Abstract Percutaneous coronary intervention (PCI) using balloon technology and stent implantation has revolutionized the interventional cardiology since the late 1970s. The plain old balloon angioplasty (POBA) was first proposed in the late 1970s as an alternative to coronary artery bypass grafting (CABG) for the treatment of coronary artery disease (CAD) such as angina pectoris and acute myocardial infarction (AMI). Thereafter, bare metal stent (BMS) was designed to overcome the problems proposed by POBA such as acute occlusion and restenosis of coronary target lesion. However, a new problem of BMS-induced in-stent restenosis (ISR) has appeared, and drug-eluting stent (DES) was introduced to resolve the problem of ISR. DES has improved the clinical outcome of patients undergoing PCI. Contemporary stent technology shows remarkable progress, and further effort continues to improve the design, structure, and materials of DES. However, DES has proposed a new problem of very late stent thrombosis. To overcome this late complication, non-stent strategy is introduced into the PCI. This article aims to review the historical development and future perspective of the PCI especially focusing on the evolution of DES.

Keywords drug-eluting stent, percutaneous coronary intervention, restenosis, thrombosis

1. Introduction

Therapeutic coronary angioplasty has begun as a plain old balloon angioplasty (POBA) using a double-lumen balloon catheter in 1977 by Dr. Andreas Grünzig. After this historical event, percutaneous coronary intervention (PCI) has evolved as a gold standard therapy of acute myocardial infarction (AMI) and angina pectoris. POBA has led to the subsequent advances in the field of PCI along with the evolving concept of infarct size reduction in patients with AMI treated in the coronary care unit (CCU).

POBA was a first coronary revascularization strategy for the patients with coronary artery disease (CAD) including AMI and angina pectoris. However, the acute occlusion and the restenosis were frequently observed as major causes of target lesion failure following POBA. Acute occlusion is derived from arterial recoil, coronary dissection, or acute thrombus formation in the target lesions especially in the multivessel and complex lesions [1]. In 1980s, bare metal stent (BMS) has emerged to overcome these clinical problems. Randomized controlled trials show a merit of patient randomization and control setting and has prevailed worldwide since 1990s in the field of clinical cardiology. Many randomized controlled trials were conducted to evaluate the efficacy and the safety of the new design, technology and material concerning BMS. Among them, STRESS study and BENSTENT study are the landmark trials, i.e., The Stent Restenosis Study (STRESS) Investigators and BENSTENT Study Group compared the effectiveness of BMS and balloon angioplasty on the angiographically detected coronary restenosis and clinical outcomes and reported the better outcomes of intracoronary stent implantation as compared with standard balloon angioplasty [2, 3]. Based on these clinical trials, BMS has become a new standard of PCI thereafter, and BMS was implanted in many patients with CAD. However, BMS has induced a new problem of stent thrombosis [4], and new technology of drug-eluting stent (DES) has appeared in clinical practice. DES is playing a pivotal role of contemporary PCI to reduce the rate of in-stent restenosis and is improved along with the development of innovation and technology (Table 1). This review
article concerning PCI describes the progress from the original pioneering procedure to modern practice in PCI and focuses mainly on the historical development and future perspective of DES.

2. Drug-Eluting Stent

BMS has emerged as a new technology of PCI in the mid-1990s. This original stent acts as a scaffold to compress the coronary vessel lumen and to keep the vessel patency. BMS has substantially overcome the problem of acute coronary occlusion after the procedure of PBOA. However, this technology has introduced a new problem of in-stent restenosis (ISR) long after the PCI procedure. ISR has a significant impact on the prognosis in patients with CAD undergoing PCI. Translational research has evolved in cardiovascular medicine and clarified the causes of ISR induced by BMS. Coronary lumen is upheld and compressed strongly by BMS scaffold, and inflammatory reaction and subsequent migration and proliferation of smooth muscle cells form neointima in response to endothelial injury caused by the mechanical compression of BMS. Thickening and protrusion of neointima into the stent lumen causes ISR. In the late 1990s, DES has emerged as a new stent technology to overcome the problem of ISR. DES is composed of three components, 1) the metal base, 2) a polymer to control the drug release, and 3) the drug to suppress ISR.

2.1 Stent Material and Design

The material of metal base in DES is fundamentally the same as that in BMS such as cobalt-chromium (CoCr), platinum-chromium (PtCr), and stainless steel. Metallic stent platform should possess several characteristics. Crossability is the ability and the characteristics for stent to pass through the narrow, irregular, or calcified lumen of the coronary target lesion. Conformability is the stent flexibility under the anatomical coronary curving, bending and tortuous movement due to cyclic cardiac motion. Durability is the endurance to avoid stent fracture. Radial force is important to keep the patency of atherosclerotic and calcified coronary lesion. Accessibility to the side branch is related to the expandability of struts (metallic meshwork) to maintain the blood supply to the side branch of the coronary lesion. Crossability and conformability improve by thinning strut thickness, which in turn limits the durability and attenuates the radial force. Coronary stent technology has produced various metallic platforms and designed the thin struts stent by improving the metal base materials. Conformability and radial strength are related to the design of metallic meshwork. As shown in Figure 1, crown is a unit structure (peak and valley structure) of a ring, and rings connect each other by link. The mode of link connection varies depending on the position of the link, i.e., there are three designs of link connection such as in-phase, out-of-phase, and offset peak-to-peak designs. Each meshwork design has its own characteristics with respect to conformability, and strength in the radial or the long-axis direction. Number of links also influences the characteristics of DES. Generally, 2-links and 3-links stents are standard. Increasing the number of the link resists the stent fracture and deformation leading to the uniform stent expanding and compression to the vessel lumen. However, this increase limits the full expanding of the struts upon the side branch, which underlies the side branch occlusion after the PCI (Figure 2).
Drug Eluting

It is important to suppress the excessive neointimal hyperplasia within the in-stent luminal space to prevent the ISR. Therefore, several drugs have been introduced into the field of DES for this purpose, and sirolimus, an immuno-suppressive agent called rapamycin, was first attempted. Paclitaxel, an anticancer agent, was introduced thereafter, but the sirolimus-eluting stent (SES) has become a mainstream due to the superiority relative to the paclitaxel-eluting stent (PES). Nowadays, a series of ‘limus’ agents such as sirolimus, zotarolimus, biolimus, everolimus are widely used as an eluting drug for DES. It has been possible to combine the eluting drugs within a DES to potentiate the anti-inflammatory and antiproliferative actions to suppress the ISR of target lesion. Furthermore, novel approach continues to coat the anti-CD34 antibody on the surface of stent metal (Figure 3). The concept of the anti-CD34 antibody coating on the surface of the stent is to capture the endothelial progenitor cells (EPCs) in blood by antigen-antibody reaction and to promote an appropriate neointimal layer formation after the differentiation of EPCs into the functional endothelial cells.

Stent Polymer

Polymer has a role of site-specific and controlled release of active drugs exerting antiproliferative and anti-inflammatory actions. However, the debris of polymer is considered as a potential chronic inflammatory stimulus. An improvement continues to minimize the inflammatory foreign matter reaction caused by polymer itself, and modern technology has developed the durable biocompatible polymer or the biodegradable polymer for this purpose (Figure 4). Polymer has a concern of detachment when DES passes through the calcified stenotic lesion [5] (Figure 5). Therefore, polymer coating is designed to show the asymmetry, i.e., bioabsorbable polymer coats the vessel wall side but not the vessel luminal side, whereas anti-CD34 antibody coats the entire surface of the stent meshwork (Figure 6).

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**Figure 1** Structure of stent and connection by link. The crown has an important role in maintaining the radial force, and the link determines the strength of stent on the long axis direction. The rings are connected by 2 or 3 links in modern stents (2-links stent or 3-links stent). How to connect the rings by links is different for each stent. In general, in-phase design has high conformability in that the distribution of stent struts tends to be uniform, and the peak can be closer to the valley in the part without a link. On the other hand, the out-of-phase design has the advantage that it is easy to cross the side branches (By courtesy of Abbott Vascular Japan Co., Ltd. (Tokyo, Japan). Partially modified).

**Figure 2** Stent strut expansion on side branch. Stents are often placed across the side branches. It is necessary to fully expand the strut on the site of branch. But doing so may cause deformation of the stent on the main branch. Generally, 2-links stent can expand the strut greatly, but 3-links stent are less likely to deform on the main side branch. Figures are diameter of stent lumen measured after the full expansion. A, B: 2-links stent. A: stent strut expansion by 3 mm balloon. B: stent strut expansion by 5 mm balloon. C, D: 3-links stent. C: stent strut expansion by 3 mm balloon. D: stent strut expansion by 5 mm balloon (By courtesy of Abbott Vascular Japan Co., Ltd.).

2.2 Drug Eluting

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Figure 3  The design of endothelial progenitor cell capture stent. A. Anti-CD34 antibody is attached to the surface of the stent. B. Endothelial Progenitor Cell (EPC) in blood is captured on the surface of the stent by an antigen-antibody reaction. C. It can be expected that the EPC attached to the stent surface differentiates into functional endothelial cells and an appropriate neointima is formed (By courtesy of OrbusNeich Medical Co., Ltd.)

Figure 4  Xience® stent polymer. A is an observation of albumin adsorption on the stent. The place where albumin is adsorbed is shining with fluorescence. The left is a Xience® stent using fluoropolymer. The right is a stent using elastomer polymer. B explains the advantages of fluoropolymer. The binding of albumin to fluoropolymers inhibits the binding of thrombotic proteins such as fibrinogen, attenuates leukocyte activation and migration, and minimizes the inflammatory response. (Cited from https://www.cardiovascular.abbott/jp/ja/hcp/products/coronary/xience-sierra.html with permission)

Figure 5  Delamination of the stent polymer. A. Coronary angiography in our case. White arrow is a severely calcified stenotic lesion. B. Scanning electron microscopy shows the delamination of the ultrathin bioabsorbable abluminal polymer in platinum-chromium everolimus-eluting stent that could not advance across the calcified stenotic lesion (cited from Ref. 3).
2.4 The First-Generation DES

The first-generation of DES available in Japan includes sirolimus-eluting stent (SES) called Cypher® stent (Cordis Corporation, Miami Lakes, FL, USA) commercialized in 1999 and paclitaxel-eluting stent (PES) called Taxus® stent (Boston Scientific Corporation, Natick, MA, USA). These two stents have reduced dramatically the rate of ISR observed after the PCI by using the BMS [6, 7]. However, a new problem has appeared as a serious complication occurring in patients undergoing PCI late after the PCI. This is very late stent thrombosis (VLST) defined as target lesion occlusion by thrombus formation within the stent lumen which occurs one year after the stent delivery [8]. VLST is caused by the delayed formation of endothelial layer within the stent lumen due to the eluted drug and by the delayed vessel healing due to persistent inflammation induced by polymer. Therefore, dual antiplatelet agents are required to prevent the VLST and administered actually to the patients undergoing PCI with this generation of DES.

2.5 The Second-Generation DES

The second-generation of DES has developed to overcome the problems presented by the first-generation. This generation of DES was commercialized in the late 2000s after reducing the amount of drug, alternating polymer, and seeking the best drug-polymer combination. This kind of refined drug-polymer relation has reduced considerably the rate of ISR and VLST.

The drug of the second-generation DES includes everolimus (XIENCE® stent, Abbott Vascular, Santa Clara, CA, and PROMUS® stent, Boston Scientific Corporation, Marlborough, MA) and zotarolimus (Resolute® stent, Medtronic Inc., Santa Rosa, CA) instead of sirolimus. Stent strut thinning from 140 μm to 80 μm was feasible to minimize the luminal space loss, and stent design was refined [9] (Figure 7). Polymer in this generation increased the biocompatibility. These revisions underlie the reduction of the rate of ISR and VLST based on the reduced proliferation of smooth muscle cells and the appropriate endothelial layer formation early after the stent implantation [10–12].

Figure 6 Polymer coating method for COMBO® stent. The luminal wall side alone is coated with the bioabsorbable polymer and the drug. The polymer is degraded within 90 days (By courtesy of OrbusNeich Medical Co., Ltd.).

Figure 7 Transition of Multi-link stent. These multi-link stent is the platform of Xience® stent (Cited from Ref. 7).
Stent strut thinning minimizes the luminal space loss and modern stent balloon have improved the stent delivery to the target lesion including the calcified stenotic lesion and other challenging lesion. Especially, evidence has accumulated with respect to the efficacy and the safety of everolimus-eluting stent (EES: XIENCE® stent), and EES is used widely today in the practical PCI applied especially to the patients with AMI.

2.6 The Third-Generation DES

Although the second-generation of DES has brought about evident reduction in the rate of ISR and VLST, this generation has left a significant problem of incomplete healing of endothelial surface caused by stent polymer. Polymer has a role of controlled release of antiproliferative drug during the period of smooth muscle cell proliferation and has no roles thereafter. Therefore, the third-generation of DES using bioabsorbable polymer has emerged. This generation of DES includes Synergy™ (Boston Scientific, Marlborough, MA, USA), Ultimaster™ (Terumo, Tokyo, Japan), Orsio (Biotronik, Erlangen, Germany), and COMBO® (OrbusNeich Medical BV, Netherlands), which have shown the non-inferiority in the randomized controlled trials to seek the efficacy and the safety of third-generation DES as compared with the second-generation DES in terms of target lesion and target vessel failures [13–15]. However, long-term clinical outcomes of the third-generation DES has not been obtained so far [16].

2.7 The Remaining Problems of DES

Although continuous effort is devoted to improve the structure and the design of DES, it does not mean no ISR and no target lesion failure at all. Current situation is to allow the neo-atherosclerosis within the stent lumen, which is considered as a sequela of allergic reaction against the polymer substance. To resolve this problem, no polymer substance left on stent surface is an ideal strategy, and vascular scaffold made of bioresorbable polymer alone has been developed. However, thickness of the scaffold limits the full expanding of the scaffold, and thrombus formation within the scaffold lumen disturbed the clinical application of bioresorbable vascular scaffold (BVS) to the patients with CAD [17].

3. Drug-Coated Balloon

Although DES is the contemporary standard modality of PCI, drug-coated balloon (DCB) has a new concept in the coronary revascularization in terms of the antiproliferative drug delivery without the use of stent. Such no-stent strategy is gradually accepted by many interventional cardiologists. DCB is consisted of a semi-compliant balloon which is coated with drug encapsulated in a polymer matrix. Antiproliferative drug is released into the target vessel wall after balloon inflation and contact with vessel surface. Drug mostly used in DCB is paclitaxel exerting an antiproliferative action by irreversible binding to the intracellular microtubules and showing the clinical effectiveness in the first-generation DES. DCB clinically available in Japan is SeQuent® Please [18] (B. Braun, Melsungen, Germany). Lipophilic paclitaxel admixed with hydrophilic iopromide as a contrast medium (Ultravist™) is an effective coating matrix formulation to prevent drug release into the blood before inflation and to deliver the drug reliably to the vessel wall during single balloon inflation alone. This non-stent balloon technology

Figure 8 Drug coated balloon system. A. SeQuent balloon on which the lower catheter is coated with paclitaxel, a balloon on which the upper catheter is not coated. B. Paclitaxel is coated with iopromide using a technique of Paccocath. C. The contrast agent iopromide functions as a spacer and serves to remind paclitaxel to the vessel wall when the balloon is inflated (Cited from reference-16).
is now registered as Paccocath® technology (Figure 8). Paclitaxel-coated balloon under the Paccocath® formulation aims at the fast and homogeneous delivery of paclitaxel during the single balloon inflation to reduce the risk of ISR and very late thrombus formation based on the concept of targeted drug delivery mediated by balloon technology without stent implantation. The indication of DCB is the revascularization of the stent-related restenosis, bifurcation lesion, and de novo lesion in relatively small coronary arteries, where stent implantation causes significant luminal loss leading to ISR [19].

4. Conclusions

The concept of PCI was introduced at first as POBA without stent more than 40 years ago to normalize the coronary blood flow, keep the coronary patency, reduce the infarct size in patients with AMI, and improve the prognosis in patients with CAD. After POBA presented the problems of acute occlusion and restenosis, BMS partially overcame these problems, whereas the other problem of ISR occurred. Along with an advancement of stent technology and discovery of potent antiproliferative and anti-inflammatory drugs, various types of DES have emerged in the interventional cardiology. Although DES is a mainstay of PCI, ISR and VLST have so far limited a unanimous choice of DES implantation. At present, DCB is accepted by many interventional cardiologists to treat ISR and small vessel lesion. Procedural guidance with intracoronary imaging is also important for favorable clinical outcomes of patients undergoing PCI. Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are the two major imaging modalities guiding PCI. These imaging procedures are helpful in inform the optimal size, length, expansion of balloon and stent, and to detect acute and late complications of PCI. Advancement of stent and balloon technology, drug development, and imaging modalities will improve further the appropriate PCI strategy.

Conflict of interest Authors have no conflict of interest to declare.

References


