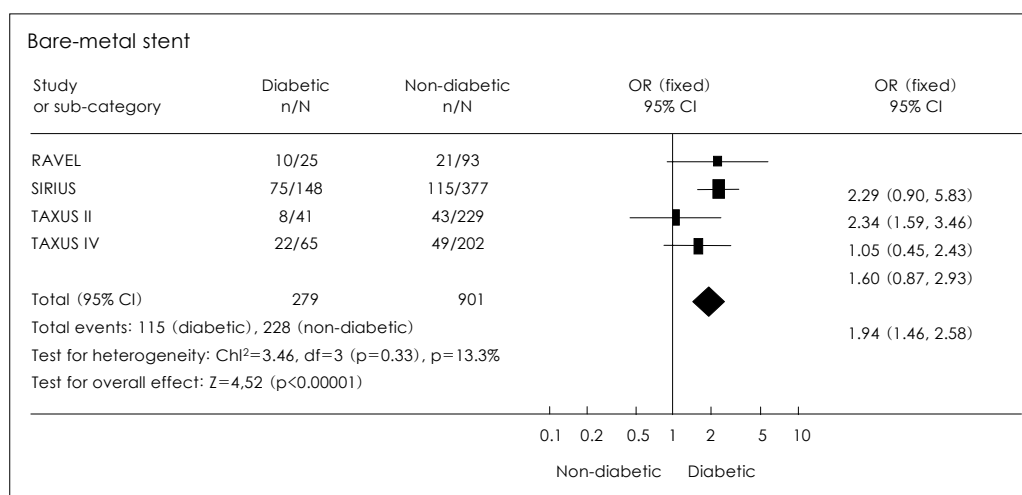


Fig. 1. Meta-analysis of the 4 trials comparing the effects of bare-metal stents on restenosis in diabetic and non-diabetic patients.

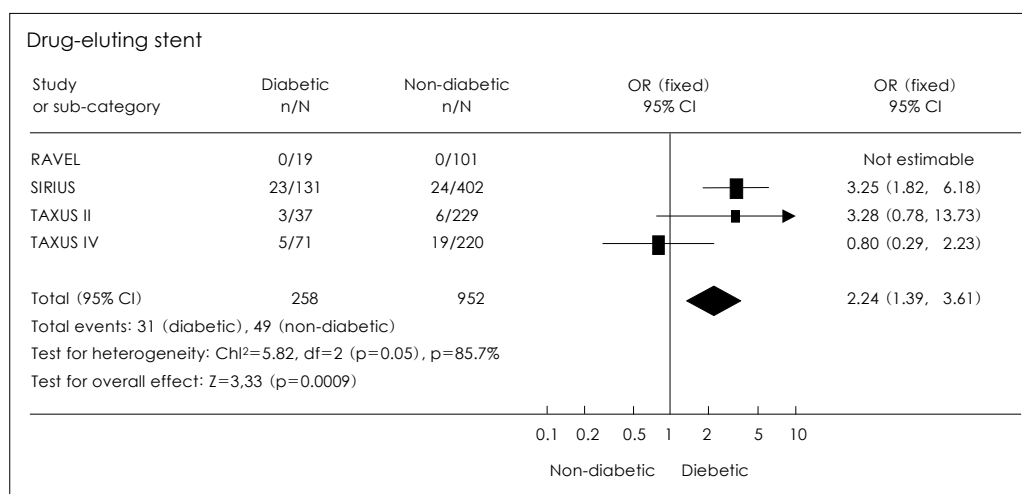


Fig. 2. Meta-analysis of the 4 trials that compared the effects of drug eluting stents on restenosis in diabetic and non-diabetic patients.

tivity and endothelial dysfunction also play a major role in the development of coronary restenosis.²⁴⁾ The coronary restenosis in diabetic patients results from neointimal hyperplasia, and this causes late luminal loss. Macrophages and polymorphonuclear neutrophils play a major role in the process of coronary restenosis. Macrophages and neutrophils release chemokines, and these chemokines serve to increase the amount of matrix metalloproteinase, which leads to remodeling of the extracellular matrix and also smooth muscle cell migration.²⁵⁻²⁹⁾ In addition, smooth muscle cells are stimulated to increase the expression of genes that are involved in cell division.³⁰⁾ Several studies have suggested genetic factors in the pathogenesis of coronary restenosis, i.e., polymorphism of the gene encoding for the angiotensin-converting enzyme correlated with diffuse coronary restenosis.³¹⁾ Diabetes are prone to coronary restenosis since neointimal hyperplasia is increased in the diabetic coronary arteries after coronary intervention, which results in greater late in-stent lumen loss.³²⁾ It has been assumed that the hyperglycemic state may induce, modify or accentuate the biologic mechanisms that contribute to the greater tissue proliferation and more diffuse restenotic pattern seen in diabetics.¹⁹⁾ Specifically, the vascular thickening may be related to glycosylation of vascular collagen and elastin.¹⁹⁾ Insulin could stimulate the mitogen-activated protein kinase (MAPK) signaling pathway, thereby activating the ERK1 and ERK2 isoforms that are able to stimulate vascular smooth muscle cells, growth factors and cell migration. In the physiological state of insulin resistance, insulin signaling through the PI3K pathway is decreased, whereas the MAPK pathway remains intact.³³⁾ Takagi et al.³⁴⁾ have shown that the neointimal index that was measured six months after coronary stenting correlated with the fasting and post-glucose load insulin levels. Babalik et al.³⁵⁾ have demonstrated that hyperinsulinemia during the OGTT was a strong predictor of restenosis at the six month follow-up. Insulin resistance in diabetics aggravates coronary restenosis through a direct growth factor-like effect of insulin on the vascular smooth muscle and neointimal cells.³⁶⁾

Moreover, increased leptin levels (leptin is a hormone related to both fat metabolism and insulin resistance), have been considered as an independent predictor of restenosis. Chronic hyperleptinemia could decrease the production of nitric oxide by increasing the oxidative stress in endothelial cells.²⁴⁾ The role of hyperleptinemia in the process of coronary restenosis relates to its ability to induce proliferation, differentiation and functional activation of vascular smooth muscle cells, endothelial cells and peripheral blood cells; all of this contributes to increased neointima formation.²⁴⁾ Leptin activates various signal transduction pathways in human monocytes and vascular cells such as the PI3K, protein kinase

A and MAPK pathways.³⁷⁾

Restenosis in the Era of DES

Paclitaxel vs. sirolimus

Paclitaxel and sirolimus coated stents are the currently available DESs on the market. Paclitaxel is a derivative of taxol, a compound with antimitotic properties. It inhibits microtubule depolymerization, arrests the cell cycle and stops proliferation. Since paclitaxel modulates cell mitogenesis downstream from Ras/Raf/MAP kinase and it does so independently from the PI3 kinase/PKb/mTOR signal-transduction pathway, it may be effective for treating the diabetic patients with insulin-resistance as it inhibits both the insulin-dependent and insulin-independent pathways that mediate neointimal hyperplasia.³⁸⁾ Microtubules, in addition to their central role for cell division, they control cell signaling, cell activation, cell secretory processes and the cell migration that's involved in coronary restenosis.³⁹⁾⁴⁰⁾

Sirolimus (rapamycin) is a macrolide antibiotic that was discovered in a microorganism on Easter Island. Sirolimus exerts antiproliferative effects on smooth muscle cells by inhibiting growth-factor induced and cytokine-induced cell division.⁴¹⁾ The mTOR (mammalian target of rapamycin) is an enzyme located in the nonparticulate region of the cell cytoplasm; this enzyme plays a major role in conducting extracellular signals to the intracellular pathways that adjust cell division and proliferation.⁴²⁾ For activated smooth muscle cells to progress from the G1 phase into the S phase of the cell cycle, the mTOR dependent functions are interrupted by their interaction with the FKBP12: sirolimus complex. Sirolimus enters the cell and forms a complex with FKBP12. The FKBP12: sirolimus complex prevents the down-regulation of p27^{Kip1} and the activation of p70s6k, which ultimately results in arrest of the cell cycle at the G1 phase.⁴²⁾ Sirolimus has been coated onto the metal of a stent with an outer layer of biocompatible polymer that enable the drug to elute over a 30-day period.⁴³⁾

In a recently published ISAR-DIABETES study, the use of the sirolimus-eluting stent was associated with a decrease in the late luminal loss and clinical restenosis, as compared with the use of the paclitaxel-eluting stent, in diabetic patients with coronary artery disease.⁴⁴⁾ The use of the sirolimus-eluting stent in diabetic patients was associated with a decreased rate of restenosis, and this suggests a reduced risk of target lesion revascularization.

Restenosis pattern

Although the rate of coronary restenosis after DES implantation is less frequent when compared with that of BMSs, the prevalence of coronary restenosis is in-

creasing due to the worldwide use of DESs in “real world” interventional cardiology. The patterns of coronary restenosis have been described as either diffuse (lesion > 10 mm in length) or focal (lesion ≤ 10 mm in length).⁴⁵⁾ The SIRIUS trial that dealt with relatively longer lesion lengths than those of the previous RAVEL trial demonstrated a 9.2% rate of coronary restenosis. The coronary restenosis noted during the SIRIUS trial occurred at the stent margins or at the site of a gap in 64.5% of the cases, and 87% of the coronary restenosis was focal.⁴⁶⁾ The observations regarding the angiographic pattern of coronary restenosis after implanting SESs by Colombo A et al.⁴⁷⁾ revealed that all the restenotic lesions were focal. This observation was concordant with the findings in the SIRIUS trial. All the restenotic lesions, except for 1 multifocal restenosis that involved the distal margin of the stent, were reported to be located in the body of the stent. This finding was different from the SIRIUS and TAXUS II trials where most of the restenotic lesions were located near the stent margins or at the site of a gap between 2 stents (64.5% in the SIRIUS trial and 83.3% in TAXUS II trial).⁴⁶⁾ Moreover, 4 of 6 multifocal coronary restenoses occurred in diabetic patients.⁴⁶⁾ For the diabetic patients with coronary restenosis in the TAXUS IV trial, the diffuse type of coronary restenosis was reduced by more than 90%; therefore, most of coronary restenosis were the focal type when angiographic restenosis did occur.¹⁹⁾ The proportion of patients with the diffuse type of coronary restenosis, if it occurs at all, has clearly been reduced in the era of DESs.

Predictors of Restenosis after DES Implantation in Diabetes

Several studies have demonstrated the clinical and angiographic factors of coronary restenosis after BMS implantation,⁴⁸⁻⁵¹⁾ and the various factors associated with coronary restenosis after BMS implantation have been reported for the diabetic populations.^{52,53)} Several clinical and angiographic predictive factors of coronary restenosis after BMS implantation were reported by Mercado et al.,⁴⁸⁾ and diabetes was a major independent predictive factor of restenosis. Moreover, a large preprocedural reference diameter (RD) and a minimal postprocedural lumen diameter (MLD) were favorable predictive factors after BMS implantation. The stent length was found to be a significant predictor of coronary restenosis in BMSs, and for each millimeter of increased stent length, the risk of developing coronary restenosis increased by 4%.⁴⁸⁾ The risk factors of coronary restenosis after BMS implantation include the length of the stented segment and the size of the vessel, with smaller vessels having a higher rate of coronary restenosis.⁵⁴⁾ Since diabetes is known to be a major pre-

dictor of coronary restenosis after BMS implantation, several studies reported on the predictors of coronary restenosis in diabetic patients after BMS implantation. The study published by Mazeika et al.⁵³⁾ has reported that poor glycemic control and the vessel size were independent predictors of coronary restenosis in diabetic patients. Another study published by West et al.⁵²⁾ has reported that the vessel caliber, the stented length of the vessel and a lower body mass index were predictors of restenosis in diabetic patients. One of the major risk factors for coronary restenosis is diabetes, which doubles the its incidence when compared to non-diabetic patients.⁵⁵⁾ Most of the studies concerning coronary restenosis after BMS implantation have emphasized the reference vessel diameter, the stent length and diabetes as major predictive factors for restenosis. However, the clinical and angiographic parameters of coronary restenosis in diabetic patients after DES implantation have not yet been reported on.

In our preliminary study that included stented patients (n=840) with DESs from the Multicenter PCI Database Registry, we sought to identify the factors that had an influence on the likelihood of restenosis after DES implantation in diabetic patients. From this database, out of 840 patients with a minimum of six months angiographic follow-up, 211 (25.1%) had diabetes. The predictive factors of coronary restenosis were identified by performing multivariate logistic regression analysis. Restenosis occurred in 92 of 629 (14.6%) nondiabetic patients and in 44 (20.9%) of 211 diabetic patients ($p < 0.001$). The factors found on multivariate analysis for predicting restenosis in the diabetic group were current smoking, and current smoking increased the risk of coronary restenosis by 92%; a higher C-reactive protein (CRP) level increased the risk of coronary restenosis by 31%, the use of the paclitaxel-eluting stent (PES) increased the risk of coronary restenosis by 164%, a longer stent length increased the risk of coronary restenosis by 65%, a smaller reference diameter before DES implantation increased the risk of coronary restenosis by 50%, a smaller reference diameter increased the risk of coronary restenosis by 46%, and a minimum lumen diameter at baseline increased the risk of coronary restenosis by 45% after DES implantation. We could well observe that diabetes remains a significant predictor of coronary restenosis especially in the cases with a small baseline vessel size, a small post-PCI vessel size, a longer stent length, the use of the PES, a current smoker and a high level of CRP even in this era of DES.

Adjunctive Therapy

Adjunctive therapy with glycoprotein IIb/IIIa inhibitor, maintenance of aspirin therapy and adminis-

ring a thienopyridine for longer than 1 year should be considered for those diabetic patients who have multiple predictive factor for restenosis.⁵⁶⁾ Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker and HMG (3-hydroxy-3-methylglutaryl)-CoA reductase inhibitor should administered when clinically indicated. Moreover, the thiazolidinediones may further reduce coronary restenosis in diabetic patients by activating the nuclear transcription factor peroxisome proliferator-activated receptor (PPAR)- γ .⁵⁷⁾ In addition to the optimal adjunctive pharmacotherapy to prevent coronary restenosis in diabetic patients, instituting strict glycemic control may decrease the restenosis rate in diabetic patients.⁵³⁾⁵⁸⁾ These data suggest that strict control of diabetes to achieve hemoglobin A1C levels $\leq 7.0\%$ may reduce the restenosis rate and so it may improve the clinical outcomes after PCI.

Conclusions

The small reference vessel diameter with a longer lesion length in diabetic patients was noted to increase the rates of coronary restenosis after DES implantation.¹⁸⁾¹⁹⁾ The immediate gain in blood flow was often less optimal in diabetic patients, and this was probably due to the large plaque burden; in addition, the neointimal hyperplasia increased in diabetic patients after coronary intervention, resulting in greater late lumen loss.⁵⁹⁾ Using new devices such as DESs reduces the restenosis rate compared with BMSs in diabetic patients by decreasing the late luminal loss. By reducing the coronary restenosis, DESs significantly improved the major limitation of BMS implantation in diabetic patients. Many studies have shown that a blockade of smooth muscle cell proliferation with DESs results in the preservation of the normal vessel phenotype and function, thereby decreasing the rate of both neointimal hyperplasia and in-stent restenosis.^{60,64)} Since the introduction of paclitaxel and sirolimus-eluting stents, these devices are regarded by many physicians and scientists to be the standard of treatment for diabetic patients undergoing stent implantation. Even though DESs could lower the restenosis rates by preventing smooth-muscle cell proliferation at the stented site, atherosclerosis could progress at other coronary sites. Therefore, combined approaches that use systemic therapies are required to prevent neointimal proliferation and to prevent atherosclerosis progression at the other coronary sites in diabetic patients.

BMS implantation significantly reduces the coronary restenosis rates and the target lesion revascularization (TLR) rate in the diabetic patient when compared to balloon angioplasty alone, and DESs further reduce the coronary restenosis rates and the TLR rate in the diabetic patient as compared to the BMSs. However,

the rate of coronary restenosis is still higher in diabetic patients, when compared with non-diabetic patients, and even after DES implantation. Diabetes still remains a major risk factor for coronary restenosis after DES implantation, and so aggressive risk factor management with the concomitant pharmacotherapy should be done to reduce the risk of coronary restenosis, and especially in diabetic patients who have undergone DES implantation.

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