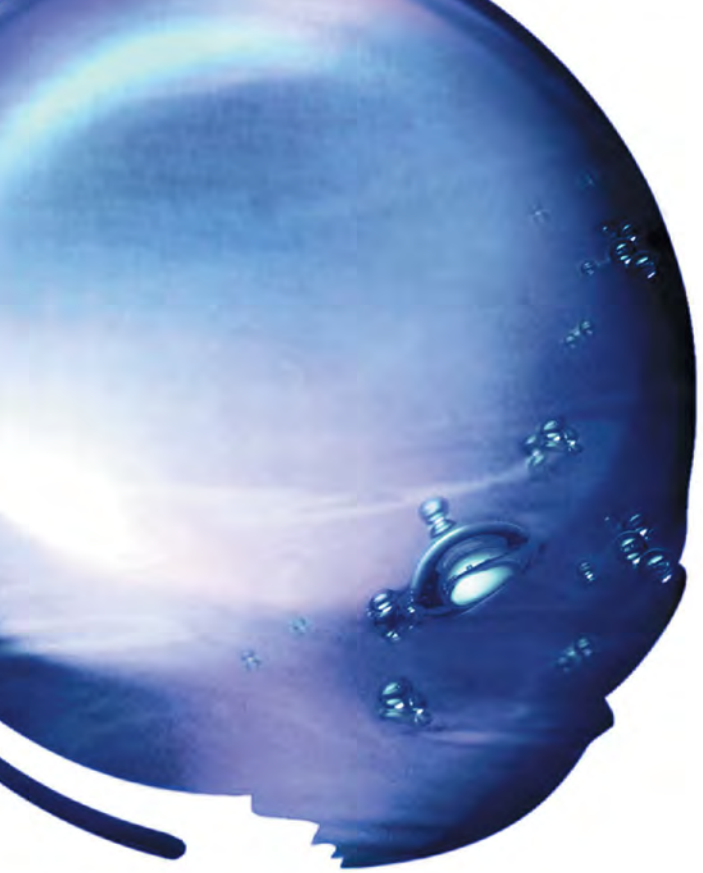


Complex Catheter Therapeutics 2005

CCT2005 in Kobe

September 26 mon.-29 thu., 2005

Course Directors

Osamu Katoh
Toyohashi Heart Center

Shigeru Saito
Shonan Kamakura General Hospital

Takahiko Suzuki
Toyohashi Heart Center

Hideo Tamai
Shiga Medical Center for Adults

Highlights

CCT Website http://www.cct.gr.jp/

CONTENTS

Changing the face of PCI!!
Satellite Symposium

The CCT Satellite Symposium entitled "Changing the face of PCI!!" co-sponsored by Johnson & Johnson, was held in the day before the meeting this year. In this session, Japanese experts from all over the country discussed their latest clinical data of the Cypher Sirolimus-Eluting stent.

Dr. Takeshi Kimura from Kyoto University School of Medicine, a principle investigator of the j-Cypher registry, reported the preliminary six-month clinical outcome of the j-Cypher registry. By August 2005, 5530 patients were enrolled in this registry. The data from 1259 patients were available for the six-month follow-up. Clinical sub-acute thrombosis (occurring within 30 days after the procedure) was reported in 0.32% of the patients. Similarly, clinical late stent thrombosis (occurring from day 31 to day 180 after the procedure) was also observed in 0.32% of them. Together, the rate of clinical stent thrombosis at six-month follow-up period was 0.64% for the entire cohort in this registry. Furthermore, the TLR free rates at the six-month and eight-month follow-up were 97.3% and 92.3% respectively.

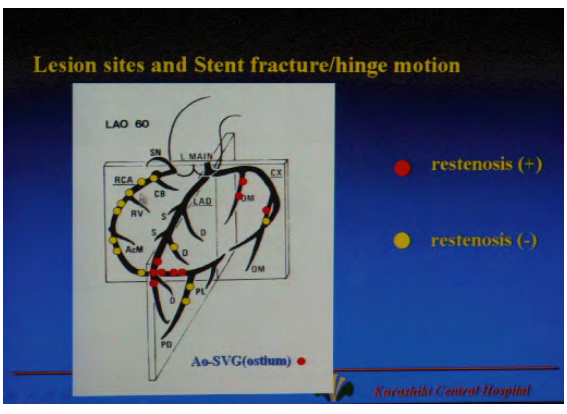
Dr. Toshiya Muramatsu from Kawasaki Social Insurance Hospital reported the indications and follow-up for the Cypher stent in his center. Dr. Muramatsu currently uses the Cypher stent for all patients except those who are unable to receive ticlopidine or those who have small vessel diseases (less than 2.0mm). 1481 Cypher stents were placed in 1110 lesions of 876 patients. Only three patients (0.27%) experienced sub-acute thrombosis, which is similar to the rate of the j-Cypher registry. Binary restenosis and TLR rates were the same, which represented 4.56% of the patients (focal 11, diffuse 0, proximal edge 6, distal edge 1, and total occlusion 3). He concluded that the Cypher stent significantly reduced major adverse coronary events (MACEs) in the field of coronary intervention.

In his presentation, **Dr. Yuji Ikari from Tokai University School of Medicine** reported the mid term results of the Cypher PMS study for the Japanese patients. Until August 2005, 992 patients were enrolled. An eight months clinical follow-up was obtained in 880 patients. The rate of MACEs was 4.2% (37 patients), and the TLR rate was 2.7% (24 cases). Stent thrombosis occurred in 0.23% (2 patients/880 patients) of the patients. Those results demonstrate again the safety and efficacy of the Cypher stent.

Dr. Kazushige Kadota from Kurashiki Central Hospital reported Cypher stent failures in his center. Between November 2002 and December 2004, Cypher stents were implanted in 649 patients at the Kurashiki Central Hospital. Out of the 556 lesions (85.7%) who received an angiographic follow-up, the rate of restenosis at a six or eight-month follow-up was 10.3% (57/556). Most of them occurred in complex lesions. The analysis of restenotic lesions demonstrated the presence of stent under-expansion and stent fracture. He emphasized the issue of hinge-like motion caused by heart beating. Indeed, ISR occurred frequently at location where a hinge-like motion was present. Dr. Kadota and his colleagues suspect that the hinge-like motion plays a significant role in DES failures.

Finally, **Dr. Tetsuo Matsubara from Toyohashi Heart Center** reported the clinical experience of the Cypher stent in Toyohashi Heart Center. Between August 2004 and August 2005, PCI was performed in 1092. In the BMS era, stents were implanted in less than 50% of all PCIs (42%). Since the advent of Cypher stents, the implantation rate increased to 67 %. Clinical and angiographic outcomes were both obviously improved. Prior to the DES era, the rates of restenosis and TLR were 33.0% and 23.7% respectively. After the introduction of DES, they decreased to 13.7% and 11.6%.

Dr. Takahiko Suzuki from Toyohashi Heart Center concluded that the preliminary data on SES in Japan are encouraging with a reduced rate of restenosis and a low overall MACE. Further data are necessary to confirm the safety and efficacy of the Cypher stent in the Japanese population.



Bifurcation stenting: Results of DES implantation in the unprotected left main

According to **Dr. Antonio Colombo from Centro Cuore Columbus / San Raffaele Hospital,** several important clinical trials involving the treatment of unprotected left main trunk (ULMT) using drug-eluting stents (DESs) have been published in all over the world. RESEARCH study from the Netherlands, Milan experience from Italy, and Korean experience from Korea are well-known studies in this field, and have contributed to expand indications of the PCI.

Dr. Park at Asan Medical Center in Korea is an authority of the LM-PCI. Dr. Park and his colleagues demonstrated a significant effectiveness of the Cypher Sirolimus-eluting stent (SES) compared to the bare metal stents (BMS). In this historical comparison study, more patients with severe lesion characteristics were presented in the SES group. Angiographic restenosis of the BMS group and SES group were 30.3% and 7.0% respectively (P<0.001). Dr. Park divided the locations of restenosis into three segments: ostium, shaft, and bifurcation. Restenosis rates at the ostium, shaft, and bifurcation of the BMS and SES were 27.0% vs. 0% (P=0.007), 22.0% vs. 0% (P=0.305), and 35.7% vs. 9.8% (P=0.001) respectively.

In sub-analysis of LM-PCIs of RESEARCH and T-SEARCH studies, researchers from the Rotterdam included 86 BMS patients (protected LM: 9) and 95 DES patients (protected LM: 15). Five hundred and three days (range: 331 to 873) follow-up study revealed a non-significant difference on mortality between the BMS group and DES group (16% and 14% respectively). However, myocardial infarction and TVR rates in the BMS group and DES group demonstrated significant differences, indicating 12% vs. 4% and 23% vs. 6%. The event rate of the BMS group was higher than that of DES group (45% vs. 24%).

Dr. Colombo and his colleagues have been conducted a study called "Milan experience", demonstrating a significant effectiveness of DESs. In this study, 85 patients with DESs and 64 patients with BMSs were registered. Proportions of lesion locations in Milan experience were 81% (69) for distal, 17% (14) for ostium, and 2% (2) for mid segment.

The Cypher stent and Taxus stent were used for the study (Cypher: 41 (48%), Taxus 44 (52%).) For the treatment of bifurcation lesions, 51 cases (74%) and 8 cases (11%) were treated by stenting and POBA respectively. The other 10 cases (15%) remained untreated. In bifurcation stenting technique, crush stenting, culottes stenting, Y-stenting, and T-stenting were performed for 30(59%), 5(9%), 12(25%), and 4(7%) cases respectively. Final kissing balloon inflation was performed for 38 cases (65%).

In-hospital outcomes showed non-significant differences between the BMS group and the DES group. In a six-month follow-up result, the DES group revealed 20% (17) of the total MACE rate while the BMS group demonstrated 36% (23) of it (0.039). The higher mortality was associated with the higher MACE rate (DES: 3.5% (3) and BMS: 14.1% (9). Other factors such as cardiac death, TLR, and TVR did not show significant differences. Angiographic follow-up was performed for 80% of the patients (DES: 63 patients, BMS: 49 patients), demonstrating restenosis rates of 19% (12) for the DES group and 31% (15) for the BMS group(NS). Late loss was lower for the DES group than for the BMS group (0.58mm and 1.08mm) (P=0.001).

Restenosis and TLR rates of crush stenting technique without final kissing balloon in main branch were 13% and 5% respectively. In side branch, restenosis and TLR rates were considerably higher (46% and 19%). Restenosis and TLR rates of crush stenting technique with final kissing balloon inflation in main branch were similar to those of crush stenting technique without final kissing balloon technique (10% and 5%). However, in side branch, restenosis and TLR rates were lower (19% and 9%), suggesting the importance of final kissing balloon technique.

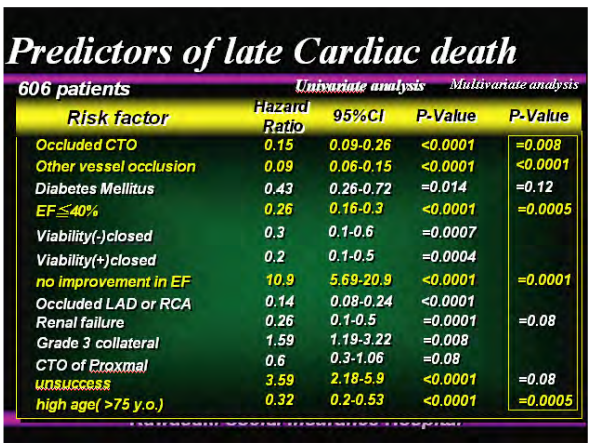
For the results in the above, restenosis can be reduced by the use of DESs in the left main trunk stenosis. Restenosis, when it occurred, they are focal and easily treated. Restenosis is commonly presented in the Lcx ostium, but does not affect on mortality.

CTO club international 2

Chairs: Dr. Antonio Colombo and Dr. Yasushi Asakura
Dr. Osamu Katoh
Dr. Toshiya Muramatsu
Dr. Masahiko Ochiai
Dr. Antonio Colombo
Dr. Gerald Werner

Dr. Katoh from Toyohashi Heart Center presented his current treatment strategies for complex CTOs. Mental condition and patience are the first important factors to success CTO-PCIs. Then, appropriate devices selections according to the lesion characteristics are key factors for a successful CTO treatment. "An 80% of CTOs are treatable with the combination of current treatment strategies," said Dr. Katoh. The remaining 20% of complex CTOs include lesions with bending, calcification, and/or shrinkage (negative remodeling). Specific guidewire techniques such as the IVUS-guided technique or the retrograde wire technique are used to handle these complex CTOs. The IVUS guided technique is a bailout technique in which an IVUS catheter is advanced over a first wire in a false lumen, and then a second wire is handled under the guidance of the IVUS images. However, the IVUS catheter often enlarges the false lumen. This technique requires expertise and it is difficult to handle the wire. In the retrograde wire technique, a wire is manipulated through a retrograde channel using a collateral vessel. Though this approach is easier, it has the risk of occluding or damaging the collateral vessel. "The retrograde approach was initially considered to be a bailout strategy, but I currently use this technique as a first step," said Dr. Katoh.

Dr. Muramatsu from Kawasaki Social Insurance Hospital reported the long-term clinical outcomes of CTOs in his center. Between January 1996 and December 2004, Dr. Muramatsu and his colleagues treated 1145 CTO lesions in 606 patients. Patients with successful revascularization were divided in 2 groups according to the long-term patency (Group P = patent, 436 patients; group O = occluded, 170 patients) and compared the survival rate in each groups. Mean age of group P and group O were 68±10 and 69±11 years respectively.
Approximately 90% of the patients in the group P experienced survival through 5000 days. However, the survival of the group O dramatically declined through 2000 days to 3000 days (P<0.0001) (Kaplan-Meier Method). Multivariable analysis at follow-up demonstrated that occlusive CTOs, other vessel occlusions, and EF<=40% were independent predictors of cardiac death. Long-term prognosis was strongly associated with maintenance of its patency. Today, the combination of various devices improved the success rate of CTO-PCIs. "DES is a promising device to maintain patency. Therefore, the combinations of these devices will further improve long-term prognosis," said Dr. Muramatsu.



Dr. Ochiai from Show University Northern Yokohama Hospital explained the importance of the identification of a CTO entry in abrupt type. He supported the penetration strategy using the Conquest Pro guidewires to handle CTOs. Penetration strategy is composed of three important elements. First, the distal tip of a guidewire should be stiffer than the calcification of a CTO lesion.

Second, the position of the guidewire should be identified by biplane angiography. The operator should construct 3D image using this biplane angiography. Finally, the operator should carefully analyze structures of the CTO.
Proximal fibrous cap has three types: 1) tapered type with stump, 2) tapered type without stump, and 3) abrupt type involved bifurcation. IVUS plays a significant role to identify a CTO entry. Once the CTO entry is identified, a guidewire is then advanced. The IVUS guided technique could be useful to handle the abrupt type. He then reported the result of IVUS analysis after dilatation with a 1.5mm balloon catheter in sixty-seven native coronary CTOs. In this study, Dr. Ochiai and Dr. Fujii at Columbia University counted a number of calcium deposit and performed quantitative analysis of maximum arc and each calcium deposition. As a result, the detection of calcium deposit was identified in 96% of the CTO lesions.

Dr. Antonio Colombo from Centro Cuore Columbus / San Raffaele Hospital first emphasized on the importance of guidewire selection in the CTO treatment strategy. He then introduced a new technique called the STAR technique (subintimal tracking and reentry). In this technique, a subintimal dissection plane is created usually with a hydrophilic wire (e.g. Whisper) with a loop supported by an 1.5mm OTW or monorail balloon. The wire is advanced keeping the loop configuration along the anatomical direction of the vessel toward the distal true lumen. The balloon is used to support the wire when necessary. Then distal reentry in the distal true lumen is performed. Of twenty-one patients who were treated by the STAR technique, six patients (28.6%) experienced restenosis while five patients (23.8%) suffered occlusive restenosis. The remaining ten patients (47.6%) were free from restenosis.

Then he explained the Milan CTO registry. Comparison of 122 patients treated by the Cypher stent with 290 patients treated by BMSs. At six-month follow-up angiography demonstrated a 9.9% (11/111) restenosis rate in the DES group. On the other hand, restenosis was observed in 33.5%(76/227) in the BMS group (P=0.000). Also, occlusion rates in the six-month follow-up period in the DES group and BMS group were 2.7%(3/111) and 6.6% (15/227) respectively.

The last speaker in this session was **Dr. Werner from Medizinische Klinik I / Klinikum Darmstadt, Germany** who reported the long-term angiographic results of the TAXUS stent in CTO lesions. This single center trial is called "PACTO". Primary endpoint of the trial was the evaluation of MACEs. The control group was a group of 148 CTO patients who received treatment with BMSs between 1999 and 2002. The study group included 129 CTO patients who underwent treatment with Taxus stents between Jan 2003 and March 2005. Baseline characteristics had no significant difference between the groups. Six-month angiographic follow-up demonstrated restenosis rates of 49% and 10% in the control and DES group respectively. Re-occlusion rates were also significantly different, with 1% and 18% in the DES and the control group respectively. The BMS group in 2-years experienced 38% of MACE free survival, while the TAXUS group indicated 86% of MACE free survival. "DESs have demonstrated a significant effectiveness in CTO lesions, but it in CTOs the cost-effectiveness is higher than in nonocclusive lesions with only 3 lesions to be treated to prevent one revascularization " Dr. Werner concluded.

Intervention for CTO. Why not?

According to **Dr. Etsuo Tsuchikane from Toyohashi Heart Center,** the importance of revascularization can be divided into two phases in the treatment of CTOs: acute and chronic phase. Removal of symptoms, avoidance of bypass surgery, and maintenance of safety areas of other vessels are the main objectives in acute phase. On the other hand, improvement of left ventricular function, maintenance of collateral vessel, and improvement of long-term prognosis are the main goals in chronic phase.

Regardless of the presence or absence of its viability, significance of the CTO treatment excluding distal and small vessels is to inflate occluded vessels and to maintain patency of opened vessels. Patency rate in the BMS era was not satisfactory despite the successful implantation of coronary stents. However, restenosis and TLR rates have been dramatically declined in the DES era as shown in various clinical registries and trials. Therefore, treatment of occluded vessels plays a significant role in this era.

The CTO club in Japan was established to improve treatment outcomes of the total occlusion. The first meeting was held in Kyoto in 1999, and until 2002, live demonstration and CTO lectures were mainly included in programs. Since 2003, the meeting has been held in Toyohashi, and live demonstration becomes the main focus of the meeting.

Over the past three years, sixty-five CTO cases were treated in the CTO club. Of those, 43%(28), 28%(18), 17%(11), 1%(1), 8%(5), 3%(2) of lesions were located in the RCA, LAD, LCX, LMT, CIA/EIA, and SFA respectively. More than 90% of the cases were considered occluding for more than one year or unknown. Re-try was performed in 18% (12) of the cases, and the total success rate was 92.3%.

Characteristics of steerable guidewires and techniques of operators play significant roles in success of CTO lesions. Miracle series and Conquest series are guidewires specific for the treatment of CTO lesions. Approximately a half of the CTO lesions in the CTO club was handled by the Miracle series while the use of Conquest series accounted one fourth of the lesions. Intermediate guidewires and others were used to handle the remaining cases. The use of stiffer wires relatively increased the success rate.

Today, techniques of Japanese operators have been improved along with the advancement of devices. New techniques used in CTO lesions are known such as the anchor wire technique, parallel wire technique, side branch technique, retrograde technique, and IVUS-guided technique. Today, retrograde and IVUS guidewire techniques are considered to be the last wiring techniques to handle complex CTO lesions.

The advent of DESs certainly changed the current practice. Favorable outcomes are expected when DESs are successfully implanted in CTO lesions. Success rates have been also improved due to the advancement of guidewire and operators' techniques. To obtain similar success rates as with non-CTO lesions, the characteristics of these new devices and technologies should be understood.

Six-month outcomes for sirolimus-eluting stents: Preliminary results from the J-Cypher registry

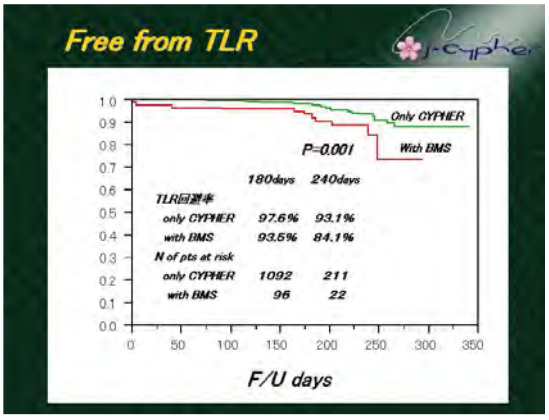
Dr. Yoshihisa Nakagawa from Kyoto University School of Medicine reported the result of 5530 patients who received the Cypher stent by September 20. The j-Cypher registry, leaded by Drs. Kazuaki Mitsudo and Takeshi Kimura, is the first physician-directed registry of consecutive patients undergoing SES implantations in Japan. This registry is focused on assessing the safety of Sirolimus-eluting stent (SES) in routine clinical use with combined aspirin and Ticlopidine anti-platelet regimen as well as the evaluation of the efficacy of SES in routine clinical practice encompassing a large number of patients with high-risk lesions in Japan.

Until now, forty-one Japanese leading centers have been registered in this study with targeting at a recruitment of 15000 patients. Patients will be followed at 30 days, 6 months, 1, 3, and 5 years. Angiographic follow-up is not mandatory. By September 20 2005, 14,350 patients received PCIs in these centers. The Cypher Sirolimus-eluting stent was implanted in 7315 cases. Three thousand five hundred seventy-five patients completed a 30-day follow-up. Only one third (1259 patients) underwent a six-month follow-up.

Mortality rates at 30 day and 180 day were 1.1% and 2.9% respectively. TLRs were 0.3% and 2.6% at 30 day and 180 day respectively. MACE rates at 30 day and 180 day were 1.8% and 5.8% respectively.

The main finding of the j-Cypher registry is its low stent thrombosis rate. The 30-day sub-acute thrombosis rate was 0.32% while the same percent (0.32%) of patients experienced late stent thrombosis. Thus, a total stent thrombosis rate at 180 day was significantly lower than previous studies (0.64%). TLR free rates at 180 day and 240 day were considerably high with 97.3% and 92.3% respectively.

The j-Cypher registry encompasses a large number of patients with high-risk characteristics and could be a very powerful clinical tool to evaluate adequacy of expanding indication of PCI using SES. SES implantation under Ticlopidine anti-platelet regimen seemed not to be associated with exaggerating the incidence of stent thrombosis as compared to those reported in previous randomized clinical trials and registries using clopidogrel. Off-label use of SES is quite prevalent in the real world clinical practice in Japan. Finally, the TLR rate is lower than the one in BMS era. Longer follow-up (up-to 1year) is mandatory to confirm true TLR rate.



Target lesion failure after SES implantation: Insights from IVUS

Dr. Kenichi Fujii from Colombia University Medical Center reviewed a three-year follow-up data of the US SIRIUS trial in his presentation. In the SIRIUS three-year follow-up, TLR free rates in the bare metal stent (BMS) and Sirolimus-eluting stent (SES) were 76.0% and 92.9% respectively, indicating extremely superior outcome of the SES (P<0.001). In-stent restenosis was also common in the BMS group, demonstrating 91% of reduction in this study (BMS; 35.4% and SES; 3.2%). This significant reduction of the restenosis rate was also demonstrated in both stent proximal and distal segments.

However, some negative data regarding the Cypher stent have been also reported. Dr. Fujii emphasized three mechanisms of the DES failure identified by the IVUS finding. The Cypher stent has been currently reported to have three causes of the DES failure: 1) intra-stent restenosis, 2) edge restenosis, and 3) stent thrombosis. To identify them more carefully, Dr. Fujii and his colleagues in Colombia University performed an extensive IVUS analysis.

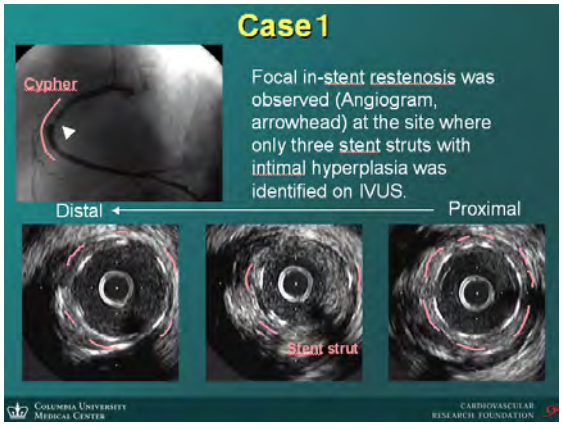
First, intra-stent restenosis is caused by a gap between two stents. Six to seven stent struts of the Cypher stent should be identified on an IVUS analysis when it is fully expanded. In contrast, a number of stent struts was not identified in restenotic lesions, revealing neointima hyperplasia in strut free areas. This phenomenon is called a strut mal-distribution or stent fracture. Stent fracture is considered to be caused by cardiac and vascular constriction. Dr. Fujii and his colleagues evaluated lumen cross-sectional area, stent cross-sectional area, and neointima cross-sectional area of 24 non-restenotic and 25 restenotic lesions. The results indicated significant differences between the groups.

Second, another DES failure is restenosis at edges of the stent. In SIRIUS study, the rates of proximal edge restenosis in the SES group and BMS group were 5.8% and 8.1% respectively. On the other hand, the rates of distal edge restenosis demonstrated a significant difference demonstrating 2.0% and 7.2% respectively.

The restenosis rate of the Cypher stent in proximal edge was considerably higher than that of the Cypher stent in distal edge, which suggests the cause of vascular circulation from upper stream to down stream. In a study published in "Circulation", a higher concentration of Sirolimus was found in vascular circulation of down stream than that of up stream. This was suggested to be the cause of this effect.

The last DES failure is a stent thrombosis. Previous reports revealed that stent under expansion was the most important factor associated with stent thrombosis. Based upon the analysis of previous data that evaluated those who experienced stent thrombosis and those who do not, stent thrombosis was reported to be influenced by minimal lumen diameter and minimum cross-sectional area. Multivariable analysis demonstrated that reference stenosis and stent under expansion were independent predictors of the Cypher stent thrombosis

Understanding the mechanisms of a target lesion failure was very important. Local drug concentration is lower for the insufficient stent strut distribution, and it promotes neointima hyperplasia. Stent under expansion should be avoided when the Cypher stent is placed. A gap between two SESs is also suggested to affect local neointima hyperplasia. Consideration of these issues will help overcome the DES failure of the Cypher stent.



Detection of vulnerable plaque by 64 MSCT

Dr. Mariko Ehara from Toyohashi Heart Center presented the utility and applications of 64 MSCT for coronary artery disease through several case examples. 64 MSCT has been used for several months in Japan for the diagnostic of coronary heart disease.

The 16 MSCT, the former generation scanner of MSCT, has been already known as an useful non-invasive diagnostic modality. In the USA, the Time Magazine focused on the non-invasive characteristics of this modality. Diagnostic challenges include the detection of significant stenosis, of in-stent restenosis, and recently, special emphasis has been put on the identification of vulnerable plaques. Preliminary data shows an excellent accuracy for the detection of de novo stenosis when compared to invasive coronary angiography. This was also the case for ISR, although limited data are available up to date.

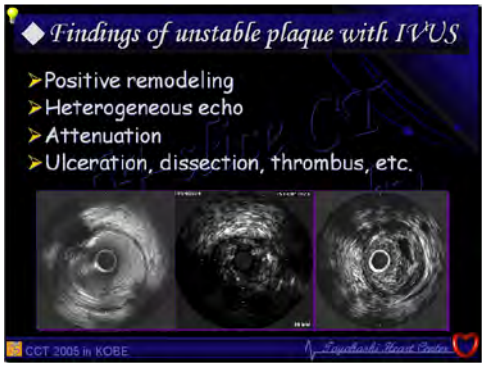
Vulnerable plaques have been described to have the following characteristics:
1) Positive remodeling
2) Eccentric distribution
3) Lipid-rich
4) Ruptured or ulcerative tissue
5) Thrombus
6) Thin fibrous cap
7) Macrophase mobilization
8) Others

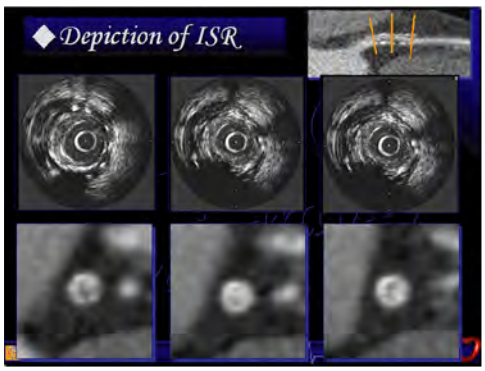
Positive remodeling, eccentric distribution, and ulceration of coronary artery can be identified by MSCT. However, 64 MSCT has not enough resolution to visualize and identify lipid-rich, ruptured tissue, thrombus, thin fibrous cap and/or macrophase mobilization. A large number of investigators in the world are trying to identify vulnerable plaque by MSCT.

Based upon the analysis of lesion size and CT density, plaque characteristics identified by 64 MSCT were closely related to those by IVUS.

Dr. Ehara showed coronary images of unstable angina, a typical case of unstable angina with heterogeneous CT density, positive remodeling and eccentric distribution of culprit site. They were similar to those of IVUS images. Plaque characterization may become possible with MSCT.

Dr Ehara concluded that 64 MSCT has a potential to depict and distinguish vulnerable plaques.



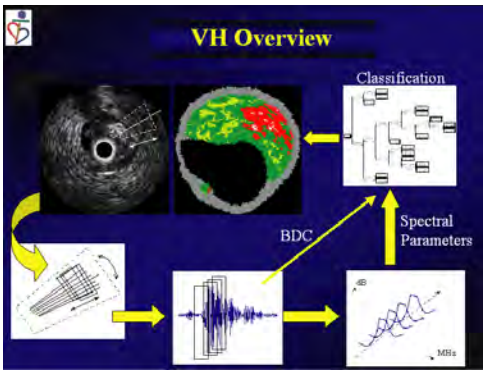


Detection of vulnerable plaque by using Virtual Histology IVUS

"DESs have overcome the Achilles' heel of a PCI, commonly known as restenosis", said **Dr. Kenya Nasu from Toyohashi Heart Center.** Now, the interest of interventionalists is shifted to the diagnosis and treatment of unstable or vulnerable plaque. Though the DES showed a significant reduction on restenosis rates, they failed to demonstrate the effectiveness of mortality and myocardial infarction in large randomized trials such as SIRIUS and TAXUS IV. This fact led the interventionalists to pay more attention on the identification of vulnerable plaque during a percutaneous coronary intervention procedure. Smith el al. reported a relationship between diameter stenosis and patients who experienced ACS. The data from 195 patients, proportions of patients who experienced acute coronary syndrome (ACS) had less than 50% stenosis, 50-70% stenosis, and more than 70% stenosis were 68%, 18%, and 14% respectively. Therefore, this study indicated that most ACS occurs on mild stenosis. This reflects the fact that non-significfnat stenosis by far outnumber significant stenosis. ACS demonstrated the higher mortality rate and many mechanisms remained unknown.

The Virtual Histology™ IVUS system developed by Volcano Therapeutics is a new modality that possibly allows the detection of vulnerable plaque. This technology uses radiofrequency backscatter signals and can reconstruct a tissue map of plaque components. Previous study reported 80-92% of accuracy rate in vitro to detect four different plaque components. By the use of VH-IVUS, a patient can receive an earlier detection of vulnerable plaque and initiate prophylactic treatment to prevent the incidence of ACS.

However, the detection of vulnerable plaque is not directly associated with the reduction of mortality rate. The most important issue in this field is to identify vulnerable plaque that has a higher risk of rupture in near future. Dr. Nasu and his colleagues currently initiated a study called "the SPECIAL" trail (Study of Prospective Events in Coronary Intermediate Atherosclerotic Lesions). The SPECIAL is target at the recruitment of 2000 patients in up to 100 centers.



Primary endpoint is the safety of the IVUS procedure evaluated by MACE (defined as cardiac death, cardiac arrest, re-hospitalization, MI, clinical driven revascularization) and the identification of plaque progression and regression evaluated by VH-IVUS. Dr. Etsuo Tsuchikane at Colombia University and Dr. Tadanori Aizawa at Roppongi Cardiovascular Institute are co-principle investigators in this study. The study is planned to begin on January 2006. "This study will potentially enlighten the diagnosis and treatment of vulnerable plaque, one of the remaining issues in the field of coronary intervention," said Dr. Nasu.

OCT: Toyohashi experience

At first, **Dr. Yoshihiro Takeda from Toyohashi Heart Center,** explained the history of Optical Coherence Tomography (OCT). Huang and his colleagues first succeeded imaging coronary atheromatious plaques in vitro by using OCT in 1991, and over the past decade, OCT has been developed and slowly but surely used in the clinical practice. OCT is a light-based imaging modality with a high resolution (10 μm). Catheter-based intravascular OCT imaging has been shown to obtain qualitative information about arterial anatomy and plaque composition in vitro and in vivo with a high accuracy. "OCT can possibly identify the mechanism of re-occlusion, restenosis, and plaque rupture after the DES implantation," said Dr. Takeda.

DESs had overcome the Achilles's heel of the PCI known as restenosis. Angiographic restenosis rate is less than 10% when DESs are implanted in simple lesions. Under this circumstance, evaluating the effectiveness of "new" DESs comparing to currently available DESs requires a large sample size, at least 1000 to 2000 patients. OCT can quantify especially small amounts of neointimal hyperplasia, which possibly offers a significant advantage in the clinical evaluation of DESs.

The <Picture A> showed the OCT image of the incomplete stent apposition immediately after stent implantation. In this OCT image, stent struts failed to appose vascular wall. The <Picture B> demonstrated the resolution of the stent incomplete apposition at 2-month follow-up study of OCT imaging. IVUS was not able to visualize such detailed morphological information. Therefore, OCT will possibly be a new modality offering a detailed analysis even after the implantation of coronary stent.

OCT is not only useful to detect vulnerable plaque, but it also possibly to offer information on incomplete stent apposition after a DES implantation, tissue prolapse, thrombosis, and an accurate quantification of neointimal hyperplasia. "Further studies will verify the usefulness of OCT in real-world clinical practice," said Dr. Takeda.

Intravascular Imaging Modalities for Detection of Vulnerable Plaque

Imaging Modality	Resolution	Penetration
IVUS	100 μm	Good
Angioscopy	Unknown	Poor

Imaging Modality	Fibrous Cap	Lipid Core	Calc	Thrombus
IVUS	+ ++	+++	+	
Angioscopy	+		++	-
+++				

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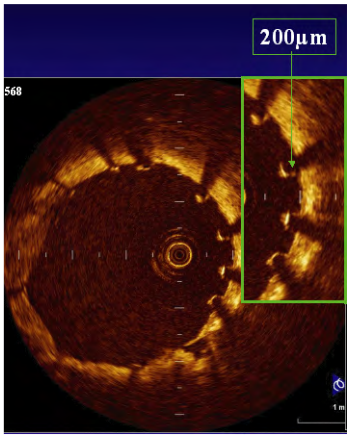
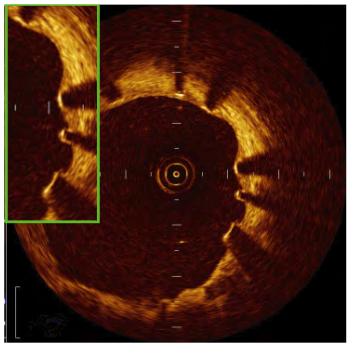


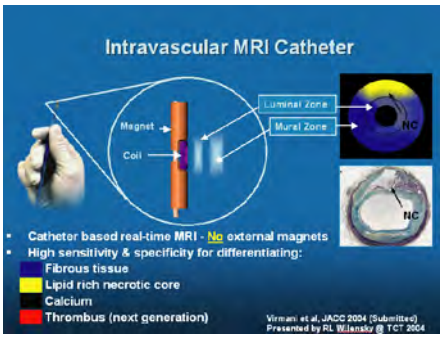
Picture A: Immediately after stenging (DES)



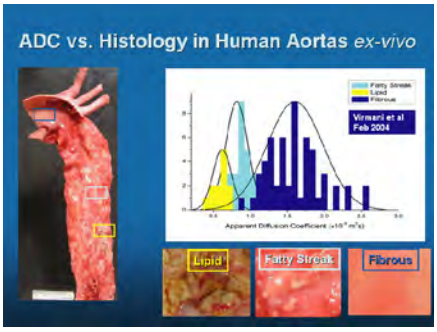
Picture B: 2 Mo FU

Intravascular MRI to detect lipid content

In his presentation, **Dr. Ron Waksman from Washington Hospital Center** emphasized that early detection of vulnerability of a coronary plaque is useful to predict future events. Angiography is limited in its possibily to detect vulnerable plaques. Today, new modalities that easily detect progressive or unstable plaque are strongly demanded. Dr. Waksman introduced a new percutaneous intravascular MRI called "Top-spin™ IVMRI" miniature hand held catheter for local high resolution MRI. This is a catheter based real-time MRI with no external magnets. The catheter has high sensitivity and specificity for differentiating fibrous tissue, lipid rich necrotic core, calcium, and thrombus (next generation). IVMRI catheter can be used like an IVUS or other intravascular image catheters. Magnet and coil are attached to a tip of the catheter and information received from this catheter tip is transmitted in outside monitor.



Dr. Waksman reported an ex-vivo human aortic study. The purpose of this study was the ex-vivo determination of arterial plaque lipid content and thickness of fibrous cap correlated to histology. Sixteen aortic arch specimens from subjects dying suddenly were used in this study (6 normal and 10 atherosclerotic.) The result in figure below showed a positive correlation.



He also reported the safety and efficacy of the IVMRI system during catheterization procedures. Subject is a group of patients who underwent coronary angiography for the suspicion of coronary artery diseases in their native arteries. Twenty-nine patients from four European centers were registered in this trial. Dr. Wijns (PI) at Aalst, Belgium, Dr. Serruys at Rotterdam, Netherlands, Dr. Hennsen at Homburg, Germany, and Dr. Grube at Siegburg, Germany are co-investigators in this study. A 30-day follow-up demonstrated no device related adverse events. Catheter is easily maneuvered and retracted. IVMRI results demonstrated a range of fibrous to lipid rich lesions.

Today, another study involving two other US and an Israel centers is planned, adding Dr. Wiensky, Dr. Waksman, and Dr. Leon. Further study assessing lipid content, fibrous cap, inflammation, angiogenesis, and thrombosis is also considered to be examined.

Expert's Opinion

Left Main Trunk Stenosis in the DES era

Dr. Takahiko Suzuki
Toyohashi Heart Center

Question
What are the standard indications of LM-PCI in the DES era?

Answer
The indications of the LM-PCI are basically cases assuming to receive similar acute and chronic outcomes with the bypass surgery. Hence, LM-PCIs in the DES era are currently paid a strong attention in all over the world.

More than a year has been passed after the advent of the Cypher stent in Japan. Today, its positive short and mid-term outcomes gradually led to expand indications. One of them is the application of a left main (LM) disease. However, the discussion regarding the LM disease should not consider to be the same as other diseases. No one guarantees the success of a LM-PCI. Success or failure is strongly depending on the operator skill. In general, LM-PCI is not a difficult procedure, however, unskilled or inexperienced operators should not perform LM-PCI because the incidence of complications in left main trunk directly causes death.

Some studies currently demonstrated their positive outcomes to treat LM stenoses in randomized clinical trials, but they do not completely represent the "real-world" practices due to the limitations of different inclusion and exclusion criteria in the trials.

Since the LM-PCI is associated with higher procedural risks, unskilled operators who are not able to manage unexpected complications should not handle the LM-PCI.

Stenoses located at the ostium and body of the LM are relatively less technically challenging than those at the LAD/LCx bifurcation. Intermediate skilled operators, who have experienced more than a few hundred stent implantations, can handle the ostium and body LM-PCI without difficulty. Clinical outcomes of the LM-PCI in these areas are favorable if stents are appropriately implanted.

The rate of the PCI, compares to the rate of the CABG for LM treatment, after the advent of a DES has obviously changed in Toyohashi Heart Center. The DES certainly expanded the indications of the PCI in this setting.

In Toyohashi Heart Center, percentages of LM-PCI performed in the body, ostium, and bifurcation are approximately 10%, 10%, and 80% respectively. Stenoses located at the LAD/LCx bifurcation are technically more challenging, and DCA might be performed to maximize treatment outcomes, which requires more skills of operator. Thus, only skillful operators should perform this challenging LM-PCI to handle any complications.

Question
When a coronary stent is implanted in a LM ostium, how long does the stent strut project to aorta?

Answer
At first, one of the most important aspects associated with a LM stenting is the incidence of stent slipping during balloon inflation. A stent should be positioned by reference to aorta side (the roof side) of ostium when stenoses extent a wide range of LMT. In general, the aorta side and Sinus Valsalva side (the bottom side) of ostium are not coaxially located, and valsalva side is shorter than aorta side. The ideal stenting of the LM ostium is protrusions of 1-2mm stent strut in aorta side and 2-3mm in Valsalva side.

Question
What are differences between the implantation of coronary stent in a LM and a RCA ostium?

Answer
Stent positioning at a RCA ostium is considerably harder than a LM ostium. Therefore, multiple projections are recommended. I normally consider 1-2mm strut protrusion to the aorta. Protrusion of 1mm is an ideal, but it is difficult in most cases. Hence, 2mm protrusion to the aorta is recommended.

Question
How do you treat if restenosis occurs after having placed a coronary stent protruding to the aorta in an LM ostium? Please tell me a ways to engage a guiding catheter.

Answer
The engagement of a guiding catheter (even a diagnostic catheter) is challenging when a coronary stent is projected to an aorta ostium. This is especially true when the projected stent from the ostium is longer or the guiding catheter destructs the projected stent strut. In this case, a steerable guidewire is advanced to the stent strut. Then, the guiding catheter is placed a position to be a coaxial to the entry of the stent. Another guidewire is then advanced from the actual entry of the stent. If the stent strut is destructed, it should be required to debulk with a rotational atherectomy. Then, a balloon dilatation is performed.

Question
What is your stenting strategy for LMTs involving bifurcation lesions?

Answer
Single stenting is a basic stenting strategy for the treatment of bifurcation lesions in Toyohashi Heart Center.

Crush stenting is not preferred due to the presence of stent free zones. In other word, stent strut in the carina is not fully apposed and drug free zone remains. Though final kissing balloon technique is said to improve clinical outcomes, at the area where the stent is bended, stent fails to appose the vessel walls.

This is the technique that a first stent is crushed by a second stent. The simplicity is an advantage of the crush stent technique, however, drug distributions to vessel walls are not uniform. Also it could be assumed that the occurrence of stent thrombosis would be higher in the area of 3 struts compare to 1 strut. Thus, we prefer to single stenting technique. If second stent implantation is necessary, we perform provisional Y-stenting. Because a second stent theoretically crosses into the strut of a first fully expanded stent, the second stent is completely covered vessel walls.

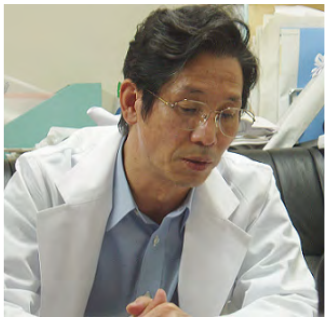
Question
What is an optimal atmosphere for a final KBT in a LMT stenosis?

Answer
The operator should be paid a special attention to advance a guidewire in a LCx artery after a coronary stent was implanted in a LM-LAD. I first advance a guidewire across the LCx artery and pull it back to select the closest point to the carina. A balloon catheter with flexible distal tip should be selected to cross the stent strut in the LCx artery. The size of balloon catheter should be optimal. The atmosphere of final kissing balloon in the LM and LCx is preferred to be more than 12 atm (a 15 atm is preferred.)

Expert's Opinion

Bifurcation Lesions in the DES era

Dr. Hideo Tamai
Shiga Medical Center for Adults



Question

Please tell us your opinions about various bifurcation stenting strategies. How and when do you perform them?

Answer

"Y", "T", "Kissing" and "Crush" stenting are techniques in which two stents are implanted in bifurcation lesions. Some studies demonstrated negative outcomes of these two stenting strategies. Single or provisional "Y"/"T" stenting is a basic bifurcation treatment strategy in our center. Final kissing balloon dilatation is performed in any strategies immediately after the placement of the DES.

Some operators prefer crush stenting; however, a lot of issues still remain unsolved in this technique. For example, some researchers reported higher restenosis or sub-acute thrombosis rates in this strategy if final kissing balloon technique (KBT) was not performed. Final KBT reduces the incidence of these unfavorable outcomes, however, a balloon catheter often fails to cross the struts of three overlapping stents. Although this technique is a simple, and cosmetically shows favorable angiographic views, the issues of long-term outcomes in regards to restenosis and thrombosis remains unknown, especially after the discontinuation of anti-thrombotic agents.

Question

Is the DCA still an effective strategy to receive the optimal result in the DES era? Do you still perform DCA in the DES era? If yes, has the DES changed your current debulking strategy?

Answer

We have been supporting the use of DCA since it was first introduced. DCA is an effective strategy to reduce an acute recoil and plaque shift in bifurcation lesions. We also use this debulking device in the DES era.

Result of the DESIRE study supports the efficacy of DCA. In this multi-center study, subjects were divided into two groups: POBA + stent (BMS) group and DCA+ stent group. The Results were favored in the DCA + stent group. Restenosis rates of LAD bifurcation sites in the DCA + stent group, and stent + POBA group were 7% and 26% respectively (P=0.059)."

This outcome supported our belief and enhanced the motivation to implantation of the DES followed by the DCA. Restenosis can be significantly suppressed by the combination of DCA + DES if the drug of the DES extends over stenoses. The most favorable outcome is predicted when the edges of a side branch is successfully debulked with DCA. However, this challenging debulking technique needs a higher skill.

In AMIGO study led by Dr. Antonio Colombo, the DCA group in all centers except Dr. Colombo's institution demonstrated negative outcomes. This result revealed that the technique and outcome were depending upon the skill of operators. This was also true for the DESIRE study. For example, patients with more than 60% of the remaining plaque area after the atherectomy experienced 15.3% of a TVR rate, and the TVR rate was 6.9% for those who had less than 60% of the remaining plaque area. Surprisingly, TLR rate was 2.8% for those who had less than 50% of the remaining plaque area.

Question

Should direct stenting be performed when a stent is implanted in an ostium lesion of side branch?

Answer

Pre-dilatation is recommended to prevent a polymer destruction of the DES. Direct stenting in the BMS era has been reported to reduce restenosis due to the reduction of vascular injury caused by the pre-dilatation. However it is difficult that the stent implantation in the side branch ostium after the stenting in main branch. So that it would be recommended to pre-dilate the side branch for the case of stenting. DES decreases the response of vascular injury. Thus, the issue of vascular injury should not be considered if it is intended to implant a DES.

Question

What is optimal pressure when you implant the Cypher stent?

Answer

A Cypher stent is often failed to attain the complete expansion over the 18 atmospheres. In this case, 20 atmospheres should be applied to receive the full expansion. For example, a 2.5mm Cypher stent is inflated to 18 to 20 atmospheres in 2.5 mm vessel, however lower pressure should be applied when a larger stent is placed in a smaller vessel size.

Question

How do you treat ISRs when they occur in the branch of bifurcation lesions?

Answer

I prefer to use a DCA to treat restenosis in a main vessel, and then pre-dilation is performed. If necessary, a Cypher stent is placed to cover the restenosis. Single stenting strategy with final KBT is a basic treatment strategy to manage ISRs of bifurcation lesions.

A Cypher stent implantation after cutting balloon angioplasty is another choice to treat ISRs of bifurcation lesions. Provisional "Y" stenting is performed if necessary, since this technique allows the stent to make good result and the drug to distribute equally. A simple strategy is the best way to treat bifurcation lesions.

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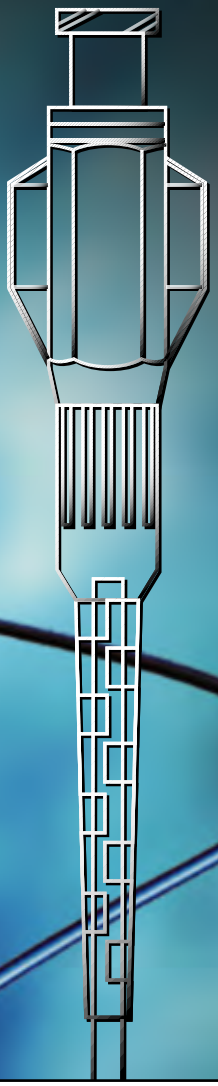

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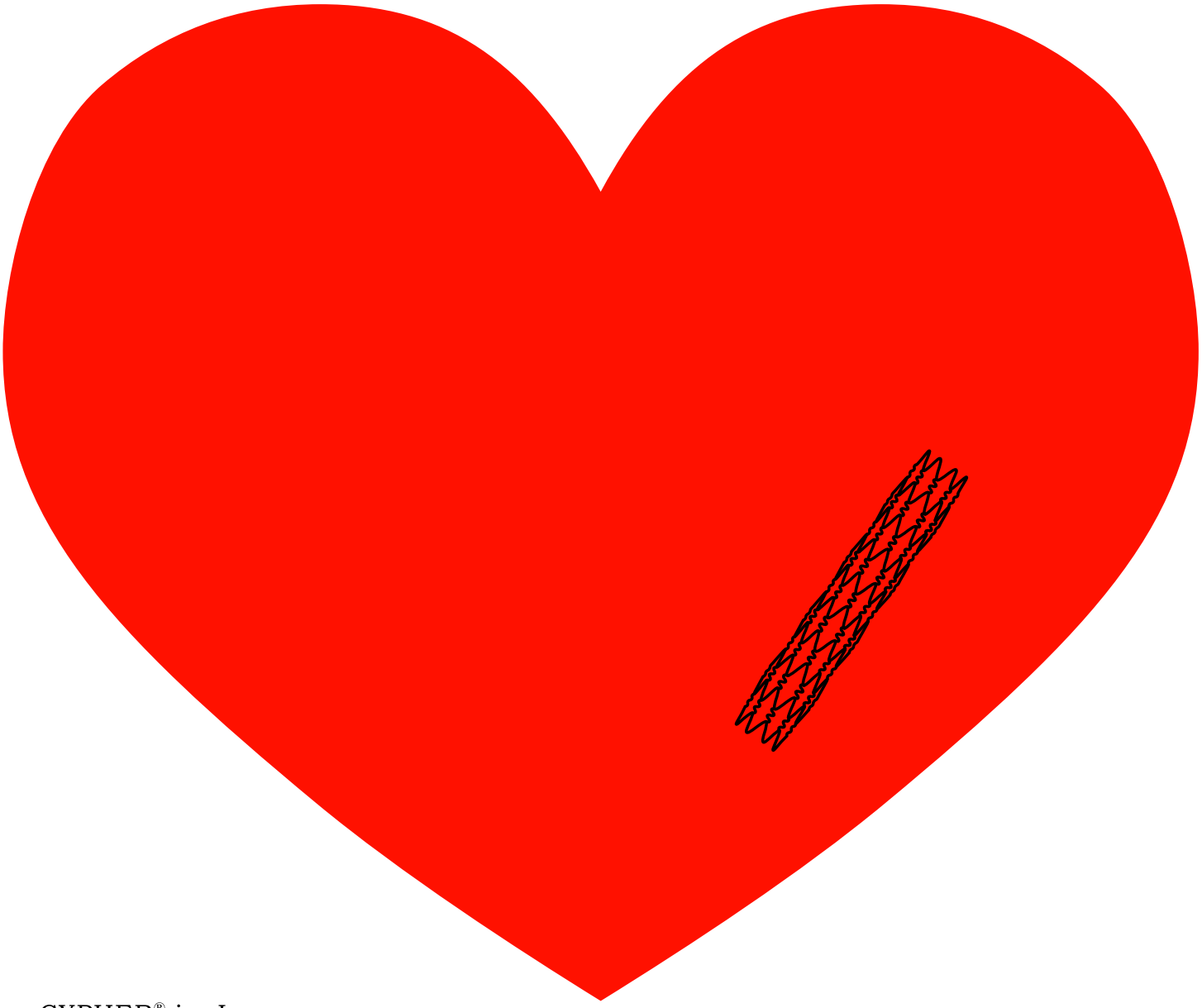

CYPHER® in Japan

Japan was one of the last countries in the world to approve CYPHER®. Market approval was received over 2 years after the EU and Asian countries and over 1 year after approval in the United States. CYPHER® was launched in Japan in August of 2004. Since clopidgrel is not an approved medication for cardiovascular indications here in Japan, ticlopidine is the required anti-platelet medication to be used along with aspirin prior to implanting CYPHER® and for 3 months after the implantation procedure. Thereafter, aspirin is to be continued indefinitely to reduce risk of thrombosis.

In collaboration with physicians, medical societies and the Japanese government, we have been working closely to ensure patient safety with use of CYPHER®. Since the introduction of CYPHER® through the end of 2005 (for approximately 17 months)*, over 210,000 units of CYPHER® have been implanted in an estimated 120,000 patients or more. Currently, the incidence of thrombosis is 0.2-0.3%, which appears to be lower than the incidence historically observed with bare metal stents.

Patient safety remains the highest priority for Cordis Cardiology Japan.

*The number of stents used is based on clinical usage reports submitted to Johnson & Johnson K.K. as of December 16, 2005.

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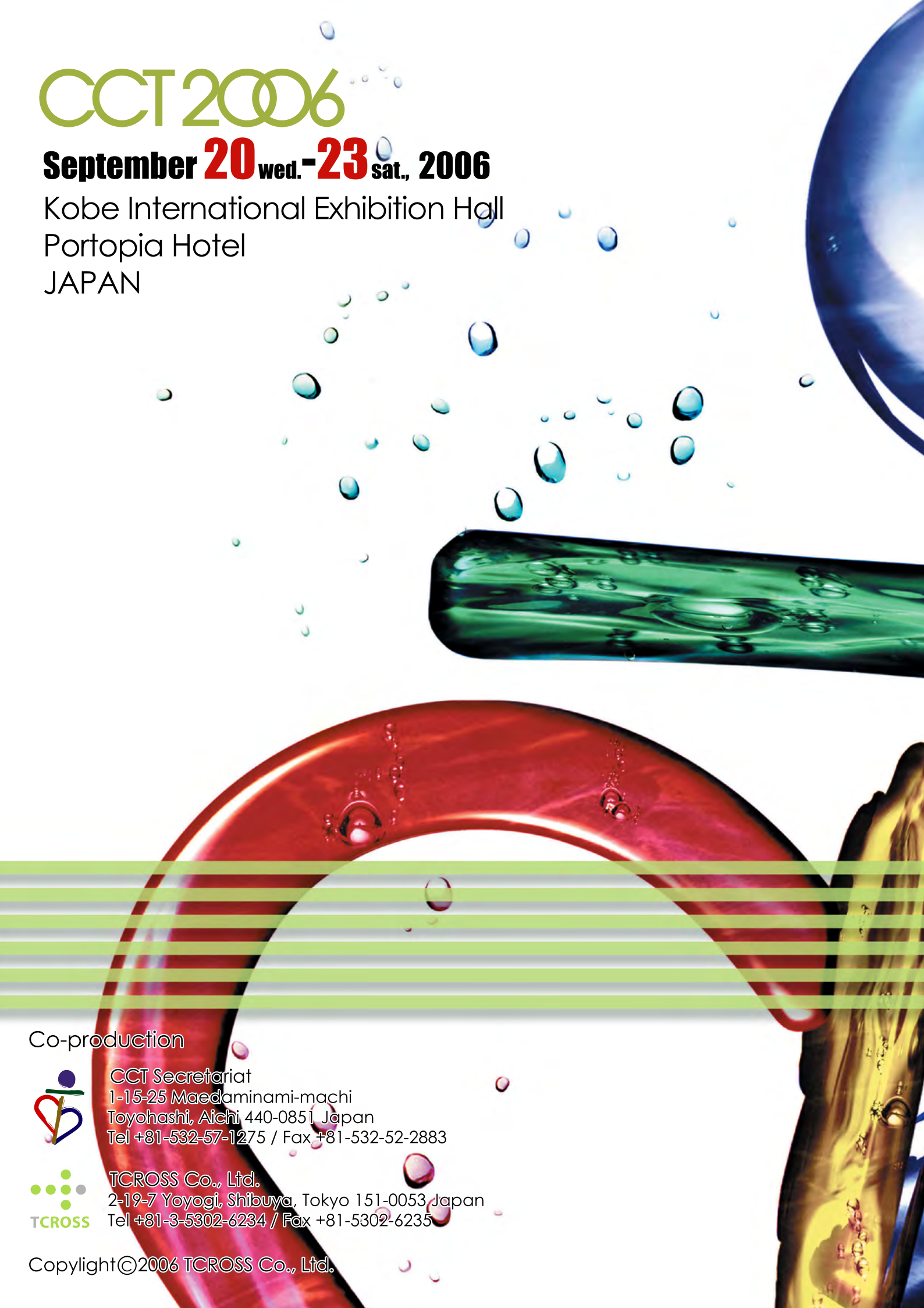

Co-production

CCT Secretariat
1-15-25 Maedaminami-machi
Toyohashi, Aichi 440-0851 Japan
Tel +81-532-57-1275 / Fax +81-532-52-2883

TCROSS Co., Ltd.
2-19-7 Yoyogi, Shibuya, Tokyo 151-0053 Japan
Tel +81-3-5302-6234 / Fax +81-5302-6235