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Research article

Effectiveness and Safety of Polymer-free Biolimus-eluting Stents (PF-BES): a 1-year Single-center Study

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Abstract

Background: An estimated one-fifth of patients undergoing percutaneous coronary intervention are at high bleeding risk (HBR), which has a high mortality rate. Most of these HBR patients are excluded from stent trials. In response, many studies have used polymer-free Biolimus-eluting stents (PF-BESs), mainly for HBR patients. However, there is a lack of data on the clinical outcomes of the effectiveness and safety of PF-BESs in Thailand. **Objectives:** To evaluate the effectiveness and safety profile of PF-BES in real-world, all-comer patients with coronary artery disease undergoing percutaneous coronary intervention at the Central Chest Institute of Thailand. **Methods:** An observational, retrospective (chart review), single-arm study was conducted. All consecutive patients who were implanted with a PF-BES at the Central Chest Institute of Thailand were included in the analysis. **Results:** A total of 208 patients were enrolled. Half of these patients (54.3%) had an HBR according to the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria. Within 1 year following the indexing procedure, the primary endpoint (a composite of cardiac death, target-vessel myocardial infarction, and clinically driven target lesion revascularization) was reached by 3.8% of the patients. Notably, there was no occurrence of stent thrombosis. Bleeding per the Bleeding Academic Research Consortium 5 definition was not seen for any patient. **Conclusion:** The PF-BES is safe and effective for real-world patients, irrespective of HBR status.

Keywords: Polymer-free Biolimus-eluting stents, High bleeding risk, Dual antiplatelet therapy

Introduction

An estimated one-fifth of patients undergoing percutaneous coronary intervention (PCI) are at high bleeding risk (HBR) with associated mortality hazards (1,2). Most of these HBR patients are excluded from many stent trials. In the past, bare-metal stent (BMS) implantation followed by 1 month of dual antiplatelet therapy (DAPT) was adopted to minimize the bleeding risk; however, this regimen is associated with a higher risk of restenosis and reintervention than the use of a drug-eluting stent (DES) (3,4). The standard management supported by current guidelines (5–8) favors using a second-generation DES with a shortened course of DAPT.

A polymer-free Biolimus-eluting stent (PF-BES), namely the BioFreedom stent (Biosensors Europe), has been developed to transfer Biolimus A9, a highly lipophilic sirolimus agent, into the vessel wall over a period of 1 month. In a prior study, the use of a Biolimus-eluting stent resulted in less neointimal proliferation and inflammation at 180 days than did the use of a sirolimus-eluting stent (9). Furthermore, in a first-in-human evaluation, the Biolimus-eluting stent was non-inferior to a paclitaxel-eluting stent in terms of in-stent late lumen loss at 12 months (10).

The results of the Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle BMS in Patients at HBR (LEADERS FREE) trial showed that the PF-BES was superior to a BMS in terms of the primary safety and efficacy endpoints when used with a 1-month course of DAPT (11). The results were maintained for 2 years (12). In addition, the Randomized Trial Comparing a Polymer-Free Coronary DES with an Ultra-Thin Strut Bioresorbable Polymer-Based DES in an All-Comers Patient Population (13) found that PF-BES was not non-inferior to an ultra-thin strut bioresorbable polymer-based drug-eluting stent.

In Thailand, there are no available safety or effectiveness data for PF-BESs implanted in HBR patients (13–16). The present study evaluated the effectiveness and safety profile of PF-BESs for real-world, all-comer patients with coronary artery disease (CAD) undergoing PCI at the Central Chest Institute of Thailand (CCIT).

Methods

Objectives

The purpose of this study was to evaluate the effectiveness and safety profile of the PF-BES in real-world, all-comer patients with CAD undergoing PCI at the CCIT.

Study Design and Patient Selection

This research was an observational, retrospective (chart review), single-arm study. The study protocol was approved by the Human Research Ethics Committee of the CCIT. All consecutive patients who underwent PCI and were implanted with a PF-BES at the CCIT from August 2015 to July 2020 were included in the study.

To assess the safety and effectiveness of the PF-BES in patients, the clinical composite endpoint of cardiac death, target-vessel myocardial infarction (TVMI), and clinically driven target lesion revascularization (CD-TLR) within 1 year of the indexing procedure was used. Secondary outcomes included stent thrombosis per Academic Research Consortium (ARC) definitions, heart failure requiring admission, stroke, bleeding per Bleeding Academic Research Consortium (BARC) definitions, and the incidence of the clinical composite endpoint from the indexing procedure to 12 months (all deaths and any coronary revascularization).

Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m2 for more than 3 months. Data collected included baseline characteristics, duration of medication, indications of PCI, lesion features, and procedural characteristics.

Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD) or median (interquartile range), whereas categorical variables were reported as n (%). Clinical follow-up was censored at the date of death or the latest available follow-up date. Data for patients who were lost to follow-up were censored at the time of last contact. Adverse events were reported as the observed number of events and Kaplan–Meier estimated rates. Statistical analyses were performed using STATA/IC version 14.0 (StataCorp, College Station, TX, USA).

Results

From August 2015 to July 2020, 208 patients (267 lesions) received 327 PF-BESs. Most patients in this study were male (66.3%), and the patient age was 70.4 ± 12.8 years. Risk factors of CAD included dyslipidemia (93.3%), hypertension (84.1%), and diabetes mellitus (41.8%). The group CRUSADE score was 36.1 ± 14.9, with 63 of the 208 patients (30.3%) having a CRUSADE score exceeding 40 points and thus being categorized as at a high risk of bleeding. Interestingly, 113 patients (54.3%) were at a high risk of bleeding according to ARC-HBR criteria (Table 1). According to the ARC-HBR criteria, this study's high proportion of bleeding risk factors included age greater than 75 years, anemia, and chronic kidney disease (Figure 1).

All patients were prescribed aspirin, with clopidogrel being the most commonly prescribed concomitant P2Y12 inhibitor (79.8%). DAPT was prescribed for 88.5% of patients at discharge and 69.2% at 1-year follow-up (Figure 2), whereas triple therapy was used for 11.5% at discharge and 7.2% at 1-year follow-up. In our study, the mean DAPT duration was 365.5 ± 87.3 days (Table 2).

The indication for PCI was chronic coronary syndrome in 59.6% of the patients. The left anterior descending artery (40.1%) was the most frequently treated target vessel (Table 3). The Synergy between PCI with Taxus and Coronary Artery Bypass Surgery (SYNTAX) score was 28.1 ± 14.7 (Table 1). PF-BESs were used at rates of 21.4% for ostial lesions, 21.0% for bifurcation lesions, and 38.7% for calcified lesions. According to the ACC/AHA lesion classification system, most lesions were classified as type B (90.6%). Half of them, 135 lesions (50.6%), were longer than 20 mm, with a lesion length of 26.5 ± 14.4 mm. The use of the fractional flow reserve was only 3.0%, and rotablation was adopted for 4.1% of patients (Table 3).

The primary endpoint was a composite of cardiac death, TVMI, and CD-TLR within 12 months of the indexing procedure and was reached by 3.8% of the patients (Figure 3). The secondary endpoints of death from any cause, myocardial infarction (MI), and ischemic stroke were respectively reached by 0.9%, 3.6%, and 1.5% of the patients at 1 year. Notably, there was no occurrence of stent thrombosis in our study. Only 4.4% of patients who presented with heart failure required admission. For the bleeding endpoints, no patient presented with BARC 5 bleeding (Table 4).

Discussion

The PF-BES was designed to eliminate the inflammatory pro-thrombotic trigger of polymer coatings (17). Porcine models showed less neointimal proliferation and inflammation at 180 days with PF-BESs

than with sirolimus-eluting stents (9,18). In the LEADERS FREE trial (2), 2466 patients with HBR were randomized to PF-BES or BMS groups, each with 1-month DAPT. In that trial, the PF-BES outperformed the BMS in terms of both primary efficacy (CD-TLR) and safety (cardiac death, MI, and definite/probable stent thrombosis) endpoints.

In Thailand, there has been no real-world investigation of PF-BESs. The present study was the first to examine the use of PF-BESs in real-world, all-comer patients. Compared with the LEADERS FREE trial, our study group had comparable gender and age proportions, a higher proportion of diabetes mellitus (41% vs. 34%), and a comparable proportion of HBR patients according to the CRUSADE score (36.1 ± 14.9 vs. 34.1 ± 0.4). Half of our patients (54.3%) were HBR patients as per ARC-HBR criteria.

In terms of device effectiveness, for the real-world use of PF-BESs, our study showed less unfavorable outcomes, such as cardiac death, MI, TVMI, and clinically driven TLR, compared with the LEADERS FREE trial (1.4% vs. 4.2%, 3.6% vs. 6.1%, 0% vs. 5.7%, and 2.4% vs. 5.1%, respectively) (2). An interesting result of our study was that there was no occurrence of stent thrombosis during the 1-year follow-up.

Another interesting point was that our study had a long DAPT duration of 365.5 ± 87.3 days. This result is attributed to the following. (1) Our study was a retrospective review and not a dedicated HBR trial with a mandated 1-month DAPT regimen. (2) Forty percent of patients in our study had acute coronary syndrome, and guidelines recommended a DAPT regimen 12 months for this group of patients. (3) Approximately 9.4% of the patients in our study received non-PF-BES stents (34 stents), and these stents have not been evaluated for a 1-month DAPT regimen. (4) Most of our patients were under universal health coverage (the 30 Baht scheme), and there was little economic impetus for physicians to shorten the duration of DAPT in stable patients with no bleeding event.

In HBR patients, a 1-month DAPT regime following the implantation of PF-BESs has been shown to reduce the risk of re-intervention, MI, and stent thrombosis compared with the implantation of a BMS without DAPT (2,19). In addition, favorable results of the implantation of PF-BESs in non-HBR patients have been reported, such as in the RUDI-FREE study (20). Furthermore, positive results of a short DAPT regimen following the implantation of DES were reported for the Onyx ONE study (5) and the XIENCE Short DAPT Clinical Program: XIENCE 90/28 (21). Current European guidelines (19,22–24) recommend a new-generation DES with a 3- or 1-month course of DAPT for HBR patients. The guidelines also state that a 1-month DAPT may be considered for chronic coronary syndrome with HBR (Class of recommendation IIb, Level of evidence C).

Regarding the safety of the short duration of DAPT in HBR patients, there were only three patients in our study who participated in a 1-month DAPT regimen like the patients in the LEADERS FREE trial. Two of these patients had atrial fibrillation and needed long-term anticoagulants, whereas one of the patients had anemia and was planned for surgery owing to suspected colon cancer. Our study showed minor bleeding per BARC definitions in contrast with the more major bleeding in the LEADERS FREE trial, without bleeding mortality, despite a longer DAPT regimen (of approximately 1 year).

The present study was limited in that it was an observational, retrospective study with a limited number of patients receiving 1-month DAPT as in the LEADERS

FREE study. However, the mean age and prevalence of diabetes mellitus, chronic kidney disease, and acute coronary syndrome were comparable to those in other DES studies.

The real-world effectiveness of the PF-BES was demonstrated in this study in terms of less incidence of unfavorable outcomes, such as cardiac death, MI, TVMI, and clinically driven TLR, and there was no stent thrombosis during a year-long period. The safety of the PF-BES was shown in this study in that there was only minor bleeding per BARC definitions compared more major bleeding in the LEADERS FREE trial. We expect that our real-world data on the effectiveness and safety of the PF-BES will encourage interventional cardiologists to use the PF-BES in HBR patients with more confidence.

Conclusion

The PF-BES is safe and effective for real-world patients irrespective of HBR status.

Conflict of interest

The authors declare that there is no conflict of interest.

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Table 1. Baseline characteristics

Characteristic	n (%) (*n* = 208)
Age (years)	70.4 ± 12.8
Female	70 (33.7)
BMI	24.4 ± 4.2
Hypertension	175 (84.1)
Diabetes mellitus	87 (41.8)
Dyslipidemia	194 (93.3)
Chronic obstructive pulmonary disease	22 (10.6)
Current smoker	28 (13.5)
Current drinker of alcohol	23 (11.1)
Family history of coronary artery disease	29 (13.9)
History of heart failure	38 (18.3)
Atrial fibrillation	24 (11.5)
SYNTAX score	28.1±14.7
CRUSADE score	36.1±14.9
HAS-BLED score	1.9 ± 1.0
ARC-HBR criteria	113 (54.3)

ARC-HBR criteria: Academic Research Consortium-High Bleeding Risk criteria; BMI: body mass index; SYNTAX score: Synergy between percutaneous coronary intervention with Taxus and Coronary Artery Bypass Surgery score

Table 2. Antithrombotic therapy

Antithrombotic therapy	*n* = 208 (%)
Antithrombotic treatment at discharge	
DAPT	184 (88.5)
Triple therapy	24 (11.5)
Antithrombotic treatment at 1 year	
No antithrombotic treatment	6 (2.9)
SAPT	37 (17.8)
DAPT	144 (69.2)
Dual therapy	6 (2.9)
Triple therapy	15 (7.2)
ASA duration, mean ± SD	385.0 ± 61.5
DAPT duration, mean ± SD	2365.5 ± 87.3

ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy; SAPT: single antiplatelet therapy

Table 3. Lesions and procedural characteristics

Lesion and procedural characteristic	*n = 267 (%)*
Indication of PCI	
Chronic coronary syndrome	159 (59.6)
STEMI	66 (24.7)
NSTEMI	39 (14.6)
Unstable angina	2 (0.7)
Staged PCI	1 (0.4)
Extent of coronary vessel disease	
SVD	40 (15.0)
DVD	74 (27.7)
TVD	115 (4.1)
LM with SVD	1 (0.4)
LM with DVD	9 (3.4)
LM with TVD	27 (10.1)
SVG	1 (0.4)
Target vessel at segment:	
RCA	104 (39.0)
LM	11 (4.1)
LAD	107 (40.1)
LCx	45 (16.8)
Lesion features:	
Lesions per patient	1.3
Ostial lesions	57 (21.4)
Bifurcations	56 (21.0)
Tortuous lesions	10 (3.8)
Calcifications	103 (38.7)
Chronic total occlusions	19 (7.1)
Characteristics of ACC/AHA type	
Type A	10 (3.8)
Type B	242 (90.6)
Type C	15 (5.6)
Lesion length (mm)	26.5±14.4
Procedural features	
Stent length (mm)	25.1 ± 7.8
Direct stenting	7 (2.6)
FFR used	8 (3.0)
Rotablation use	11 (4.1)
Post-dilatation	140 (52.4)

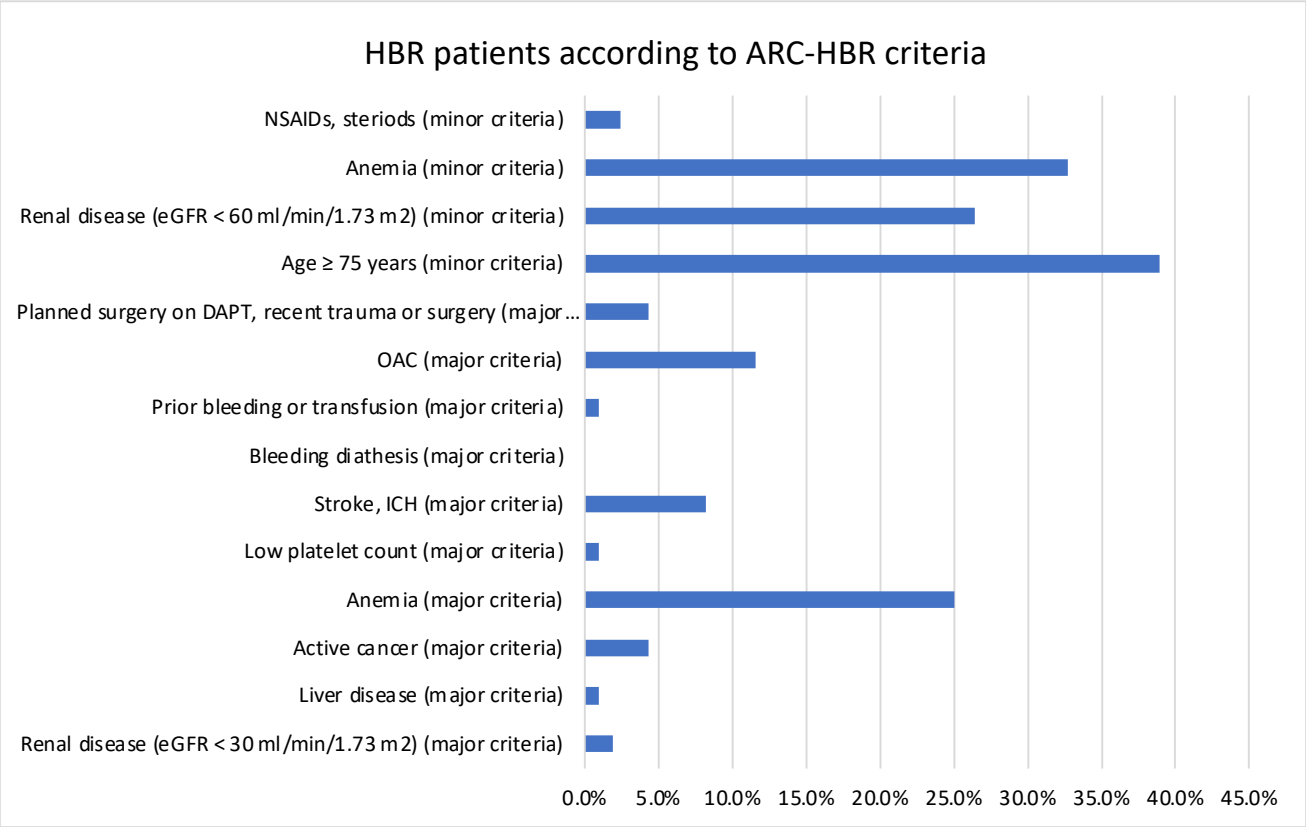
DVD: double vessel disease; FFR: fractional flow reserve; LAD: left anterior descending artery; LCx: left circumflex artery; LM: left main; NC: non-compliant; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; RCA: right coronary artery; STEMI: ST-elevation myocardial infarction; SVD: single vessel disease; SVG: saphenous vein graft; TVD: triple vessel disease

Table 4. Incidence of the clinical composite endpoint

Incidence of the clinical composite endpoint	*n* (%)	95% CI
Cardiac death	3 (1.4)	0.3-4.2
Death from any cause	2 (0.9)	0.1-3.5
Myocardial infarction	8 (3.6)	1.7-7.5
Target-vessel myocardial infarction	0 (0)	-
Clinically driven TLR within 12 months from the indexing procedure	5 (2.4)	0.8-5.6
Ischemic stroke	3 (1.5)	0.3-4.2
Hemorrhagic stroke	0 (0)	-
Heart failure required admission	9 (4.4)	2.0-8.1 3
Bleeding per BARC definitions type 1	3 (1.5)	0.3-4.2
Bleeding per BARC definitions type 2	1 (0.5)	0.1-2.7
Bleeding per BARC definitions type 3	5 (2.4)	0.8-5.6
Bleeding per BARC definitions type 4	0 (0)	-
Bleeding per BARC definitions type 5	0 (0)	-
Stent thrombosis	0 (0)	-

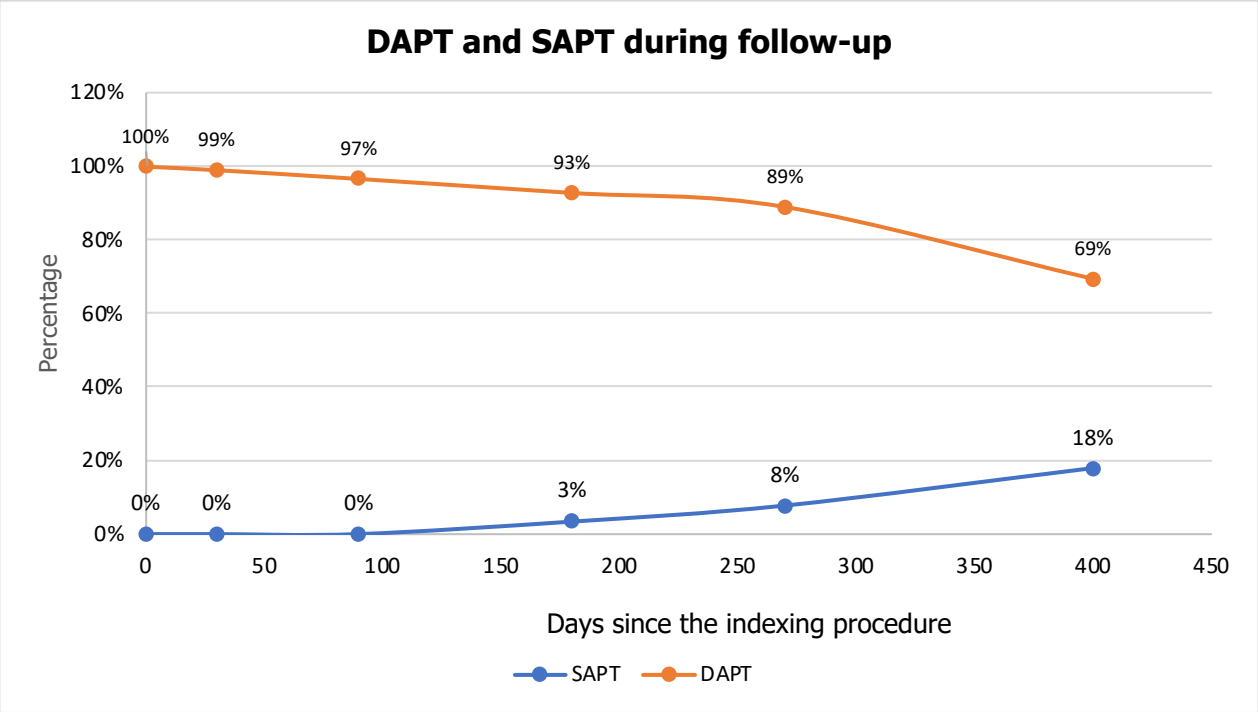
BARC: Bleeding Academic Research Consortium; TLR: target lesion revascularization

Figure 1. High-bleeding-risk patients according to Academic Research Consortium-High Bleeding Risk criteria



DAPT: dual antiplatelet therapy; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; HBR: high bleeding risk; ICH: intracranial hemorrhage; NSAIDs: non-steroidal anti-inflammatory drugs; OAC: oral anticoagulant

Figure 2. Dual antiplatelet therapy and single antiplatelet therapy during follow-up



DAPT: dual antiplatelet therapy; SAPT: single antiplatelet therapy

Figure 3. Cumulative incidence of the primary endpoint (cardiac death, target vessel myocardial infarction, and clinically driven target lesion revascularization within 12 months of the indexing procedure)