A Randomized Comparison between Everolimus-Eluting Stent and Cobalt Chromium Stent in Patients with Acute ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention Using Routine Intravenous Eptifibatide: The X-MAN (Xience vs. Multi-Link Stent in Acute Myocardial Infarction) Trial, A Pilot Study

Surya Dharma, MD, PhD, FIHA, FICA, FAPSIC, FESC, FSCAI¹ Alexander J. Wardeh, MD, PhD²
 Sunarya Soerianata, MD, FIHA, FESC, FACC, FSCAI, FASCC¹ Isman Firdaus, MD, FIHA¹
 J Wouter Jukema, MD, PhD, FESC, FACC³

¹ Department of Cardiology and Vascular Medicine, Faculty of Medicine, University of Indonesia, National Cardiovascular Center Harapan Kita, Jakarta, Indonesia

² Department of Cardiology, M.C. Haaglanden, The Hague, The Netherlands

³ Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

Address for correspondence Surya Dharma, MD, PhD, FIHA, FICA, FAPSIC, FESC, FSCAI, Department of Cardiology and Vascular Medicine, Faculty of Medicine, University of Indonesia, National Cardiovascular Center Harapan Kita, Jalan Letjen S. Parman Kav 87, Slipi, Jakarta Barat, Jakarta, Indonesia 11420 (e-mail: drsuryadharma@yahoo.com).

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Abstract

The objective of this study is to determine the efficacy and safety of an everolimus-eluting stent (EES/Xience; Abbott Vascular, Santa Clara, CA) compared with a cobalt chromium stent (CoCr/Multi-Link Vision; Abbott Vascular) in patients with acute ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) with routine administration of eptifibatide infusion. This is a prospective, single center, randomized trial comparing EES ($n = 75$) and CoCr stent ($n = 75$) implantation in patients with acute STEMI undergoing primary PCI. Intravenous eptifibatide administration was mandatory by protocol in this pilot study. The primary efficacy endpoint was major adverse cardiac events (MACE) at 30 days, defined as the composite of death, reinfarction, and target vessel revascularization. Secondary safety endpoints were stent thrombosis at 30 days and in-hospital bleeding event. Acute reperfusion parameters were also assessed. One-month MACE rate did not differ between EES and CoCr group (1.3 vs. 1.3%, $p = 1.0$). No stent thrombosis cases were observed in the EES group. The groups did not differ with respect to in-hospital bleeding events (5 vs. 9%, $p = 0.37$), achievement of final thrombolysis in myocardial infarction flow 2 or 3 ($p = 0.21$), achievement of myocardial blush grade 2 or 3 ($p = 0.45$), creatine kinase-MB level at 8 to 12 hours after stenting ($p = 0.29$), and left ventricular ejection fraction ($p = 0.21$). This pilot study demonstrates that after one-

Keywords

- everolimus
- cobalt chromium
- eptifibatide
- STEMI
- primary PCI
- stent

month follow-up, the use of EES is as safe and effective as the use of CoCr stents in patients with acute STEMI undergoing primary PCI with routine administration of intravenous eptifibatide.

Currently, primary percutaneous coronary intervention (PCI) as part of mechanical revascularization therapy has become a preferred option in the treatment of acute ST-elevation myocardial infarction (STEMI) patients with its fast and efficient re-establishment of coronary blood flow resulting in a reduction of mortality of 5 to 15% at 12 months compared with fibrinolytic therapy.^{1–5} One of the unresolved issues in the setting of primary PCI is the stent choice between drug-eluting stent (DES) and bare metal stent (BMS).

We hypothesized that in STEMI patients undergoing primary PCI with routine administration of eptifibatide, implantation of an everolimus-eluting stent (EES) is as safe and effective as implantation of a BMS in 30-day follow-up. Until now, there are no randomized studies specifically investigating the role of EES and cobalt chromium (CoCr) stent in acute STEMI patients undergoing primary PCI with routine administration of eptifibatide. The present X-MAN study was performed to compare the efficacy and safety of EES (Xience stent; Abbott Vascular, Santa Clara, CA) and BMS (Cobalt Chromium/Multi-Link Vision stent) in acute STEMI patients (≤ 12 hours of symptom onset) undergoing primary PCI, in whom routine intravenous eptifibatide was mandatory by protocol.

Patients and Methods

The X-MAN study was designed as a single-center, prospective, randomized pilot study, performed at the emergency department and catheterization laboratory of National Cardiovascular Center Harapan Kita, Jakarta, Indonesia, in the period of February 2011 to November 2012. All eligible patients were randomized into two groups of stents: the EES group consisting of patients who received Xience V or Xience Prime (Abbott Vascular) and the CoCr group (CoCr stent/Multi-Link or Vision stents; Abbott Vascular). Patients were randomized in the emergency department before primary PCI. Only a single type of stent was allowed in each patient. The study protocol was approved by the local ethical committee. All patients provided written informed consent before randomization. The trial was performed according to the declaration of Helsinki.

Inclusion criteria were: presence of acute myocardial infarction with ≤ 12 hours of symptom onset (chest pain of more than 20 minutes, not relieved by sublingual nitrates), ST-segment elevation in two or more contiguous leads (≥ 2 mm in precordial leads, ≥ 1 mm in limb leads), and planned for primary PCI with stent implantation.

Patients with left main disease, previous PCI, history of fibrinolytic treatment, past coronary artery bypass surgery, cardiogenic shock, renal failure, recent major bleeding, known hemorrhagic diathesis, and end-stage chronic diseases were excluded. From 410 patients who underwent primary PCI in the period of February 2011 to November 2012,

a total of 150 patients were recruited who fulfilled the inclusion criteria.

Primary PCI was performed according to the standard techniques. Stenting, if feasible, was performed only in the infarct-related coronary artery (IRA). Technical considerations, such as direct stenting or balloon predilation, were left to the operator's discretion.

Manual Thrombus Aspiration Protocol

Manual thrombus aspiration was recommended. After the guide wire has crossed the lesion, thrombus aspiration was routinely performed in a totally occluded culprit vessel (thrombolysis in myocardial infarction [TIMI] flow of 0). If preprocedural TIMI flow 1 to 3 was observed, the aspiration judgment was based on the presence or absence of a large thrombus burden. If a large thrombus burden was visualized, manual thrombectomy was performed. Direct stenting was advised if a lesion with a small thrombus burden was present.⁶ The most commonly used thrombus aspiration catheter was a 6F Thrombuster II (Kaneka, Japan).

Administration of GPI (Eptifibatide)

After arrival in the emergency department, patients received intravenous eptifibatide using a weight-adjusted dose (a single intravenous bolus of 180 $\mu\text{g/kg}$ followed by a continuous infusion of 2.0 $\mu\text{g/kg/min}$ up to 12–18 hours) as soon as primary PCI had been planned. Additional intracoronary eptifibatide was given at the operator's discretion.

Antiplatelet and Anticoagulant Regimen

All patients were pretreated with 160 to 320 mg acetylsalicylic acid and 600 mg clopidogrel orally before primary PCI, followed by daily administration of 75 mg clopidogrel planned for at least 1 year after discharge and 80 to 100 mg acetylsalicylic acid indefinitely. Before PCI, all patients received an intravenous bolus of unfractionated heparin (50–60 IU/kg).

Microvascular Perfusion Evaluation

Diagnostic modalities that were used to evaluate microvascular perfusion were the angiographic measurement of coronary flow and tissue perfusion (TIMI flow and myocardial blush grading [MBG]) in all patients following primary PCI, applying the following definitions:

1. **TIMI flow grading:** TIMI flow grade 0: absent antegrade flow; TIMI flow grade 1: partial contrast penetration beyond an occlusion with incomplete distal filling; TIMI flow grade 2: patent epicardial artery with opacification of the entire distal artery although contrast filling or washout is delayed; TIMI flow grade 3: patent epicardial artery with normal flow.⁷
2. **MBG:** MBG 0: failure of dye to enter the microvasculature; MBG 1: dye slowly enters but fails to exit the

microvasculature; MBG 2: delayed entry and exit of dye from the microvasculature; MBG 3: normal entry and exit of dye from the microvasculature.⁸

Cardiac Markers

Creatine kinase-MB (CK-MB) level in plasma was measured by immunoinhibition assay (Roche Hitachi 912, Mannheim, Germany) after arrival in emergency department and 8 to 12 hours after stent implantation. Serum troponin T concentration was measured with the cTnT assay from Roche Diagnostics (Mannheim, Germany). The lowest cTnT value to be measured reliably with this assay is 0.03 µg/L which is the lowest cTnT concentration that can be measured reproducibly with the between-run coefficient of variation of 10%.

Echocardiography Evaluation

Left ventricular ejection fraction (LVEF) was calculated using Simpson's method from a two-dimensional transthoracic echocardiography evaluation,⁹ performed at the second day of admission by dedicated personnel who were blinded to the treatment allocation.

Study Endpoints

The primary endpoint (efficacy endpoint) of this pilot study was the major adverse cardiac event (MACE) rate at 1-month follow-up, defined as the composite of all-cause death, re-infarction, and clinically indicated target vessel revascularization (TVR). Secondary endpoints (safety endpoints) were stent thrombosis rate at 30-days and in-hospital bleeding event. Acute reperfusion parameters (TIMI flow and MBG),

CK-MB level at 8 to 12 hours after stenting, and LVEF were also assessed.

Two independent interventional cardiologists blinded to the treatment assignment of the patients verified the assessment of TIMI flow and MBG. One month clinical follow-up was judged by an independent clinical event committee, blinded to the allocated stent type.

Definitions

Death was defined as all-cause death during 1-month follow-up. Re-infarction during follow-up was defined as a troponin T rise > 0.03 µg/L with symptoms, or a second rise of troponin T > 25% after recent MI in the presence of symptoms or the development of new Q waves on electrocardiography.^{10,11} We defined TVR as a re-intervention driven by any lesion located in the IRA and included coronary artery bypass surgery involving the IRA.¹² Stent thrombosis criteria were according to the Academic Research Consortium classification.¹³

In-hospital bleeding criteria were according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria¹⁴ and described as: (1) Severe or life-threatening bleeding: intracranial bleeding or bleeding that causes substantial hemodynamic compromise requiring treatment; (2) Moderate bleeding: bleeding that needs blood transfusion; (3) Minor bleeding: other bleeding, neither requiring transfusion nor causing hemodynamic compromise.

Door-to-device time was defined as the time from patient arrival at the emergency department to the introduction of the first device, either a thrombus aspiration catheter or a balloon catheter into the IRA.

Fig. 1 Flowchart of the study. STEMI, ST-segment elevation myocardial infarction; CK-MB, creatine kinase-MB; PPCI, primary percutaneous coronary intervention; ED, emergency department; TIMI, thrombolysis in myocardial infarction; MBG, myocardial blush grade; MACE, major adverse cardiac event.

Procedural success was defined as completion of the planned procedure without associated with catheterization laboratory major clinical complications (e.g., stroke, death or coronary artery perforation).¹⁵ The flowchart of the study is presented in ►Fig. 1.

Statistical Methods

Data were expressed as mean $\pm$ standard deviation for normally distributed continuous variables. If data were distrib-

uted not normally, data were expressed as median and interquartile range. Continuous variables were compared with Student *t*-test or Mann-Whitney *U* test. Chi-square test or Fisher exact test were used to compare categorical variables. Cox proportional hazards models were used to examine the association of stent type with the risk of clinical events (MACE).

As data regarding the use of EES in patients with eptifibatide treatment are lacking, we decided to enroll 150 patients

Table 1 Baseline characteristics

	EES group (N = 75)	CoCr group (N = 75)	P value
Demographic characteristics			
Age, years	56 $\pm$ 9.6	54 $\pm$ 9.5	0.16
Male	67 (89%)	61 (81%)	0.17
BMI, kg/m ²	24 (23–27)	25 (23–27)	0.9
Risk factors			
Hypertension	37 (49%)	37 (51%)	1.0
Diabetes mellitus	22 (29%)	17 (23%)	0.35
Dyslipidemia	36 (48%)	37 (49%)	0.87
Smoking	46 (61%)	48 (64%)	0.86
Family history of CAD	20 (27%)	20 (27%)	1.0
Location of infarction			
Anterior wall	37 (49%)	39 (52%)	0.74
Onset of infarction			
$\leq$ 2 hours	6 (8%)	3 (4%)	0.49
2–6 hours	44 (59%)	51 (68%)	0.24
> 6 hours	25 (33%)	21 (28%)	0.48
Risk stratification			
Killip class I	63 (84%)	62 (83%)	0.83
Door-to-reperfusion time			
Door-to-device time, minutes	86 (70–114)	90 (70–106)	0.82
Door-to-device time $\leq$ 90 minutes	41 (55%)	35 (47%)	0.33
Laboratory parameter			
Creatinine, mg/dL	1.0 (0.9–1.2)	1.0 (0.8–1.2)	0.4
Glucose, mg/dL	146 (123–207)	146 (122–195)	0.97
Hemoglobin, g/dL	14 $\pm$ 1.4	14 $\pm$ 1.6	0.49
Medication at discharge			
ACE inhibitor or ARB	62 (83%)	61 (81%)	0.83
Clopidogrel	74 (99%)	75 (100%)	1.0
Acetylsalicylic acid	74 (99%)	74 (97%)	1.0
Beta blocker	58 (77%)	52 (69%)	0.27
Statin	74 (99%)	71 (95%)	0.37
Medication at 1 month			
Acetylsalicylic acid	74 (99%)	75 (100%)	1.0
Clopidogrel	75 (100%)	75 (100%)	1.0

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CoCr, cobalt chromium; EES, everolimus-eluting stent.

(75 patients for each arm) in this pilot study before recruiting a larger population. Thus, study equivalence is not being tested.

A p value of < 0.05 was considered statistically significant. All statistical analyses were performed using a statistical package (SPSS version 17.0, SPSS Inc., Chicago, IL).

Results

Baseline Characteristics

► **Table 1** shows the baseline clinical characteristics of the patients in the two study groups. Most patients (85%) were male. The study groups were well balanced in terms of baseline clinical characteristics and risk factors. ► **Table 2** shows angiographic characteristics and procedural results. The two groups had similar anatomical and procedural characteristics. Thrombus aspiration was performed in 59% of the patients. PCI only on IRA was performed in the majority of the patients (93%). Procedural success was obtained in all patients (100%).

Study Endpoints

During 1-month follow-up, MACE rates did not differ between the EES and the CoCr group (1.3 vs. 1.3%, $p = 1.0$) (► **Table 3**). A single case with probable stent thrombosis was observed in the CoCr group and none in the EES group. In-hospital bleeding event rates were similar in the EES and CoCr groups (5 vs. 9%, $p = 0.37$) (► **Table 4**).

Acute Reperfusion Parameters

The EES and CoCr stent groups showed no significant differences in the achievement of final TIMI flow 2 or 3 (99 and 93%, $p = 0.21$) and MBG 2 or 3 (72 and 77%, $p = 0.45$) (► **Table 4**).

Creatine kinase-MB Level and Left Ventricular Ejection Fraction

CK-MB level in serum obtained 8 to 12 hours after primary PCI did not differ between EES and CoCr stent group ($p = 0.29$). Echocardiographic findings revealed a nonsignificant difference in LVEF between the groups (53 vs. 50%, $p = 0.21$) (► **Table 5**).

Discussion

The most important finding of this study is that the short-term (30 days) efficacy and safety of EES in acute STEMI patients (≤ 12 hours of onset) undergoing primary PCI with routine administration of intravenous eptifibatide are as good as the short-term efficacy and safety of the CoCr stent. These results contribute to the knowledge of efficacy and safety of DES in acute STEMI patients treated by primary PCI.

Drug-Eluting Stent in Acute STEMI

The use of first generation DES in the setting of primary PCI for acute STEMI remained controversial due to an increased risk of late stent thrombosis,¹⁶ possibly related to delayed culprit vessel healing after DES implantation¹⁷ and late acquired stent malapposition.^{18,19} Second generation DES have been developed to overcome the disadvantages related to first generation DES. Since several trials have shown an improve-

ment of clinical outcomes during mid- to long-term follow-up in patients who received second generation DES,^{20–22} the use of DES have been widely used for off-label indications.²³ In acute STEMI, the use of EES has been investigated in several trials which showed favorable results compared with first generation DES^{24,25} or BMS.²⁶

The European Society of Cardiology (ESC) 2012 guidelines on the management of STEMI has qualified the use of DES for STEMI patients as class IIa recommendation.²⁷ However, data regarding efficacy and safety of second generation DES after primary PCI are still relatively scarce.

Our study showed that the use of EES after primary PCI is safe and does not increase the risk of MACE during 30-day follow-up. Furthermore, we did not find any stent thrombosis case in the EES group. Concordant with this result, a recent meta-analysis showed that EES was associated with a significant reduction in early (30 days) definite stent thrombosis (relative risk = 0.28; $p < 0.0001$) and early definite/probable stent thrombosis (relative risk = 0.54; $p = 0.005$) compared with pooled paclitaxel, sirolimus, and zotarolimus-eluting stents.²⁸

Optimizing Acute Reperfusion Treatment

Acute reperfusion parameters (TIMI flow and MBG) during primary PCI are important tools for immediate evaluation of a successful reperfusion treatment.²⁹ The use of routine glycoprotein IIb/IIIa inhibitor (GPI) administration in combination with manual thrombus aspiration during primary PCI resulted in the achievement of final TIMI flow 2 or 3 and MBG grade 2 or 3 in 96% and 74% of the study population, respectively. These results strengthen the findings from Burzotta et al who used the combination of GPI and thrombus aspiration during primary PCI and showed that the combination was associated with a lower mortality rate than GPI alone and thrombus aspiration alone.³⁰

Administration of GPI and manual thrombus aspiration during primary PCI are recommended by the 2011 ACCF/AHA/SCAI (American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular and Angiography Interventions) guideline for PCI³¹ and the 2012 ESC guideline on management of STEMI patients²⁷ (class IIa). However, routine precatheterization use of GPI has been indicated as a class IIb recommendation. In the EXAMINATION trial,²⁶ GPI (predominantly abciximab) was used in 52% of the study population, whereas in our study, eptifibatide was administered to all patients of the study population. Moreover, in our study, the similar MACE rate in the EES and CoCr groups can be explained by equal success to achieve reperfusion (final TIMI flow and MBG), which leads to similar CK-MB rises ($p = 0.29$) and similar LVEF ($p = 0.21$). The choice to use CK-MB level at 8 to 12 hours after stenting was based on the fact that in patients with reperfused infarcts, serial CK-MB values in serum peak after 8.7 and 12.6 hours after onset of chest pain in patients with early and late reperfusion, respectively.³²

Several reasons may explain the low MACE rate and the absence of stent thrombosis associated with EES in our study. First, it is postulated that stenting of a highly thrombotic lesion in a patient with acute STEMI may result in undersizing

Table 2 Procedural and angiographical characteristics

	EES group (N = 75)	CoCr group (N = 75)	p value
Access site			
Transradial approach	36 (48%)	39 (52%)	0.62
Procedural-related variables			
Thrombus aspiration	38 (51%)	50 (67%)	0.06
Direct stenting	31 (41%)	25 (33%)	0.31
Predilation before stenting	45 (60%)	50 (67%)	0.39
IRA only PCI	68 (91%)	72 (96%)	0.19
Maximal inflation pressure, atm	13.6 ± 2.9	13.5 ± 3.2	0.85
Number of stents at target lesion	1.1 ± 0.3	1.0 ± 0.2	0.35
Total stent length, mm	23 (18–28)	23 (18–28)	0.38
Lesion characteristics			
Total occlusion	44 (59%)	51 (68%)	0.24
Bifurcation	31 (41%)	26 (35%)	0.4
Reference vessel diameter, mm	3.1 ± 0.4	3.2 ± 0.4	0.62
Initial TIMI flow grade			
0/1	42 (56%)	49 (65%)	0.24
2	6 (8%)	4 (5%)	0.51
3	17 (23%)	14 (19%)	0.54
Final TIMI flow grade			
0/1	1 (1.3%)	5 (7%)	0.21
2	15 (20%)	18 (24%)	0.55
3	59 (79%)	52 (69%)	0.19
IRA			
LAD	42 (56%)	41 (55%)	0.87
LCX	5 (7%)	2 (3%)	0.44
RCA	28 (37%)	32 (43%)	0.5
Number of diseased vessels			
Single vessel	30 (40%)	29 (39%)	0.87
Multivessel	45 (60%)	46 (61%)	
Procedural success	75 (100%)	75 (100%)	1.0

Abbreviations: CoCr, cobalt chromium; EES, everolimus-eluting stent; IRA, infarct-related artery; LAD, left anterior descending artery; LCX, left circumflex artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

Table 3 Primary endpoint

Primary endpoint	EES (N = 75)	CoCr (N = 75)	HR (95% CI)	p value
Death/re-MI/TVR at 30 days	1 (1.3%)	1 (1.3%)	0.9 (0.06–15.8)	1.0

Abbreviations: CI, confidence interval; CoCr, cobalt chromium; EES, everolimus-eluting stent; HR, hazard ratio; MI, myocardial infarction; TVR, target vessel revascularization.

of the applied stent or incomplete stent apposition (which is known to be a predictor of stent thrombosis),³³ probably due to the masking effect of thrombus in the vessel. In our study, the treatment with eptifibatide alone or in combination with manual thrombus aspiration was expected to dissolve thrombus and minimize distal embolization, which: (1) allows clear

visualization of the true vessel diameter, (2) allows the choice of an appropriate stent size, and (3) eliminates early stent malapposition. Second, the maximal stent inflation pressures applied in the EES and CoCr groups were similar (→ **Table 2**), which may indicate adequate stent deployment with well-opposed stent struts in the EES group. Third, it is postulated

Table 4 Secondary endpoints

	EES (N = 75)	CoCr (N = 75)	p value
Secondary endpoint			
Stent thrombosis at 30-days			
Definite	0	0	1.0
Probable	0	1 (1.3%)	
Possible	0	0	
In-hospital bleeding ^a			
Severe	0	0	0.37
Moderate	0	3 (4%)	
Mild	4 (5%)	4 (5%)	
Other endpoints			
Postprocedural TIMI flow grade 2/3	74 (99%)	70 (93%)	0.21
Myocardial blush grade 2/3	54 (72%)	58 (77%)	0.45

Abbreviations: CoCr, cobalt chromium; EES, everolimus-eluting stent; TIMI, thrombolysis in myocardial infarction.

Table 5 CK-MB and LVEF

	EES (N = 75)	CoCr (N = 75)	p value
CK-MB, U/L			
At baseline	44 (26–110)	44 (31–80)	0.95
After 8–12 hours	281 (168–475)	358 (160–536)	0.29
LVEF (%)	53 (45–61)	50 (45–58)	0.21

Abbreviations: CK-MB, creatine kinase-MB; CoCr, cobalt chromium; EES, everolimus-eluting stent; LVEF, left ventricular ejection fraction.

Note: Values are expressed as median (interquartile range).

that EES may have a rapid and complete endothelialization. Finally, the stent design of the Xience stents with thin struts, fracture-resistant CoCr stent struts, and low polymer and drug load³⁴ may also yield specific advantages.

Study Limitation

The present study has several limitations. First, the observation period of this study was 1 month only, and to observe differences with respect to MACE rates and (very) late stent thrombosis rates between the two groups, we need longer follow-up periods. Second, this study was underpowered to detect small-scale benefits of EES in 1-month follow-up, particularly when the MACE rate in the group of patients treated with the CoCr stent is very low. However, this is the first study that has investigated EES using routine administration of eptifibatide in STEMI patients and therefore this preliminary report may encourage the start of larger randomized trials.

Conclusion

The results of this pilot study indicate that, in a 1-month observation period, the use of EESs is as safe and effective as

CoCr stents in patients with acute STEMI undergoing primary PCI with routine administration of intravenous eptifibatide. Future trials with much larger sample size and longer follow-up are necessary to confirm these results.

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