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Long term clinical outcomes of brachytherapy, bare-metal stenting, and drug-eluting stenting for *de novo* and in-stent restenosis lesions: Five year follow-up

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Abstract

Background: *We aimed to investigate the effects of brachytherapy, drug-eluting stent (DES) and bare metal stent (BMS) applications in the treatment of coronary artery disease, on five--year clinical outcomes and mortality.*

Methods: *Two hundred and seventeen patients who were treated in our clinics between January 2000 and December 2003 with brachytherapy, DES, or BMS for both* de novo *and in--stent restenosis lesions were included in this cohort study. Of these 217 patients, 69 received brachytherapy, 80 were given BMS and 68 were given DES. The clinical outcomes of the patients during hospitalization and over a long-term follow-up were evaluated. Cardiovascular events, revascularizations and mortality rates were compared among the three groups over a five-year follow-up.*

Results: *The mean age was 60.1 ± 9.5 years in the brachytherapy group, 55.7 ± 9.2 years in the BMS group, and 58.9 ± 9.8 years in the DES group ($p = 0.44$). All-cause mortality rates were 20 (29%) brachytherapy patients, 22 (27.5%) BMS patients, and four (5.9%) DES patients ($p = 0.01$). Cardiovascular event was the cause of death for 14 (20.3%) brachytherapy patients, 16 (20%) BMS patients and four (5.9%) DES patients ($p = 0.001$). All-cause mortality rates were 20 (29%) brachytherapy patients, 22 (27.5%) BMS patients and four (5.9%) DES patients. All-cause and cardiovascular mortality rates were significantly lower in the DES group compared to both the BMS and the brachytherapy groups ($p = 0.01$ and $p = 0.001$, respectively).*

Conclusions: *DES application for in-stent restenosis and* de novo *lesions was superior to brachytherapy and BMS application with respect to all-cause and cardiovascular mortalities.* (Cardiol J 2011; 18, 6: 654–661)

Key words: intracoronary brachytherapy, drug-eluting stent, bare-metal stent, cardiovascular mortality

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Introduction

While stent application is effective in reducing early-stage complications after balloon angioplasty, it cannot completely overcome late-stage restenosis. Therefore, researchers performing intracoronary brachytherapy studies have recently focused on the effects of ionized radiation on restenosis and *de novo* lesions. Studies on intracoronary brachytherapy have demonstrated that it reduces neointimal formation, especially during the initial months, and leads to negative remodeling [1–5]. Failure to completely prevent restenosis with stent procedures or brachytherapy has resulted in the development of drug-eluting (paclitaxel, sirolimus coated) stent (DES) applications. Randomized studies have shown that DES cause less restenosis than bare-metal stents (BMS) [6–9].

Although the ability of brachytherapy and DES to lessen restenosis has been demonstrated in some studies, their contribution to clinical end-points is an issue of greater importance. There is no data in the literature comparing long-term (five years) clinical outcomes of intracoronary brachytherapy, DES and BMS applications.

Therefore, in the present study we aimed to investigate the effects of brachytherapy, DES and BMS applications in the treatment of coronary artery disease (CAD), on five-year clinical outcomes and mortality.

Methods

Patient population

A total of 270 patients were treated with brachytherapy, BMS or DES applications for coronary artery lesions in our clinics between January 2000 and December 2003, of whom 217 were available for five year follow-up. Patients re-presenting with angina and/or objective evidence of coronary artery lesion in native vessel or by-pass graft as demonstrated angiographically and who had undergone successful elective percutaneous revascularization were included in the study. In patients with multiple artery disease, only one lesion was operated per artery. Patients re-presenting with arteries of diameters between 2.5 and 4.0 mm, at high risk for restenosis (diffuse, > 20 mm diseased segment, chronic total occlusion, saphenous graft or presence of in-stent restenosis) and having *de novo* or marked restenotic lesion (> 50%) were considered eligible. Patients with acute myocardial infarction (MI), new thrombotic lesions as evidenced by angiography, and patients in whom aspirin or clopidogrel was contraindicated and who received both brachytherapy and stenting were excluded. Patients were treated with only one of the following: beta--radiotherapy, BMS or DES. The drug in the DES was paclitaxel. Written informed consent was obtained from all patients before inclusion in the study and the study was approved by the Ethics Committee of Erciyes University Medical Faculty.

Procedural details

All patients were given aspirin (100 mg, oral) and clopidogrel (75 mg) at least a week before the procedure, and 5,000 u heparin was administered just before the procedure. Based on standard applications, percutaneous coronary intervention (PCI) was performed using a femoral 8 Fr guiding catheter. In all procedures, brachytherapy, BMS or DES were applied after an adequate opening was achieved by balloon angioplasty.

BMS and DES stent application was carried out in accordance with international guidelines which set the basis for standard applications in our clinics. Patients who received combined BMS and DES were excluded from the study. Successful PCI was defined as a lack of major complications after stent implantation, < 30% decrease in target lesion and TIMI flow grade being 3. The choice as to DES or BMS was left to the operating physician. All DES stents were paclitaxel-eluting.

Transfer-device enclosed strontium/yttrium beta source was used for VBT and a 5 Fr catheter (Novoste Beta-Cath) was used for intravascular transfer. Complete administration (> 90%) of the radiation dose, including interruptions, was considered successful brachytherapy. Recommended radiation dose, determined based on arterial and stent diameters, was administered from a distance of 2 mm. Following successful PCI, transfer catheter was inserted to the arterial region through the wire. The position of the radiation source was angiographically documented. The source device was 40 mm long. A pull-back procedure was applied in case the diseased segment could not be covered by the radiation source. After completion of the radiation therapy, the transfer catheter was removed along with the beta source and the procedure was completed with angiographic imaging following administration of intracoronary nitrate. Procedural success was defined as the presence of 30% or less residual narrowness at the final angiogram.

Measurable coronary angiography

Measurable coronary analysis was performed offline using a CAAS 2 system. Measurements were

performed before and after the operation. Minimal lumen diameter was estimated from the lesion borders and the reference diameter was automatically calculated. The percentage stenosis diameter was calculated using minimal lumen and reference diameters.

Hospitalization and long term follow-up

Acute clinical success was accepted as a successful procedure without a major cardiac event during hospitalization. A major cardiac event was defined as: death, MI or repeated revascularization in any coronary arteries (PCI or CABG). MI was diagnosed in the presence of two of the following symptoms: chest pain lasting for at least 30 min; newly developing pathological q waves; at least doubling of the the normal CK-MB isoenzyme levels.

Myocardial infarcts, cardiovascular or all-cause related morbidities, and revascularization procedure for the target vessel (PTCA, CABG) data during the five year follow-up were obtained from hospital records, death certificates and direct contact via telephone.

Statistical analysis

Chi-square tests and Fisher's exact tests were used for categorical variables. For continuous variables, the three groups were compared using ANOVA. Correlation analyses were performed using the Pearson coefficient of correlation. A probability value of $p < 0.05$ was considered significant. Kaplan-Meier survival analysis was performed for survival analysis of all patients. All statistical analyses were carried out using statistical software (SPSS, version 15.0 for Windows; SPSS, Chicago, IL, USA). Survival curves with a 95% confidence interval (CI) were computed using the Kaplan-Meier method. Cox regression was used to model five year mortality. The start-point was treatment with brachytherapy or BMS or DES, and the end-point was either death or the end of the fifth year of treatment. For multivariate analysis, only variables with a p value < 0.05 were entered into a Cox proportional hazards model and selected using a stepwise selection procedure. Hazard ratios (HR) and 95% CI were computed from the estimated parameters of the final regression model. Software package Stata 11 (StataCorp, College Station, TX, USA) was used for the analysis.

Results

General clinical characteristics

General clinical characteristics are set out in Table 1. There were no significant differences among the three groups with respect to general characteristics including age, gender, history of MI and revascularization, clinical presentation, or cardiovascular risk factors. Also, there were no significant differences in mean baseline blood urea nitrogen or left ventricular ejection fraction (LVEF). All patients were given clopidogrel (75 mg) at least six months after the procedure, and the duration of clopidogrel treatment did not vary between the groups ($p > 0.05$; Table 1).

Angiographic properties

There were no significant differences among the three groups with respect to parameters such as vessel localization, in-stent restenosis/*de novo* ratio and lesion characteristics (length, width, type and narrowing percentage; Table 1).

Acute success and in-hospital events

Acute success was achieved in all patients. No cases of death, new MI or revascularization were seen in any of the three groups (Table 2).

Long-term follow-up results

Mean follow up duration was 5.1 ± 1.1 years in the brachytherapy group, 4.7 ± 1.0 years in the BMS group, and 4.9 ± 0.2 years in the DES group.

During the five year follow-up period, 25 patients (20 PTCA, five CABG) in the brachytherapy group, 22 patients (14 PTCA, eight CABG) in the BMS group, and 11 patients (eight PTCA, three CABG) in the DES group, had undergone revascularization of the target vessel. Totals in terms of revascularization, PTCA or CABG were not significantly different between the groups ($p = 0.29$, 0.01 and 0.53, respectively; Table 2).

During the five year follow-up period, 22 (31.9%) patients in the brachytherapy group, 20 (25%) patients in the BMS group, and seven (10.1%) patients in the DES group were hospitalized due to MI. MI was significantly less frequent in the DES group compared to both the BMS and the brachytherapy groups ($p = 0.03$; Table 2).

During the five year follow-up period, the all-cause mortality figure was 20 (29%) in the brachytherapy group, 22 (27.5%) in the BMS group, and four (5.9%) in the DES group. Cardiovascular event was the cause of death for 14 (20.3%) patients in the brachytherapy group, 16 (20%) patients in the BMS group and four (5.9%) patients in the DES group. All-cause mortality and cardiovascular mortality rates were significantly lower in the DES group compared to both the BMS and the brachytherapy groups ($p = 0.01$ and $p = 0.001$, respectively; Table 2).

Table 1. Demographic, clinical and angiographic characteristics of the patients (n = 217).

	Brachytherapy (n = 69)	BMS (n = 80)	DES (n = 68)	P
Age [years]	60.1 ± 9.5	55.7 ± 9.2	58.9 ± 9.8	0.44
Gender (male/female)	49/20	54/26	51/17	0.61
Prior MI	20 (29%)	20 (25%)	14 (20.6%)	0.25
Prior PCI	13 (18.8%)	10 (12.5%)	8 (11.8%)	0.23
Prior CABG	7 (10.1%)	6 (7.5%)	4 (5.9%)	0.35
Presentation:				
STEMI	25 (36.2%)	22 (27.5%)	18 (26.5%)	0.21
Non-STEMI/UAP	27 (39.1%)	33 (41.3%)	27 (39.7%)	0.94
Stable angina	17 (24.6%)	25 (31.3%)	23 (33.8%)	0.24
LVEF, mean [%]	50.3 ± 10.3	48.6 ± 10.5	51.5 ± 9.7	0.22
NYHA				
1	46 (66.7%)	57 (71.3%)	51 (75%)	0.28
2	17 (24.6%)	18 (25%)	12 (17.6%)	0.32
3	6 (8.7%)	5 (6.3%)	4 (5.9%)	0.51
BUN [mg/dL]	19.3 ± 8.5	17.3 ± 7.3	18.2 ± 8.3	0.35
Clopidogrel use [months]	15.1 ± 3.4	15.5 ± 3.6	16.3 ± 3.7	0.13
Cardiovascular risk factors:				
Diabetes mellitus	21 (30.4%)	28 (35%)	30 (44.1%)	0.09
Hypertension	24 (34.8%)	32 (40%)	32 (47.1%)	0.14
Hyperlipidemia	34 (49.3%)	32 (40%)	34 (50%)	0.93
Smoker	37 (53.6%)	54 (67.5%)	44 (64.7%)	0.18
In-stent restenosis/*de novo*	28/41	32/48	30/38	0.67
Location of lesions:				
LAD	26 (37.7%)	32 (40%)	30 (44.1%)	0.67
RCA	22 (31.9%)	28 (35%)	18 (26.5%)	0.43
CX	16 (23.2%)	16 (20%)	16 (23.5%)	0.96
Saphenous graft	5 (7.2%)	4 (5%)	4 (5.9%)	0.78
Width of lesions	2.97 ± 0.40	3.15 ± 0.35	3.0 ± 0.37	0.17
Length of lesions	13.8 ± 7.6	16.0 ± 5.0	15.5 ± 6.0	0.36
Type of lesions:				
A	10 (14.5%)	18 (22.5%)	19 (27.9%)	0.65
B1	28 (40.6%)	26 (32.5%)	14 (20.6%)	0.23
B2	16 (23.2%)	20 (25%)	21 (30.9%)	0.47
C	15 (21.7%)	16 (20%)	14 (20.6%)	0.83
Percentage of narrowing (QCA):				
50–70%	10 (14.5%)	2 (2.5%)	0	0.11
70–90%	31 (44.9%)	38 (47.5%)	34 (50%)	0.78
90–99%	11 (15.9%)	22 (27.5%)	21 (30.9%)	0.28
99% (subtotal)	7 (10.1%)	8 (10%)	9 (13.2%)	0.77
100% (total)	10 (14.5%)	10 (12.5%)	4 (5.9%)	0.53

MI — myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass grafting; STEMI — ST elevation myocardial infarction; UAP — unstable angina pectoris; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; BUN — blood urea nitrogen; LAD — left anterior descending coronary artery; RCA — right coronary artery; CX — circumflex coronary artery

Table 2. Clinical five year follow-up of all patients.

	Brachytherapy (n = 69)	BMS (n = 80)	DES (n = 68)	P
Repeated revascularization	25 (36.2%)	22 (27.5%)	11 (16.8%)	0.29
PTCA	20 (29%)	14 (17.5%)	8 (11.8%)	0.01
CABG	5 (7.2%)	8 (10%)	3 (4.4%)	0.53
Myocardial infarction	22 (31.9%)	20 (25%)	7 (10.1%)	0.03
Death (all-causes)	20 (29%)	22 (27.5%)	4 (5.9%)	0.01
Cardiovascular death	14 (20.3%)	16 (20%)	4 (5.9%)	0.001

PTCA — percutaneous transluminal coronary angioplasty; CABG — coronary artery bypass grafting; BMS — bare-metal stent; DES — drug-eluting stent

Table 3. Demographic, clinical and angiographic characteristics of the death and survival groups (n = 217).

	Death group (n = 46)	Survival group (n = 171)	P
Age [years]	61.4 ± 11.4	57.2 ± 8.9	0.02
Gender (male/female)	28/18	126/45	0.09
Prior MI	17 (37%)	37 (21.6%)	0.03
Prior PCI	7 (15.2%)	24 (14%)	0.83
Prior CABG	5 (10.9%)	12 (7%)	0.38
Presentation:			
STEMI	22 (42.8%)	43 (25.1%)	0.003
Non-STEMI/UAP	14 (30.4%)	73 (42.7%)	0.13
Stable angina	10 (21.7%)	55 (32.2%)	0.17
LVEF, mean [%]	46.6 ± 11.1	51.0 ± 9.8	0.01
NYHA:			
1	27 (58.7%)	127 (74.3%)	0.04
2	12 (26.1%)	35 (20.5%)	0.41
3	7 (15.1%)	8 (4.7%)	0.01
BUN [mg/dL]	17.9 ± 6.8	18.3 ± 8.3	0.77
Treatments:			
Brachytherapy group (n = 69)	22 (47.8%)	47 (27.5%)	0.009
BMS group (n = 80)	20 (43.5%)	60 (35.1%)	0.29
DES group (n = 68)	4 (8.7%)	64 (37.4%)	< 0.001
Cardiovascular risk factors:			
Diabetes mellitus	23 (50%)	56 (32.7%)	0.02
Hypertension	16 (34.8%)	72 (42.1%)	0.23
Hyperlipidemia	26 (56.5%)	74 (43.3%)	0.07
Smoker	29 (63%)	106 (62%)	0.51
In-stent restenosis/*de novo*	24/22	66/105	0.07
Location of lesions:			
LAD	14 (30.4%)	74 (43.3%)	0.22
RCA	12 (26.1%)	56 (32.7%)	0.45
CX	17 (37%)	31 (18.1%)	0.12
Saphenous graft	3 (6.5%)	10 (5.8%)	0.64
Width of lesions	3.03 ± 0.41	3.05 ± 0.35	0.78
Length of lesions	14.5 ± 6.8	15.8 ± 5.7	0.25
Type of lesions:			
A	12 (26.1%)	35 (20.5%)	0.44
B1	17 (37%)	51 (29.8%)	0.25
B2	10 (21.7%)	47 (27.5%)	0.71
C	7 (15.2%)	38 (22.2%)	0.37
Percentage of narrowing (QCA):			
50–70%	1 (2.2%)	11 (6.4%)	0.21
70–90%	27 (58.7%)	76 (44.4%)	0.33
90–99%	9 (19.6%)	45 (26.3%)	0.51
99% (subtotal)	4 (8.7%)	20 (11.7%)	0.62
100% (total)	5 (10.9%)	19 (11.1%)	0.81

Abbreviation as in Table 1

Demographic, clinical, and angiographic characteristics of the death and survival groups are detailed in Table 3. Regarding the basic clinical and demographic characteristics, the death and survival groups were similar in terms of gender, history of PCI and CABG, lesion localization, in-stent restenosis/*de novo* ratio and lesion characteristics (length, width, type and narrowing percentage; $p > 0.05$). Additionally, smoking, hypertension and hypercholesterolemia were similar in the two groups ($p > 0.05$; Table 3). However, the prevalence of diabetes mellitus and prior MI were significantly higher in the death group than in the survival group ($p = 0.02$; Table 3). Similarly, mean age was higher in the death group ($p = 0.02$; Table 3). Also, admission with ST elevation MI (STEMI) and NYHA class III were the most frequent clinical presentations in the death group ($p = 0.003$; Table 3).

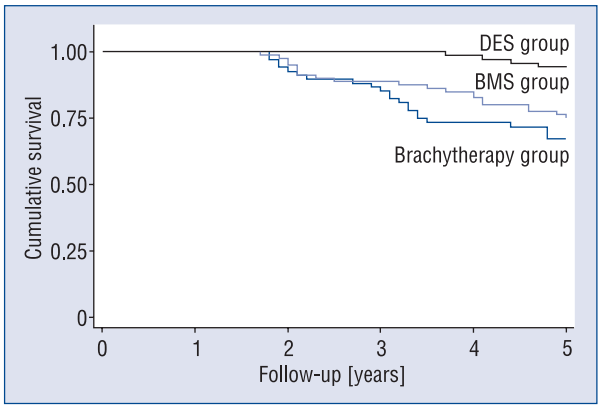

Figure 1. Kaplan-Meier survival estimates by treatment. The patients with DES treatment have the highest probability of survival.

Significantly fewer patients were treated with DES in the death group, and additionally, mean LVEF was significantly lower in the death group compared to the survival group (46.6 ± 11.1 *vs* 51.0 ± 9.8; p = 0.01; Table 3).

Patients treated with DES had the highest probability of survival (Fig. 1). Estimated standard error, p value, and HR as a function of the risks of the variables according to the Cox proportional hazards model are set out in Table 4. Significant relations with total mortality were observed for increasing age, DES use and admission with STEMI (Table 4).

Discussion

Percutaneous angioplasty is one of the commonest treatment procedures for CAD. Stent technology has developed over recent decades, in order to prevent both coronary dissections and long-term restenosis development following balloon angioplasty. Initially, the use of non-drug-eluting stents resulted in problems including restenosis, which led to the development of drug-coated stents and the use of brachytherapy with beta radiation. Although brachytherapy is now considered an outdated approach, the literature does not include many long-term studies which have clinically compared this approach to stent technology.

Ours is the first study comparing brachytherapy, BMS and DES with regards to survival. Our results have demonstrated the superiority of DES in groups of patients with *de novo* and in-stent restenosis lesions.

Previous studies have compared brachytherapy to DES in in-stent restenosis cases. In their study of 50 patients, Feres et al. [10] showed the superiority of DES to brachytherapy in in-stent restenosis. During the initial 12-month follow-up period, revascularization was required in almost one-third of the patients who received beta radiation for in-stent lesions. Pohl et al. [11] also demonstrated the superiority of drug coated stents to brachytherapy in terms of repetitive revascularization rates and the prevention of angiographic lumen loss in patients with in-stent restenosis. In contrast to these studies, the present study is the first to compare DES use to brachytherapy in a patient group including not only in-stent restenosis cases, but also cases with *de novo* lesions. Despite these two groups being similar with respect to in-hospital events, there were significant differences at the clinical end-points of the long-term follow-up.

At the end of the five year follow-up period, all-cause and cardiovascular event related mortality rate, mainly including non-fatal MIs, was significantly lower in the DES group. There was no signifi-

Table 4. Estimated standard error (SE), p value, and hazard ratio (HR) as a function of the risks of the variables according to the Cox proportional hazards model.

Risk factors	SE	P	HR	95% CI
Brachytherapy	0.34	0.92	1.03	0.54–1.97
BMS	0.33	0.90	0.96	0.50–1.85
DES	0.09	0.001	0.18	0.06–0.49
Age	0.02	0.007	1.05	1.01–1.08
STEMI	0.02	0.003	2.43	1.36–4.34
NYHA class 1	0.27	0.47	0.77	0.39–1.54
NYHA class 3	0.49	0.95	0.96	0.35–2.66
LVEF	0.01	0.08	0.97	0.94–1.00

CI — confidence interval; BMS — bare-metal stent; DES — drug-eluting stent; STEMI — ST elevation myocardial infarction; NYHA — New York Heart Association; LVEF — left ventricular ejection fraction

cant difference between the groups with respect to revascularization rate. The observation of fewer deaths, but a similar revascularization rate in the DES group compared to the other groups, suggests that MI events recorded in this group were mostly non-fatal.

In their study of 235 patients (150 BMS and 85 DES), Yang et al. [12] did not record any in-hospital event. Similarly to the study of Condado et al. [13] of 21 patients, no cardiac event was noted following brachytherapy in the present study.

Repeating MIs in patients who had undergone angioplasty is the most important cause of mortality and morbidity. In their study of 61 patients who received brachytherapy, Nikas et al. [14] reported an 8% MI rate during 43 months of follow-up. Pfisterer et al. [15] reported a 13% MI rate during three years of follow-up of 545 patients who had received DES. In the present study, the MI rate during the five-year follow-up was 32% in the brachytherapy group and 10% in the DES group.

We believe that the most important reason for the higher MI rate reported in the brachytherapy group is the high DM rate recorded in this group and the longer follow-up duration. Given that DES may introduce significant benefits, especially to diabetic patients, its superiority to brachytherapy is an expected outcome.

In their studies on brachytherapy, Feres et al. [10] reported that beta radiation causes acellularity in the vessel segments where it is applied, resulting in aggregation of macrophages and thrombocytes on these regions, especially after the first six months, which leads to an increased tendency for late-stage thrombosis. It has also been demonstrated that adequate radiation of the whole area of vessel damage seen after balloon procedure results in plaque formation originating especially from the lesion borders. These factors may have led to the high MI rates recorded in the brachytherapy group in the present study.

The SISR study [16] has demonstrated the clinical and angiographic benefits of drug-coated stents compared to vascular brachytherapy. The superiority of drug coated stents seen during long term clinical follow-ups may also be associated with the presence of in-stent stenosis in these patient groups. The operated lesions of some patients in this study were in-stent restenosis. Currently, DES is preferentially indicated in this patient group.

Meta-analyses of randomized trials and large registry studies demonstrate that the use of DES generally leads to better clinical outcomes for patients with or without diabetes mellitus [17–19]. Additionally, another study observed a low rate of late stent thrombosis and superior efficacy results in DES patients [20]. Less late stent thrombosis may be the plausible explanation of the low death rates observed in the DES treatment group.

LVEF is well-known to predict outcomes in patients with CAD [21]. The magnitude of functional status (NYHA) before stenting differed between the groups.This study showed that mean LVEF was significantly lower in the death group compared to the survival group.

The present study is the first to clinically compare brachytherapy to BMS. The use of BMS did not lead to a significant difference in the rates of MI, revascularization, cardiovascular or all-cause mortalities during in-hospital and long-term follow-up compared to brachytherapy.

Limitations of this study

Limitations were the small number of patients, the retrospective nature, the incomplete follow-up, the single-center design, the mixed cohort of both in-stent restenosis and *de novo* lesions, and the potential bias in the non-randomized selection of treatment strategy. Additionally, the BNP/NT-proBNP levels were not measured.

Conclusions

Among the treatment options available for CAD, DES application provides lower all-cause mortality and cardiovascular mortality rates compared to BMS or brachytherapy. These findings support the cessation of brachytherapy application, as one which although previously used with enthusiasm, has not achieved the desired outcomes.

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