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Clinical outcomes with 6 months dual antiplatelet therapy after implantation of Biolimus-A9 drug eluting coronary stents ☆

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ABSTRACT

Introduction: Duration of dual antiplatelet therapy (DAPT) following drug eluting stent (DES) implantation remains poorly defined. Endothelialisation of biodegradable polymer biolimus-eluting stents occurs early, and 6 months DAPT may be adequate.
Aims: We evaluated long term outcome in patients treated with biolimus-eluting stents who were treated with 6 months DAPT. Endpoints included cardiac death and non-fatal stent thrombosis occurring 6 to 12 months after stent implantation.
Methods: 692 patients (77.2% male), aged 65.6 ± 12.5 years received biolimus-eluting DES (March 2008 – November 2011). Vital status was tracked through the Medical Research Information Service. Episodes of non-fatal stent thrombosis, (Academic Research Consortium definition) between months 6 and 12 were tracked via systematic database searches (5 PCI centres).
Results: Presentations included acute coronary syndrome (47.2%) and stable coronary disease (52.8%). Vessels treated included left main stem (6.8%), left anterior descending (37.4%), circumflex (19.1%), right coronary artery (34.5%) and saphenous vein graft (2.1%) respectively. High-risk subsets included diabetes (15.6%); AHA type C lesions (35.1%) and chronic total occlusions (12.8%). During median follow-up of 700 days (0 to 1392) there were 42 deaths (6.1%); 4.2% at 0–6 months, 1.0% at 6–12 months and 0.9% at >12 months. Of the 7 deaths between 6 and 12 months, one death was adjudicated as possible stent thrombosis. There were no cases of non-fatal known stent thrombosis. All cause mortality accrued with smooth decremental incidence. Statistical examination showed no evidence of event clustering between 6 and 12 months.
Conclusions: After implantation of biodegradable polymer biolimus-eluting coronary stents, 6 months DAPT appears to be adequate, safe and effective.

1. Introduction

Significant controversy remains with regard to appropriate duration of dual anti-platelet therapy (DAPT) after implantation of drug eluting stents (DES). Although guidelines advise use of DAPT for ≥12 months [1–4], this recommendation is not based on prospective randomised trial evidence associating extended duration of DAPT with a reduction in adverse events or late stent thrombosis (ST). The recommendation reflects concerns about stent thrombosis using first generation drug eluting stents [5], and observational trials and studies involving bare metal stents (BMS) [6–10] There is now emerging evidence that shorter duration (6 months) DAPT may be non-inferior to extended treatment (12 months), with regard to incidence of death and myocardial infarction (MI) [11–13].

Furthermore, studies of second and third generation DES using optical coherence tomography (OCT), demonstrate that complete endothelialisation and neo-intimal coverage occurs as early at 3 to 6 months, suggesting that there may be no need for extended DAPT [14,15].

The BioMatrix (Biosensors Inc., Newport Beach, California) stent is a third generation DES. It consists of stainless steel stent struts, and an abluminal biodegradable polymer infused with biolimus. The LEADERS trial compared this novel DES system with the sirolimus-eluting durable polymer Cypher stent in a large randomised all-comers controlled trial, where patients were treated with 12 months DAPT [16]. The BioMatrix stent was found to be non inferior to the sirolimus-eluting Cypher stent with regard to death, myocardial infarction (MI) and target vessel revascularisation (TVR) at 9 months, and out to 4 years [17].

☆ Conflicts of interest: DHS - Advisory Boards and Consultancy for BioSensors and Terumo, RG - Advisory Boards and Consultancy for Medtronic, Sanofi-Aventis, AstraZeneca.

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Similarly, the Nobori (Terumo, Tokyo, Japan) stent consists of a different stainless steel stent strut matrix but with the same abluminal biodegradable polymer infused with biolimus. The NOBORI II trial assessed the safety and efficacy of this platform in a large all comer registry ($n \geq 1000$), with a primary endpoint of target lesion failure, a composite of cardiac death, q and non-q wave MI and clinically driven TVR. At 12 months cardiac death occurred in 1.2%, MI in 2.2% and TVR in 2.2% respectively. Stent thrombosis rates were 0.7% [18].

The aim of this study was to report outcomes out to a maximum of 3 years for a large all-comer population ($n = 692$), with varied patterns of coronary disease, treated with both BioMatrix and Nobori stents where the length of DAPT was limited to 6 months, and to examine specifically adverse events between 6 months and 12 months, to see if there was a detectable spike in events between 6 and 12 months when DAPT had been discontinued and patients were maintained on long term antiplatelet mono-therapy.

2. Methods

2.1. Study design and patient population

We undertook a retrospective review of all PCI cases undertaken at the Sussex Cardiac Centre from March 2008 to November 2011, following introduction of the BioMatrix and the Nobori stent platforms to the department. Data regarding procedural details are prospectively entered by the operator at the end of each case, and are updated by an independent audit officer at the end of the hospital admission. Cases of cardiogenic shock were excluded from this analysis; all other cases were included. All patients were routinely prescribed 6 months DAPT, with additional written confirmation to the general practitioner in all cases.

2.2. Procedures

Patients were pretreated with clopidogrel 600 mg and aspirin 300 mg as required, depending on prior chronic antiplatelet use. Patients were treated with balloon angioplasty and stent implantation as per standard techniques. There was no mixing of DES type during the index procedure, but a proportion of patients had previous non-biolimus stent implants. Intravenous heparin 70 iu/kg was given and the activated clotting time was maintained at >250 s. Glycoprotein IIb/IIIa inhibitors or bivalirudin were used according to operator discretion.

After coronary stenting, patients were treated with six months DAPT followed by continuation of a single antiplatelet agent (usually aspirin). This regime was maintained irrespective of the location of the lesion (e.g. left main stem) or the length of stent implantation (e.g. chronic total occlusions). Patients who were also taking anticoagulant medication had individually-tailored antiplatelet treatment, depending on the absolute indication for anticoagulation, but similarly had DAPT for ≤6 months.

2.3. Endpoint definitions

2.3.1. All cause mortality

This was defined as death due to immediate cardiac aetiology (MI, fatal arrhythmia) related to the procedure or following the procedure, death related to any concomitant treatment, un-witnessed death and death of unknown cause. This definition has been widely used within the literature [16].

2.3.2. Stent thrombosis

Stent thrombosis (ST) was defined according to the Academic Research Consortium (ARC) definitions [19].

2.4. Data collection

All PCI cases are entered into the Sussex Cardiac Centre Patient Analysis & Tracking System (PATS, Dendrite). This is a bespoke and dedicated database filled in by the operator at the time of the index procedure, and cross-checked and updated by an independent audit officer at the end of the hospital admission. Follow up information relating to mortality was obtained via the Medical Research Information Service (MRIS).

Data consistency is assured by internal audit undertaken by an independent data officer within the hospital. Morbidity and mortality meetings additionally track adverse events. All data is cross-checked prior to uploading to the UK Central Cardiac Audit Database (CCAD).

Specific attention was paid to events occurring between 6 months and 12 months, including death and ARC defined non fatal stent thromboses. Non-fatal stent thrombosis was identified by cross checking the patient cohort for any re-interventions against the regional databases, made up of all five PCI centres in Sussex.

Table 1
Patient demographics.

Variable	$n = 692$%
Mean age (±SD)	65.6 ± 12.4
Male	77.8 (668)
Ethnicity	
Caucasian	79.8 (667)
Non-Caucasian	20.1 (667)
Diabetes	15.6 (653)
Hypercholesterolemia	72.5 (612)
Hypertension	62.2 (612)
Family history of CAD	37.9 (572)
Obesity	16.6 (613)
Peripheral vascular disease (PVD)	5.2 (610)
Cerebrovascular disease (CVD)	2.9 (612)
Valvular heart disease (VHD)	4.4 (612)
Previous myocardial infarction (MI)	31.0 (600)
Previous coronary artery bypass grafting (CABG)	9.3 (667)
Previous percutaneous intervention (PCI)	29.1 (666)
Smoking status	
Never smoked	29.2 (565)
Former smoker	54.2 (565)
Current smoker	16.6 (565)
Ejection fraction	
Good	84.5 (667)
Moderate	12.0 (667)
Poor	3.4 (667)
Renal disease	
Normal renal function	95.8 (640)
Functioning transplant	0.2 (640)
Creatinine >200	2.3 (640)
Longterm dialysis	1.7 (640)

2.5. Statistics

Data for continuous variables were expressed as mean ± SD. Survival curves were calculated using the Kaplan–Meier method and Cox proportional hazard modelling. A plot of the hazard rate, used to calculate the rate of death, against time was produced to examine the possibility of any "spike" in events following the cessation of DAPT at 6 months.

Further pre-specified analyses were undertaken to look for any spike in events during the 6–12 month period under investigation. This included locally weighted scatterplot smoothing using a Lowess smoother, and Weibull modeling respectively. Analyses were done on an intention-to-treat basis using Stata 10.1 software. A p value of <0.05 was considered significant.

2.6. Results

Between March 2008 and November 2011, 692 patients aged 65.6 ± 12.4 years underwent PCI using biolimus-eluting DES (BioMatrix, BioSensors $n = 638$, Nobori, Terumo $n = 54$). Patient demographics and procedural data are shown in Tables 1 and 2, respectively.

Median follow-up was for 700 days, (range 0 to 1392).

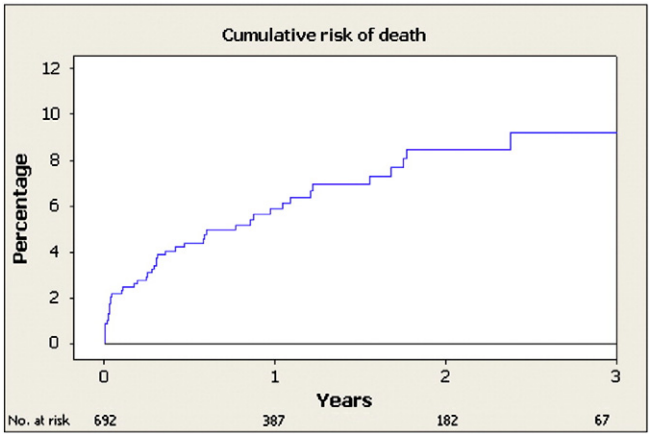

Fig. 1. Freedom from primary endpoint (all cause mortality).