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Heart 2010 96: 415-418
doi: 10.1136/hrt.2009.170571
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OVERVIEW OF THE DEVELOPMENT OF PERCUTANEOUS CORONARY INTERVENTION IN CHINA

Since the introduction of percutaneous transluminal coronary angioplasty (PTCA) into China in 1985 with a first report in 1986, there has been exponential growth in annual numbers of percutaneous coronary interventions (PCI, figure 1), and the expansion and technical evolution of interventional cardiology in China can be roughly divided into three phases. During the first phase, spanning 1985 to 1996, PCI could only be performed in a few centres by a few cardiologists. According to a national survey organised by the Chinese Society of Cardiology, a total of only 6213 PCI cases had been performed by the end of 1996 in 51 hospitals nationwide with a success rate of 91.9%. The most common procedure was balloon angioplasty, while rotational atherectomy cases numbered only in the hundreds and rare cases of directional coronary atherectomy and excimer laser angioplasty were performed in a few centres. Also during this first phase, coronary stenting was introduced in 1992 and first reported in 1994; by 1996, coronary stents had been implanted in 51.3% of patients undergoing PCI in China. The second phase from 1997 to 2001 witnessed a rapid growth of PCI in China with a 40% yearly increment in the number of cases. For instance, in 2001, 16 345 PCI cases were performed in 112 hospitals with a success rate of 97%; this number of cases was larger than the combined figures for the previous 15 years. During this time, stents were implanted in more than 80% of PCI patients, while there were only 115 cases of intracoronary brachytherapy for the treatment of in-stent restenosis from its introduction in 1999 to the end of 2001. During the third phase, from 2002 until now, case numbers continue to increase. In 2007, a total of 144675 cases were performed in 670 hospitals in 30 provinces. Drug-eluting stents (DES) were introduced in 2001, and currently account for about 90% of stents implanted, including the Cypher sirolimus-eluting stent (Cordis, Johnson & Johnson, Roden, Netherlands), Taxus paclitaxel-eluting stent (Boston Scientific, Galway, Ireland), Endeavor zotarolimus-eluting stent (Medtronic, Galway, Ireland) and domestically manufactured sirolimus-eluting stents (SES), such as the Firebird SES (MicroPort, Shanghai, China), Excel biodegradable polymer SES (Jiwei, Weihai, China) and Partner SES (Le Pu, Beijing, China), among others. Based on clinical practice experience and evidence from international multicentre trials, the first Chinese PCI guidelines were issued in 2002 and updated in 2009. Clinical research and device development have also flourished alongside the accumulation of clinical experience and increases in case number.

PCI IN ST-SEGMENT ELEVATION ACUTE MYOCARDIAL INFARCTION

Emergent PCI after failure of thrombolytic therapy in ST-segment elevation myocardial infarction (STEMI) was initiated in 1989 and shortly thereafter in 1990, primary PCI was introduced, including treatment of STEMI complicated by cardiogenic shock. According to a prospective nationwide survey of acute coronary syndromes conducted from 2004 to 2005 (CPACS), among STEMI patients presenting within 12 hours of onset of chest pain, 56% received reperfusion therapy, including 16.5% who underwent primary PCI in hospitals with cardiac catheterisation laboratories; in tertiary hospitals, the median door-to-balloon time was 90 minutes (60–175 minutes). A later shorter survey (BRIG) which took place from March 2006 to July 2006 in 65 hospitals revealed that reperfusion therapy was used in 50.3% of STEMI patients, with 12% undergoing primary PCI; even when solely considering tertiary hospitals, only 21.2% of STEMI patients underwent primary PCI with a median door-to-balloon time of 105 minutes (40–126 minutes). In recent years, primary PCI has become the treatment of choice for STEMI in cases presenting within 12 hours of symptom onset to hospitals equipped with a cardiac catheterisation laboratory, especially those in large cities. A registry from Beijing showed that among 803 STEMI patients, 80.9% received reperfusion therapy; 15.4% were treated with thrombolysis and 65.5% with primary PCI with a median door-to-balloon time of 132 minutes; however, only 22% of patients had PCI performed within 90 minutes. Although primary PCI has experienced a tremendous expansion in China during recent years, there remains room for improvement in its practice. To this end, the ongoing Clinical Pathway for Acute Coronary Syndrome in China (CPACS)-Phase-2 study is aimed at implementing and evaluating quality improvement measures for the care of patients with acute coronary syndrome (ACS); reducing the identified evidence-practice gap in the management of ACS; and improving clinical outcomes among ACS patients in China.

Although over 1000 hospitals in China are equipped with angiographic facilities, many hospitals lack operators qualified to perform PCI procedures independently, thereby limiting the number of hospitals with actual PCI capability. Previous studies have underscored transfer of patients for primary PCI as a superior strategy to local administration of thrombolysis in patients presenting more than 3 hours after symptom onset; however, transfer of STEMI patients to specialised facilities.
continues to encounter significant challenges in China, including traffic and public awareness, among others. For this reason, a prospective multicentre randomised trial by Zhang et al comparing outcomes from physician-transfer (ie, a physician transferring to a centre with PCI facilities but without qualified interventionalists) versus patient transfer for primary PCI showed that despite similar procedure success rates between both groups totalling 334 STEMI patients, the physician-transfer strategy provided shortened door-to-balloon time and improved MACE-free survival at 30-day follow-up.17

**STUDIES ON INTERVENTIONS IN COMPLEX LESIONS**

**The registries of unprotected left main coronary artery stenting**

Because a high-quality cardiac surgery service is not available in many geographic regions and many patients refuse to undergo coronary artery bypass graft surgery, PCI with stenting for the treatment of unprotected left main coronary artery (ULMCA) stenosis is relatively more popular in China than in some other parts of the world.

To approach the safety and efficacy of ULMCA stenting, the Chinese Registry of Unprotected Left Main Coronary Artery Stenting enrolled 224 cases of ULMCA stenting performed from 1997 to 2003 in 23 hospitals.18 Analysis of long-term outcomes revealed a Kaplan-Meier method-derived 4-year survival rate of 92.9%, and a 4-year major adverse cardiac event (MACE)-free survival rate of 68.4% in this highly selected patient group. This experience underscores ULMCA stenting as a viable option in inoperable or low-risk patients with left ventricular ejection fraction (LVEF) ≥40% and isolated ULMCA disease, or in ULMCA disease combined with multivessel disease in which complete revascularisation can be achieved.

Although in the era of bare-metal stents (BMS) ULMCA stenting became relatively safe and feasible, in-stent restenosis remained a major limitation to long-term effectiveness and safety. To evaluate the immediate and long-term outcomes of elective DES implantation for ULMCA stenosis in a Chinese population, outcomes among 220 consecutive patients with ULMCA disease who had undergone elective stenting with DES at Fu Wai Hospital, Beijing, from April 2003 to February 2006 were analysed19 and compared with those of a historically matched BMS control group who had been included in the Chinese Registry of ULMCA stenting.18 The study revealed that the in-hospital MACE rate was significantly higher in the DES than in the BMS group (4.1% vs 0.9%, p=0.030), an observation that is probably related to the higher procedural complexity characteristics of DES recipients. During the follow-up period with a mean duration of 15 months, cumulative rates of cardiac death (0.5 vs 4.9%, p=0.004), target-vessel revascularisation (TVR) (5.9% vs 11.6%, p=0.034) and MACE (9.5% vs 16.5%, p=0.029) were significantly lower in the DES group than in the BMS control group. No significant difference in ARC-defined total stent thrombosis rates was demonstrated between the DES and BMS groups. DES implantation for ULMCA therefore appears safe and more effective in preventing major adverse cardiac events compared to BMS implantation in the mean time period studied of 15 months. Another retrospective analysis also reported that the incidences of MACE, TVR and angiographic restenosis in the DES group were significantly lower than in BMS group.20 ULMCA complex bifurcation stenting with DES using current techniques, such as ‘T stenting, crush stenting and ‘V’ stenting for patients with larger and diseased left circumflex (LCX) coronary artery may be feasible owing to the larger vessel size compared to those of other vessels.19

**Modification of the crush technique for bifurcation stenting**

Stent crush is one of the commonly used techniques for true bifurcation lesions with large and diseased side branches. A modified double-kissing and double-crush (ie, DK Crush) technique by Chen et al has shown potential for increasing rates of successful final kissing balloon inflation, reducing rates of stent thrombosis, and further reductions of rates of TVR and cumulative MACE at 8 months compared with the classic crush approach.21

**Treatment of chronic total occlusion lesions**

Recent years have seen witnessed significant progress in the treatment of chronic total occlusion (CTO) lesions thanks in great part to the efforts of interventional cardiologists, especially those of Japanese colleagues, owing to improvement in wires and catheters, novel devices (such as the Tornus catheter, etc) and new techniques such as the paralleled wire technique, retrograde approach and STAR technique, among others. These new techniques were rapidly introduced into China, which led to increases in the success rates of CTO lesion treatment to 70—90% in some centres.22 Among developments in this area in China, Han et al reported that multiwire plaque crushing is effective in facilitating the passage of the balloon catheter through occluded sites.23
DES ‘REAL-WORLD’ REGISTRIES AND STUDIES

The China Cypher select registry

The prospective multicentre (20-centre) China Cypher select registry (CCSR)24 enrolled 1189 consecutive patients who underwent implantation of at least one Cypher Select stent during routine interventional practice from July 2004 to November 2004. Patients who underwent emergency stenting for acute myocardial infarction (MI) were excluded. The results showed that the 12-month rates of target-lesion revascularisation (TLR, 5.14%), and MACE (including cardiac death, non-fatal MI and TLR, 6.51%) were similar to those reported in randomised trials and ‘real-world’ registries of the Cypher-Bx stent. The 12-month overall Cypher Select stent-related thrombosis rate was 1.2% (ie, 14 cases). Angiographic follow-up at 9 months revealed that binary restenosis rates were 4.8% in-stent and 9.6% in-segment. In-stent and in-segment late loss was 0.14±0.09 mm and 0.11±0.40 mm, respectively. The safety and efficacy of the Cypher Select stent in this registry are consistent with those in Cypher-Bx stent studies.

Excel biodegradable polymer-coated SES registry (CREATE)

In the CREATE registry, a multicentre prospective post-marketing surveillance study that enrolled 2077 ‘real-world’ patients from 59 centres in four countries25 who underwent implantation of only Excel biodegradable polymer-coated SES (Ji Wei, Weihai, China) with recommended duration of clopidogrel treatment of 6 months post index procedure, the MACE rate was 3.1% and the stent thrombosis rate was 0.67% at 18 months; the 9-month follow-up angiogram revealed a mean in-stent late lumen loss of 0.21 mm, and in-stent and in-segment restenosis rates of 3.8% and 6.7%, respectively.

Other registry experiences

The Firebird SES is extensively used in China. A prospective multicentre registry of the Firebird stent (Firebird in China, FIC) that enrolled 1561 patients has completed 2-year follow-up, while a Firebird registry focusing on the treatment of complex lesions in over 1000 patients (Fireman registry) is ongoing.

A multicentre registry on Taxus and Taxus Liberty stents (Boston Scientific, USA) has been completed, the Endeavor Stent (Medtronic, USA) China registry has completed patient enrollment, a Cypher Select+ registry focused on diabetic patients (The Care China-Diabetes Registry) recently has been started, and a randomised trial to compare Excel SES with the Cypher Select+ stent (Evolution trial) also is ongoing.

RESEARCH AND DEVELOPMENT OF NEW DES

To improve clinical outcomes with a stent with greater radial strength and thinner stent struts, a cobalt-alloyed SES, Firebird 2, was developed by MicroPort, Shanghai, China. After pre-clinical studies revealed favourable efficacy and safety features, a First-in-Man Study was conducted.26 Sixty-seven patients with de novo or non-stented restenotic coronary lesions were treated with the Firebird 2 stent, and compared with 49 consecutive patients who had been treated with bare cobalt-alloyed stents (Driver, Medtronic) within the previous 6 months who served as historical controls (control group). MACE rates were significantly lower in the Firebird 2 group than in the control group at the 6-month and 12-month follow-up. Late lumen loss at 6-month angiographic follow-up (as primary endpoint) was significantly reduced in the Firebird 2 group compared to the control group (in-stent: 0.05±0.09 mm vs 0.98±0.61 mm; in-segment: 0.05±0.18 mm vs 0.72±0.59 mm; p<0.0001, respectively). One patient (1.5%) in the Firebird 2 group developed in-segment restenosis, and the restenosis rate was significantly lower than that in the control group (38.1%, p<0.0001). Intravascular ultrasound examination revealed that the percentage of volumetric obstruction was 1.26%±1.05%. No stent thrombosis was observed in either group at 12-month follow-up. The results showed that use of the Firebird 2 cobalt-alloyed SES is safe and feasible in treating patients with coronary artery disease. This clinical benefit and significant lower rates of TLR and MACE were sustained up to 2 years post-stenting.27 The Firebird 2 SES received regulatory approval and it is extensively used in daily clinical practice in China. A multicentre prospective post-marketing surveillance study of Firebird 2 SES (Forcus registry) has completed a 5000 patient enrolment. The third generation of DES, targeted release biodegradable polymer SES (Firehawk, MicroPort, Shanghai, China), has completed pre-clinical studies, and a First-in-Man clinical study has been started.

To avoid the possible hypersensitivity reaction induced by the durable polymer of the first generation of DES, a polymer-free paclitaxel-eluting stent (Yin Yi, Dalian, China) has been developed and commercially launched. New biodegradable polymer-based SESs also have been developed, and First-in-Man clinical trials are ongoing.

STUDY ON ADJUNCTIVE ANTIPLATELET THERAPY AFTER PCI

Dual antiplatelet therapy is crucial after stent implantation. Although aspirin combined with a thienopyridine (clopidogrel or ticlopidine) is considered optimal therapy, if the patient cannot tolerate a thienopyridine, is there an alternative drug? Cilostazol has been used for antiplatelet therapy after stent implantation; however, this practice has been debated. In the RACTS (A Randomised Prospective Antiplatelet Trial of Cilostazol Versus Ticlopidine in Patients Undergoing Coronary Stenting) trial,28 the efficacy of cilostazol for the prevention of late restenosis and acute or subacute stent thrombosis after bare-metal stent implantation was compared with that of ticlopidine. Patients scheduled for stent implantation were randomly assigned to receive either cilostazol (100 mg twice daily for 6 months, n=201) or ticlopidine (250 mg twice daily for 1 month, n=196). All patients also received oral aspirin (100 mg once daily for 6 months). There was no significant difference in the composite incidence of death, MI, stroke and stent thrombosis between the cilostazol and ticlopidine groups (1.5% vs 5.6%, p=0.216), but the TLR rate at 9 months post-coronary stenting was significantly lower in the cilostazol group compared to the ticlopidine group (22.9% vs 32.7%, p=0.030). The results showed that aspirin plus cilostazol is a comparable antithrombotic regimen. In clinical practice, cilostazol is often prescribed to patients who cannot tolerate aspirin or clopidogrel as an alternative. For patients who have stent thrombosis, triple antiplatelet therapy (aspirin, clopidogrel plus cilostazol) sometimes is useful for prevention of thrombosis recurrence. Han et al reported in a randomised trial of 813 cases that a high maintenance dose of clopidogrel improved short-term clinical outcomes in patients with acute coronary syndrome (ACS) undergoing DES. A loading dose of 600 mg followed by 150 mg daily for 50 days reduced the risk of stent thrombosis compared with a maintenance dose of 75 mg daily (0 vs 1.5%, p<0.05), while rates of death, MI and bleeding were not significantly different between the two groups.29

‘HYBRID’ REVASCULARISATION: MIDCAB COMBINED WITH STENTING

Since 1999 a hybrid revascularisation procedure has been approached at Fu Wai Hospital, Beijing, in patients with a totally
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occluded left anterior descending (LAD) coronary artery not amenable to recanalisation by PCI, or with an LAD lesion that is not suitable for PCI but with lesions in other vessels that are good candidates for PCI. In this approach, the surgeon first performs minimally invasive direct coronary artery bypass (MIDCAB) grafting of a left internal mammary artery (LIMA) to the LAD through a minithoracotomy without cardiopulmonary bypass, after which a cardiologist confirms the patency of the LIMA graft by angiography and implants stents in other vessels as necessary. The preliminary results of this approach are encouraging, and a randomised study comparing the safety and efficacy of a hybrid procedure with traditional bypass graft surgery is ongoing.

PERSPECTIVE

Although great progress has been achieved in China in the field of interventional cardiology, especially in recent years, the case number totals achieved thus far remain too small to satisfy the local medical needs of patients with coronary artery disease. There also are imbalances in terms of training and use of PCI techniques among different geographic areas. For instance, according to a recent survey, in 2007 more than 40% of PCI cases were performed in six provinces or cities (15.4% in Beijing, 8.0% in Guangdong, 6.9% in Liaoning, 6.9% in Shandong, 6.1% in Shanghai, and 5.8% in Henan). Although the largest PCI centres can perform more than 5000 cases each year, only in 13 hospitals did PCI case numbers exceed 1000 cases per year, while in 299 hospitals annual PCI case numbers exceeded 100 cases and in more than 60% of the hospitals the annual case loads were fewer than 100. Therefore, technique training remains very important. Besides training and academic exchanges, institutional and personal criteria for performance of PCI need to be outlined, and regulation of administration and supervision needs to be expanded to standardise technique and to create an effective programme of PCI in China. International and domestic academic exchanges need to be continuously strengthened as well as active participation in international multicentre trials or registries encouraged while local studies must continue to be organised. There is confidence among Chinese interventionalists that the use of PCI will continue to expand and that in the near future it will homogenise in numbers and quality across China to levels achieved in other countries.

Acknowledgements

The author sincerely thanks Roberto Patarca, MD, for revising the manuscript.

Competing interests

None.

Provenance and peer review

Not commissioned; not externally peer reviewed.

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