Rev Esp Cardiol. 2013;66(6):483–496

Update: Innovation in cardiology (V)

Progress in Treatment by Percutaneous Coronary Intervention: The Stent of the Future

Takashi Muramatsu,[a] Yoshinobu Onuma,[a] Yao-Jun Zhang,[a] Christos V. Bourantas,[a] Alexander Kharlamov,[a] Roberto Diletti,[a] Vasim Farooq,[a] Bill D. Gogas,[b] Scot Garg,[c] Hector M. García-García,[a] Yukio Ozaki,[d] and Patrick W. Serruys[a,*]

[a] *Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands*
[b] *Department of Interventional Cardiology, Andreas Gruentzig Cardiovascular Center, Emory University School of Medicine, Atlanta, Georgia, United States*
[c] *Department of Cardiology, East Lancashire, NHS Trust, Lancashire, United Kingdom*
[d] *Department of Cardiology, Fujita Health University, Toyoake, Japan*

Article history:
Available online 4 May 2013

Keywords:
Bioresorbable scaffold
Coronary artery disease
Drug-eluting stent
Vascular reparative therapy

ABSTRACT

First generation drug-eluting stents have considerably reduced in-stent restenosis and broadened the applications of percutaneous coronary interventions for the treatment of coronary artery disease. The polymer is an integral part of drug-eluting stents in that, it controls the release of an antiproliferative drug. The main safety concern of first generation drug-eluting stents with permanent polymers—stent thrombosis—has been caused by local hypersensitivity, delayed vessel healing, and endothelial dysfunction. This has prompted the development of newer generation drug-eluting stents with biodegradable polymers or even polymer-free drug-eluting stents. Recent clinical trials have shown the safety and efficacy of drug-eluting stents with biodegradable polymer, with proven reductions in very late stent thrombosis as compared to first generation drug-eluting stents. However, the concept of using a permanent metallic prosthesis implies major drawbacks, such as the presence of a foreign material within the native coronary artery that causes vascular inflammation and neoatherosclerosis, and also impedes the restoration of the vasomotor function of the stented segment. Bioresorbable scaffolds have been introduced to overcome these limitations, since they provide temporary scaffolding and then disappear, liberating the treated vessel from its cage. This update article presents the current status of these new technologies and highlights their future perspectives in interventional cardiology.

Avances en el tratamiento mediante intervención coronaria percutánea: el *stent* del futuro

Palabras clave:
Estructura bioabsorbible
Enfermedad coronaria
Stent liberador de fármaco
Tratamiento de reparación vascular

RESUMEN

Los *stents* liberadores de fármacos de primera generación han reducido considerablemente las reestenosis en el *stent* y han ampliado las aplicaciones de las intervenciones coronarias percutáneas en el tratamiento de la enfermedad coronaria. El polímero es parte integrante de los *stents* liberadores de fármacos, ya que controla la liberación de un fármaco antiproliferativo. La principal preocupación respecto a los *stents* liberadores de fármacos de primera generación con polímeros permanentes—la trombosis del *stent*—se ha debido a la hipersensibilidad local, la cicatrización tardía del vaso y la disfunción endotelial. Esto ha llevado al desarrollo de *stents* liberadores de fármacos de nueva generación con polímeros biodegradables o incluso sin polímero. En ensayos clínicos recientes se ha observado la seguridad y la eficacia de los *stents* liberadores de fármacos con polímero biodegradable, que han mostrado una reducción demostrada de la trombosis de *stent* muy tardía, comparados con los de primera generación. Sin embargo, el concepto de utilizar prótesis metálicas permanentes tiene importantes inconvenientes, como la presencia de un cuerpo extraño en el interior de la arteria coronaria nativa, que causa inflamación vascular y neoaterosclerosis e impide también el restablecimiento de la función vasomotora del segmento tratado con el *stent*. Para superar esas limitaciones, se han introducido las estructuras de base bioabsorbible, que proporcionan un armazón temporal y luego al desaparecer liberan el vaso tratado de la jaula que le imponían. En este artículo de puesta al día se presenta el estado actual de estas nuevas tecnologías y se resaltan sus perspectivas futuras en cardiología intervencionista.

* Corresponding author: Department of Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, Ba583, Dr. Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands.
E-mail address: p.w.j.c.serruys@erasmusmc.nl (P.W. Serruys).

1885-5857/$ – see front matter
http://dx.doi.org/10.1016/j.rec.2012.12.009

Abbreviations

BMS: bare metal stent
BRS: bioresorbable scaffold
DES: drug-eluting stent
LLL: late lumen loss
MACE: major adverse cardiac events
MI: myocardial infarction
SES: sirolimus-eluting stent
ST: stent thrombosis

INTRODUCTION

Coronary stents were first developed in the mid 1980s to overcome the inherent limitations of balloon angioplasty, including elastic recoil and vessel closure in the acute phase, as well as constrictive remodeling and restenosis in the late phase.[1–3] In the 1990s, this technology became widely accepted as a promising treatment strategy for patients with coronary artery disease after the landmark Belgian Netherlands Stent trial, which demonstrated the superiority of the bare metal stent (BMS) over balloon angioplasty.[4] Although coronary stenting improved angiographic results and clinical outcomes, neointimal hyperplasia and restenosis continued to be major limitations of this technology.[5] In order to minimize neointimal hyperplasia and thereby reduce repeat revascularization, drug-eluting stents (DES) were developed. Early pivotal trials of the first generation DES showed excellent results with respect to the reduction of in-stent restenosis, such that they rapidly replaced BMS.[6,7] In the year 2006, safety concerns were raised with DES following reports linking their use to an increased risk of stent thrombosis (ST).[8,9] First generation DES, with permanent polymers, have been associated with delayed endothelialization, endothelial dysfunction, and local hypersensitivity reactions, resulting in an increased risk of ST and the need for prolongation of dual antiplatelet therapy.[10,11]

Newer generation DES, with thinner struts and more biocompatible polymers, have considerably improved their safety profile.[12–15] However, concerns still persist over the presence of durable polymers, as evidence from animal and human studies still suggest that these durable polymers may cause persistent arterial wall inflammation and delayed vascular healing, both of which may subsequently have a potential role in precipitating ST and delayed in-stent restenosis (ie, late catch-up phenomenon).[16] Newer generation DES, coated with biodegradable polymers, offer the attractive combination of controlled drug elution in parallel with biodegradation of the polymer into inert monomers. After the completion of biodegradation, only a "BMS" remains, thereby reducing the long-term risks associated with the presence of a permanent polymer.[17] An extension of this concept has brought the development of newer DES that are completely free of polymer, or come with novel coatings. In addition, bioresorbable metallic (ie, magnesium) and polymeric scaffolds have been developed, which initially safeguard the patency of the treated vessel and then disappear. The aim of this article is to review new stent technologies that are currently undergoing clinical investigation and discuss their future perspectives in interventional cardiology.

NEW GENERATION METALLIC DRUG ELUTING STENT

Drug Eluting Stent With Biodegradable Polymers

Biodegradable polymeric coatings facilitate drug delivery to the vessel wall and are then resorbed without any long-term sequelae. Since their introduction in the year 2004,[18] many DES with biodegradable polymers have been developed, particularly after it was hypothesized that this technology would potentially reduce the risk of very late ST (VLST), an adverse event which has been associated with durable-polymer DES. The randomized ISAR-TEST 4 trial was conducted to test the noninferiority of a biodegradable-polymer rapamycin-eluting stent (RES; Yukon Choice PC, Translumina; Hechingen, Germany) to a durable-polymer DES (ie, the first generation Cypher sirolimus-eluting stent [SES] or the second generation Xience V everolimus-eluting stent [EES]), with respect to clinical outcomes. A total of 2603 patients were enrolled in the trial. At 3-year follow-up, there were no significant differences in a composite of cardiac death, target-vessel myocardial infarction (MI), and target lesion revascularization (TLR) (RES 20.1% vs DES 20.9%, *P*=.59), as well as the incidence of definite/probable ST (RES 1.4% vs DES 1.9%, *P*=.51).[19] Longer-term clinical follow-up is required to evaluate the potential superiority of RES over the traditional DES in reducing the risk of VLST.

Biolimus-eluting Stent With Biodegradable Polymer

Biolimus A9 is a semisynthetic limus-drug designed for stent application which has a similar potency to sirolimus, but is 10 times more lipophilic. It is immersed at a concentration of 15.6 μg/mm into a polylactic acid biodegradable polymer that covers the abluminal stent surface. Polylactic acid is coreleased with biolimus and completely metabolized into carbon dioxide and water over 6 months to 9 months. The stainless steel stent platform has a strut thickness of 112 μm, with a quadrature link design. Currently, the stent platforms utilizing this technology are the BioMatrix Flex (Biosensors Inc.; Singapore), NOBORI (Terumo Corp.; Tokyo, Japan), and Axxess (Biosensors Inc.).

In the LEADERS trial, the BioMatrix stent was shown to be noninferior to the first generation durable-polymer Cypher SES, with respect to a composite end point of cardiac death, MI, and ischemia-driven target vessel revascularization at 12-month follow-up (BioMatrix 10.6% vs Cypher 12.0%, *P*=.37).[20] This noninferiority has recently been confirmed at 5-year follow-up.[21] Importantly, the BioMatrix stent showed a significantly lower incidence of definite VLST at 5-year follow-up (hazard ratio=0.26 [0.10-0.68]). A pooled data analysis of the randomized ISAR-TEST 3, ISAR-TEST 4, and LEADERS trials also showed that the DES with biodegradable polymers were associated with a lower risk of VLST as well as MI compared to the Cypher SES.[22] The LEADERS trial not only provided the first evidence of improved clinical outcomes compared to the first generation DES, but is also the proof of concept in terms of biodegradable-polymer DES.

Everolimus-eluting Stent With Biodegradable Polymer: SYNERGY Stent

The SYNERGY stent (Boston Scientific; Natick, Massachusetts, United States) consists of a thin-strut (74 μm), platinum-chromium platform that delivers everolimus from a bioabsorbable polylactide-co-glycolide polymer applied to the abluminal surface. In the randomized, EVOLVE trial, the safety and efficacy of 2 dose formulations (standard dose [SD], 113 μg/20 mm, and half dose [HD], 56 μg/20 mm) of the SYNERGY stent were compared to the durable-polymer PROMUS Element EES (Boston Scientific).[23] A total of 291 patients were randomly assigned in a 1:1:1 ratio to SYNERGY, SYNERGY HD, and EES. The primary clinical endpoint was the 30-day rate of target lesion failure (TLF), defined as a composite of cardiac death, MI related to the target vessel, and TLR. TLF occurred in 3.1%, 1.1%, and 0% of patients in the SYNERGY, SYNERGY HD, and EES groups, respectively. The 6-month in-stent