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Effects of Thiazolidinediones on In-Stent Restenosis: A Review of IVUS Studies

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1. Introduction

Patients with metabolic syndrome or type 2 diabetes are at high risk of in-stent-restenosis, although drug-eluting stents reduce the in-stent restenosis rate and target lesion revascularization rate to less than half compared with bare metal stents.(Mintz GS, et al. J Am Coll Cardiol 2006) Most clinical trials of systemic pharmacotherapies with ACE inhibitors, statins and antiplatelet agents to reduce restenosis have yielded disappointing results. Proliferation of vascular smooth muscle cells is the predominant mechanism of neointimal hyperplasia leading to restenosis. Insulin resistance is a major factor in metabolic syndrome and type 2 diabetes, and has been demonstrated to represent an independent risk factor for in-stent-restenosis.(Piatti P, et al. Circulation 2003) Thiazolidinediones are insulin-sensitizing agents, and reportedly inhibit proliferation of vascular smooth muscle cells in vitro and in animal studies. Recent studies, including our own, (Katayama et al. Am Heart J 2007; Takagi et al. J Am Coll Cardiol Intv 2009) have highlighted the beneficial effects of thiazolidinediones in reducing neointimal growth after stent implantation. We review herein IVUS studies regarding the effects of thiazolidinedione therapy on in-stent restenosis after coronary stent implantation.

2. Effects of thiazolidinedione beyond anti-diabetic actions

Thiazolidinediones activate peroxisome proliferator-activated receptor (PPAR)-γ in adipose tissue, improving insulin sensitivity and glucose control in patients with type 2 diabetes mellitus and metabolic syndrome. The first thiazolidinedione described, troglitazone, was removed from the market because of hepatotoxic effects. Two glitazones, pioglitazone (Actos; Takeda/Lilly,) and rosiglitazone (Avandia; GlaxoSmithKline) are now commercially available for treatment of diabetes mellitus. Glitazones have been shown to improve specific lipid abnormalities associated with insulin resistance. Treatment with glitazones elevates serum levels of high-density lipoprotein (HDL) cholesterol, decreases triglyceride levels, and changes the size of low-density lipoprotein (LDL) cholesterol from small particles to large ones, less atherogenic particles. (Hanefeld M, et al. Diabetes Care 2004) Beyond the anti-diabetic activity, thiazolidinediones inhibit inflammatory activity, and migration and

proliferation of vascular smooth muscle cells by decreasing matrix metalloproteinase production and inducing cell cycle arrest or apoptosis and atherosclerotic effects in vascular cells in vitro and in diseased animal models. (Marx N, et al. Circ Res 2004)

2.1 Effects of thiazolidinedione on atherosclerosis and cardiovascular events

In the PROactive study, a double-blinded, placebo-controlled investigation, pioglitazone significantly reduced the composite of all-cause mortality, non-fatal myocardial infarction, and stroke in patients with type 2 diabetes, who have a high risk of macrovascular events. (Dormandy JA, et al. Lancet 2005) Nissen et al. conducted a double-blinded, randomized, multicenter trial in 543 patients with coronary disease and type 2 diabetes to compare the effects of an insulin sensitizer, pioglitazone, with an insulin secretagogue, glimepiride, on the progression of coronary atherosclerosis in patients with type 2 diabetes. (Nissen SE, et al. JAMA 2008) Treatment with pioglitazone resulted in a significantly lower rate of progression of coronary atherosclerosis as assessed by intravascular ultrasound (IVUS) compared with glimepiride in patients with type 2 diabetes and coronary artery disease. A meta-analysis showed that pioglitazone did not increase the risk of myocardial infarction or cardiovascular mortality. (Lincoff, et al. JAMA 2007)

In contrast, controversy persists regarding the effects of rosiglitazone therapy on myocardial infarction and cardiovascular mortality. A meta-analysis of 4 randomized controlled trials (N=14 291, including 6421 receiving rosiglitazone and 7870 receiving control therapy, with a follow-up duration of 1-4 years) showed that rosiglitazone use for $\geq$12 months is associated with a 42% increased risk of acute myocardial infarction and a doubling in the risk of heart failure among patients with impaired glucose tolerance or type 2 diabetes. (Singh S, et al. JAMA 2007) The most recent systematic review by Nissen and Wollski reported that rosiglitazone therapy significantly increased the risk of myocardial infarction (odds ratio (OR), 1.28; 95% confidence interval (CI), 1.02-1.63; P=.04), but not cardiovascular mortality (OR, 1.03; 95% CI, 0.78-1.36; P=.86). (Nissen SE, et al. Arch Intern Med 2010)

Both thiazolidinediones have been shown to increase the risk of heart failure compared with treatment with placebo or other antidiabetes medications. In order to compare the risk of serious cardiovascular harm by rosiglitazone and by pioglitazone, Graham DJ et al. conducted a nationwide, observational, retrospective, inception cohort of 227, 571 Medicare beneficiaries aged 65 years or older who initiated treatment with rosiglitazone or pioglitazone. The adjusted hazard ratio for rosiglitazone compared with pioglitazone was 1.06 (95% confidence interval [CI], 0.96-1.18) for AMI; 1.27 (95% CI, 1.12-1.45) for stroke; 1.25 (95% CI, 1.16-1.34) for heart failure; 1.14 (95% CI, 1.05-1.24) for death; and 1.18 (95% CI, 1.12-1.23) for the composite of AMI, stroke, heart failure, or death. Compared with prescription of pioglitazone, prescription of rosiglitazone was associated with an increased risk of stroke, heart failure, and all-cause mortality and an increased risk of the composite of AMI, stroke, heart failure, or all-cause mortality in patients 65 years or older. (Graham DJ et al. JAMA. 2010)

2.2 Effects of pioglitazone on in-stent restenosis in metabolic syndrome

We first demonstrated that treatment with pioglitazone reduces intimal index as assessed by IVUS as a parameter of neointimal hyperplasia after bare metal stent implantation in patients with non-diabetic metabolic syndrome using an open-labeled randomized

controlled study. (Katayama, et al. Am Heart J 2007) Before coronary stenting, 32 patients were randomly assigned to two treatment groups: the pioglitazone group; and the control group. All patients were successfully treated using IVUS-guided coronary stenting. After coronary stenting, patients in the pioglitazone group were treated with 30 mg/day of pioglitazone in addition to standard medications for 6 months, whereas patients in the control group were treated using only standard medications. After intracoronary administration of isosorbide dinitrate, a 40-MHz IVUS catheter was advanced to the distal side beyond the target lesion, and IVUS images were recorded using automatic pullback (0.5 mm/s). The lesion was defined as the site with smallest lumen, and the reference points were defined as the sites with the largest lumen within 10 mm proximal and distal to the lesion. Bare metal stents were implanted based on IVUS measurements. In accordance with the American College of Cardiology Task Force on Clinical Expert Consensus Documents on IVUS, (Mintz S, et al. J Am Coll Cardiol 2001) quantitative IVUS measurements were performed by a single observer who was blinded to the treatment assignments of patients. (Figure 1)
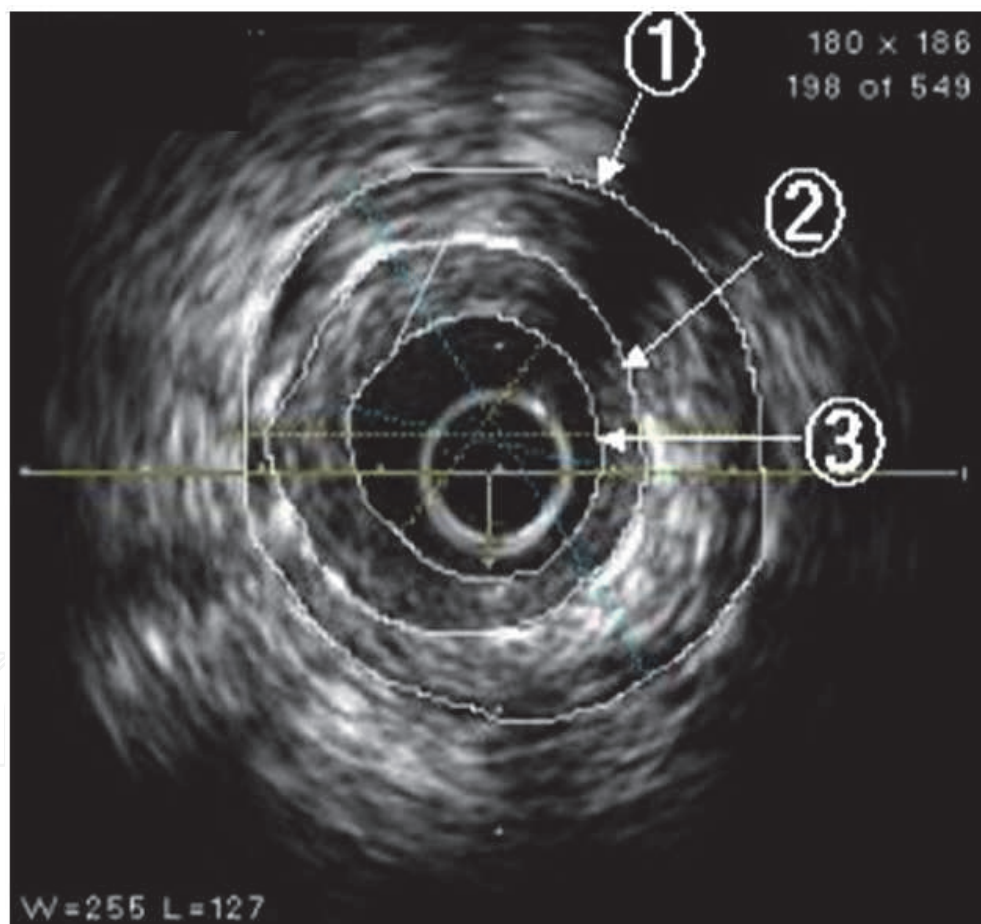

Fig. 1. The following parameters of IVUS were measured at 0.5-mm intervals through the stent site immediately and 6 months after stent implantation. 1) External elastic membrane cross-sectional lumen areas (mm^2); 2) Stent cross-sectional lumen areas (mm^2); 3) Lumen cross-sectional lumen areas (mm^2). Intimal area was calculated as the stent cross-sectional lumen area minus the lumen cross-sectional lumen areas, and the intimal index was defined as the intimal area divided by the stent cross-sectional lumen areas.

Two-dimensional tomographic images from IVUS allowed direct visualization of the 360° characterization of the coronary arterial lumen and neointimal hyperplasia at stent sites. IVUS is a safe, accurate and reproducible method and has thus been recognized as the reference method for quantification of restenosis in trials of anti-restenosis therapeutic interventions. Conversely, angiographic studies of progression/regression are limited because angiography shows the opacified silhouette of only the lumen. Furthermore, the variability of vascular remodeling prevents reliable assessment of plaque dimensions on the basis of lumen narrowing.

The primary end point of this study was the reduction of neointimal hyperplasia as evaluated by intimal index, a prespecified parameter for evaluating neointimal hyperplasia by IVUS. (Katayama, et al. Am Heart J 2007) Intimal index rather than intimal area is considered as a more reliable parameter for the assessment of neointimal hyperplasia. (Mintz GS, et al. J Am Coll Cardiol 2006) Secondary end points were intimal area, late loss of minimal lumen diameter, percentage diameter stenosis, binary restenosis rate, and target vessel revascularization.

Mean intimal index and maximal intimal index by IVUS were significantly reduced in the pioglitazone group compared with controls (Figure 2, panel a). Mean intimal area and maximal intimal area also tended to be reduced in the pioglitazone group compared with controls, but this difference was not significant (Figure 2, panel b). Late loss of minimal lumen diameter and percentage diameter stenosis by quantitative coronary angiography were significantly decreased in the pioglitazone group compared with controls (Figure 2, panels c, d).

The binary restenosis rate was 0% in the pioglitazone group, compared to 31% in controls (P=.043). Three patients in the control group underwent target vessel revascularization, whereas no patients in the pioglitazone group required such interventions. No significant differences in fasting plasma glucose levels, 2-h plasma glucose levels, or hemoglobin (Hb)A1c levels at baseline or follow-up were seen between the 2 groups. On the other hand, fasting insulin levels at baseline were significantly higher in the pioglitazone group compared with controls, and 2-h insulin levels at follow-up were lower in the pioglitazone group than in controls (67.1 ± 28.8 µU/mL vs. 151.9 ± 185.7 µU/mL; P=.027). Visceral fat areas as measured by abdominal computed tomography were significantly decreased at follow-up in the pioglitazone group compared with controls, although no significant differences in plasma lipid profiles (including total cholesterol, LDL, HDL and triglyceride levels) between groups. Pioglitazone treatment improved insulin resistance and decreased visceral fat accumulation, which is closely associated with insulin resistance, without significant changes in glucose or HbA1c levels, or lipid profiles. Our results indicate that reductions in neointimal hyperplasia by pioglitazone in non-diabetic patients with metabolic syndrome are likely attributable to improvements in insulin resistance. Our findings are consistent with previous reports of randomized controlled trials and meta-analyses in patients with impaired glucose tolerance or type 2 diabetes. However, no RCTs have demonstrated that rosiglitazone significantly reduces the risk of repeat target vessel revascularization following implantation of bare metal stents. A meta-analysis by Nishio et al. showed that rosiglitazone does not reduce the risk of repeat target vessel revascularization following PCI (Nishio et al. Cardiovasc Revasc Med 2010). The reasons behind these differing results for prevention of in-stent-restenosis by two thiazolidinediones remain unclear.
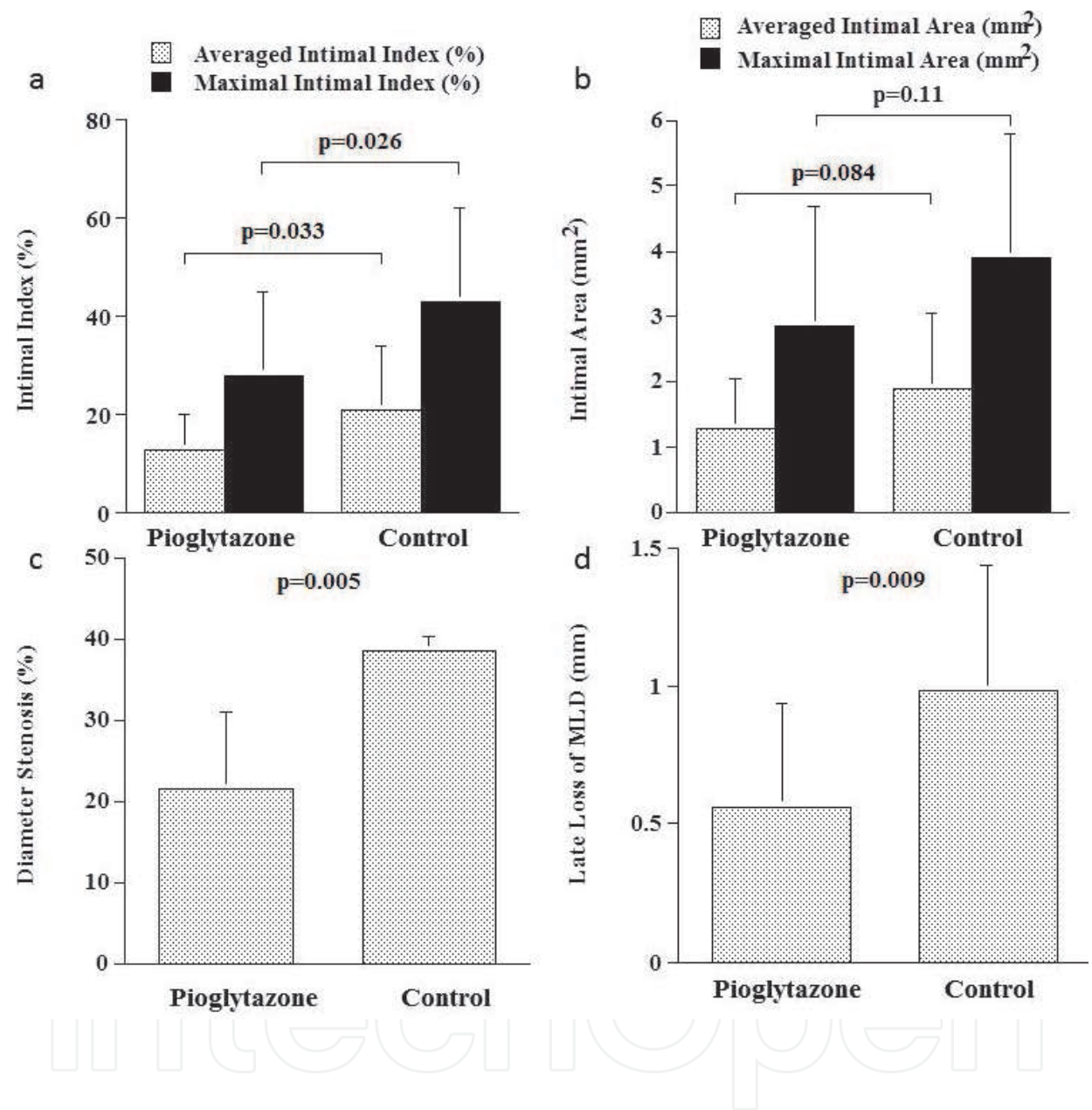
Fig. 2. Intimal index (a) and intimal area (b) as measured by IVUS and late loss (c) and diameter stenosis (d) as assessed by coronary angiography at 6-month follow-up. Mean intimal index and maximal intimal index (a) were significantly reduced in the patient group treated using pioglitazone (n=14) compared with controls (n=14). A non-significant reduction in intimal area was seen in the pioglitazone group compared with controls (b). Late loss of minimum lumen diameter and percentage diameter stenosis as assessed by quantitative coronary arteriography at 6-month follow-up. Late loss of minimum lumen diameter (c) and percentage diameter stenosis (d) were significantly decreased in the pioglitazone group compared with controls.

3. Conclusion

Thiazolidinediones, agonists of peroxisome proliferator-activated receptor (PPAR)-γ, improve insulin sensitivity in patients with type II diabetes mellitus and metabolic syndrome. Beyond the anti-diabetic actions, thiazolidinediones exert anti-inflammatory and anti-atherosclerotic effects in vascular cells in vitro and in diseased animal models. Pioglitazone shows reductions in neointimal hyperplasia leading to in-stent-restenosis after implantation of bare metal stents in patients with type 2 diabetes and metabolic syndrome by IVUS, without unfavorable effects such as increases in myocardial infarction or cardiovascular death. Rosiglitazone shows not only no significant reduction of in-stent-restenosis, but also a strong possibility of increased risk of myocardial infarction and cardiovascular death.

Two-dimensional tomographic imaging by IVUS allows direct visualization of the 360° characterization of coronary arterial lumen and neointimal hyperplasia at the stent sites. IVUS is a safe, accurate and reproducible method and has thus been recognized as the reference method for quantification of restenosis in trials of anti-restenosis therapeutic interventions.
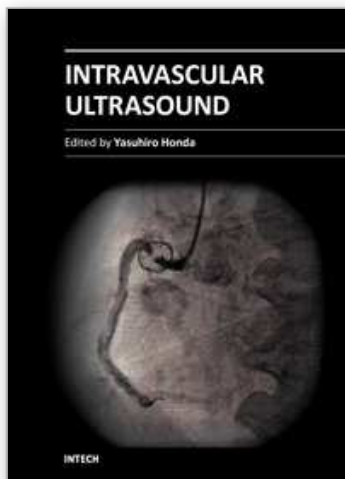
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Intravascular Ultrasound

Edited by Dr. Yasuhiro Honda

Intravascular ultrasound (IVUS) is a cardiovascular imaging technology using a specially designed catheter with a miniaturized ultrasound probe for the assessment of vascular anatomy with detailed visualization of arterial layers. Over the past two decades, this technology has developed into an indispensable tool for research and clinical practice in cardiovascular medicine, offering the opportunity to gather diagnostic information about the process of atherosclerosis in vivo, and to directly observe the effects of various interventions on the plaque and arterial wall. This book aims to give a comprehensive overview of this rapidly evolving technique from basic principles and instrumentation to research and clinical applications with future perspectives.

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Takanori Yasu, Hiroto Ueba,Takuji Katayama and Masanobu Kawakami (2012). Effects of Thiazolidinediones on In-Stent Restenosis: A Review of IVUS Studies, Intravascular Ultrasound, Dr. Yasuhiro Honda (Ed.), ISBN: 978-953-307-900-4, InTech, Available from: http://www.intechopen.com/books/intravascular-ultrasound/effects-of-thiazolidinedione-on-in-stent-restenosis-a-review-of-ivus-studies-

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