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Impact of intravascular ultrasound guidance in routine percutaneous coronary intervention for conventional lesions: data from the EXCELLENT trial

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ABSTRACT

Background: Intravascular ultrasound (IVUS) offers tomographic images of coronary artery, helping physicians refine percutaneous coronary intervention (PCI) procedures. However, it is still controversial whether routine use of IVUS in conventional lesions leads to improvement in clinical outcomes after PCI.
Methods: From the EXCELLENT trial, patients were grouped into IVUS-guided versus IVUS-non-guided PCI (619 and 802 patients, respectively). The crude patients as well as the propensity score matched pairs were compared with regard to clinical outcomes.
Results: Baseline characteristics showed younger age and lower incidence of comorbidities in the IVUS group. IVUS-guided PCI was associated with more aggressive treatment such as longer stenting length, larger stent diameter, and greater number of stents implanted. In the total population, IVUS guidance was associated with a significantly higher risk of periprocedural MI with no significant differences in other outcomes. In the matched cohort (463 matched pairs, 926 patients), IVUS guidance was associated with significantly increased risk of target lesion failure (4.3% vs. 2.4%; $p = 0.047$ by conditional logistic regression) and major adverse cardiovascular events at 1 year almost exclusively due to increased risk of periprocedural myocardial infarction (MI) (1.6% vs. 0.2%; $p = 0.050$), while the rates of cardiac death, spontaneous MI, and target lesion revascularization did not differ significantly between the two groups.
Conclusions: The adjunctive use of IVUS during PCI was associated with more stents implanted, longer stenting, and bigger stenting. There were no significant advantages of IVUS guidance, but rather a significant increase in periprocedural enzyme elevation, reflecting more aggressive procedures performed with IVUS guidance.

1. Introduction

Intravascular ultrasound (IVUS) has contributed greatly to the comprehension of coronary artery disease and advances in percutaneous coronary intervention (PCI), such as progression of vulnerable plaque, mechanism of restenosis after stenting, and the concept of stent apposition and high pressure post-dilation [1–5]. While conventional angiography provides only 2-dimensional projections, IVUS, which offers tomographic images of the coronary vessel wall, has become a widely-used adjunct to angiography helping refine PCI procedures.

However, it is still controversial whether PCI guided by IVUS leads to better clinical outcomes after PCI. Studies in the bare metal stent (BMS) era have suggested clinical benefit of IVUS in reducing restenosis [6–9]. Whereas IVUS use in complex lesions such as bifurcation and left main coronary artery disease has been shown to reduce the rates of mortality and/or myocardial infarction (MI) [10,11], the benefit of routine use of IVUS in conventional lesions is not yet clear [12–14]. Recent advances in coronary intervention including the routine use of high pressure adjunctive ballooning techniques and the introduction of drug-eluting stents (DES) warrant updated clinical data. The aim of this study was to determine the impact of IVUS use on the prognosis of patients undergoing PCI, using the database from the prospective randomized EXCELLENT trial.

2. Materials and methods

2.1. Patients

The Efficacy of Xience/promus versus Cypher in rEducing Late Loss after stENTing (EXCELLENT) trial was a prospective, randomized, multicenter trial which enrolled 1443 patients in order to compare the efficacy of everolimus-eluting versus

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sirolimus-eluting stent in reducing late loss in patients undergoing PCI. The study design and the primary results have been reported previously [15,16]. Exclusion criteria included ST-elevation myocardial infarction within 72 h, significant left main coronary artery stenosis, and true bifurcation lesions requiring 2 stents. The study protocol was approved by the Ethics Committee at each participating center, and was conducted according to the principles of the Declaration of Helsinki. All patients provided written, informed consent for participation in the trial. This was an investigator-initiated trial and the funding source of the study had no role in study, design, data collection, monitoring, analysis, interpretation of the data, or writing of any manuscript. Patients were grouped according to the use of IVUS during PCI: IVUS group versus no IVUS group.

2.2. Procedures and follow-up

Balloon angioplasty and stent implantation was performed according to standard techniques. Before index procedure, all patients received at least 300 mg of aspirin and a 300–600 mg loading dose of clopidogrel. Heparin was administered throughout the procedure to maintain an activated clotting time of 250 s or longer. Administration of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. At discharge, all patients were maintained on at least 75 mg/day of aspirin and 75 mg/day of clopidogrel for at least 6 months. Clinical follow-up was performed at 1, 3, 9, and 12 months after index PCI and all patients were recommended to undergo angiographic follow-up at 9 months. Patients were followed up by telephone contacts or office visits. At follow-up, patients were specifically questioned regarding the occurrence of any adverse events or the presence of anginal symptoms.

2.3. Quantitative coronary angiography (QCA)

Quantitative analysis of coronary angiographic images was performed at a central core laboratory, the Seoul National University Hospital Cardiovascular Clinical Research Center Angiographic Core Laboratory by specialized QCA technicians unaware of the purpose of this study. The Cardiovascular Angiography Analysis System (CAAS) 5.7 QCA system (Pie Medical Imaging, Maastricht, Netherlands) was used for automated contour detection and quantification. Using the guiding catheter for calibration, the minimal luminal diameter (MLD) and reference vessel diameter were measured before and after index procedure, and at first and second angiographic follow-ups. Diameter stenosis (DS) was defined as the ratio of MLD to the diameter of reference segment (RD), and angiographic binary restenosis as DS >50% within the target lesion. Acute gain was defined as the increment of MLD immediately after index procedure. Late luminal loss (LL) was the difference in MLD between immediately after index procedure and 9-month follow-up.

2.4. Study endpoints

The prespecified primary endpoint of the EXCELLENT trial was target lesion failure (TLF), a composite of cardiac death, target-vessel-related myocardial infarction (MI), and clinically-driven target lesion revascularization (TLR), at 1 year. Secondary key endpoint was in-segment binary restenosis at 9 months as measured by QCA. Secondary clinical endpoint included all-cause death, cardiac death, all-cause MI, target vessel-related MI, target vessel revasculization, TLR, and definite or possible stent thrombosis. All definitions of clinical events followed the consensus of the Academic Research Consortium (ARC) [17]. Specifically, cardiac death was defined as any death due to proximate cardiac cause, unwitnessed death and death of unknown cause, and all procedure-related deaths. MI included those occurred during the immediate periprocedural period (within 48 h after PCI) and long after the procedure. Diagnosis of periprocedural MI was established when cardiac biomarkers increased above the 99th percentile of upper reference limit with or without new ST-T abnormalities [18]. TLR was defined as any repeat percutaneous intervention of the target lesion, which means the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent. The occurrence of 'definite' and 'probable' stent thrombosis (ST), according to ARC definition, was recorded. Major adverse cardiovascular events were defined as a composite of all-cause death, all-cause myocardial infarction, target vessel revascularization, and ST.

2.5. Statistical analysis

Baseline data are presented as frequencies or mean ± SD. Differences between patients with and without IVUS guidance were compared using χ^2 test or Fisher's exact test for categorical variables and Student's *t*-test or Mann–Whitney *U* test for continuous variables. QCA data were compared with generalized estimating equations, taking into account correlation of within-subject variables. The event-free survival rates were analyzed by the Kaplan–Meier method, and the differences in survival curves between the groups were assessed with the log-rank test. In order to minimize selection bias in this study, propensity score matching was performed [19]. Details of propensity score matching is described in the Supplement file. A 2-sided P value less than 0.05 was considered significant for all tests. All statistical analyses were performed using R programming language.

3. Results

3.1. Patient characteristics

The EXCELLENT study enrolled a total of 1443 patients, 22 of whom with any missing values listed in Table 1 were excluded in this analysis. Out of a total of 1421 patients, 619 (43.6%) were treated with IVUS-guided PCI. Baseline characteristics of crude study population are summarized in the left panel of Table 1. There were 199 (14.0%) patients with true bifurcation involvement, and 66 (4.6%) with chronic total occlusion, while left main vessel disease was excluded by protocol. Compared with control group, IVUS-guided treatment group was associated with younger age, and had lower incidence of comorbidities including hypertension, current smoking, history of myocardial infarction, and acute coronary syndrome. Angiography showed that the IVUS group had less severe coronary artery involvement, higher frequency of ostial lesions, and more high risk lesions based on American College of Cardiology/American Heart Association criteria. In order to minimize selection bias between the two groups, propensity score matching was performed with all the 32 variables listed in Table 1 to create 463 matched pairs. All features were well-matched after matching as shown in the right panel of Table 1. Comparison of all 32 baseline characteristics used in the propensity score matching is detailed in Supplement table.

3.2. Clinical study endpoints

Comparison of clinical adverse events between the IVUS versus no IVUS groups is summarized in Table 2. Comparisons of clinical outcomes in total population showed no significant differences between the two groups, except for target vessel-related MI. The rate of MI was significantly higher in the IVUS group, mainly driven by the increase in periprocedural MI, but not spontaneous MI. In the matched cohort, the rate of the primary endpoint, TLF, was significantly higher in the IVUS group (4.3% vs. 2.4%; p = 0.047 by conditional logistic regression). The increase in TLF was mainly driven by the higher risk of MI in the IVUS group, especially during the periprocedural period (p-value for periprocedural MI = 0.050). The rates of cardiac death, TVR, and ST did not differ significantly between the two groups, both in the total and matched population. Fig. 1 depicts Kaplan–Meier curves of clinical adverse events in the propensity score-matched group. No significant interaction for the effect of IVUS was observed across any subgroups, as illustrated in Fig. 2.

3.3. Angiographic and procedural data

Angiographic follow-up with QCA at 9 months was performed in 1059 out of a total of 1421 patients (74.5%). In matched population, 685 (74.0%) performed QCA at 9-month follow-up, 347 (74.9%) in the IVUS group and 338 (73.0%) in the no IVUS group. Table 3 compares QCA results of the two groups, revealing lesions treated with IVUS-guided PCI were longer in total length, broader in RD and MLD, and narrower in %DS than those without IVUS. Immediate post-PCI angiogram showed in-stent %DS was less than 10% in both groups, while the IVUS group showed a significant increase in acute gain after procedure. The secondary endpoint, binary restenosis at 9 months, did not differ between the two groups (1.7% vs. 1.1% for the IVUS vs. no IVUS group, respectively; p = 0.373). In Table 4 describing procedural details, the IVUS group was associated with longer treatment length, larger stent diameter, and greater number of stents implanted. Numerically, the mean difference in the total stent length was 5.9 ± 1.7 mm (mean ± s.e.), whereas the lesion length before PCI differed by no more than 1.4 ± 0.7 mm.