CLINICAL RESEARCH
CORONARY INTERVENTIONS

Long-term outcomes with Biolimus A9-eluting stents in real-world, all-comers Asia Pacific patients. Final 5-year report of the BEACON (Biolimus Eluting A9 Coronary Stent Obviating Luminal Narrowing) II clinical registry

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KEYWORDS

- biodegradable polymer
- drug-eluting stent
- major adverse cardiac events
- stent thrombosis

Abstract

Aims: To evaluate and report the final five-year clinical outcomes of treatment with BioMatrix DES in a real-world, all-comers population of Asian Pacific patients.

Methods and results: BEACON II is a prospective observational registry at 12 sites with 497 patients enrolled in six Asia Pacific countries. The primary endpoint was a composite of cardiac death, myocardial infarction (Q and non-Q-wave) or target lesion revascularisation at 12 months. Secondary endpoints included extending the primary endpoint to five years and rates of stent thrombosis. Analysis was performed according to the intention-to-treat principle. Patients in the BEACON II registry were relatively young with a mean age of 59.8 years and a high prevalence of diabetes mellitus (32.5%). In spite of many complex lesion subsets, acute procedural success was achieved in 98% of patients. At five years, the hierarchical major adverse cardiac events (MACE) rate was 11.2%, the cumulative incidence of cardiac death 4.4%, myocardial infarction 4.5%, and target lesion revascularisation 3.8%, respectively. Although this was an all-comers population excluding the enrolment of patients with left main disease, the five-year definite stent thrombosis cumulative incidence was low (1.2%), and definite very late stent thrombosis (VLST) events were rare (0.4%). There were no VLST in native coronary arteries; indeed, VLST was limited to saphenous vein grafts (SVGs).

Conclusions: The low hierarchical MACE incidence and the absence of VLST in native coronary arteries suggest an excellent safety profile up to five years for the BioMatrix stent when used in routine clinical practice in an Asian Pacific population.

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Introduction

The efficacy of drug-eluting stents (DES) over bare metal stents (BMS) has been demonstrated in large randomised clinical trials leading to their widespread use in clinical practice[1,2]. However, major concerns regarding the long-term safety of the first-generation DES include the increased risk of late stent thrombosis (LST), very late stent thrombosis (VLST)[3-6], and the need for prolonged dual anti-platelet therapy (DAPT) with its inherent risk of bleeding. Although the cause of LST/VLST is probably multifactorial, the durable polymer surface coating of DES may play a role. The durable polymer carrier can cause persistent inflammatory response which leads to poor healing due to delayed re-endothelialisation, positive remodelling with late acquired malapposition and the risk of LST/VLST[7-10]. Other concerns with durable polymer are the ongoing inflammatory response which may induce the "late catch-up" phenomenon[11,12] and an acceleration of neoatherosclerosis which may also trigger a subsequent risk of late device failure (stenosis and thrombosis)[13].

Second-generation DES are designed to improve the safety and efficacy profile of earlier-generation stents. One of these innovations has been the development of biodegradable polymer which is often abluminally coated. This ensures the polymer is applied in the minimum amount necessary for its function and is then removed over time, theoretically limiting the delay in arterial healing.

The BioMatrix™ drug-eluting coronary stent system (Biosensors Europe SA, Morges, Switzerland) comprises the active pharmaceutical ingredient Biolimus A9™ (BA9) (Biosensors) which is a proprietary, semi-synthetic analogue that is chemically related to both sirolimus and everolimus. It is highly lipophilic and rapidly absorbed in tissues. BA9 is encapsulated in the biodegradable polymer, polylactic acid (PLA), to bind the drug mechanically to the primer of the stent surface and also regulate drug release from the stent to the surrounding tissue. The coating mixture is applied solely to the abluminal surface of a flexible 316L stainless steel stent. The PLA coating was previously demonstrated in an *in vivo* study to convert fully to lactic acid after six to nine months; thereafter, the stent has a profile like a BMS.

The objective of this registry was to assess the clinical outcomes in patients receiving the BioMatrix biodegradable polymer DES during treatment of real-world, all-comer patients.

Methods

This was a prospective, multinational multicentre observational, patient data registry conducted in 12 centres in six Asia Pacific countries: Singapore (3), Thailand (1), Indonesia (2), Australia (2), New Zealand (1), and Malaysia (3).

The patient population consisted of men and non-pregnant women who were at least 18 years old, with a diagnosis of stable angina, unstable angina or silent ischaemia, including one or more *de novo* or restenotic lesions (>50%) in a native coronary artery or saphenous vein graft (SVG). Angiographic lesion requirements included a reference vessel diameter visually estimated to be ≥2.5 mm and ≤4.0 mm, while there was no limit to the lesion length

or the number of treated lesions or vessels. There was also no limit to disease/lesion morphology.

Patients were excluded when antiplatelet and/or anticoagulation therapy was contraindicated. Patients with known hypersensitivity to stainless steel, contrast agents, sirolimus or biolimus were excluded. Patients considered for non-registry DES implant during a procedure or having a lesion located in a protected/unprotected left main coronary artery were also excluded.

This study received approval from the local ethics committee at each site, as well as approval of an informed consent text specific to the registry.

ENDPOINTS AND FOLLOW-UP DEFINITION

The primary endpoint per protocol was the cumulative number and rate of major adverse cardiac events (MACE), defined as a composite of cardiac death, myocardial infarction (MI), and target lesion revascularisation (TLR) at 12 months post procedure. The definition of cardiac death included any death due to an immediate cardiac cause (e.g., myocardial infarction, low-output failure, fatal arrhythmia), procedure-related deaths including those related to concomitant treatment, unwitnessed death and death of unknown cause, where cardiac causes could not be excluded. Myocardial infarction was defined using the electrocardiographic criteria of the Minnesota Code or as an elevation of CK levels to more than two times normal with positive levels of CK MB or troponin I or T. TLR was defined as any repeat percutaneous coronary intervention of the target lesion or bypass surgery of the target vessel. These are clinically driven revascularisations in which the patient had a positive functional study, ischaemic ECG changes at rest in a distribution consistent with the target vessel, or ischaemic symptoms, and an in-lesion diameter stenosis >50% by quantitative coronary angiography (QCA). Revascularisation with an in-lesion diameter stenosis >70% (by QCA) in the absence of the above-mentioned ischaemic signs or symptoms was also considered clinically driven. In the absence of QCA data, the clinical need for revascularisation would be adjudicated using the presence or absence of ischaemic signs and symptoms. QCA assessment was not mandatory and up to the discretion of the investigator.

The secondary endpoints were: ischaemia-driven target lesion failure (TLF), a composite of cardiac death, target vessel MI (Q- and non-Q-wave) and ischaemia-driven TLR at 12 months; the rates of definite stent thrombosis up to five years according to the Academic Research Consortium (ARC) definition[14]; and MACE at 30 days, 90 days, six months, and two to five years annually.

Clinical follow-up visits were performed at one month, and telephone follow-ups at three months, six months, and one to five years annually. The Kaplan-Meier method was used to calculate time-to-event in the patient population. Data were captured using an Electronic Data Capture (EDC) system in compliance with the FDA requirement.

Event adjudication was performed by an independent clinical events committee (CEC) composed of cardiologists not involved in the study.

STATISTICAL ANALYSIS

There were no *a priori* statistical considerations for deriving the sample size of this registry. The primary analysis sample was based on the principle of intention-to-treat (ITT). All patients who met the registry entry criteria and signed the written informed consent were counted in the primary analysis. The enrolment period for each participating site was about six months.

Survival analyses were carried out using the time to the first event. Cumulative incidence rates were estimated using the Kaplan-Meier method. Kaplan-Meier estimates can be interpreted as the proportions of patients with a given clinical outcome. In the survival analyses, the number of patients with the event of interest was reported together with the number at risk. The number of patients at risk at time t is the number of patients who may experience the event of interest at t.

Results

BEACON II patients had a high prevalence of cardiovascular risk factors: 32.5% had diabetes, and 46.2% had a history of smoking, while 62.1% had hypertension, 74.4% had hypercholesterolaemia and 29% had a family history of coronary artery disease (CAD). A large percentage of patients (38.6%) had a history of myocardial infarction **(Table 1)**. The follow-up rate for each time point is specified accordingly: 98.6% at 30 days, 98.4% at three months, 97.8% at six months, 97.2% at one year, 97.6% at two years, 93.6% at three years, 94.2% at four years and 93.8% at five years.

In total, 742 lesions were treated. Sixty-three percent of the patients had one lesion treated, 27% two lesions, and 10% more than two lesions. ACC/AHA lesion classification was 10.1% type A, 32.3% type B1, 28.3% type B2, and 29.2% type C. Lesion

distribution among the three primary epicardial arteries was 46% left anterior descending (LAD), 31.3% right coronary artery (RCA), 21.6% left circumflex coronary artery (LCX), and 1.2% saphenous vein graft (SVG). Most lesions (94.5%) were *de novo* lesions; only 5.5% were restenotic lesions. Relatively small vessel diameter lesions, that is with a diameter smaller than 2.75 mm, accounted for 33.7% of the lesions. Other complex lesions included long lesions (>20 mm; 31.4%) and those with moderate to severe calcification (23.9%) **(Table 2)**.

Table 2. Lesion characteristics.

Parameter	Number of lesions (n=742)
Target lesion coronary artery, n (%)	701 (94.5)
Bifurcation lesion (side branch >2 mm), n (%)	101 (13.6)
with moderate/severe calcification, n (%)	32 (4.3)
Moderate/severe calcification, n (%)	177 (23.9)
Lesions >20 mm, n (%)	232 (31.4)
Reference vessel diameter <2.75 mm, n (%)	250 (33.7)
Total occlusion, n (%)	69 (9.3)
De novo lesions, n (%)	701 (94.5)
Restenotic lesions, n (%)	41 (5.5)

Device success, defined as achievement of less than 30% residual in-segment percent diameter stenosis and either TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure using the assigned device only, was achieved in 98.8% of patients. Lesion success, defined as achievement of less than 30% residual in-segment percent diameter stenosis and either TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, was achieved in 98.9% of patients. Procedure success, defined as achievement of less than 30% residual in-segment percent diameter stenosis and either TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure with the assigned stent and without the occurrence of death, MI or repeat revascularisation of the target vessel during the hospital stay, was achieved in 98% of patients **(Table 3)**.

Table 1. Patient demographics.

Parameter		Number of patients (n=497)
Male, n (%)		399 (80.3)
Age, mean±SD		59.8±10.75
Diabetes mellitus, n (%)		156 (32.5)
Hypertension, n (%)		306 (62.15)
Hypercholesterolaemia, n (%)		338 (74.45)
Smoking, n (%)		215 (46.25)
Family history of CAD, n (%)		126 (29)
Previous MI, n (%)		184 (38.65)
Previous PCI, n (%)		54 (27.55)
Previous CABG, n (%)		27 (5.55)
Current angina status	Asymptomatic, n (%)	78 (15.7)
	Stable angina, n (%)	268 (53.9)
	Unstable angina, n (%)	151 (30.4)
LVEF %, mean±SD		52.43±14.07
LVEF <30%, n (%)		18 (6.84)

Data are mean (SD) or number (%). CABG: coronary artery bypass graft; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention

Table 3. Procedure characteristics.

Parameter	Number of lesions (n=742)
Lesions per patient, mean±SD	1.49±0.74
Stents per patient, mean±SD	1.73±0.96
Stents per lesion, mean±SD	1.16±0.47
Lesion length (mm), mean±SD	18.7±9.7
Total stent length per lesion (mm), mean±SD	22.6±10.9
Stent length (mm), mean±SD	19.2±6
Glycoprotein IIb/IIIa inhibitor use, n (%)	81 (10.9)
Lesion success, n (%)	734 (98.9)
Device success, n (%)	733 (98.8)
Procedure success, n (%)	727 (98)

Outcomes for clinical events are reported using Kaplan-Meier estimates. The number of events are given in parentheses. Hierarchical MACE rates at one and five years were 4.3% (21) and 10.9% (52), respectively **(Figure 1)**. For five years the cumulative incidence of all death was 8.5% (41). The cumulative incidence of cardiac death was 4.4% (21), with about half of the total deaths occurring during the first year **(Figure 2)**. The cumulative incidence of MI at five years was 4.5% (21), of which 3.6% (17) and 1% (5) were non-Q-wave and Q-wave MI, respectively, with a Q-wave MI plateau at 1% **(Figure 3)**. The TLR rate at five-year follow-up was 3.8% (18). Most of the TLR occurred during the first two years, with a tendency to plateau after two years. Interestingly, for TVR and non-TLR TVR, the rates increased linearly **(Figure 4)**. Target lesion failure (TLF), defined as a composite of cardiac death that could not be clearly attributed to a non-target vessel, target vessel MI or TLR, had a cumulative incidence of 8.2% (39) at five-year follow-up **(Figure 5)**. The five-year definite stent thrombosis (ST) cumulative incidence was only 1.2% (6). Most of the ST occurred during the first year (0.8%), and after two years it plateaued at 0.4% **(Figure 6)**.
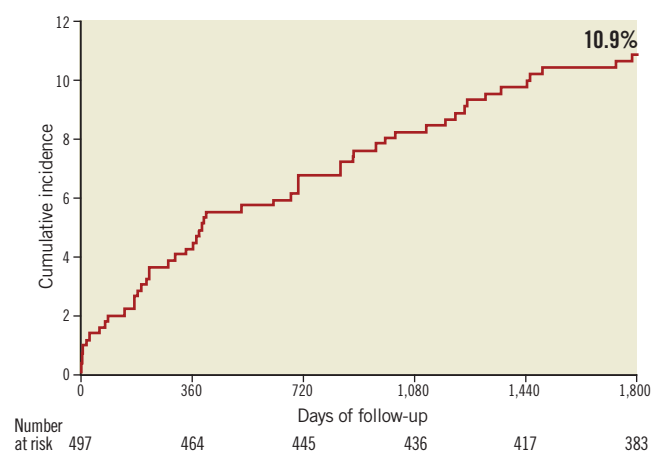

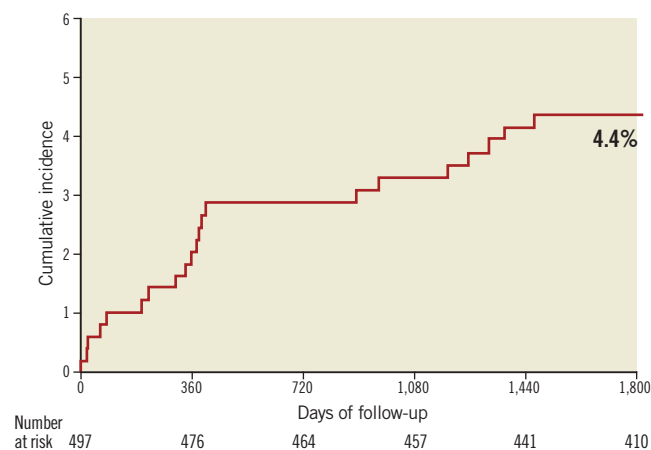**Figure 1.** *Hierarchical MACE. Cumulative incidence rate at 5 years.*

Figure 2. *Cardiac death. Cumulative incidence rate at 5 years.*
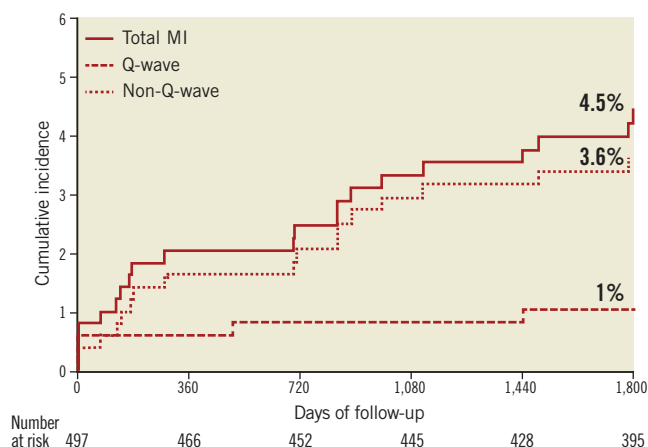

Figure 3. *Myocardial infarction, stratified by Q-wave and non-Q-wave MI. Cumulative incidence rate at 5 years. MI: myocardial infarction*
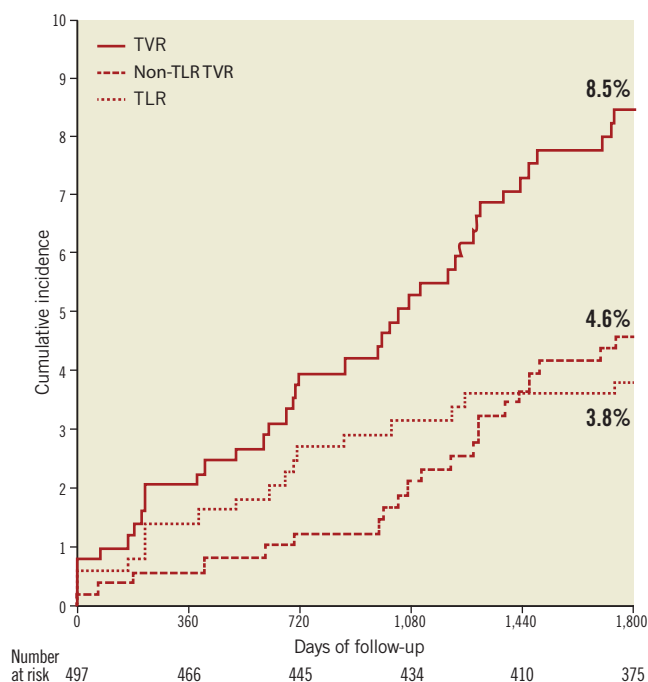

Figure 4. *Revascularisation stratified by TVR, TLR only and non-TLR TVR only. Cumulative incidence rate at 5 years. TVR: target vessel revascularisation*

Discussion

The final five-year follow-up results of the LEADERS trial using a similar Biolimus A9-eluting stent have been published[15-19]. The results showed that a biodegradable polymer-based Biolimus A9-eluting stent (BES) was non-inferior to a durable polymer sirolimus-eluting stent (SES). Compared with a durable polymer SES, the biodegradable polymer-based BES was linked to a significant reduction in very late (>1 year) ST and associated composite clinical endpoints. The safety benefit of the biodegradable polymer-based BES appeared to occur in more complex CAD and was secondary to a reduction in MI and repeat revascularisation.
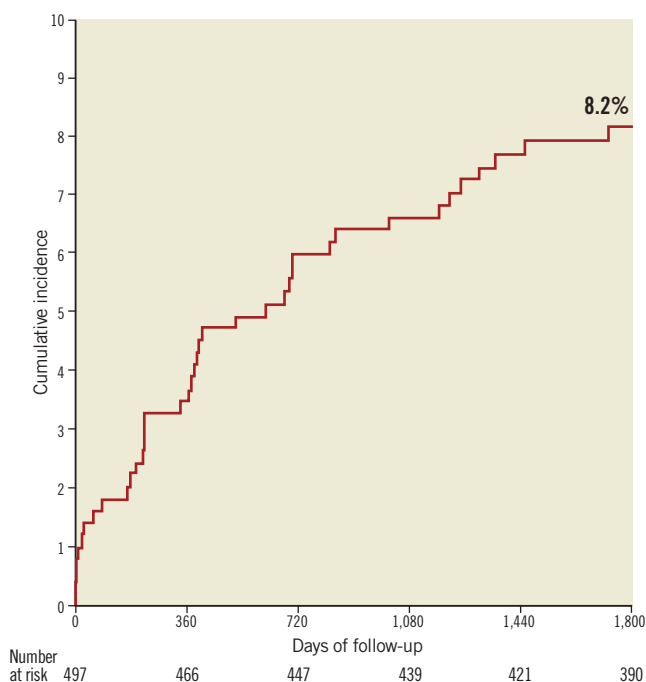
Figure 5. *Target lesion failure. Cumulative incidence rate at 5 years.*
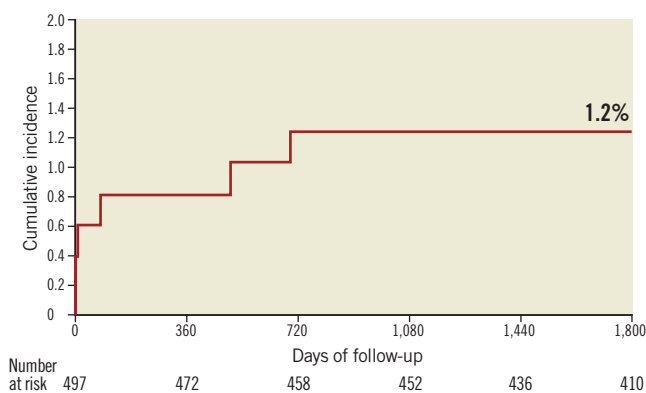

Figure 6. *Definite ST. Cumulative incidence rate at 5 years. ST: stent thrombosis*

Patient demographics and characteristics differed across LEADERS and BEACON II. Asian patients undergoing percutaneous coronary intervention (PCI) were usually much younger with a high prevalence of CV risk factors[20]. BEACON II patients, as compared to LEADERS patients, were younger (59.8 vs. 64.6), had a higher prevalence of diabetes (32.5% vs. 26.0%) and hypercholesterolaemia (74.4% vs. 65.3%) and a higher rate of multivessel disease (58.1% vs. 24.4%). In LEADERS[15], the MACE rate at nine months was 9.1%, while in BEACON II the rate at one year was 4.9%.

Patient compliance with DAPT and follow-up rates were similar at five years. Follow-up was available in 96% of patients in the BES arm of the LEADERS trial and in 94% of patients

in BEACON II at five years. The final five-year report of the LEADERS trial[19] demonstrated that there was a significant interaction between treatment effect and time (zero to one year, and one to five years, p-value for interaction=0.022). Specifically, there was a significantly lower risk of definite ST for the biodegradable polymer BES compared with the durable polymer SES, from years one to five (RR: 0.26 [95% CI: 0.10 to 0.68]; p=0.003), whereas, at year zero to one year, the incidence of definite ST was similar between the two groups. Similar findings were noted in BEACON II for ST: there was a significant interaction between treatment effect and time (zero to one year, and one to five years, p-value for interaction=0.043). The Kaplan-Meier cumulative incidence percentage at zero to one year, and from one to five years was 0.8% and 0.4%, respectively.

A favourable advantage of the biodegradable polymer BES stent seems to occur after one year, in particular the rare incidence of VLST. Both LEADERS and BEACON II showed similar low very late event rates for BES, in particular very late definite stent thrombosis from one to five years.

Another biodegradable polymer BES is the Nobori® (Terumo Corporation, Tokyo, Japan). The only difference between the BioMatrix and the Nobori stent is the slight modification in stent design, the delivery catheter and the coating method. The use of the Nobori stent results in better endothelial recovery, with normal coronary vasodilatation in the adjacent stent segment after implantation, contrasting with the paradoxical vasoconstriction seen with first-generation DES[21]. A recently pooled analysis based on individual patient data from the ISAR-TEST 3, ISAR-TEST 4 and LEADERS trials[22] showed that biodegradable DES (BioMatrix Flex™, n=857; and biodegradable polymer SES, n=1,501) improved safety and efficacy compared with durable polymer SES during long-term follow-up to four years. In this meta-analysis, the efficacy endpoint of interest was TLR and the safety endpoint of interest was definite ST. At four years, the risk of TLR was significantly lower with biodegradable polymer DES vs. durable polymer SES (hazard ratio [HR] 0.82, 95% CI: 0.68-0.98, p=0.0029). In addition, the risk of ST was also significantly reduced with biodegradable polymer DES vs. durable polymer SES (HR 0.56, 95% CI: 0.35-0.90, p=0.015), driven by a lower risk of VLST (HR 0.22, 95% CI: 0.08-0.61, p=0.004). The incidence of MI between one and four years was lower with biodegradable polymer DES vs. durable polymer SES (HR 0.59, 95% CI: 0.73-0.95, p=0.031). In the COMPARE II and NEXT trials, biodegradable polymer BES have been shown to be as safe and efficacious as the current standard of a thin-strut everolimus-eluting stent with a durable biocompatible polymer at one-year follow-up[23,24]. Longer-term follow-up will show whether the beneficial effect of the biodegradable polymer BES on late stent thrombosis also applies when compared to newer-generation DES.

The concept of polymer-free stents and bioresorbable vascular scaffolds looks very interesting. Preclinical studies support their use, but robust clinical data are still lacking. Until then, biodegradable polymer BES/DES will have a major role to play in our daily PCI practice.

Limitations

Several limitations should be underlined. First of all, this is a single-group, non-randomised design, which has some degree of selection bias. Data analysis is hence descriptive in nature and inferior to a randomised trial as no direct comparison can be made versus a control group. Secondly, the results reported here may have been affected by the type of bias inherent in all registries, namely the selective inclusion of lower-risk patients, together with less exhaustive monitoring than that applied in randomised controlled trials, potentially contributing to an overall under-reporting of events. Additionally, the SYNTAX score was not common practice at all study sites at the time of the study and was not calculated for all patients as part of the screening process. Patients with left main disease were excluded during the enrolment period in 2008 as the choice of treatment then was CABG. This was before the ACCF/AHA/SCAI guidelines for left main PCI were established in 2011. Last but not least, our sample size was small and was not calculated to determine predictive factors for MACE, revascularisation and stent thrombosis outcome.

Conclusions

The BEACON II registry confirms the findings of the LEADERS trial and other trials involving biodegradable polymer BES. Indeed, the BioMatrix stent has a good safety profile up to five years when used in routine clinical practice in an Asian Pacific population. There appears to be a significant interaction between treatment effect and time zero to one year and from one to five years. After one year, the rate of definite ST (VLST) was very low and was maintained up to five years.

Impact on daily practice

In daily clinical practice we often encounter complex lesions and Asian patients in particular have a high prevalence of diabetes mellitus. The findings from the BEACON II registry, which indicate a good safety profile in the BioMatrix drug-eluting stent, at least up to five years, give us great reassurance in using this stent in our routine clinical practice.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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