International Journal of Cardiology 224 (2016) 317–322

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Review: The outcomes of different vessel diameter in patients receiving coronary artery stenting

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ARTICLE INFO

Article history:
Received 22 June 2016
Received in revised form 8 September 2016
Accepted 15 September 2016
Available online 17 September 2016

Keywords:
Coronary Artery Disease
Topic:
Stent
Bare metal stent
Drug eluting stent

ABSTRACT

Compared to bare metal stent (BMS) implantation, drug-eluting stents (DES) is significantly better in attenuating intimal hyperplasia and reducing the rate of revascularization. However, the requirement of prolonged dual antiplatelet therapy (DAPT) and the economic cost have been the major disadvantages of DES. Studies have shown that the use of DES in small vessels decrease revascularization rate, but the results in large vessels vary. Previous studies have shown that the extent of late loss is unrelated to vessel diameter, and that late loss is easily accommodated in large vessels, thus resulting in decreased clinical benefit of DES in this setting. No definite cut-off point value of the vessel size has yet been demonstrated. Series studies aimed at evaluating the clinical outcomes of DES versus BMS in large vessels, but their results have been controversial. In this review, we evaluate the latest studies on clinical outcomes for different vessel sizes and clinical conditions. Nonetheless, further large clinical trials are warranted to address the clinical results of newer stents in different size vessels, especially in large vessels.

1. Introduction

Percutaneous transluminal coronary angioplasty (PTCA) has been practiced for coronary artery disease (CAD) since the 1970s. The conventional plain balloon angioplasty (POBA) increased vessel lumen by compression of the soft atheromatous material, stretching the arterial wall, and finally disrupting the intima with the tradeoff of intimal dissections and acute vessel closure [1,2]. In order to overcome the problems related to elastic recoil, angioplasty-related coronary dissection, and higher restenosis rate of POBA, researchers developed bare metal stent (BMS) [3–7]. The drug-eluting stent (DES) was later launched to overcome the neointimal hyperplasia after BMS implantation [8,9], and was significantly better in attenuating intimal hyperplasia and reducing the rate of revascularization [10–12].

However, the major disadvantages of DES were the requirement of longer duration of dual antiplatelet therapy (DAPT) and the economic costs. The prolonged DAPT could also be associated with higher bleeding risk and treatment interruptions at times of surgery [13], and the absolute benefit of DES in patients with a low risk of restenosis is reduced [14]. Previous studies on BMS demonstrated a similar late lumen loss irrespective of vessel sizes [15], which suggested that the same extent of late loss was easily accommodated in large vessels. It is a potential benefit of BMSs when they are applied to large vessels. Furthermore, though the mean late luminal loss of about 0.17 mm reported with DES is potentially beneficial compared to that of about 1.0 mm with BMS implantation [11,16], the extent of restenosis is critically dependent on the reference vessel diameter. Series studies have shown that restenosis rate is low (<10%) in large coronary arteries after BMS implantation [15,17,18], which is similar to the restenosis rate of DES. A previous cost-effectiveness analysis suggested that DES would only become a cost-effective treatment strategy when the rate of BMS restenosis exceeds 18.5% [19]. Although several studies have been conducted to figure out the clinical outcome of different vessel diameters in patients receiving coronary artery stentings, the results have been controversial.

2. The mechanism of post-stenting restenosis

Restenosis after coronary artery stenting has been studied for decades. Earlier studies in patients receiving BMSs reported restenosis rates of about 22% to 32% [5,6]. The reduction in lumen diameter following stent implantation has been thought to be the result of arterial damage with subsequent neointimal tissue proliferation and hyperplasia [20–22]. Neointimal proliferation has been discovered as a process of differentiation of smooth muscle cells associated with macrophage accumulation and extensive neovascularization [23]. DES has been developed to overcome this issue. DES enables anti-inflammatory, immunomodulatory, and antiproliferative agents to be released and

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http://dx.doi.org/10.1016/j.ijcard.2016.09.061
0167-5273/

distributed at the site of arterial injury during the initial 30-day healing period [24]. And clinically, DES has been found to lower the rate of target lesion revascularization (TLR) by 50–70% when compared to BMS; though the restenosis rate was significantly lower in DES than BMS, it still accounts for 5–15% [8,25,26].

A later study suggested that vessel diameter influences restenosis rate with BMS [27]. With a similar degree of neointimal proliferation around a stent of any diameter, neointimal growth occurring in a large vessel is less likely to cause a significant restenosis, either clinically or angiographically. Such difference may be translated into a different binary restenosis and a different extent of vascular patency to maintain hemodynamics and prevent further intervention in various sizes of vessels. The subgroup analysis in TAXUS-IV demonstrated that the benefit of DES over BMS was limited to vessels smaller than 3.0 mm [12]. Further, in the TAXUS-V study, TLR and target vessel revascularization (TVR) in vessels treated with 4.0 mm BMS were very low (5.0% and 7.9%, respectively) and equivalent to the vessels treated with Taxus paclitaxel-eluting stents (PES) [28]. These studies suggested that the higher restenosis rate of BMS were less observed in large diameter vessels and thus achieved a comparable clinical result as that of DES.

3. Clinical impact of small vessel size

3.1. BMS and mixed generation DESs in small vessels

Earlier clinical studies showed worse outcomes of patients with BMS implantation at small vessel size from the BENESTENT and STRESS trials [29,30]. In 1998, Shpend et al. compared the outcome among patients who received coronary BMSs with different vessel sizes [15]. The study enrolled 2602 patients and demonstrated a significant difference of 1-year event-free survival for different vessel sizes (<2.8 mm, 69.5%; 2.8–3.2 mm, 77.5%; >3.2 mm, 81%; $p < 0.001$), and the restenosis rate of small vessels was ≥1.5X higher than that noted in large vessels. Because of the superiority over BMS, DES has been largely adopted in small vessel disease. Subgroup analysis on first generation DES, such as PES and sirolimus-eluting stent (SES), showed that DES was beneficial to angiographic restenosis and TLR. In TAXUS IV, the TLR rate of vessel diameter < 2.5 mm at 12-month in PES group were significantly lower than that in BMS group (5.6% vs. 20.6%, respectively; $P < 0.001$) [31]. The subgroup involving small vessels (≤2.75 mm) in SIRIUS trial showed significantly lower TLR rate when comparing SES with BMS (6.6% vs. 22.3%; $P < 0.0001$) [32]. These earlier studies supported the use of DES in reducing TLR relative to BMS among small vessels size. Stent thrombosis with DES implantation in small vessels was another issue. Nakamura et al. found that the incidence of stent thrombosis in the Asian population was relatively low (0.5% with DES and 0.6% with BMS of subacute stent thrombosis), and the 7-year analysis disclosed higher late stent thrombosis in DES than in BMS (0.18% vs. 0.1% respectively, $p = 0.001$) [33]. However, other studies presented that the incidence of stent thrombosis in small vessel DES implantation did not differ from the result of BMS [34].

Puymirat et al. conducted a comparison study between DES and BMS at vessels diameter < 3 mm. The result showed that DESs had significantly lower major adverse cardiac event (MACE) (HR: 0.51, 95% CI: 0.33–0.78) and TVR (HR: 0.44, 95% CI: 0.25–0.78) than BMS in 645 patients with 3 years follow-up results [35]. Further study from the Asian population also supported the superior outcome of DES. A 9 months follow-up study from Japan enlisted 335 patients to compare the results of DES and BMS in small vessels (2.5 mm stent) [36]. Although DES group included more severely diseased small coronary arteries, the in-stent restenosis (ISR) rate was significantly lower than BMS group (24% vs. 27%; $p = 0.001$). The result of 1-year registry database with 669 DES and 686 BMS patients also supported the use of DESs in small coronary arteries (2.50–3.00 mm) [37]. Compared to patients treated with BMS, the use of DESs was associated with significantly lower rates of both repeat revascularization and MACE at one year follow-up, though there was no significant difference between DES and BMS regarding death and myocardial infarction (MI). Another 293 elderly (≥75 years old) patients demonstrated a better result of DES than BMS among native small coronary arteries (<3 mm). This 3.5 years follow-up study revealed significantly lower adjusted MACEs (HR: 0.42, 95% CI: 0.24–0.72; $p = 0.002$) and TVR (HR: 0.33, 95% CI: 0.14–0.76; $p = 0.009$) in DES group [38], but no significant differences were observed in death, MI, stent thrombosis or bleeding. These real-world analyses suggested that patients treated with DES had significantly lower rates of repeat revascularization and MACE comparing to those treated with BMS. (See Table 1.)

3.2. Second generation DES in small vessels

Even though the data of comparison between second generation DES and BMS in small vessels are limited, some studies showed that the second generation DES remained superior to BMS in small vessels. The subgroup analysis of ENDEAVOR II trial reported 171 patients with vessels size of <2.5 mm, and revealed that 8-month angiographic restenosis rate favored the use of zotarolimus-eluting stents (ZES) over BMS (18.2% vs. 38.6%; $p = 0.0037$) [39]. A subgroup analysis of SPIRIT IV trial enrolled 1352 patients with small vessel disease (≤2.75 mm) showed a better result of everolimus-eluting stent (EES) than PES. EES group demonstrated a significantly less target vessel failure (TVF) (3.9% vs. 6.8% respectively; OR: 0.57, 95% CI: 0.35–0.91) [40]. A 2-year clinical study from Japan also supported the better outcome of EES over PES in small vessels (<2.5 mm) [41]. The 509 patients enrolled clinical study displayed a significant better result of EES than PES in TVR (8.0% vs. 13.9%; $p = 0.03$) and MACE (8.7% vs. 14.3%; $p = 0.05$). The subgroup analysis of ENDEAVOR IV also demonstrated the trend of

Table 1
Articles comparing clinical outcomes of stenting for small vessels.

First author, year	No. of patients	Cut-off diameter (mm)	Stent types	Length of follow-up	Favorable result for death or MI	Favorable result for TLR/TLF/TVR/ISR
Stone, 2004	176	2.5	PES/BMS	1 year	NS	DES
Fajadet, 2006	171	2.5	ZES/BMS	8 month	NS	DES
Leon, 2010	516	2.5	ZES/PES	1 year	NS	ZES
Sugihara, 2013	335	2.5	SES/PES/BMS	9 month	NS	DES
Nasu, 2015	509	2.5	EES/PES	2 years	NS	EES
Jinnouchi, 2015	1132	2.5	BES/EES	2 years	NS	NS
Holmes, 2004	522	2.75	SES/BMS	1 years	NS	DES
Stone, 2010	1352	2.75	EES/PES	1 years	NS	EES
Puymirat, 2011	645	3.0	SES/PES/ZES/EES/BMS	3 years	NS	DES
Parikh, 2014	1355	3.0	SES/PES/BMS	1 year	NS	DES
Puymirat, 2013	293	3.0	SES/PES/ZES/EES/BMS	3.5 y	NS	DES

BES: biolimus-eluting stent; BMS: bare-metal stent; DES: drug-eluting stent; EES: everolimus-eluting stent; ISR: In-stent restenosis; MI: myocardial infarction; NS: non-significant difference; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; TLR: target lesion revascularization; TLF: target lesion failure; TVR: target vessel revascularization; ZES: zotarolimus-eluting stent.