ORIGINAL ARTICLE

Mid-term clinical outcomes of new generation drug-eluting stents for treatment of diffuse coronary artery disease

Yaygın koroner arter hastalığında yeni kuşak ilaç salınımlı stentlerin kullanımının orta vadeli klinik sonlanımı

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ABSTRACT

Objective: Diffuse coronary artery disease (CAD) is a challenging issue in clinical cardiology practice. There are limited data about percutaneous revascularization in these patients.

Methods: This study was an observational clinical evaluation. The records of patients with diffuse CAD revascularized with new-generation drug-eluting stents (DES) were researched retrospectively. Patients treated with multiple, overlapping new-generation DES (at least 60mm in length per vessel) were included. The incidence of major adverse cardiac events (MACE), defined as cardiac death, stent thrombosis, non-fatal myocardial infarction, and target lesion revascularization (TLR), at the end of the first year following the index procedure was recorded.

Results: A total of 71 patients (with 75 coronary vessels) treated with new-generation DES for diffuse CAD were enrolled in the study. Zotarolimus-eluting stents were used in 48 vessels and biolimus A9-eluting stents were used in 27 vessels. The median total stent length per vessel was 75.0 mm (60.0–106.0) and the median number of stents implanted was 3 (2–4) for each vessel. The cumulative incidence of MACE at the end of the first year was 11.2% (8 patients). The presence of diabetes mellitus (DM) and ST-segment elevated myocardial infarction (STEMI) were defined as independent clinical risk factors related to MACE development.

Conclusion: Coronary artery revascularization with new-generation drug-eluting stents can be a good choice in the treatment of selected patients with diffuse CAD. DM and STEMI were found to be related to poorer clinical outcomes with this treatment option in our study.

ÖZET

Amaç: Yaygın koroner arter hastalığı tedavisi klinik kardiyolojinin sıkıntı yaratan durumlarından biridir. Bu hastaların perkütan revaskülarizasyonu ile ilgili veriler sınırlıdır.

Yöntemler: Çalışmamız gözlemsel bir klinik değerlendirmedir. Yaygın koroner arter hastalığı olup yeni kuşak ilaç salınımlı stentler (DES) ile revaskülarize edilmiş hastalar geriye dönük incelendi. Çoklu, üst üste gelecek şekilde yerleştirilmiş yeni kuşak DES'ler (her damar için en az 60 mm uzunlukta olacak şekilde) ile tedavi edilmiş hastalar çalışmaya alındı. Girişim sonrasındaki ilk yılın sonunda önemli istenmeyen kardiyak olay (MACE) sıklığı araştırıldı. MACE kavramı kardiyak ölüm, stent trombozu, ölümcül olmayan miyokart enfarktüsü ve hedef lezyon revaskülarizasyonu ihtiyacı (TLR) olarak tanımlandı.

Bulgular: Çalışmaya yaygın koroner arter hastalığı nedeniyle yeni kuşak DES'ler ile tedavi edilen 71 hasta (75 koroner damar) dahil edildi. Zotarolimus DES 48 koroner damarda, biolimus A9 DES 27 koroner damarda kullanıldı. Her koroner damar için kullanılan ortalama stent uzunluğu ortalama 75.0 mm (60.0–106.0) ve yine her damar için kullanılan stent sayısı üç 3 (2–4) olarak bulundu. İlk yıl sonunda toplam MACE sıklığı %11.2 olarak izlendi (sekiz hasta). Diabetes mellitus ve ST segment yükselmeli miyokart enfarktüsü (STEMI) MACE gelişimi ile ilişkili bağımsız klinik risk faktörleri olarak belirlendi.

Sonuç: Yaygın koroner arter hastalığında yeni kuşak DES'lerin kullanımı ile gerçekleştirilecek koroner arter revaskülarizasyonu seçilmiş olgularda uygun bir seçenek olarak görülmektedir. Çalışmamızda diabetes mellitus ve STEMI varlığı bu tedavi seçeneğinde olumsuz klinik sonlanım ile ilişkili bulunmuştur.

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Diffuse coronary artery disease (CAD) poses a significant problem in clinical cardiology practice.[1] Despite advances in medical treatment and surgical revascularization techniques, long-term clinical outcomes can be suboptimal.[2–4] In past decades, during the era of balloon angioplasty and bare metal stents (BMS), restenosis and stent thrombosis were frequently seen.[5,6] With the advent of drug-eluting stents (DES), interventional cardiologists were able to treat longer segments and diffuse coronary lesions.[7,8] However, we have limited data about the clinical outcomes of the treatment approach to diffuse coronary lesions using DES that is known as the full metal jacket strategy. The aim of this study was to investigate the efficacy and safety of treatment of diffuse coronary artery stenosis with multiple, overlapping DES.

Abbreviations:

ACS	*Acute coronary syndrome*
BES	*Biolimus A9-eluting stent*
BMS	*Bare metal stent*
CAD	*Coronary artery disease*
CI	*Confidence interval*
DAPT	*Dual antiplatelet therapy*
DES	*Drug-eluting stent*
DM	*Diabetes mellitus*
HR	*Hazard ratio*
LAD	*Left anterior descending artery*
MACE	*Major adverse cardiac event*
NSTE-ACS	*Non-ST-segment elevation-acute coronary syndrome*
RCA	*Right coronary artery*
STEMI	*ST-segment elevation myocardial infarction*
TLR	*Target lesion revascularization*
ZES	*Zotarolimus-eluting stent*

METHODS

Study population

A retrospective search of the hospital database was conducted to identify patinets with diffuse coronary artery stenosis who were treated with a full metal jacket approach. Full metal jacket is defined as a stent length ≥60 mm without a gap in a single coronary artery.[7] The inclusion criterion for this study was implantation of multiple, overlapping new-generation DES, ≥60 mm in total stent length per vessel treated. Patients who were treated with a full metal jacket approach in a single coronary artery and were followed up in the cardiology outpatient clinic through the end of the first year following the index coronary intervention were included in the present study.

Exclusion criteria were defined according to the coronary anatomy and the coronary artery percutaneous intervention:

- BMS implantation (alone or with DES)
- Saphenous vein graft intervention
- Bioabsorbable stent implantation
- Intervention for in-stent restenosis
- DES implantation with former generation platforms
- Patients who were lost to follow-up or did not have a clinical non-invasive coronary ischemia evaluation in the post-interventional follow-up period.

In our center, 2 kinds of new-generation DES are used: zotarolimus-eluting stents (ZES) with durable polymers (Resolute Integrity, Resolute Onyx; Medtronic, Inc. (Minneapolis, MN, USA)) and biolimus A9-eluting stents (BES) with biodegredable polymers (Biomatrix Flex; Interventional Technologies Pte Ltd., Singapore). ZES were used exclusively at our center until late 2015; since then, both ZES and BES have been in use. The type of stent deployed is the choice of the primary operator. Demographic, clinical, and angiographic data were collected from the hospital database or from patients during clinical visits.

Stenting procedure and angiographic evaluation

Patients with multiple, overlapping DES longer than 60 mm in length in a single coronary artery were enrolled retrospectively and evaluated for major adverse cardiac events (MACE). As a general approach, the stent diameter and stent length were decided upon after repeated dosages of intracoronary nitroglycerin. The overlapping areas of the consecutive stents were to be 2 to 4 mm in length. Chronic total occlusion was defined as a lesion assumed to be occluded more than 3 months. The decision to perform coronary intervention for chronic total occlusion was driven by documentation of coronary ischemia using myocardial perfusion scintigraphy. A bifurcation intervention was defined as any side branch greater than 2 mm jailed under the stented segment of the main branch. The type of dual antiplatelet therapy (DAPT), glycoprotein IIb/IIIa antagonist usage, and postdilatation after stenting were decided by the primary operator. In our institution, the general approach is postdilatation with non-compliant balloons. Angiographic data were evaluated by 2 independent cardiologists retrospectively.

Endpoint definition and clinical follow-up

A composite endpoint for MACE was defined as cardiac death, stent thrombosis (definite or probable), re-

current myocardial infarction, or target lesion revascularization (TLR). Overall survival was also investigated and all deaths were accepted as cardiac death if there was no proof of another underlying etiological factor. TLR was defined as repeat revascularization via percutaneous intervention or surgically for a previously stented area or 5 mm proximal or distal to the stent. Routine coronary angiography was not encouraged. A TLR designation was based on clinical evidence of ischemia. The Third Universal Definition of Myocardial Infarction guideline defines perioperative myocardial infarction associated with percutaneous coronary intervention as an elevation of cardiac troponin values more than 5 times the 99th percentile upper reference limit in patients with normal baseline values.[9] Obviously, diagnosis of myocardial reinfarction may be difficult in patients with acute coronary syndrome (ACS) as a result of the baseline cardiac troponin elevation. The Third Universal Definition of Myocardial Infarction guideline defines myocardial reinfarction as an additional >20% increase of cardiac troponin values following the peak and decrement curve in ACS patients.[9] Stent thrombosis was categorized according to the Academic Research Consortium definitions.[10]

Statistical analysis

For discrete and continuous variables, descriptive statistics (mean, SD, median, minimum value, maximum value, and percentile) were calculated. In addition, the homogeneity of the variances, which is one of the prerequisites of parametric tests, was assessed using Levene's test. The assumption of normality was tested via the Shapiro-Wilk test. To compare the differences between the 2 groups, the Student's t-test was used when the parametric test prerequisites were fulfilled, and the Mann-Whitney U test was used when such prerequisites were notmet. Cumulative event rates were calculated using the Kaplan-Meier method and groups were compared with a log-rank test. Risk factors were established using the Cochran-Mantel-Haenszel chi-square test. The data were evaluated using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). $P<0.05$ and $p<0.01$ were used as the levels of significance.

RESULTS

Demographic and clinical characteristics

A total of 136 patients were treated with multiple, overlapping stents longer than >60 mm in length. Sixty-five patients were excluded from evaluation due to the defined study exclusion criteria: 26 patients with earlier DES platforms, 17 patients with BMS+DES, 4 patients with BMS alone, 2 patients with saphenous vein graft intervention, 2 patients with bioabsorbable stents, and 2 patients with in-stent restenosis intervention were excluded. Five patients were also excluded from the study as a result of loss to follow-up, and 7 patients were excluded because of the lack of a non-invasive coronary ischemia evaluation in the follow-up period. In all, 71 patients (with 75 coronary arteries) were ultimately included for MACE evaluation. The demographic and clinical characteristics of the patients are provided in Table 1. The mean age of the study population was 65 years (39–92 years) and 73.2% of the study patients were male. The diabetes mellitus (DM) frequency in the study population was 29.6%. Nearly 70% of the patients were admitted with an ACS presentation (15.5% unstable angina, 21.1% non-ST-segment elevation-acute coronary syndrome [NSTE-ACS], 32.4% ST-segment elevation myocardial infarction [STEMI]). Twenty-two cases (31.0%) were admitted with stable angina pectoris.

Angiographical and procedural results

The right coronary artery (RCA) was the vessel most often requiring intervention. There were 48 (64.0%) RCA and 22 (29.3%) left anterior descending (LAD) artery procedures. The chronic total occlusion rate was 24% (18 vessels). The rate of bifurcation intervention rate was 41.3% (31 vessels). Ten of these 31 vessels had undergone kissing ballon dilatation (13.3%) and 4 needed 2 stents (5.3%). In our institution, there is a tendency to perform postdilatation in these long segment-stented patients as a routine procedure, and the postdilatation rate was 94.7% (71 vessels) in this study population. Routine glycoprotein IIb/IIIa inhibitor use is not preferred, and in this study population, glycoprotein IIb/IIIa inhibitors were used in only 7 cases (9.3%). A median of 3 (2–4) stents were used for each vessel treated and the median total stent length per vessel was 75.0 mm (60.0–106.0 mm). Peri-interventional myocardial infarction diagnosed as defined cardiac marker elevation was seen in 16 interventions (21.3%) (Table 2).

There was a tendency to use more stents per vessel and a longer stented segment in the ZES group compared with the BES group, but this difference did not

Table 1. Demographic and clinical characteristics of the study population

	Study population
Age (years)	65.0 (39.0–92.0)
Gender-male, n (%)	52 (73.2)
Diabetes mellitus, n (%)	21 (29.6)
Smoking, n (%)	44 (62.0)
Hypertension, n (%)	49 (69.0)
Hyperlipidemia, n (%)	31 (43.7)
Family history of premature coronary artery disease, n (%)	12 (16.9)
History of previous myocardial infarction, n (%)	29 (40.8)
History of previous revascularization (PCI or CABG), n (%)	20 (28.2)
Chronic kidney failure, n (%)	4 (5.6)
Chronic obstructive pulmonary disease, n (%)	9 (12.7)
Previous TIA or stroke, n (%)	3 (4.2)
Previous peripheral artery disease, n (%)	5 (7.0)
Admission creatinine (mg/dL)	0.9 (0.6–10.7)
Admission ejection fraction (%)	56.0 (25.0–72.0)
Clinical presentation, n (%)	
Unstable angina pectoris	11 (15.5)
NSTE-ACS	15 (21.1)
STEMI	23 (32.4)
Stable angina pectoris	22 (31.0)

CABG: Coronary artery bypass graft; NSTE-ACS: Non-ST-segment elevation-acute coronary syndrome; PCI: Percutaneous coronary intervention; RCA: Right coronary artery; STEMI: ST-segment elevation myocardial infarction; TIA: Transient ischemic attack.

Table 2. Angiographical data of the study population

	Study population
Target vessel, n (%)	
Right coronary artery	48 (64.0)
Left anterior descending artery	22 (29.3)
Circumflex artery	5 (6.7)
SYNTAX score	16.0 (7.0–31.5)
Chronic total occlusion, n (%)	24% (18)
Bifurcation, n (%)	31 (41.3)
Bifurcation intervention ended with kissing balloon dilatation, n (%)	10 (13.3)
Bifurcation intervention ended with 2 stents, n (%)	4 (5.3)
Preintervention percentage of stenosis	99.0 (90.0–100.0)
Predilatation, n (%)	67 (89.3)
Postdilatation, n (%)	71 (94.7)
Glycoprotein IIb/IIIa usage, n (%)	7 (9.3)
Number of stents per vessel	3 (2–4)
Total length of stent per vessel (mm)	75.0 (60.0–106.0)
Mean diameter of stents (mm)	2.83 (2.33–3.25)
Peri-interventional myocardial infarction, n (%)	16 (21.3)
P2Y12 inhibitor	
Clopidogrel	40 (56.3)
Ticagrelor	20 (28.1)
Prasugrel	11 (15.4)

reach statistical significance (Table 3). Furthermore, there was no statistically significant difference in the mean diameter of the stents implanted between the ZES and BES groups.

Peri-interventional complications and in-hospital follow-up

There was no instance of in-hospital mortality. All of the study patients were discharged in safe clinical condition. One (1.3% of all interventions) case of subacute stent thrombosis was observed during the in-hospital follow-up 36 hours after the index procedure, and it was treated successfully with balloon angioplasty. In addition, there was 1 case of retroperitoneal hemorrhage, and the patient was stabilized after a blood transfusion. It was not necessary to discontinue DAPT for hemorrhagic complications. The peri-interventional myocardial infarction rate was 21.3%, which was quite high compared with similar studies, but this cardiac marker elevation did not lead to worse clinical outcomes.

Clinical outcomes at the end of 1 year

The cumulative incidence of MACE at the end of 1 year was 11.2% (8 patients). Two patients died within the follow-up period (all-cause death rate: 2.8%), 1 of which was a cardiac death (cardiac death rate: 1.4%) at the fifth month after index coronary intervention. There was no significant difference in MACE rate between the 2 groups with different types of DES (p=0.387). TLR-related MACE had occurred in 3 patients by the end of the first year (4% of total study population).

Table 3. Comparison of zotarolimus and biolimus A9-eluting stent data

	Zotarolimus-eluting stents	Biolimus A9-eluting stents	*p*
	Median (Min-Max)	Median (Min-Max)	
SYNTAX score	15.0 (7.0–31.0)	16.0 (7.0–31.5)	0.858
Number of stents per vessel	3 (2–4)	2 (2–4)	0.112
Total length of stented segment (mm)	78.0 (60.0–100.0)	72.0 (60.0–106.0)	0.147
Mean diameter of stents per vessel (mm)	2.78 (2.33–3.25)	2.87 (2.50–3.00)	0.351
Composite MACE rate at the end of 1 year	4 (8.3%)	4 (14.8%)	0.387
Overall follow-up period (months)	23 (12–40)	13 (5–18)	<0.001

MACE: Major adverse cardiac events; Min: Minimum; Max: Maximum.

All of the patients enrolled in the study remained in follow-up for more than 1 year. The mean length of follow-up of the patients enrolled in the study was 18 months (5–40 months) and at the end of this follow-up period, the cumulative MACE rate was 13.3% (10 patients). TLR-related MACE was experienced in only 5 patients (6.7% of total study population) at the end of the overall follow-up period (nearly 2 years). No additional cardiac death or instance of stent thrombosis was observed beyond the end of the first year.

Various factors thought to potentially be related to adverse clinical outcomes were evaluated using the Cochran-Mantel-Haenszel chi-square test. The presence of DM, STEMI, STEMI+NSTE-ACS, age, gender, chronic total occlusion intervention, target vessel (RCA *vs*. non-RCA), total stent length per vessel, number of stents per vessel, mean diameter of stent, type of DES and perioperative myocardial infarction were used in relation analysis, and after adjustment for the study population basal characteristics, DM and STEMI were found to be associated with MACE development. DM was strongly related with MACE occurence (1.9% *vs*. 30.4%; hazard ratio [HR]: 2.958; 95% confidence interval [CI]: 0.904–5.012; p=0.005) (Fig. 1). STEMI presence was also determined to be related to adverse clinical outcomes during the fol-

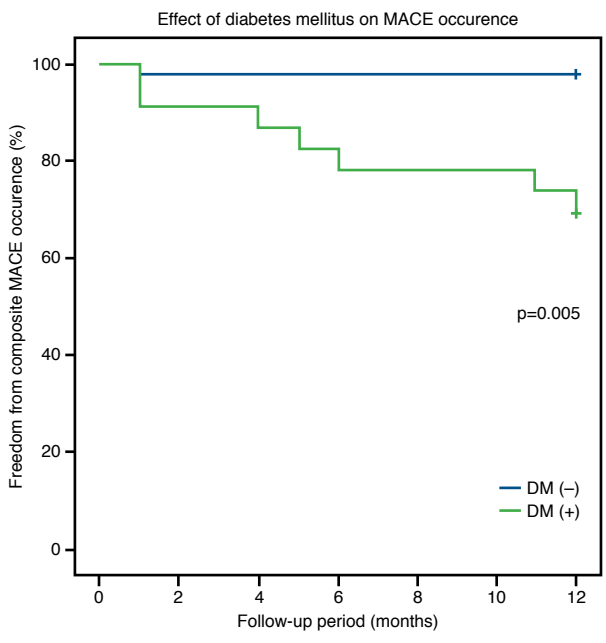

Figure 1. Effect of presence of diabetes mellitus on the development of major adverse cardiac events.

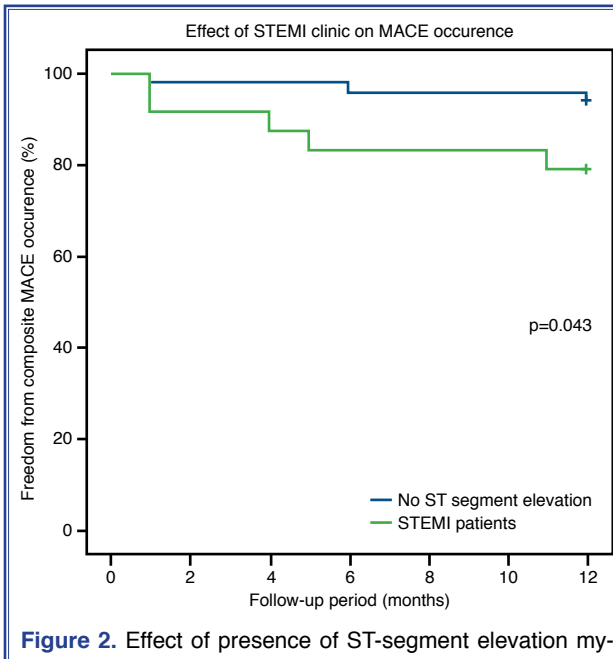

Figure 2. Effect of presence of ST-segment elevation myocardial infarction on the development of major adverse cardiac events.

low-up period (5.8% *vs*. 21.7%; HR: 1.629; 95% CI: 0.048–3.211; p=0.043) (Fig. 2).

DISCUSSION

New-generation DES decreased the prevalance of stent restenosis; however, late-term stent thrombosis still remains a question. In theliterature, the total length of implanted stents and reference stent diameter were defined as predictors of late stent thrombosis and stent restenosis for DES. In a study evaluating the effect of DES length on adverse outcomes during clinical follow-up, stent length greater than 31.5 mm was found to be related to poorer clinical outcomes, including stent thrombosis, death, and myocardial infarction.[11] Overlapping areas for multiple, sequential DES were also evaluated as high risk regions for adverse clinical outcomes.[12,13] However these studies were performed with first-generation DES and we do not have enough clinical evidence of the efficacy and safety of new-generation DES. Ahn et al.[14] examined clinical outcomes of Zotalimus and Sirolimus DES in the treatment of long-segment coronary artery disease and reported that Zotarolimus DES were determined to be non-inferior to the Sirolimus DES and both groups had good clinical outcomes. Recently, a study has been published that evaluated the MACE rates of long-segment CAD patients treated with Zotarolimus DES via a full metal jacket stenting approach.[15] Researchers reported acceptable clinical MACE rates at the end of a mean of 3 years of clinical follow-up. However, we still do not have enough clinical studies to evaluate the effect of new generation DES. In this study, we evaluated the clinical outcomes of patients with diffuse CAD treated with Zotarolimus DES and Biolimus A9 DES (with biodegradable polymer) via a full metal jacket approach. We did not find any difference in composite MACE rates between the ZES and BES groups.While ZES have been in use longer at our institution, we performed a MACE comparison between these 2 DES at the end of 1 year of clinical follow-up.

Previous studies evaluating the efficacy and safety of earlier generation DES used in a full metal jacket approach found that the total stent length, reference stent diameter, and the number of stents (in other words, the number of overlapping areas) were related to adverse MACE rates in clinical follow-up.[16,17] We did not find any significant relationship between total stent length, mean stent diameter, or the number of stents per lesion and clinical MACE rates. This difference from previous studies may be related to advanced polymer technology, new-generation biodegredable polymers (used in Biolimus A9 DES) and new generation antiplatelet treatment choices. In earlier studies, DAPT had been used for 3 to 6 months,[16,17] while in our study we aimed to continue DAPT at least for the first year following the index procedure. The longer duration of DAPT in our study may provide protection from clinical MACE with respect to stent-related factors, such as total stent length, mean stent diameter, and the number of stents per lesion.

DM is a well known clinical risk factor for target lesion failure in CAD patients, even those treated with new-generation DES.[18] Long-term evaluation of patients treated with a full metal jacket strategy using former generations of DES, DM was found to be an independent risk factor for the development of clinical MACE.[19] We found a close relationship between presence of DM and clinical MACE rates (1.9% *vs*. 30.4%; p=0.005). Although there were few diabetic patients in this study, adverse events were seen in almost one-third of the diabetic segment of the study group within the first year. This high percentage of clinical MACE in diabetic patients has prompted concerns about the efficacy of full metal jacket stenting in the diabetic population. DM can delay tissue healing and endothelization of stent polymers. Overlapping stent areas are the most probable points of stent-related clinical MACE development. Tissue healing may be further disturbed at these overlapping sites in the presence of DM. Furthermore, impaired glucose metabolism and poor diabetic condition have been found to be related to increased neointimal proliferation following DES implantation in animal based studies.[20] New-generation antiplatelet agents or a longer duration of DAPT may be a solution for better clinical outcomes in diabetic patients.

In our study, 52 patients (69.3%) were admitted in an ACS setting (STEMI or NSTE-ACS). Only 22 patients (31.0% of all study population) were admitted to the cardiology outpatient clinic with stable angina pectoris. In previous studies, an ACS setting was found to be related to a worse clinical MACE rate than stable angina pectoris.[21,22] We did not find any significant difference in the composite MACE rates between ACS and stable angina pectoris patients. Although there was a tendency to have more adverse

clinical events in the ACS group, this tendency did not reach the level of statistical significance. We compared STEMI patients with non-ST segment elevated patients (NSTE-ACS plus stable angina pectoris patients) using the composite MACE rates, and we found a higher MACE rate in patients admitted with STEMI (5.8% *vs*. 21.7%; p=0.043). STEMI was found to be associated with a 1.6 times higher rate of MACE development compared with all non-ST segment elevated patients.

Correct apposition of stent struts to the coronary arterial wall is very important for proper endothelization. Stent underexpansion is a well-known factor related to adverse clinical outcomes, and in a previous study, stent length was found to be directly related to suboptimal stent expansion.[23] In our institution, we generally use postdilatation with non-compliant balloons to provide correct apposition, and particularly in cases with long segment or multiple, overlapping stents. In our study population, the postdilatation percentage was higher than that of other, similar studies:[15,22] 94.7% of all patients (71 of 75 cases). Although intravascular ultrasound[24] is the preferred technique to evaluate apposition of an implanted stent to the arterial wall, in our study population, the stenting procedure were performed with the guidance of angiography alone. Therefore, even in the absence of intravascular ultrasound, postdilatation with a properly sized balloon can provide better stent apposition and is essential in patients treated with a full metal jacket strategy.

In our study population, we experienced more peri-procedural myocardial infaction following the index procedure compared with similar studies. This might be related to several factors: 1) relatively large number of ACS, 2) regular usage of postdilatation, and 3) infrequent use of glycoprotein IIb/IIIa antagonists. In a recently published study, peri-procedural myocardial infarction and injury were found to be related to increased composite MACE rates at the end of the first year following the index procedure.[25] We did not find any significant difference in the composite MACE rates at the end of 1 year regarding the development of peri-procedural myocardial infarction. This absence of an impact of peri-procedural myocardial infarction development on the composite MACE rates might be related to the relatively small number of patients in our study population.

We also examined favorable clinical results in our study population, particularly in terms of the low TLR rate compared with earlier studies. This improvement may be related to advanced stent technology, longer DAPT duration, and new-generation antiplatelet agents. Zotarolimus and Biolimus A9-eluting stents have been introduced to cardiology practice recently.

Conclusion

Our clinical evaluation found that these new generation DES provide high efficacy and safety. However, a full metal jacket stenting approach may still raise concerns for diabetic patients or in patients presenting in a STEMI setting. We observed higher MACE results at the end of the first year in these 2 patient groups.

Study limitations

First of all, this is a retrospective clinical study and we did not have a control group for comparison of the full metal jacket approach to optimal medical treatment or to surgical revascularization options. Our study population was also relatively small in size because these new-generation DES were introduced to the market only recently. The small size of the study group may generate difficulties in the evaluation of the statistical results about clinical risk factors related to MACE occurence.

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