ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Comparison of drug-eluting stents to bare-metal stents in ST-elevation myocardial infarction in long-term follow-up

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Abstract

Background: Recent data from "real world" registries and some randomised trials concerning the safety and efficacy of drug-eluting stents (DES) in patients with acute ST-elevation myocardial infarction (STEMI) are equivocal.

Aim: We sought to compare DES with bare-metal stents (BMS) in STEMI patients treated with primary percutaneous coronary intervention in terms of safety and efficacy parameters in long-term follow-up.

Methods: 895 consecutive STEMI patients admitted between 2003 and 2006 were included in this observational study. The clinical and procedural characteristic as well as long-term outcome of 327 patients treated with DES were compared with 568 patients treated with BMS. Combined primary endpoint consisted of: death, myocardial infarction (MI) and target vessel revascularisation (TVR).

Results: Age, sex, risk factors, presence of 3-vessel disease, left ventricular ejection fraction and the use of IIb/IIIa antagonist were comparable in both groups. During a mean follow-up of 570 ± 490 days, the mortality rate was 8.9% in the DES group vs. 15.5% in the BMS group ($p = 0.005$). In the DES group, lower incidences of both death and MI (9.5% vs. 16%, $p = 0.006$) as well as the combined endpoint of death, MI and TVR (19.3% vs. 31.3%, $p < 0.001$) were recorded. Target lesion revascularisation was more frequently performed in the BMS group (13.4% vs. 8.6%, $p = 0.03$). However, patients who received BMS more frequently had history of MI and coronary interventions, Killip class > 1 on admission, lower level of haemoglobin and HDL-cholesterol and higher level of troponin than those who received DES. After adjustment, the use of BMS was no longer significantly associated with worse clinical outcome with a trend in favour of DES. The only independent factor associated with increased risk of the combined endpoint was the Killip class > 1 ($p = 0.003$).

Conclusions: In STEMI patients, DES are not inferior in comparison to BMS in terms of safety and efficacy parameters and seem to be associated with a lower rate of target lesion revascularisations. Additionally, Killip classification remains a simple and important classification used to stratify risk in patients with acute MI.

Key words: ST-segment elevation myocardial infarction, primary percutaneous coronary intervention, drug-eluting stents

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INTRODUCTION

The main goal of primary percutaneous coronary intervention (PPCI) in ST-elevation myocardial infarction (STEMI) is to restore blood flow in infarct-related artery as soon as possible, but equally important is maintaining its patency after recanalisation. Primary PCI proved to be significantly more efficient in mortality reduction compared to pharmacological therapy [1] and PCI with bare metal stent (BMS) implantation was better than balloon angioplasty in reducing repeat revascularisation rates [2]. Introduction of drug eluting stents (DES)

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into elective percutaneous interventions led to significant reduction of restenosis and need for repeat revascularisation [3]. The status of DES implantation during PPCI is not so unequivocally established. This is because first reports based on large unselected groups of patients suggested increased risk of thrombosis, especially late after implantation, which might translate into increased mortality [4].

The results of the majority of randomised clinical trials comparing DES and BMS in STEMI did not confirm increased mortality after DES implantation and showed reduction of repeat target vessel revascularisation (TVR) [5], although this was not consistent with data from some other trials [6–8]. Data from non-randomised "real world" registries are even more unequivocal. Some of these registries indicate that there are no differences between DES and BMS [9] while others suggest the reduction in the rates of repeat revascularisation and deaths after DES implantation [10] or contrary — increased mortality related with DES, particularly in long-term observation [11].

The aim of our study was to compare safety and efficacy parameters of DES and BMS implantation during PPCI in patients with STEMI in 18-month follow-up.

METHODS

Studied population

This observational study included 895 consecutive patients (aged 64 ± 12 years, 27 women) who were hospitalised in Herz-Zentrum Bad Krozingen, Germany between 2003 and 2006 due to STEMI and underwent PPCI. In 327 (37%) of patients DES and in 568 (63%) of patients BMS were implanted. Tables 1–3 present detailed clinical characteristics of patients.

Inclusion criteria included anginal pain and ST segment elevation in at least 2 adjacent leads, primary or rescue coronary angioplasty performed within 12 hours after the onset of myocardial infarction (MI) symptoms, and age ≥ 18 years. Since no exclusion criteria were adopted, the study group included patients with cardiogenic shock, those who survived sudden cardiac arrest, elderly patients and with many comorbidities.

Study design

Coronary angioplasty was performed with the use of BMS and DES. Decision according the type of stent implanted was subjectively made by operator, without randomisation, based on the anatomy of coronary artery lesions and clinical characteristics of patients. DES was more frequently used in more complex lesions and in patients without contraindications for chronic double antiplatelet therapy. In the DES group, stents eluting paclitaxel (Taxus, Boston Scientific) and sirolimus (Cypher, Cordis) were used. In each patient physical examination was performed at admission, blood samples were drawn for basic laboratory parameters assessment and standard pharmacological therapy was applied to stabilise clinical status; the therapy was modified according to clinical picture. During the first 24 hours of hospitalisation and before discharge, cardiac ultrasonography was performed. In the same time, demographic data, disease history, and risk factors as well as data related to the procedure itself were analysed. Patients were given antiplatelet treatment with loading doses of aspirin and thienopyridine (clopidogrel or in some patients ticlopidine) and recommended to continue aspirin indefinitely and thienopyridines for at least 1 month after BMS implantation, 3 months after implantation of stent eluting sirolimus and 6 months after implantation of stent eluting paclitaxel. Information concerning occurrence of cardio-vascular episode during follow-up was obtained directly from patients or their relatives or from hospital database.

Combined primary endpoint consisted of: all-cause death, nonfatal recurrent MI and repeat TVR.

Statistical analysis

In statistical analysis continuous variables were presented as means ± standard deviation. For categorised parameters, percentage distribution in studied population was presented. For between-group comparisons, t-Student test was used; the differences in frequency distributions in study groups were tested with χ^2 test.

Univariate Cox model was applied to assess the relationship between cardiovascular episode occurrence and following parameters: baseline demographic (age, sex, body mass index) and clinical (previous MI, previous coronary artery bypass grafting or PCI) parameters, left-ventricular ejection fraction, risk factor and comorbid conditions (smoking, dyslipidaemia, hypertension, diabetes, positive family history), the results of basic laboratory tests (blood count, lipid profile, blood levels of creatinine, glucose, and troponins), haemodynamic status at admission (Killip class), basic parameters related with PCI procedure (length of the stent, TIMI coronary blood flow scale before and after PCI, the type of lesion, presence of 3-vessel disease, local complications), and the type of stent implanted. Multivariate Cox model included all variables that were significantly associated with survival in univariate analysis.

Subsequently, Kaplan-Meier curves estimation was performed to assess 18-months survival according to type of stent implanted; the differences in survival were analysed with Cox-Mantel test.

P value < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS (version 13.0, SPSS Inc., Chicago, IL, USA).

RESULTS

The study included 895 consecutive patients diagnosed with STEMI. There were no differences between BMS and DES groups in terms of age, sex, cardio-vascular risk factors, presence of 3-vessel disease, left ventricular ejection fraction and the use of IIb/IIIa antagonist (Table 1). Patients who received

Table 1. Clinical characteristics of studied patients according to the type of implanted stent.

	DES group (n = 327)	BMS group (n = 568)	P
Age [years]	63 ± 11	64 ± 13	0.542
Women [%]	25.7	27.6	0.526
Body mass index [kg/m^2]	27 ± 3	27 ± 4	0.862
LVEF < 30% [%]	12	16	0.316
Previous MI [%]	15.4	26.5	< 0.001
Previous CABG [%]	3.4	3.7	0.811
Previous PCI [%]	13.5	7.7	0.006
Smoking [%]	34.9	36.5	0.635
Dyslipidaemia [%]	82.7	80.7	0.492
Hypertension [%]	66.8	68.4	0.626
Diabetes [%]	23.7	25.1	0.644
Family history [%]	27.2	30.5	0.322
Q wave formation [%]	21.2	24.7	0.243
Killip class 2 [%]	16.2	29.9	< 0.001
Killip class 3 [%]	4.9	7.4	< 0.001
Killip class 4 [%]	4.6	7.2	< 0.001
VF before PCI [%]	5.2	7.9	0.145
Reanimation before PCI [%]	7	8.6	0.817
GPIIb/IIIa before PCI [%]	64.6	67.8	0.437
Fibrinolysis before PCI [%]	2.7	5.6	0.054

Data are presented as means ± SD or % of patients. DES — drug eluting stent; BMS — bare metal stent; LVEF — left ventricular ejection fraction; MI — myocardial infarction; CABG — coronary artery bypass grafting; PCI — percutaneous coronary intervention; VF — ventricular fibrillation

Table 2. Laboratory parameters according to implanted stent

	DES group (n = 327)	BMS group (n = 568)	P
C-reactive protein [mg/L]	1.86 ± 3.91	2.19 ± 4.73	0.264
Platelets [G/μL]	245 ± 73	248 ± 96	0.102
Fibrinogen [g/L]	406 ± 136	400 ± 142	0.519
Haemoglobin [g/dL]	14.2 ± 1.8	13.9 ± 1.69	0.019
Creatinine [mg/dL]	0.96 ± 0.31	0.96 ± 0.42	0.902
Glucose [mg/dL]	152 ± 57	159 ± 68	0.083
LDL cholesterol [mg/dL]	132 ± 42	130 ± 44	0.524
HDL cholesterol [mg/dL]	52 ± 15	48 ± 14	< 0.001
Triglicerides [mg/dL]	147 ± 102	119 ± 74	0.052
Total cholesterol [mg/dL]	199 ± 47	201 ± 52	0.573
Troponins at admission [ng/mL]	0.04 ± 0.07	0.69 ± 0.4	< 0.001

Data are presented as means ± SD or % of patients. DES — drug eluting stent; BMS — bare metal stent

BMS had more prior MI, more prior PCI, and worse haemodynamic status (more often Killip class > 1) on admission (Table 1). Patients from the DES group had higher level of haemoglobin and HDL-cholesterol and lower level of troponin at admission (Table 2). In the DES group, type C lesion according to ACC/AHA classification was more frequently observed, whereas in the BMS group more frequent was type B2 lesion (Table 3).

During mean follow-up of 570 ± 490 days (18 months) the mortality rate was 8.9% in the DES group vs. 15.5% in the BMS group (p = 0.005). Lower incidences of both death and MI were observed in the DES group (9.5% vs. 16%, p = 0.006) as well as the combined endpoint of death, MI and TVR (19.3% vs. 31.3%, p < 0.001). Repeat TVR was more frequently performed in the BMS group (13.4% vs. 8.6%, p = 0.03). Figure 1 present Kaplan-Meier survival curves reflecting redu-

Table 3. Procedural parameters according to implanted stent

	DES group (n = 327)	BMS group (n = 568)	P
Stent length [mm]	22 ± 10	22 ± 11	0.905
Inflation pressure [atm]	14 ± 3	16 ± 3	0.533
Stenosis before PCI [%]	94 ± 10	95 ± 10	0.116
Stenosis after PCI [%]	0.9 ± 8	1 ± 8	0.949
TIMI 0/1 before PCI [%]	63.8	59.1	0.399
TIMI 3 after PCI [%]	91.6	87.4	0.127
Bifurcation [%]	24.7	25.2	0.915
Local complications [%]	3.1	4.2	0.379
Type B2 lesion [%]	24.1	33.5	0.002
Type C lesion [%]	60.4	46.4	0.002
Three-vessel disease [%]	33.1	32.7	0.744

Data are presented as means ± SD or % of patients. DES — drug eluting stent; BMS — bare metal stent; PCI — percutaneous coronary intervention; TIMI — coronary blood flow scale

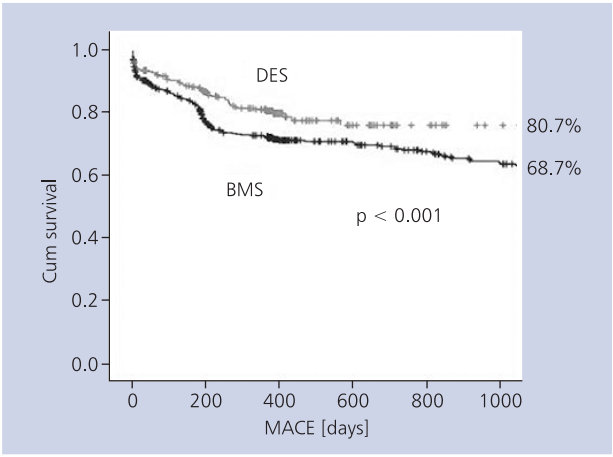

Figure 1. Kaplan-Meier curves of combined end point-free survival according to the type of implanted stent; DES — drug eluting stent; BMS — bare metal stent; MACE — major adverse cardovascular events

ced frequency of composite end-point in the DES group compared to the BMS group.

Survival analysis showed that following parameters were associated with the risk of combined end-point (death, MI, TVR): BMS stent implantation, decreased level of HDL-cholesterol, increased troponin level at admission, previous MI, previous PCI, type B2 or C lesion according to ACC/AHA classification, and Killip class > 1 at admission ($p < 0.05$ for all parameters). After multivariate analysis, the only independent factor associated with increased risk of composite end-point was Killip class at admission > 1 ($p = 0.003$; Table 4). Thus, multivariate analysis including the factors significantly associated with survival based in univariate analysis did not confirm that the use of BMS is related with poorer prognosis and showed statistical trend in favour of DES in terms of combined end-point frequency (HR = 0.79, 95% CI 0.576–1.104, $p = 0.173$).

Table 4. Factors associated with increased risk for combined end-point — the results of multivariate analysis with the use of Cox model

	HR	95% CI	χ^2	P
BMS vs. DES implantation	0.80	0.57–1.10	1.86	0.173
HDL cholesterol, every 1 mg/dL	1.01	1.00–1.02	3.29	0.071
Troponins at admission, every 0.01 ng/mL	1.00	0.99–1.01	0.1	0.752
Previous PCI, yes/no	1.02	0.64–1.63	0.01	0.929
Previous myocardial infarction, yes/no	1.17	0.83–1.66	0.82	0.365
Type B2 or C lesion, yes/no	2.32	0.31–17.25	0.68	0.410
Killip class ≥ 2, yes/no	1.74	1.26–2.40	11.5	0.001
Killip class ≥ 3, yes/no	2.09	1.28–3.40	8.76	0.003
Killip class 4, yes/no	6.81	4.33–10.69	69.39	< 0.001

HR — hazard ratio; CI — confidence interval; BMS — bare metal stent; DES — drug eluting stent; PCI — percutaneous coronary intervention

DISCUSSION

Primary PCI with stent implantation is the treatment of choice in STEMI. Adverse effects after stent implantation are thrombosis and restenosis. Thrombosis is related with increased mortality and may occur both after DES and BMS implantation [12]. Recently some data emerged from general population suggesting that thrombosis may occur more frequently after DES implantation [4]. Increased risk of stent thrombosis is influenced by various factors including stent malapposition, delayed endothelial healing, and increased inflammatory parameters, which may occur more frequently after DES implantation than after BMS implantation, and by many other factors that are unrelated to stent, including the presence of thrombus, resistance to antiplatelet drugs or premature withdrawal of antiplatelet therapy [13]. Many of these factors may coexist in MI. However, our study showed that DES are not inferior to BMS — they do not increase the risk of cardiovascular episodes: death, MI, and the need of repeat TVR (combined end-point) compared to BMS. In the same time, repeat TVR was performed significantly more frequent in the BMS group. Although the clinical burden was higher in the BMS group, the risk factors were not typically related to the development of thrombosis and need for re-intervention.

The results of first non-randomised registries did not show any differences between DES and BMS in STEMI [9]. Further registry data suggested the benefits from DES implantation, mainly in terms of repeat TVR reduction in short-term follow-up. However, in long-term follow-up the number of cardiac events was comparable, with a trend towards more frequent occurrence of thrombosis in DES [14]. Additionally, while data from Global Registry of Acute Coronary Events (GRACE) did not reveal differences between DES and BMS during 180 days after MI, there was significant increase in mortality after DES implantation between 180 and 730 day after MI [11]. Recently published data from long-term follow-up of large population of patients after STEMI showed higher frequency of late (> 1 year) thrombosis and recurrent MI after DES implantation [15]. Contrary to these data, other large registries showed mortality reduction after implantation of DES compared to BMS [10]. On the background of these inconsistent data, in our registry we showed significant reduction of deaths, MI and repeat TVR after DES implantation compared to BMS in 18-months follow-up, however there were differences between groups in some clinical parameters. After adjusting for factors significantly associated with survival, in multivariate analysis there was only trend towards superiority of DES.

Many randomised trials comparing the 2 types of stents in STEMI were also performed. Important results provided one of the largest trials including more than 3,500 patients, with a follow-up period of more than 3 years — Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI). This study compared bivalirudin and heparin with receptor IIb/IIIa antagonist and paclitaxel eluting stents with BMS. No differences were demonstrated in the rate of major cardiovascular events between DES and BMS groups, while there were significant reduction in repeat target lesion revascularisations (TLR) in the DES group [16].

The results of previous studies also suggested the superiority of DES [17–20]. Despite some discrepancies in the study design and adjuvant therapy, no significant differences between groups were observed in the number of deaths, recurrent MI or stent thrombosis, while in most trials there was a reduction in the rate of repeat revascularisations after DES implantation (TVR or TLR). This was confirmed by large meta-analyses of several randomised clinical trials [5, 21]. Abovementioned results are consistent with the data from our registry. However, in randomised clinical trials, specified inclusion and exclusion criteria are adopted, hence the study participants does not fully reflect the population of non-randomised registries.

The results of long-term follow-up (more than 12 months) in several abovementioned randomised clinical trials confirmed the lack of increased risk of adverse cardiovascular events after DES implantation, with reduced number of repeated revascularisations. However, in some trials increased cardiovascular mortality that was not directly related to MI [6] and trend towards increased rate of late and very late stent thrombosis in 5-years follow-up [7, 8] was observed after DES implantation. In our registry, mean follow-up period was 18 months, however interesting would be data from longer observation (several years).

Guidelines of cardiac societies recommend that DES should be used with caution in STEMI. Recent guidelines of European Cardiac Society on myocardial revascularisation allow their use in patients without contraindications for long-term dual antiplatelet therapy, however further long-term observations are needed [22]. Current guidelines of American cardiologic societies recommend the use of DES in patients with STEMI (class IIa recommendation, previously IIb) [23]. Experts from Polish Cardiac Society do not exclude the use those DES, which efficacy was confirmed in selected population of patients with STEMI (Cypher, Taxus) [24].

Finally, it should be noted that Killip classification (that was proposed in 1967 for risk stratification in patients with acute MI) still plays an important role [25]. Although this was not the aim of our study, Killip class at admission > 1 was the only independent factor for increased risk of composite endpoint in our analysis. Such established factors like diabetes, kidney failure or LDL cholesterol level were not associated with poorer prognosis. Although many years have passed and modern treatment of MI have been introduced, Killip classification remains valuable information for physician responsible for admitting and taking care of patient with STEMI.

Limitations of the study

The study has some limitations. First, this was an observational study, which allows to draw rather hypothetical than definite conclusions. Furthermore, decision concerning the type of stent

was made by the operator, without randomisation, which might result in the choice of BMS in patients with higher risk of haemorrhagic complications and poorer prognosis. Moreover, the study included population of patients admitted between 2003 and 2006, when aspiration thrombectomy was not yet routinely performed in patients with STEMI. Nowadays, new DES generations with better safety profile replace sirolimus- or paclitaxel-eluting stents. Besides aspirin, antiplatelet treatment included thienopyridines (some patients received ticlopidine) taken for 1 month after BMS implantation and for 3–6 months after DES implantation, which is inconsistent with current guidelines. Furthermore, no additional statistical analysis of combined end-point components was performed, regarding the differences between groups. Another limitation is lack of assessment of the frequency of suspected and confirmed stent thrombosis, which was undoubtedly the reason of many MI and deaths during the follow-up period.

CONCLUSIONS

In the population of patients with STEMI, DES are not inferior to BMS in terms of safety and efficacy in 18-months observation. DES do not increase the risk of cardiovascular events compared to BMS, while they reduce the rate of repeat revascularisation. Additionally, it was shown that Killip classification remains simple and important classification for risk stratification in patients with acute myocardial infarction.

Conflict of interest: *none declared*

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Porównanie stentów uwalniających leki ze stentami metalowymi zastosowanymi w ostrym zawale serca z uniesieniem odcinka ST w obserwacji odległej

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Streszczenie

Wstęp: Wprowadzenie stentów uwalniających leki (DES) do elektywnych interwencji przezskórnych spowodowało znaczące zmniejszenie zjawiska restenozy i potrzeby ponownych rewaskularyzacji. Pozycja DES zastosowanych podczas pierwotnej przezskórnej angioplastyki wieńcowej (PPCI) nie jest jednoznacznie ustalona, na co wpływały doniesienia oparte na niewyselekcjonowanych grupach pacjentów, wskazujące na zwiększone ryzyko zakrzepicy, zwłaszcza później po ich implantacji, co może się przekładać na zwiększoną śmiertelność. Wyniki większości randomizowanych badań klinicznych porównujących DES ze stentami metalowymi (BMS) w zawale serca z uniesieniem odcinka ST (STEMI) nie potwierdziły zwiększonej śmiertelności po implantacji DES, przy jednoczesnej redukcji ponownych rewaskularyzacji. Wyniki nierandomizowanych rejestrów i części randomizowanych badań klinicznych nie są jednak tak jednoznaczne.

Cel: Celem pracy było porównanie DES z BMS zastosowanymi podczas PPCI u pacjentów ze STEMI, pod względem parametrów bezpieczeństwa i skuteczności w obserwacji 18-miesięcznej.

Metody: Badaniem obserwacyjnym objęto 895 kolejnych pacjentów (w wieku 64 ± 12 lat, 27% kobiet) hospitalizowanych w latach 2003–2006 z rozpoznaniem STEMI, u których wykonano PPCI. U 327 (37%) osób implantowano DES, a u 568 (63%) BMS. Jako pierwotny złożony punkt końcowy badania przyjęto: śmiertelność całkowitą, ponowny zawał serca nieprowadzący do zgonu oraz ponowną rewaskularyzację w obrębie naczynia dozawałowego.

Wyniki: Nie stwierdzono różnic między grupą pacjentów, u których implantowano BMS, a grupą pacjentów, u których implantowano DES, m.in. pod względem wieku, płci, obecności czynników ryzyka sercowo-naczyniowego, choroby 3-naczyniowej, frakcji wyrzutowej lewej komory oraz użycia antagonistów receptora IIb/IIIa. Pacjenci z grupy BMS częściej przebyli w przeszłości zawał serca, częściej przeprowadzano u nich rewaskularyzację przezskórną, a stan hemodynamiczny przy przyjęciu był cięższy. Pacjenci z grupy DES charakteryzowali się wyższymi wyjściowymi wartościami hemoglobiny i cholesterolu HDL oraz niższymi stężeniami troponin przy przyjęciu. W grupie DES częściej występowała zmiana typu C wg klasyfikacji ACC/AHA, natomiast w grupie BMS częściej zmiana typu B2. Podczas 570 ± 490 dni (śr. 18 miesięcy) obserwacji śmiertelność wyniosła 8,9% w grupie DES i 15,5% w grupie BMS ($p = 0,005$). W grupie DES rzadziej występowały łącznie zgony i zawały serca (9,5% *vs.* 16%; $p = 0,006$) oraz rzadziej występował złożony punkt końcowy (zgon, zawał, ponowna rewaskularyzacja tętnicy dozawałowej) — 19,3% *vs.* 31,3%; $p < 0,001$. W grupie BMS częściej przeprowadzano ponowną rewaskularyzację zmiany dozawałowej — 13,4% *vs.* 8,6%; $p = 0,03$. Wśród analizowanych parametrów z podwyższonym ryzykiem wystąpienia złożonego punktu końcowego wiązały się: implantacja BMS, obniżone stężenie cholesterolu HDL, podwyższone stężenie troponin przy przyjęciu, przebyty zawał serca, przebyte PCI, typ zmiany B2 lub C wg ACC/AHA oraz klasa Killipa przy przyjęciu > 1 (wszystkie $p < 0,05$). Po zastosowaniu analizy wieloczynnikowej jedynym niezależnym czynnikiem związanym ze zwiększonym ryzykiem wystąpienia złożonego punktu końcowego była klasa Killipa przy przyjęciu > 1 ($p = 0,003$). Analiza wieloczynnikowa nie wykazała, żeby zastosowanie BMS wiązało się z gorszym rokowaniem, utrzymując statystycznie trend na korzyść użycia DES, pod względem występowania złożonego punktu końcowego (HR = 0,798; 95% CI 0,576–1,104; $p = 0,173$).

Wnioski: W populacji chorych ze STEMI DES nie są gorsze w porównaniu z BMS pod względem parametrów bezpieczeństwa i skuteczności w obserwacji 18-miesięcznej, nie zwiększają ryzyka wystąpienia incydentów sercowo-naczyniowych w porównaniu z BMS, redukując jednocześnie liczbę ponownych rewaskularyzacji. Dodatkowo wykazano, że klasyfikacja Killipa pozostaje prostym i ważnym narzędziem służącym do stratyfikacji ryzyka u pacjentów z ostrym zawałem serca.

Słowa kluczowe: zawał serca z uniesieniem odcinka ST, pierwotna przezskórna angioplastyka wieńcowa, stenty uwalniające leki

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