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Review article

Bioabsorbable stents – Has the concept really translated to clinical benefits? – Concept to clinical – Update: 2012

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ABSTRACT

Bioabsorbable stents have altogether opened a new perceptive in coronary interventions and a debate on benefits over bare metallic stents and drug eluting stents. There had been difference of opinion from experts in this state of art over the technology, indications of usage, clinical benefits and economics. The review enumerates material and technical related issues of so for developed bioabsorbable stents and the players involved. Unbiased, categorical information on the clinical trials of the stents – till date are also discussed.

1. Introduction

Coronary stents are used as a mechanical means to overcome the major limitations of balloon angioplasty with adequate scaffolding, preventing early recoil and late vascular remodeling.[1,2] Bare Metal Stents (BMS) have been associated with relatively high rates of restenosis requiring additional procedures for target vessel revascularization. This lead to the development of the Drug Eluting Stents (DES) composed of a polymer layer and an anti-proliferative drug to prevent restenosis.[3] However DES were reported to be associated with delayed healing, inflammation, hypersensitivity due to drug/polymer and endothelial dysfunction which have contributed to late thrombosis and prolonged dual antiplatelet therapy.[4–7]

Bioabsorbable stents came in to the arena to offer several potential advantages over BMS or DES. These include abolished late stent thrombosis, improved lesion imaging, reduction in revascularization procedures, restoration of vasomotion, freedom from side-branch obstruction and strut fracture-induced restenosis.[8,9]

2. Materials and technical specifications

There are several polymeric bioabsorbable stents that have been tested. One of the first bioabsorbable stent tested was the Igaki-Tamai (Igaki Medical Planning Co.Ltd., Kyoto, Japan) made of a high-molecular-weight poly L-lactic acid, without any drug.[10] Two other companies, Bioabsorbable Therapeutics

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Table 1 – Comparative – technical specifications of bioabsorbable stents.

Company	Stent name	Stent material	Drug	Strut thickness (μm)	Absorption time (months)	Stent radio-opacity	Design	Current status of development
Kyoto Medical	Igaki tamai	PLLA	None	170	24	Gold markers	Zig-zag helical coils with straight bridges	Stopped
Biotronik	AMS	Magnesium alloy	None	165	<4	Nil	Sinusoidal in-phase hoops linked by straight bridges	Ongoing clinical trials
REVA Medical	REVA DES	Tyrosine derived polycarbonate	Paclitaxel/ Sirolimus	200	36	Covalently bound iodine	Slide and lock	Ongoing clinical trials
BTI	IDEAL	Polyanhydride ester	Sirolimus/ Salicylicacid	200	6	Nil	Tube with laser cut voids	Under development
Abbott	BVS	PLLA	Everolimus	156	24	Platinum markers	Out-of-phase/in-phase hoops with straight and direct links	Ongoing clinical trials

AMS-absorbable metallic stent; BTI-Bioabsorbable Therapeutics Inc; BVS-bioabsorbable vascular solutions.

Inc (BTI) and Reva Medical *Inc* have tested bioabsorbable stents, coated with sirolimus and paclitaxel respectively. The BTI sirolimus-eluting stent uses a poly (anhydride ester) salicylic acid polymer that gives the stent physical structure and a polymer coating that controls release of sirolimus. During absorption, the bonds between salicylic acid and linker molecules are hydrolyzed releasing the anti-inflammatory drug, salicylic acid.[11] While REVA paclitaxel stent uses an absorbable tyrosine-derived polycarbonate polymer that metabolizes to amino acids, ethanol and carbon dioxide. The stent possesses high radial strength and negligible recoil with standard balloon deployment.[12] Biotronik's magnesium-alloy stent without drug had been tested in the PROGRESS-AMS study.[13]

Till now the most successful bioabsorbable stent was the BVS stent from Abbott Vascular and it was originally developed by Bioabsorbable Vascular Solutions *Inc*. The device claimed to be fully absorbed over 2 years, has a backbone of PLLA, which was subsequently coated with a thin layer of amorphous matrix of poly-D,L-lactide (PDLLA) and 8.2 μg/mm^2 of the anti-proliferative drug everolimus in equal ratios. The PLLA enables controlled release of everolimus, such that 80% is eluted in 30 days.[14] Comparative technical specifications of bioabsorbable stents so for developed and evaluated were summarized in Table 1.

3. Clinical issues

Comparative clinical data of bioabsorbable stents is mentioned in Table 2. The Igaki-Tamai stent was implanted in 15 patients (25 stents), had re-stenosis rate of 10.5% at 6 months.[15] A second, larger study of 50 elective patients (63 lesions, 84 stents) at 4 years showed promising results with the absence of late stent thrombosis. The clinical outcomes showed MACE-free survival rates of 82.0%, but these stents promoted a thick rim of intimal thickening separating struts from lumen, a result very different from the strut protrusion or malapposition.[16] At 10-year clinical follow-up, freedom from cardiac death, non-cardiac death, and MACE were 98%, 87%, and 48%, respectively. Despite impressive results, failure of the stent for further progress was related primarily to heat induced self-expansion. There were concerns that this could cause necrosis of the arterial wall, leading to excessive intimal hyperplasia or increase platelet adhesion, leading to sub-acute stent thrombosis.[17,18]

In the FIM WHISPER trial, BTI stent was implanted in 11 patients. After 12 months there was no evidence of acute or chronic recoil, but IVUS data showed insufficient neointimal suppression,[19] and further improvisations on the BTI stent was not reported.

Table 2 – Comparative clinical data of bioabsorbable stents.

Stent	Trial	Clinical outcomes			
		MACE	TLR	Binary restenosis	Late loss (mm)
Igaki-tamai	Igaki-Tamai Coronary	–	10.5%(6M)	10.5%(6M)	0.48(6M)
Biotronik	PROGRESS AMS	26.7%(1Y)	45%(1Y)	–	0.44(1Y)
BTI	WHISPER	–	–	–	–
REVA	RESORB	–	66.7%(6M)	–	
Abbott	ABSORB	3.4%(3Y)	0%	7.7%(6M)	0.48(3Y)

MACE: Major adverse cardiac events; TLR: Target lesion revascularization, M–months, Y – years.

Table 3 – Three years clinical data of ABSORB trial.

Hierarchical	6 Months ($n = 30$)	12 Months ($n = 29$)*	24 Months ($n = 29$)*	36 Months ($n = 29$)*
Ischemia-driven TLR	0%	0%	0%	0%
By PCI	0%	0%	0%	0%
By CABG	0%	0%	0%	0%
Non Ischemia-driven TLR% (n)	3.3%(1)**	3.4%(1)**	3.4%(1)**	3.4%(1)**
Cardiac death	0%	0%	0%	0%
Non cardiac death	0%	0%	3.4%(1)	6.9%(2)
MI	3.3%(1)	3.4%(1)	3.4%(1)	3.4%(1)
Q-wave MI	0%	0%	0%	0%
Non Q-wave MI	3.3%(1)**	3.4%(1)**	3.4%(1)**	3.4%(1)**
Non ischemia driven TVR (non TLR)	6.7%(2)	6.9%(2)	6.9%(2)	6.9%(2)
Any TVR	10.0%(3)	10.3%(3)	10.3%(3)	10.3%(3)

MACE: Major adverse cardiac events; MI: Myocardial infarction; TLR: Target lesion revascularization; *-One patient withdraw consent and missed the 9, 12, 18 months and 2 and 3 year visits but the vital status of the patients in the absence of cardiac event is known through the referring physician; **-This patient also underwent a TLR, not qualified as ID-TLR (DS = 42%) followed by post procedural troponin qualified as a non-Q MI and died from his Hodgkin's disease at 888 days post procedure.

The REVA Endovascular Study of a Bioresorbable Coronary Stent (RESORB) was initiated in 2007 enrolled 27 patients. At 30-day follow-up, two patients experienced a myocardial infarction (MI) and one needed another percutaneous coronary intervention (PCI). After implantation, there was an unfavorable result with respect to target lesion revascularization (TLR) of 66.7% at 6 months.[20] The safety of a new bioresorbable ReZolve stent in native coronary arteries is under investigation and the study is expected to be completed by 2016.

The first metallic bioabsorbable stent of Biotronik, implanted in humans was studied in the PROGRESS-AMS trial with 63 patients.[21] At 12 months no stent thrombosis, myocardial infarction, or death was reported in any of the patients. However, angiographic restenosis developed in 47.5% and 45% of the patients had additional PCI[22] The safety and clinical performance of the first drug-eluting absorbable metal stent – AMS-3 in patients with *de novo* lesions in native coronary arteries (BIOSOLVE – I) is under clinical trial.

The safety and feasibility of the Abbott's BVS was assessed in 30 low-risk patients with *de novo* coronary lesions who were enrolled in the prospective, open-label, multicenter FIM ABSORB study.[23–25] The study demonstrated clinical safety of the BVS as there was only one ischemia-driven major adverse event (non–Q-wave MI) at 6 months. Angiographic follow-up demonstrated a late loss of 0.44 mm. At 2 years after implantation the stent was bioabsorbed, vasomotion restored with freedom from late thrombosis. Late luminal enlargement due to plaque reduction without vessel remodeling needs confirmation from the outcomes of ABSORB B, ABSORB EXTEND clinical investigations and ABSORB II study which are under progress.

At 3 years - stent thrombosis, MACE events were zero and angiographic follow-up demonstrated late loss of 0.48 mm similar to the values from the early DES studies. The studies have also shown reduction in scaffold area that occurred through a combination of acute and chronic scaffold recoil and non uniform vessel support. Chronic scaffold recoil occurred as a consequence of the loss of radial strength with bioresorption. The 3 years clinical data of ABSORB trials is shown in Table 3.[26]

All bioabsorbable stents so far developed are larger and bulkier than current metallic stents. In Igaki-Tamai and PROGRESS AMS studies the incidence of TLR at one-year was much higher compared to BMS, which can limit their clinical use in narrow lesions. The challenge in the development of bioabsorbable stent in the initial years was more material centric. These includes difficulties in manufacturing compatible biodegradable materials that have molecular weights capable of limiting inflammation, loss of radial strength over time that can increase the risk for stent fracture and migration of degraded products and concerns over long-term biocompatibility of breakdown products. PROGRESS-AMS trial showed loss of radial strength which resulted in high rates of restenosis due to very fast bio - absorption of the

Table 4 – Comparative clinical data of Abbott vascular cobalt chromium stent (ML Vision), everolimus eluting stent (Xience-V) and everolimus eluting bioabsorbable stent (BVS) at 6 months follow-up.

End points (6 months)	SPIRIT-first ML vision stent ($n = 29$)	SPIRIT-first Xience V stent ($n = 27$)	ABSORB BVS stent ($n = 30$)
% In-stent Binary Restenosis	25.79%	0%	7.7%
In-stent Late loss (mm)	0.85	0.10	0.43
In-segment Late loss (mm)	0.61	0.09	0.35
TLR	21.4%	3.8%	0%
MACE	21.4%	7.7%	3.3%
NIH (mm^2)	1.98	0.50	0.30

TLR: Target lesion revascularization; MACE: Major adverse cardiac events; NIH: Neointimal hyperplasia area (NIH).

material. As an alternative iron based Bioabsorbable stents with slow degradation were developed but concerns regarding systemic iron-related toxicity have so far hampered progress with this approach.

Polymeric biodegradable stents have demonstrated some limitations and long-term effects of complete polymer absorption related issues are still not well understood. Despite the advantages, there are major hurdles of using a polymer as the backbone to a coronary stent that lacks radio-opacity, reduced radial strength (necessitating thicker stent struts) and reduced ability of the stents to be deformed.

4. Conclusions

Current DES with bioabsorbable polymer has similar beneficial attributes as BMS with respect to late stent thrombosis as mentioned in Table 4. Hence the potential clinical advantages of the bioabsorbable stent as such would be limited to preservation of vessel remodeling and easier surgical revascularization at the stent site. The challenges with biodegradable stents will be – persistent mechanical resistance withstanding acute and chronic recoil and the ability to modulate hyperplasia in the first months of stent implantation. Modified devices with prolonged degradation beyond two to three years tend to lose their advantage over conventional DES. However achieving the right balance between the polymer, drug and degradation will ultimately maintain vessel patency and prevent potentially life-threatening late stent thrombosis. To this end, further continuous research and investment is imperative. However, three "mores" are needed: more patients, more follow-up, and more experience in complex lesions.

Conflicts of interest

All authors have none to declare.

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