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12-Month clinical outcomes of amphilimus drug eluting stents in an all-comers South-East Asian registry

Hee Hwa Ho [a,*,1], Dasdo Antonius Sinaga [b], Mohd Kamal Mohd Arshad [c], Sazzli Kasim [c], Jin Hyun Lee [a], Deanna Zhi Lin Khoo [a], Kwok Kong Loh [a], Fahim Haider Jafary [a], Paul Jau Lueng Ong [a], Simon Soo Siong Lo [d]

[a] Tan Tock Seng Hospital, Singapore
[b] Awal Bros Hospital, Pekanbaru, Indonesia
[c] Faculty of Medicine, Universiti Teknologi MARA, Selangor, Malaysia
[d] Gleneagles Medical Centre, Penang, Malaysia

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ABSTRACT

Background: Amphilimus-eluting stent (AES) is a novel polymer-free drug eluting stent that combines sirolimus with fatty acid as antiproliferative drug and has shown promising results in percutaneous coronary intervention.

We evaluated the clinical safety and efficacy of AES in an all-comers South-East Asian registry.

Methods: Between May 2014 to April 2017, 268 patients (88% male, mean age 60.1 ± 10.8 years) with 291 coronary lesions were treated with AES. The primary endpoint was major adverse cardiac events (MACE) ie a composite of cardiovascular mortality, myocardial infarction (MI) and target lesion revascularization (TLR) at 12-month follow-up.

Results: The majority of patients presented with acute coronary syndrome (75%) and 75% had multivessel disease on angiography. Diabetes mellitus was present in 123 patients (46%). The most common target vessel for PCI was left anterior descending artery (43%) followed by right coronary artery (36%), left circumflex (10%) and left main (6%).

The majority of lesions were type B-C (85%) by ACC/AHA lesion classification. An average of 1.25 ± 0.5 AES were used per patient, with mean AES diameter of 3.1 ± 0.4 mm and average total length of 34.8 ± 19.4 mm.

At 12-month follow-up, 4% of patients developed MACE. MACE was mainly driven by cardiovascular mortality (1.5%), MI (2%) and TLR (1.5%). The rate of stent thrombosis was 1.5%.

Conclusion: In a contemporary all-comers South-East Asian registry with high rate of diabetes mellitus, AES was found to be efficacious with a low incidence of MACE observed at 12-month follow-up.

1. Introduction

The Cre8 drug-eluting stent (CID and Alvimedica, Saluggia, Italy) is a novel polymer-free drug eluting stent (DES) [1] that combines sirolimus with fatty acid (amphilimus formulation) as antiproliferative drug and has shown promising results [2] in percutaneous coronary intervention (PCI).

The amphilimus-eluting stent (AES) utilizes abluminal reservoir technology which controls drug-elution to the vessel wall with complete drug elution within 90 days. The stent platform is made of thin cobalt chromium alloy (80-μm strut thickness) with 2 platinum markers at both ends and also features Carbofilm coating which enhances rapid cellular growth.

Several studies [3–6] have shown favourable outcomes for AES when compared to other new generation DES and also possible benefit in diabetic patients. However, there is limited data on the safety and efficacy of AES in Asian patients in contemporary clinical registries. We therefore sought to evaluate the clinical safety and efficacy of AES in an all-comers South-East Asian registry and report on the 12-month clinical outcomes.

* Corresponding author at: Department of Cardiology, Tan Tock Seng Hospital, 11, Jalan Tan Tock Seng, Singapore 308433, Singapore.
E-mail address: hee_hwa_ho@ttsh.com.sg (H.H. Ho).

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2. Methods

2.1. Study population

This study was an all-comers, multi-center registry on the 12-month clinical outcomes of consecutive South-East Asian patients with obstructive coronary artery disease undergoing emergent/urgent or elective PCI using AES in Malaysia, Indonesia and Singapore. From May 2014 to April 2017, 268 patients with a total of 291 coronary lesions were treated with AES.

2.2. Interventional procedure

All PCIs were performed using standard techniques and according to current practice guidelines. All patients were treated with Aspirin (100–300 mg daily) prior to the procedure and indefinitely thereafter. Patients also received Clopidogrel 75 mg daily or Ticagrelor 90 mg twice a day as part of the dual anti-platelet therapy (DAPT) with expected duration of 1 year.

2.3. End-Points and definitions

The primary endpoint was major adverse cardiac events (MACE) ie a composite of cardiovascular (CVS) mortality, nonprocedural myocardial infarction (MI) and target lesion revascularization (TLR) at 12 months follow-up. Secondary end-points include individual components of MACE and stent thrombosis.

Death from CVS causes was defined as death due to acute MI, cardiac perforation or tamponade, arrhythmia, a complication of the PCI procedure or as any death in which a CVS cause could not be ruled out.

Nonprocedural acute MI was defined as per current guidelines [7]. TLR was defined as any repeat revascularization (percutaneous or surgical) secondary to a stenosis >50% within the stent or within 5 mm proximal or distal to the stented segment. Stent thrombosis was defined according to the Academic Research Consortium [8] criteria. Our retrospective study conforms to the ethical guidelines of the Declaration of Helsinki and was approved by each institution's research committee.

2.4. Statistical analysis

Continuous variables were expressed as mean ± standard error of mean. Dichotomous variables were expressed as counts and percentages. Statistical comparisons were performed using Student's *t* test or Fisher's exact test, as appropriate. Cox regression analysis was used to evaluate clinical and procedural variables related to occurrence of MACE within 12 months of follow-up. Univariate logistic regression analysis was initially performed; variables < 0.2 were entered into the Cox model. Kaplan-Meier curve for freedom from MACE at 12 months follow-up was constructed when predictor(s) of MACE was identified with the difference compared with log-rank test. Calculations were performed using SPSS software (version 16.0; SPSS, Inc., Chicago, Illinois). All *p*-values were 2-sided and *p*-values < 0.05 were considered statistically significant.

3. Results

Table 1 shows the baseline clinical characteristics and angiographic findings of the study patients. The mean age of the patients at presentation was 60.1 ± 10.8 years with male preponderance (88%).

The majority of patients presented with acute coronary syndrome (75%) with 75% found to have multi-vessel disease on angiography. Diabetes mellitus (DM) was present in 123 patients (46%) with mean HbA1c level of 10.73 ± 1.95 (%). 10% of patients required Insulin therapy for glucose control. 26% of patients had history of prior MI and prior PCI. Chronic kidney disease (CKD) defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 was present in 11% of patients.

Table 1
Baseline Clinical Characteristics and Angiographic Findings.

	N = 268
Mean age, years	60.1 ± 10.8
Male:Female (%)	88:12
Clinical Presentation (%):	
Stable angina	25
ST-elevation MI	29
Non-ST elevation MI/unstable angina	46
CVS Risk Factors (%):	
Smoking	52
Diabetes mellitus	46
Insulin-dependent diabetes mellitus	10
Hypertension	65
Hyperlipidemia	71
Prior MI	26
Prior PCI	26
Prior CABG	5
CKD	11
Angiographic findings (%):	
Single vessel disease	25
Double vessel disease	38
Triple vessel disease	37
Target vessel for PCI (%):	
LAD	43
RCA	36
LCX	10
Left main	6
Others	5
Transradial access (%)	84
LVEF (%)	46 ± 14

MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, CKD: chronic kidney disease, LAD: left anterior descending artery, RCA: right coronary artery, LCX: left circumflex, LVEF: left ventricular ejection fraction.

Transradial access was used in 84% of cases. The most common target vessel for PCI was left anterior descending artery (43%) followed by right coronary artery (36%), left circumflex (10%) and left main (6%). "Others" include side branches (posterior descending arteries/posterior left ventricular branches, obtuse marginals, ramus intermedius) and saphenous venous grafts. The mean systolic left ventricular function was 46 ± 14%.

Table 2 shows the procedural and stent data of the patients during PCI.

The majority of lesions were type B-C (85%) by ACC/AHA lesion classification with chronic total occlusion accounting for 4.5% of cases. Coronary bifurcation lesions was present in 5.2% of patients undergoing PCI. Glycoprotein IIb/IIIa inhibitors were administered in 50 patients (19%).

Intracoronary imaging (mostly intravascular ultrasound) was utilised in 11% of PCI and rotablation was used in 5.2% of cases. An average of 1.25 ± 0.5 AES were used per patient, with mean AES diameter of 3.1 ± 0.4 mm and average total length of 35 ± 19 mm.

For the initial 268 patients, 9 patients died during index hospitalization. All 9 patients presented with acute coronary syndrome. 4 deaths were CVS-related and the remaining 5 deaths were due to sepsis.

Table 3 summarizes the clinical outcomes of 259 patients at 12-month follow-up (median duration follow-up was 19 months). A total of 10 patients (4%) developed MACE at 12-month follow-up.

Table 2
Procedural and Stent Data.

	N = 268
ACC/AHA Lesion Subtype (%)	
Type A	15
Type B	32
Type C	53
Coronary bifurcation (%)	5.2
Chronic total occlusion (%)	4.5
Glycoprotein 2b/3a inhibitors (%)	19
Rotablation (%)	5.2
Intracoronary imaging (%)	11
No.of stent per patient	1.2 ± 0.5
Mean stent diameter, mm	3.1 ± 0.4
Total stent length,mm	34.8 ± 19.4

ACC/AHA: American College of Cardiology/American Heart Association.

Table 3
Clinical Outcomes at 12-month follow-up.

	N = 259
MACE at 12 months, n, %	10 (4)
CVS mortality, n, %	4 (1.5)
TLR, n, %	4 (1.5)
MI, n, %	5 (2)
Stent thrombosis, n, %	4 (1.5)

MACE: major adverse cardiac event, CVS: cardiovascular, TLR: target lesion revascularization, MI: myocardial infarction.

MACE was mainly driven by CVS mortality (1.5%), myocardial infarction (2%) and TLR (1.5%). The rate of stent thrombosis was 1.5%.

Factors associated with 12-month MACE by univariate analysis (MACE group vs non-MACE group) were lower rate of transradial access (40% vs 87%, p = 0.001, impaired left ventricular function ie ejection fraction $\leq$ 35% (60% vs 24%, p = 0.01) and CKD (60% vs 8.1%, p < 0.0001) as shown in Table 4. By Cox-regression analysis, independent predictor of 12-month MACE was CKD (hazard ratio 6.7, 95% CI: 1.4–32, p = 0.02). Fig. 1 showed the Kaplan-Meier curve for freedom from MACE events over the period of 12 months for CKD and non-CKD patients (log rank test; p < 0.05). Fig. 2 case study illustrates our clinical experience with the use of AES in real world clinical practice.

Table 4
Clinical Characteristics, Angiographic Findings and Procedural Data of MACE Subgroup vs Non-MACE Subgroup.

	MACE (N = 10)	Non-MACE (N = 248)	p-value
Mean age, years	63.5 ± 10.9	59.8 ± 10.8	0.3
Male:Female (%)	90:10	88:12	1.0
Clinical Presentation (%):			
Stable angina	10	27	0.46
ST-elevation MI	20	28	0.73
Non-ST elevation MI/unstable angina	70	45	0.19
CVS Risk Factors (%):			
Smoking	57	58	0.5
Diabetes mellitus	70	45	0.19
Hypertension	90	64	0.1
Hyperlipidemia	90	71	0.3
Prior MI	30	26	0.7
Prior PCI	20	26	0.2
Prior CABG	10	4.4	0.4
CKD	60	8.1	< 0.0001*
Angiographic findings (%):			
Single vessel disease	10	25.5	0.4
Double vessel disease	50	38.5	0.5
Triple vessel disease	40	36	0.75
Target vessel for PCI (%):			
LAD	40	44	1.0
RCA	30	38	0.74
LCX	10	7	0.54
Left main	10	6	0.45
Others	10	5	0.43
Transradial access (%)	40	87	0.001*
LVEF $\leq$ 35% (%)	60	24	0.01*
ACC/AHA Lesion Subtype (%)			
Type A	20	15	0.65
Type B	20	32	0.51
Type C	60	53	0.75
No. of stent per patient	1.3 + 0.48	1.26 + 0.53	0.81
Mean stent diameter, mm	3.1 + 0.48	3.1 + 0.4	0.9
Total stent length, mm	34.0 + 20.7	35.4 + 20	0.82

MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, CKD: chronic kidney disease, LAD: left anterior descending artery, RCA: right coronary artery, LCX: left circumflex, LVEF: left ventricular ejection fraction, ACC/AHA: American College of Cardiology/American Heart Association.
* P value < 0.05.

4. Discussion

To our knowledge, this is the largest registry in the South-East Asian region evaluating the use of AES in an all-comer group of patients in the real world. We found that the use of AES was a safe and effective treatment modality and the 12-month clinical outcomes were good with a low incidence of MACE.

The advent of DES [9] has reduced the incidence of restenosis compared to bare metal stents and contemporary metallic DES represents the standard of care for patients undergoing PCI.

The newer generation DES have new metallic alloys and thinner stent struts making them more deliverable in challenging lesions. Further developments have led to emergence of polymer-free DES such as AES [1] which release the anti-proliferative agent (amphilimus formulation) from the stent surface without application of the polymer coating. The early clinical results with AES have been promising as it was associated with lower in-stent late lumen loss [2] at 6 months versus Taxus Liberte stent and optimal strut coverage [10] (a reflection of stent healing profile) of AES at 3 months was comparable to bare metal stent at 1 month. Several clinical registries [3,5–6] and one major randomized controlled trial [11] (mostly from Europe) had also demonstrated the safety and efficacy of AES in the real world when compared to new generation DES.

In our registry, the mean age of our patients at presentation was 60.1 ± 10.8 years with male preponderance (88%) and the percentage of patients with DM (46%) was quite high. Compared to previous Western studies [3,6,11], our patients were relatively younger and the rate of DM was relatively higher (rate of DM ranged from 20 to 30% in Europe). Several CVS studies [12,13] have already shown that Asian patients are relatively younger and have a higher rate of DM at presentation when compared to their non-Asian counterparts.

The majority of our patients (75%) presented with acute coronary syndrome which is higher than prior Western registries (majority being stable angina) and this is likely due to selection bias. The transradial access for PCI in our registry was 84% which reflected high adoption of contemporary PCI practice as recommended by the European Society of Cardiology (ESC) guidelines [14].

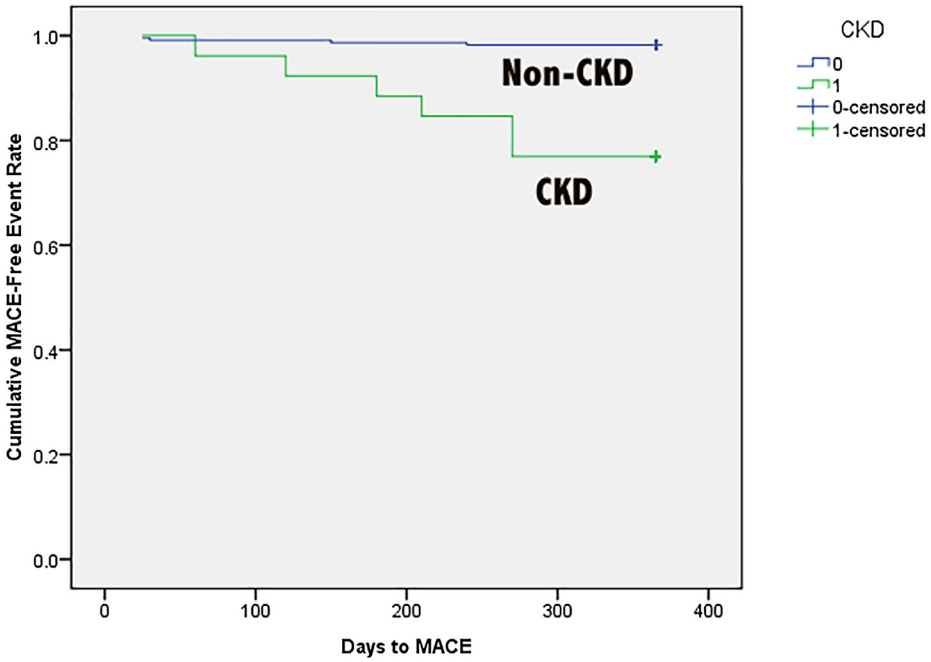

Fig. 1. Kaplan-Meier curve showing freedom from MACE for CKD versus non-CKD patients over the follow-up period of 12 months (log rank test; $p < 0.05$).

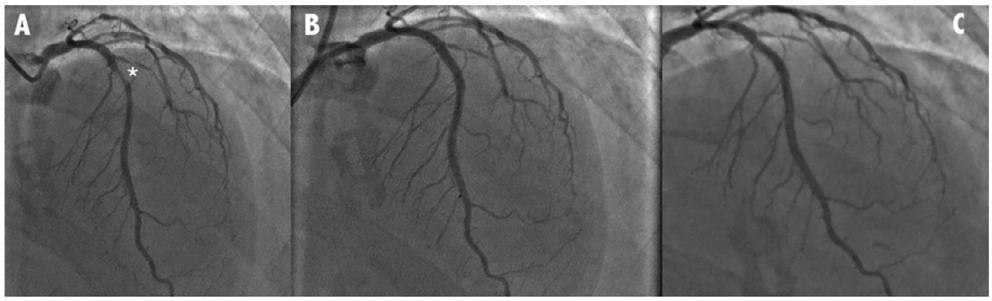

Fig. 2. (A) Baseline coronary angiography showing mid LAD stenosis (*). (B) Final angiography of mid LAD (after stenting with AES). (C) Restudy angiography of mid LAD at 20 months follow-up.

The majority of patients (85%) in our registry had complex coronary lesions by ACC/AHA lesion classification (lesion type B/C) which is comparable to Western studies. Total stent length in our study was 34.8 ± 19.4 mm which likely reflects the complexity of coronary lesions [15] treated in the real world. Total stent length was 23.3 ± 12.8 mm in the ASTUTE registry [5] (70% type B/C lesion) and was 47.7 ± 21.2 mm in the ReCre8 trial [11] (88.6% type B/C lesion). Rotablation was used in 5.2% of patients with calcified lesions and intracoronary imaging (mostly intravascular ultrasound) was used in 11% of PCIs.

In our study, a total of 10 patients (4%) developed MACE at 12-month follow-up. MACE was mainly driven by cardiovascular mortality (1.5%), myocardial infarction (2%) and TLR (1.5%). The rate of stent thrombosis was 1.5% (2 cases of subacute ST and 2 cases of possible ST). Although the number was small, we identified certain clinical factors that were predictive of 12-month MACE.

Factors associated with 12-month MACE by univariate analysis were lower rate of transradial access, impaired left ventricular function and CKD. By multi-variate analysis, independent predictor of 12-month MACE was CKD. This is consistent with the findings of recent studies [6,16,17] which have shown CKD to be significant predictor of MACE and target lesion failure.

Despite the use of new generation DES, DM remains an independent predictor of adverse clinical outcomes in patients undergoing PCI. Although the prevalence of DM in our registry was 46%, DM was not found to be a predictor of MACE in our study. Several studies [4,5,15] have shown that AES demonstrated similar efficacy and safety in DM versus non-DM patients (a unique finding among DES studies) which suggests possible incremental benefit in the DM subgroup. This could be due to the special drug formulation in AES in which the presence of fatty acids may enhance the delivery of amphilimus in diabetic cells, thus reducing neointimal proliferation. In DM subgroup analyses [3,6,18], AES have been shown to have better outcomes when compared to everolimus-eluting stent and biodegradable-polymer/polymer-free biolimus-eluting stent. These preliminary results need to be validated in large-scale randomized controlled trials.

5. Limitation

There are several limitations to our study. Our sample size was relatively small compared to prior studies. There was lack of routine angiographic follow-up in our study which may lead to overestimation of its purported clinical benefit in the "real world". There was also no data on the exact duration of DAPT regimen and patients' drug compliance which could account for the occur-

rence of stent thrombosis. Bleeding outcomes were also not evaluated in our study.

6. Conclusion

In a contemporary all-comers South-East Asian registry with high rate of diabetes mellitus, AES was found to be safe and effective with a low incidence of MACE observed at 12-month follow-up.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100469.

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