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Current status of research and application in vascular stents

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Cardiovascular diseases have been the leading cause of death in modern society. Using vascular stents to treat these coronary and peripheral artery diseases has been one of the most effective and rapidly adopted medical interventions. During the twenty-five years' development of vascular stents, revolutionary cardiovascular stents like drug eluting stents and endothelial progenitor cells capture stents have emerged. In this review, the evolution of vascular stents is summarized, aiming to provide a glimpse into the future of vascular stents. Advanced designs, focusing on the investigations of new substrates, new platforms, new drugs and new biomolecules are currently under evaluation with promising clinical studies. The concept of "time sequence functional stent" has been raised in this paper. It presents anti-proliferative properties in the first phase after implantation and subsequently support endothelialization. It also shows long-term inertness without release of toxic ions or toxic degradation products. The success of this concept is briefly presented with a clinical study in this model stents.

bare metal stent, drug eluting stent, biodegradable stent, EPC-capture stent, endothelialization

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Cardiovascular diseases (CVDs), leading major reasons of death worldwide, are a class of diseases caused by disorders of heart and the blood vessels. These disorders, which are related to a process called atherosclerosis, include numerous problems, for example the accumulation of lipid deposition and lipid-laden macrophages in atherosclerotic plaques. The primary trigger for arterial thrombosis is the rupture of such a plaque. Thus, the altered blood vessel wall interferes with the blood to flow through and increases the risks of heart attack [1]. According to statistics published by the world health organization in 2012, the annual number of deaths due to CVDs will increase from 17 millions in 2008 to 25 millions in 2030 [2]. Applying vascular stents to treat the associated coronary and peripheral artery diseases has been one of the most effective and rapidly adopted medical interventions.

Vascular stents are small expandable tubes which are mounted onto a balloon catheter, inserted and expanded at the narrowed section of the vessel, acting like a stabilizing scaffold for the artery to maintain the patency of the vessel in order to treat narrowed or weakened arteries in the body [3]. At present, the implantation of stents has been utilized as a minimally invasive treatment for CVDs and becomes the most common percutaneous coronary intervention. During the decades' development, several generations of stents have been designed with a growing knowledge of the interaction among stent, blood and endothelium. The first generation stent was named bare metal stent (BMS). Although numerous reports have suggested the increasing incidences of in-stent restenosis (ISR) after the implantation of BMS, it is still widely used in clinic today [4]. Drug eluting stent (DES), a revolutionary device to address the problem of ISR, was developed by coating a drugs-loaded polymer onto the BMS. Despite the success of DES to eliminate the ISR, long-term safety and efficacy are questioned due to the late stent thrombosis (LST) reported in

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numerous of clinical trials [5]. It has been demonstrated that the polymer coating caused persistent arterial wall inflammation and the drug delayed the vascular healing. Afterwards, scientists and biomedical engineers made every effort to construct novel stent systems to solve problems occurring in clinic. The ongoing developments of DES concern the core and the coating of the stent as well as the eluted drugs [6]. Meanwhile, novel concepts of stents are raised up such as the biodegradable stents (BDS) and endothelial progenitor cell (EPC) capture stents. Some of these products are currently in clinical evaluation and the outcomes of the studies are highly expected. In this paper, the evolution of vascular stents is discussed and new stent techniques are highlighted. Also, the concept of "time sequence functional stent" is described in detail.

1 Bare metal stents

The original strategy of percutaneous balloon dilatation dated back to 1971, at which time the first percutaneous transluminal coronary angioplasty (PTCA) was performed in patients. By passing a deflated balloon and expanding it through a catheter to the vessel, this technique can open the artery and compress the plaque against vessel wall. After 2 years, there was an overall patency rate of 70%–80% [7]. In 1987, Sigwart et al. [8] adopted intravascular stents to prevent occlusion and re-stenosis after transluminal angioplasty. Unlike the percutaneous balloon dilatation, this meshed cylindrical medical device, coronary vascular stent, serves as a mechanical support to expand the narrowed vessel wall temporarily or permanently, preventing elastic recoil and vascular negative remodeling which are the common side effects of balloon angioplasty.

Currently, over dozens of bare metal stents are available in the market. The characteristics for an ideal stent substrate are supposed to include: excellent mechanical properties for intervention and expansion, adequate radiopacity for visualization during angiography, good hemocompatibility for implantation without much side reactions [9]. Generally speaking, commonly used metals for manufacturing are 316L stainless steel (316L SS), cobalt-chromium (Co-Cr) alloy, titanium and its alloy (e.g. Nitinol). Besides, platinum-iridium (Pt-Ir) alloy and tantalum (Ta) are alternatives in some products. Among these stent substrates, 316L SS is the most commonly used metal for stents. There are overall eight coronary stents approved by the US Food and Drug Administration (FDA), most of which are made from 316L SS in both BMS and DES. While considering poor hemocompatibility of the surface and the long-term release of toxic ions such as Cr, Ni and Co, 316L SS stents are prone of ISR, limiting their applications in clinic [10].

Restenosis, which is defined as diameter stenosis of ⩾50% in the stented area of the vessel, is a multifactorial process primarily because of the vascular trauma and the denudation of endothelium after balloon angioplasty and/or stent implantation [11]. The basic biological processes of restenosis are mainly attributed to the thrombogenicity. Thrombosis involves the activation, adhesion and aggregation of platelets which is dependent on the degree of vascular damages [12]. Meanwhile, presence of vascular injury and foreign materials lead to a disorder of coagulation as well as inflammatory and complement systems. The activated neutrophils and macrophages together with the released cytokines and growth factors accelerate the hyperplasia of smooth muscle cells (SMCs), leading to remodeling of the extracellular matrix (ECM) and initiating smooth muscle cell migration [13,14]. The end results of these cascade events are the thrombus and ISR, which are the key points for consideration when novel vascular stents are designed and developed. Therefore, based on the BMS, numerous surface modification approaches and novel concept vascular stents aiming at modulating biological responses and improving the stent performance are developed. To inhibit ISR, some radioactive stents [15,16] and drug eluting stent [17,18] were reported as the effective ones. However, undergoing radiation brachytherapy or using radioactive stents have also shown that proliferation at the stent edges may be associated with higher-than-expected restenosis rates at the stent margins. As more evidence supported that radioactive stents delayed but do not prevented in-stent neointimal hyperplasia [19], scientists gradually paid much more attention on the novel designs of drug eluting stents.

2 Drug eluting stents

Among numerous methods for improving vascular stents by surface modification, there is no doubt that the drug eluting stent is the most successful one in the history of stent development. It is considered as a wonderful creation of modern medical engineering that aid physicians and surgeons in the treatment of CVDs. As a revolutionary medical device combining drug and stent, DES shows lower rates of ISR and is statistically superior to BMS. Up to date, there exist two generations of DES. Encouragingly, newer DESs are under research and clinical investigation at the same time [20]. The predominantly applied DESs approved for clinical use are summarized in Table 1.

The first generation DESs are Cypher^{TM} (Cordis, Warren, New Jersey, USA) and Taxus^{TM} (Boston Scientific, Natick, Massachusetts, USA), which received regulatory approval from both European Union Conformiteé Européenne (CE) and FDA. Cypher consists of 316L SS platform and two permanent polymer coatings of poly(ethelene-*co*-vinyl acetate) and poly(*n*-butyl methacrylate), which are the carrier of sirolimus [21]. The Taxus device also applies a 316L SS substrate and a single polymer/drug mixture layer in which poly(styrene-*b*-isobutylene-*b*-styrene) coating combined with 1 μg/mm^2 paclitaxel are adopted [22]. Both of these

Table 1 A summary of some commercial drug eluting vascular stents[a)]

Categories	Stent name	Substrate material	Coating material	Drug
Durable polymer	Cypher™	SS	PEVA, PBMA	Sirolimus
	Taxus™	SS	SIBS	Paclitaxel
	Endeavor™	Co-Cr alloy	Phospholipids co-polymer	Zotarolimus
	Xience V™	Co-Cr alloy	PBMA, PVDF-HFP	Everolimus
Biodegradable polymer	BioMatrix™	SS	PLA	Biolimus A9
	EXCEL™	SS	PLLA	Sirolimus
	NEVO™	Co-Cr alloy	PLGA	Sirolimus
Nonpolymeric	BioFreedom™	SS	Texture	Biolimus A9
	Yukon™	SS	Micropores	Sirolimus
	Janus™	SS	Reservior	Tacrolimus
EPC-capture	Combo Stent™	Absorbable polymer	Biodegradable polymer Matrix/CD34	Sirolimus
Fully degradable	BVS™	PLLA	PLLA	Everolimus
	DREAMS	Mg alloy	Bioabsorbable polymer	Paclitaxel

a) PEVA, poly(ethelene-*co*-vinyl acetate); PBMA, poly(*n*-butyl methacrylate); SIBS, poly(styrene-*b*-isobutylene-*b*-styrene); PVDF-HFP, poly(vinylidenefluoro-hexafluoropropylene); PLA: polylactic acid; PLLA, poly(L-lactic acid); PLGA, poly(lactic-*co*-glycolic acid); DREAMS, drug-eluting absorbable metal scaffold.

two stents are based on an appropriate combination of metallic platform, permanent polymer and an anti-proliferative drug. In some clinical trials and investigations, the early and midterm safety and efficacy of 1st generation DES are supported. In the 8 months follow up REALITY trials, the first generation durable polymer sirolimus eluting stent (SES) and paclitaxel eluting stent (PES) were reported that the in-segment binary restenosis rate and in-stent late loss are respectively 6.6% (SES)/11.7% (PES) and 0.09 ± 0.43 mm/0.25 ± 0.49 mm [23]. And SIRTAX trials showed the in-segment binary restenosis rate and in-stent late loss are respectively 9.6% (SES)/11.1% (PES) and 0.12 ± 0.36 mm/0.31 ± 0.44 mm after 9 months [24]. However several limitations of SES and PES have emerged. In 2003, Virmani group [25] first reported the incomplete endothelial coverage with focal platelet aggregates and persistent fibrin deposition within the necrotic core at 16 months who received Cypher stent implantation. Their following research also reported the delayed arteries healing in SES which increased the risks of late stent thrombosis, for the anti-proliferative agents impede the recovery of endothelium when they suppress the migration and proliferation of SMCs [26]. Although the molecular mechanism of these complex phenomena are still not fully understood, multiple factors including direct toxic effect from the entrapped drug and/or an acute or delayed hypersensitivity reaction from the polymer and/or drug may be involved. The released sirolimus and paclitaxel could increase production of reactive oxygen species and Nitric Oxide bioavailability may be decreased, resulting in impairment of endothelium-mediated vascular relaxation response and endothelial dysfunction in the late stage. The durable polymer from which the drug elutes may also contribute to the adhesion and activation of leukocytes, leading to the local chronic inflammation and hypersensitivity [27]. Besides, most concerns are raised up on the safety of 1st generation DES especially after discontinuation of dual antiplatelet therapy [28].

Endeavor™ (Medtronic vascular, Santa Rosa, CA, USA) zotarolimus-eluting stent (ZES) and Xience V™ (Abbott Vascular, CA, USA) everolimus-eluting stent (EES) are regarded as the second generation drug eluting stents [29]. Endeavor includes three parts. The substrate is a Co-Cr alloy with good properties in mechanics and radiopacity. The drug-polymer coating is a formation of zotarolimus and persistent anti-fouling phospholipids co-polymer, which constructs an anti-thrombogenic and anti-restenosis surface [30]. Xience V™ also adopts the Co-Cr platform. Poly(*n*-butyl methacrylate) and poly(vinylidenefluoro-hexafluoropropylene) are used in the design, separately acting as an intermediate layer and drug carrier layer [31]. In terms of reduced LST events as well as restenosis rates, clinical results of 2nd generation DES indicated that the long-term safety and promising anti-restenosis efficacy which attributed to anti-proliferative agent, the biocompatible polymer layer and the novel stent frame [32]. There is no conclusive evidence that 2nd generation DES is superior to 1st generation DES, as the problems like LST and impaired endothelial healing have been reported in both generation DESs. However, Co-Cr platforms applied in Endeavor™ and Xience V™ stents are better deliverable, more flexible with higher radial strength allowing for thinner strut design than stainless steel 316L SS, presenting better endothelial coverage and less vessel wall injury than Cypher™ and Taxus™ stents [33].

It is well known that DES is comprised of three major components as shown in Figure 1. The stent platform scaffolds the vessel to ensure the patency. Polymer coatings deliver the drugs and control the dose and release kinetics through their degradation. The drugs inhibit the neointimal growth and ECM reproduction. Therefore, the current

strategies of optimizing DES focus on preparing new platforms, new coatings and new techniques of elution [34]. Up to date, different designs of new platforms (e.g. Co-Cr alloy) and new drugs (Biolimus A9) have been evaluated, which opens a new chapter for developing new generation DES. Actually, there are only a few drugs are used in DES, mainly including three categories: mTOR inhibitors (e.g. Sirolimus, Everolimus, Zotarolimus, Biolimus A9); calcineurin inhibitors (e.g. Tacrolimus, Pimecrolimus) and microtubule stabilizer (e.g. Paclitaxel). Besides, dexamethasone, estradiol and genistein are also under investigation for the potential applications in new DES [35,36]. Compared with the development of new drugs and platforms, the methods used to combine drug and stent are far more attracting. Among new DES designs, how to load drug onto the stent surface are paid much more attention, because different drug loading methods not only have an influence on the dose and release kinetics but also on the events of stent-blood interface [37]. Besides, the presence of the drug loading polymer coating has been proved to result in the LST events [38]. Therefore, scientists trend to biodegradable polymers as drug carrier or to develop polymer-free drug loading system.

Numerous DESs with novel drug loading system are undergoing investigation in laboratories and clinical trials, some of which received CE Mark. These are referred as new generation DESs include BioMatix, Nobori, Janus, Yukon etc. [39]. BioMatrix^{TM} stent (Biosensors, Morges, Switzerland) are based on the SS platform with the thickness of 112 μm and biodegradable PLA coating with Biolimus A9. The STEALTH and LEADERS trials showed a remarkable reduction of angiographic restenosis and excellent 9-month clinical safety in all patients [40]. Later, Biosensors developed the nonpolymeric BioFreedom^{TM} DES based on the BioMatrix^{TM} stent. It loaded the same mTOR inhibitor, Biolimus A9. BioFreedom^{TM} is manufactured into micro-structures on the abluminal surface. This polymer-free local drug delivery system not only avoids the adverse effects of degradation products and non-reacted monomer

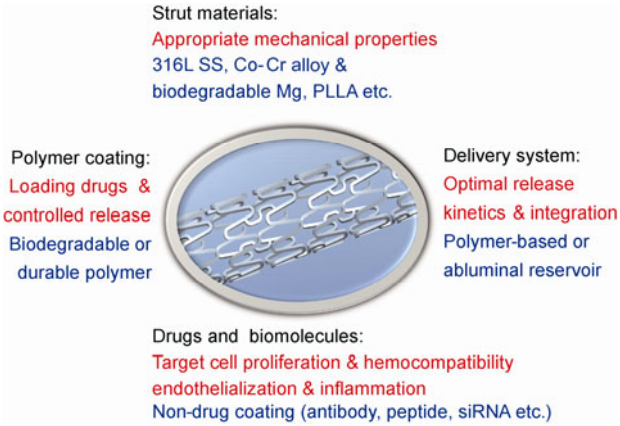

Figure 1 (Color online) Components of drug eluting stents.

compounds but also improves healing and integrity of stents [41]. Another commercial stent, Yukon^{TM} (Translumina, Hechingen, Germany) applies the similar drug loading strategy. Rapamycin is sprayed onto the microporous surface onto a bare SS stent. The micropores on the surface act as a reservoir, allowing the drugs to be released slowly. After the complete drug elution, the remaining microporous surface contributes to the adhesion and migration of endothelial cells [42]. Registry data suggested that the implantation of Yukon^{TM}-DES was feasible and safe, but binary restenosis and target vessel re-vascularization were frequently observed perhaps due to the roughness of surface [43].

3 Biodegradable stents

Although DES have obtained great success in interventional surgery, late thrombosis, delayed endothelialization, mechanical mismatch as well as the local hypersensitivity and inflammation were still considered as potential risks [44]. The fundamental cause of these phenomena lies on the fact that stent is indeed a foreign object within the vessel. A promising approach to overcome these limitations is the application of BDS, which can be also considered as bioabsorbable stents [45]. Therefore, BDS is envisaged to support the vessel wall temporarily for about 3–6 months after implantation, during which the stabilizing function of the stent is required. Then the vessel wall will be sufficiently reorganized and BDS could be degraded or absorbed following the healing process. Biodegradable cardiovascular stents can be made of both polymers (lactic acid, glycolic and caprolactone families) and metals (Mg-based or Fe-based alloys) [46]. The most frequently used cardiovascular polymer in the current biodegradable stents is PLLA, which is metabolized into lactic acid, carbon dioxide and water ultimately [47]. It is a recent idea that the metals can be identified as biodegradable materials. In terms of mechanical properties and low toxicity, pure magnesium, iron and their alloys can be applied in designs of vascular stents [48].

The Igaki-Tamai^{TM} stent (Igaki Medical Planning Company, Kyoto, Japan) is the first BDS which was developed by Tamai et al. [49] in 1999. The total stent is comprised of PLLA and a zig-zag helical coil design with straight bridges. It is worth mentioning that each end of the stent has been implanted gold markers to confer the polymer stent radiopaque. Long-term safety of the Igaki-Tamai stent was confirmed recently according to the clinical outcomes of acceptable rates of major adverse cardiac events and scaffold thrombosis, without stent recoil and vessel remodeling [50,51]. Another two representative fully BDS are named BVS^{TM} and REVA^{TM}. The BVS^{TM} (Abbott Vascular, Santa Clara, Calif, USA) everolimus eluting stent adopts PLLA as the strut coated by poly(*D*,*L*-lactide) loading everolimus. It possesses the properties of inhibiting neointimal hyperplasia

like DES and the requirement of disappearance once the stent has fulfilled its task. Whereas PLLA may need 24 months or more to degrade, mismatching the ideal implanting process of integrity for the first 6–12 months and totally degraded after 12–24 months. This kind of polymeric stent may lack sufficient radial force initially, and further decreases with bioabsorption, resulting in recoil of the stent and malapposition at follow-up [52]. The accumulated acidity production caused by the degradation of PLLA also lead to the local chronic inflammation and hypersensitivity like the adverse effect of durable drug loading coating in 1st DES. A prospective, single-group, open-label study was carried out among 30 patients. At 2 years, the in-stent late loss of 0.48 mm and a diameter stenosis of 27% are shown in angiography, which do not differ from the findings in 6 months. Consequently, the BVS stent showed excellent clinical safety with no cardiac deaths, ischaemia-driven target lesion re-vascularization, or stent thrombosis recorded, and only one myocardial infarction event by 2 years [53]. Positive vessel remodeling and restoration of vasomotion were also noted, carrying a great deal of promise of BVS^{TM} stent. The REVA^{TM} stent (REVA Medical, San Diego, California, USA) is a stent made of tyrosine poly(desamino tyrosyl-tyrosine ethyl ester) carbonate that metabolizes to amino acids, ethanol, and carbon dioxide. The radiopacity is provided by chemical modifications of tyrosine incorporated iodine with a resorption time of approximately 36 months [54]. Clinical outcomes indicate minimal acute stent recoil and injury, a non-thrombogenic response and complete endothelialization at 30 d. The long term studies also provide encouraging results.

The field of biodegradable metal stents has also gained attention from researchers around the world. Up to now, proposed biodegradable metals can be identified as: (1) Mg-based alloys, (2) pure Fe and Fe-based alloys, (3) metallic zinc, (4) metallic glasses which have been developed from both Mg-based and Fe-based alloys [55]. However, only Mg-based BDS have run to clinical tests. In the physiological environment, Mg or its alloys corrodes into soluble $Mg(OH)_2$, $MgCl_2$ and H_2 at a fast corrosion rate [56]. The released Mg ions together with the formation of hydrogen bubbles will lead to the higher local pH values which may cause chronic inflammatory reactions and blood disorder [57,58]. From a mechanical point of view, the Mg-based strut becomes thinner during the process of bio-corrosion, resulting in the loss of strength for scaffolding. Although the impacts of corrosion products on cardiovascular tissues are still not sufficiently investigated and the strength and ductility of Mg-based stents are not always satisfactory, the initial clinical success of the magnesium stent encourages the scientist to focus on the new generation BDS. The AMS^{TM} (AMS-1, BIOTRONIK, Berlin, Germany), which is the first metallic biodegradable stent implanted in human is composed of 93% magnesium and 7% rare earth metals. The PROGRESS-AMS clinical trial showed that biodegradable magnesium stents can achieve an immediate angiographic result similar to the result of other metal stents, and can be safely degraded within 4 months [59]. Subsequently, the AMS-INSIGHT clinical trial was carried out and demonstrated that the AMS technology is a safe technique to use for treating peripheral arterial disease though AMS was tested for the treatment of below-the-knee critical limb ischemia [60]. According to the clinical information back to the scientists, the focus of further development of new AMS is on prolonging stent degradation time and introducing drug eluting therapy. In 2010, the clinical evaluation of a biodegradable metallic drug eluting stent for the treatment of vascular disease has begun. This novel device is made of a proprietary magnesium alloy incorporating bioabsorbable polymer loading antiproliferative drug paclitaxel with the aim at reducing neointimal hyperplasia [61]. In May 2011, Biotronik [62] announced positive 6-month results for DREAMS. Among the first 22 patients, there was no cardiac death, no target vessel myocardial infarction and no stent thrombosis, which demonstrate a high safety profile of the novel device. Twelve-month results were reported recently to demonstrate safety and confirm vasomotion, showing the huge potential for DREAMS since it combines deployment and post-dilatation properties and long-term outcomes comparable to DES with the additional benefits of vascular restoration therapy. These promising clinical results show that the feasibility and safety of absorbable magnesium scaffolds and it might be an alternative to polymeric absorbable scaffolds. Fe-based stent does not develop as that rapidly compared with Mg-based stent. The stents made of pure Fe and its alloys are still under evaluations concerning the compatibility of ECs [63] and SMCs [64], toxicity of metabolic or degradable products [65] and gene expression profile [66]. Pre-clinical studies are carried out in the descending aorta of New Zealand rabbits [67] and coronary arteries of porcine [68]. Despite being an interesting alternative candidate for biodegradable implant material, iron mainly reacts like a permanent implant due to the very low degradation rate in physiological media. Since most biodegradable iron stent remained intact after 1 year, intense work has been done on the developing novel Fe-based alloys aiming at both an increase in degradation rate and an improvement in the mechanical properties [69]. The novel Fe-based alloys (Fe-Mn [70], Fe-Mn-Pd [71]) indicate the feasibility of achieving Fe-based BDS with enhanced degradation rate and suitable strength and ductility. Nevertheless, the long-term safety of Fe-based stents and the degradation behavior *in vivo* are still to be evaluated. What is more, zinc has been examined for the first time as a bioabsorbable cardiovascular stent material in 2013 [72]. Although a systemic evaluation of zinc applied in vascular stent needed to be carried out, the early results indicated that zinc was a promising material that could supplant magnesium as the favored base metal from the aspects of biocorrosion rate and corrosion products *in vivo*.

4 EPC-capture stent

EPCs are a small population of $CD34^+$ circulating mononuclear cells which was discovered by Asahara et al. [73] in 1997. Since the great *in vitro* and *in vivo* differentiation capacity, EPCs have the potential to upregulate the expression of endothelial specific antigens with the ability to migrate to areas of vascular injury and aid in the regeneration of damaged and dysfunctional endothelium [74]. Hence, new perspectives of rapid self-endothelialization were raised up and novel strategie of in vivo endothelialization began to be carried out by immobilizing $CD34^+$ antibody [75]. When the stent is implanted into the body, the EPCs existing in bone narrow and peripheral blood are supposed to be recruited and captured onto the stent surface. Scientists hoped that native endothelium could be reconstructed within a short period of time through this method [76]. At present, many companies and research groups are devoting lots of resources to realize this conceive.

Genous R-stent™ stent (Orbus Neich, Fort Lauderdale, Florida, USA) is the first commercial vascular stent applying EPC-capture system which received CE mark in 2005. In brief, anti-CD34 antibody is immobilized on the stainless steel substrate in order to attract EPC to the stent, accelerating natural healing to protect against thrombus and minimize restenosis [77]. Up to now, at least ten clinical trials have been carried out in different countries and ongoing trials evaluating the EPC-capture stent have begun throughout the world. In HEALING-FIM and HEALING II clinical trials, no acute or sub-acute stent thrombosis was observed, suggesting the efficacy and safety of EPC-capture technology [78]. Unfortunately, $CD34^+$ antibodies are not specific to EPC, there is possibility for an EPC-capture stent to pilot smooth muscle progenitor cells, which in turn result in neointimal proliferation [79]. Therefore, a new application of EPC-capture stent combined with DES technology is under investigation. EPC-capture technique is constructed on Combo Stent™ (OrbusNeich) together with abluminal low-dose sirolimus and a biodegradable polymer [80]. In May 2012, OrbusNeich [81] announced that 12-month follow-up data from the REMEDEE study showed favorable clinical and safety outcomes involving the use of the company's Combo Dual Therapy Stent when compared to the TAXUS Liberte® paclitaxel-eluting stent. The clinically driven target lesion failure rate was 8.9% for patients treated with the Combo stent, compared to 10.2% for those treated with the TAXUS™. Also the promising outcomes after almost 18 months support the benefits of the dual therapy approach [82].

Currently, capture of EPC and induction of EPCs homing to the stent to realize in-situ rapid endothelialization have been one of the promising strategies applied in the next generation stents. Besides anti $CD34^+$ antibody, biomolecules such as VE-cadherin [83], DNA [84] or peptide aptamers [85], and magnetic nanoparticles [86] have been reported to present the ability to specifically bind to EPC. However, considering the safety, none of these novel systems was tested in clinic. Although the efficacy of these methods have been demonstrated [87], further investigations and more experimental data from *in-vitro* and *in vivo* tests are necessary. And we are looking forward to the early trial of these strategies applied in the next generation EPC-capture stent in clinic.

5 Time sequence functional stent

Although numerous commercial stents have successfully applied in clinical tests, continuous optimizing properties of stents is still a huge task for the stent designers. With the better understanding of the pathobiology of stenting response, the failure of BMS, DES, BDS and EPC-capture stent is the mismatch between the stent behavior and biological response. For example, the proliferation of SMCs at early stage (several weeks) post-stenting leads to restenosis. Uncompleted endothelialization after drug release at the middle stage (3–6 months) results in the late thrombosis. The fast degradation rate of biodegradable magnesium stent puzzles the scientist. And the rapid endothelialization of EPC-capture stents requires healing within a few days with assist of anti-coagulant drug. Herein, the concept of time sequence functional stent is raised up. Designs of new generation stents not only focus on the property of anti-coagulation, promotion of ECs, inhibition of SMCs and the differentiation of EPC, but also pay more attention on the time sequence at global perspective. This way, the stent possesses the properties that can always match the requirements of biological environment of the host during the time sequence of healing and thus has the ability to overcome the problems above.

At the early stage (several weeks), restenosis is a predominant issue which should be suppressed. Anticoagulation and endothelialization are essential during the middle stage (3–6 months). The late stage (>9 month) should highlight the prevention of toxic ions release and maintain tissue compatibility. From this point, loading anti-coagulant molecules and anti-proliferative drugs needs precise design and synergetic effect. The passive barrier helps the bare stent to be biocompatible with the local vessel tissue. When it comes to BDS, the fast endothelialization and antithrombotic properties are given prior consideration. Suppressing restenosis and late thrombosis at the middle stage requires attention. At the late stage, in the case of fully degradable stents, tissue responses and the metabolism of degradable products need to be evaluated. Otherwise, the controlled behavior of degradation should coordinate with the healing process of stent implantation. The responses and tasks during various periods along the time sequence after stent implantation are shown in Figure 2. These spatio-temporal effects

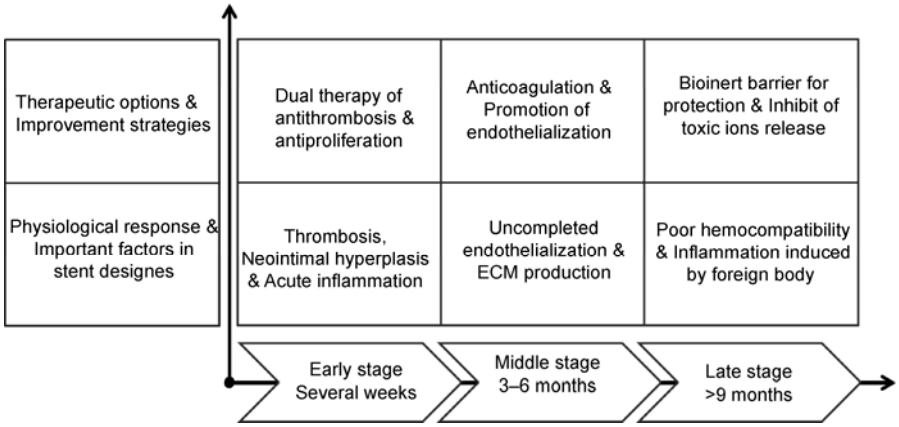

Figure 2 Responses and tasks follow stent implantation.

on the application of cardiovascular stents have been paid more and more attention in recent years. Considering the time-controlled manner, a surface that release therapeutics was achieved by Park group. The controlled release of paclitaxel from the multilayer films successfully led to the apoptosis of SMC *in vitro*, suggesting the potential application in drug-eluting systems to prevent the restenosis after surgery [88]. Yang et al. [89] construct a kind of stent surface where vascular endothelial growth factor gene and paclitaxel could be eluted at a time sequence scale. This modified stent promote early endothelium healing while inhibit smooth muscle cell proliferation compared with the control TAXUS^{TM}.

However, these designs have not been examined in clinical trials. Also, it is of great difficulties in developing novel ideally stent to solve the problems in all above stages. Authors of this paper have made an attempt on a model stent according to the above described conception and finished its clinical trial. The stent consists of metal stent, titanium oxide film, drug eluting coating (mixture layer of the biodegradable polymer PLGA and rapamycin). At the acute stage the drug release plays the role to suppress restenosis, and then the drug carrier PLGA is degraded and the Ti-O film surface with improved antithrombotic properties is exposed to blood, also supporting the endothelialization. In the long-term stage the Ti-O film coating on the stent prevents the release of deleterious elements from the surface into the surrounding tissue and increased the long-term biocompatibility. The clinical trial was performed as a multicenter randomized study in comparison with a commercial stent. The 150 patients were adopted for each stent group and totally 251 new stents and 240 reference stents were used. One year clinic results showed that the restenosis rate for the new stent was 1.1% and the late thrombus formation for the new stent was 0, both significantly lower than the control [90]. It can be concluded that the new stent with the novel structure metal stent/Ti-O film/drug eluting coating has displayed the appropriate properties according to the time stage of the vascular response after stent implantation. In addition, the realization of time sequence functional stent shows the possibility of constructing novel time-sequence functional stent with improved properties.

6 Conclusion

From the bare metal stent to drug eluting stent, and from the biodegradable stent to EPC-capture stent, twenty five years has witnessed the evolution of interventional treatment by vascular stents. Unfortunately, there is still not an ideal design for coronary stents. The relationship between these four general categories of vascular stents is summarized in the triangle from Figure 3. And the directions for improvement of vascular stents could be conjectured. At present, a large number of novel vascular stent models are constructed in the laboratory, emphasizing development of new metallic platforms, new stent bioactive coatings, new drug combinations and new alternative biodegradable substrates. At the same time, a series of clinical trials of different commercial stents are under investigation. The long term efficacy and safety of these stents on the market will be checked by doctors, patients and biomedical engineers.

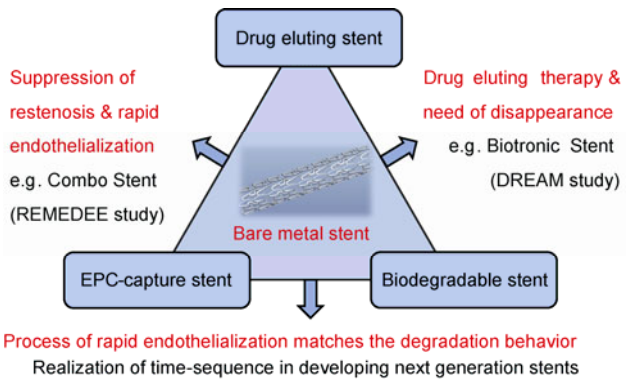

Figure 3 (Color online) Relationship between four general categories of vascular stents.

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