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A propensity score matched analysis

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Safety of drug-eluting stents compared to bare metal stents in patients with an indication for long-term oral anticoagulation: A propensity score matched analysis

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Abstract

Background: Drug-eluting stents (DES) reduce stent restenosis compared with bare-metal stents (BMS). However, their use in patients requiring long-term oral anticoagulation (OAC) is controversial owing to increased risk of bleeding associated with OAC plus antiplatelet treatment over time.

Objective: To assess the safety of DES vs BMS in patients requiring long-term OAC for any reason.

Methods: Prospective observational multicenter study conducted at 6 teaching centers of patients undergoing percutaneous coronary intervention who required OAC for any reason. Adverse outcomes were analyzed at 1 year of follow-up.

Results: We identified 1,002 patients requiring OAC (mean age: 72 years, male 72%). Six- hundred and thirteen patients (61.2%) received BMS and 389 (38.8%) DES. Diabetes, previous PCI, myocardial infarction and acute coronary syndrome at admission (P<0.0001) were more common in patients with DES. Antithrombotic prescribing was similar at discharge between groups (TT: 51.5% vs 50.9%, clopidogrel plus OAC: 7.0% vs 5.0% and DAPT: 41.4% vs 42.7%, p=0.52). DES and BMS patients showed similar rates of total bleeding (15.2% vs 13.4%, adjusted HR 0.82 [0.58-1.17, p=0.82 and major bleeding (6.2% vs 6.0%; adjusted HR 1.22 [0.71-2.09], p=0.46) and MACE (15.2% vs 18.6%, adjusted HR: 0.82 [0.57-1.17], p=0.28, while restenosis was lower in patients with DES (5.3% vs 8.5%, adjusted HR. (0.52 [0.29-0.92], p=0.02. Cox analysis after propensity score selection of 368 matched pairs demonstrated that DES use was not associated with a higher incidence of total bleeding or major bleeding.

Conclusion: DES use is safe in patients with an indication for long-term OAC.

Word count: 249.

Key words: anticoagulants, triple therapy, drug-eluting stents, bleeding.

Conflict of interests: none outside of submitted work

Highlights

- DES use is safe in patients with an indication for long-term OAC.
- DES and BMS patients showed similar rates of major bleeding and MACE.
- Restenosis rate was lower in patients with DES compared to those with BMS.

INTRODUCTION

Many patients with cardiovascular disease require antithrombotic therapy with oral anticoagulation (OAC) in combined with platelet function inhibition. Typical indications for OAC are AF, mechanical valve prosthesis, mitral stenosis, stroke, deep venous thrombosis, pulmonary embolism and hematological disorders with a thrombotic tendency[1-5]. Between 5-10% of patients undergoing percutaneous coronary stent implantation (PCI-S) are on OAC at the time of stenting and the combination of OAC with a single antiplatelet (DAT) or with dual antiplatelet therapy (triple therapy: TT)[1] is usually recommended for these patients despite the associated bleeding risk[1,2,6].

DES reduces the rate of target vessel restenosis (TVR) compared with BMS[7,8]. Historically, their higher cost and requirement for extended duration of DAPT had restricted their use to patients at higher risk of restenosis (such as those with total occlusions, in-stent restenosis, and/or diabetes mellitus)[6,9]. Current AHA/ACC/HRS guidelines recommend avoiding DES use at the time of PCI-S in patients requiring long-term OAC owing to the increased risk of bleeding associated with prolonged TT[2] and since premature interruption of DAPT may result in a higher incidence of early and late stent thrombosis[1,2,6, 7-10]. Although current US guidelines recommend avoiding DES in patients who are at high risk of bleeding, updated European guidelines indicate that second generation DES should be the default choice in those patients, [1,2] coupled with shorter duration DAPT[1]. More recently, guidelines on myocardial revascularization recommend to use DES in any PCI, irrespective of concomitant anticoagulant therapy [6]. These discrepancies exist as a result of conflicting evidence concerning the optimal choice of stent in patients requiring chronic OAC. Some studies have reported that DES use was associated with a

reduction in TVR but increased risk of bleeding, while others found no difference in the frequency of bleeding events[13-17].

The aim of the present study was to compare the safety of DES and BMS in a large prospective multicenter cohort of "real-world" patients requiring long-term OAC for any reason.

METHODS

Study population and design

We analyzed a prospective cohort study of 1,002 consecutive patients undergoing PCI-S who required OAC for any reason. The population consisted of two distinct prospective cohorts: (A) patients enrolled between January 2003 and June 2006 at six Spanish teaching hospitals and one in the United Kingdom (405 patients, 40.4%)[16] (B) patients enrolled between 2007 and 2014 at a single Spanish teaching hospital (597 patients, 59.5%).

Patients with a pre-existing diagnosis of permanent, persistent or paroxysmal AF and those who developed new-onset AF during their index admission were included in this analysis, as well as patients with any other indication for OAC (previous stroke, mechanical heart valve, venous thrombosis or pulmonary embolism). The risk of stroke or systemic embolism in AF patients was assessed using the CHA_2DS_2-VASc score[1,2] and bleeding risk estimated using the HAS-BLED score[1,2].

Choice and duration of antithrombotic therapy at discharge

Since this was an observational study, decisions concerning the intervention strategy, type of stent used, and the choice and duration of discharge antithrombotic therapies were left at the discretion of the attending Cardiologist. The exact duration of

chosen treatment was recorded in all patients. Consistent with ESC guideline recommendations, DAPT (aspirin 100 mg once a day and clopidogrel 75 mg once a day) was continued for at least 1 month following PCI with BMS and 3-12 months following PCI with DES, with use of a single antiplatelet agent until at least complete 12 months. Patients treated with OAC received vitamin K antagonists or non-VKA oral anticoagulants (DOACs, ie. Dabigatran 110 mg/b.id., rivaroxaban 15 mg/per day or apixaban 5 mg/bid) plus DAPT, or vitamin K antagonists (VKAs) with clopidogrel alone. None patient received edoxaban. All patients were followed as part of routine clinical practice at each participating hospital for 1 year as previously described [16].

End-points and definitions

The *primary end-point* was defined as the occurrence of any degree of bleeding (major and minor) during follow-up according to the BARC (Bleeding Academic Research Consortium) classification[17] (major bleeding defined as any bleeding event BARC ≥3a)[17]. We also analyzed any bleeding (BARC 1 & 2). The composite *secondary end-point* was the occurrence of any MACE, defined as death from any cause, myocardial infarction, target vessel revascularization or stent thrombosis, and death from any individual component cause [16].

The two cohort studies complied with the Declaration of Helsinki and were approved by the Institutional Review Boards of all hospitals involved.

Statistical analysis

Continuous variables are described as mean±standard deviation (SD) and range, and categorical variables as absolute and relative frequencies of patients in each

category. Comparison of continuous variables between the two treatment groups was made by Student's t-test and comparison for categorical variables by the chi-square test.

The propensity score (PS) (representing the probability of an individual patient receiving a DES) was computed using extensive non-parsimonious, logistic regression modeling with the several covariates. (Table 1).A PS matched-paired analysis was undertaken by estimation of the standardized difference between baseline characteristics in DES and BMS patients to assess the imbalance in covariates[18]. Each DES subject was matched to the closest available BMS subject using the estimated propensity score and a greedy-matching algorithm.

Survival analyses were conducted using a Kaplan–Meier method and compared using the log-rank test. In addition, we performed a Cox proportional hazard model analysis, considering the outcomes of total bleeding, major bleeding, MACE and all-cause mortality to adjust the effect of clinical variables and the PS on outcome end-points. To further ascertain whether the covariates had been successfully balanced using PS matching and to control for residual confounding, we then fitted these models with additional covariates, including potentially imbalanced demographic, clinical, cohort or procedural variables (i.e. $P \leq 0.15$ for comparison of means) [18]. All *P*-values were two-sided and a $P<0.05$ were considered statistically significant. Statistical analyses were performed using the statistical package SPSS 23.0.

RESULTS

Baseline and procedural characteristics

One thousand and two patients requiring OAC were studied (mean age: 72±10 years, male 72%). Of these, 389 (38.8%) were treated with DES (first generation paclitaxel or sirolimus stents 35.2%; second generation DES in 32.5%; third generation

DES in 32.3%) and 613 (61.2%) with BMS. Baseline and procedural characteristics are summarized in Table 1.

DES patients were more commonly diabetic with a history of stroke, PCI and previous MI. The main indication for OAC was AF in both groups but this was more frequent in patients with DES (n=842, 84%; DES vs BMS: 81.2% vs 85.8%, *P*=0.01) (Table 1). In patients with AF, the proportion with CHA_2DS_2-VASc score ≥2 was not significantly different between both stent groups; however, a HAS-BLED score ≥3 was less prevalent in DES patients.

An acute coronary syndrome as index event was more common in DES patients. Although there were no differences in lesion type, DES patients had a higher number of diseased vessels and received a greater number of stents than those treated with BMS.

A PS matched analysis of 368 pairs was performed (Supplementary Table 1).

Antithrombotic therapy

There were no significant differences in periprocedural antithrombotic treatment (low-molecular-weight or unfractionated heparin, glycoprotein IIb/IIIa receptor antagonists or level of OAC) between groups**.** Antithrombotic medications at discharge are presented in Table 1. The use of OAC was similar in both DES and BMS groups (56.8% vs 51.4%, *P*=0.29) as well as the use of TT (51.5% vs 50.9% respectively, both *P*=0.52). There was a non-significant trend towards a lower use of OAC plus clopidogrel in DES patients. The use of direct anticoagulants (DOACs) was low in our cohort (2% vs 2%) and in combination to DAPT. The mean duration of each antithrombotic strategy was substantially longer in the DES group (TT, 6.2±3 vs. 1.5±0.5 months; OAC plus clopidogrel, 6.9±2.2 vs. 1.6±1 months; all *P*<0.0001).

Drug-eluting stents and bleeding events

Follow-up was complete in 98.8% of patients. No differences were observed in total and major bleeding events between cohorts (A: 2003-2006, B: 2007-2014; 15.2% vs 12.7%, *P*=0.15; 5.8% vs 6.2%, *P*=0.45, respectively). In the overall cohort, patients with BMS and DES suffered similar rates of total, major and minor bleeding (Table 2). The incidence of major bleeding events (BARC≥3) in patients on OAC was similar in patients with DES compared with BMS (8.9% vs 8.6%, p=0.52). Likewise, the incidence of bleeding events in patients receiving TT was similar (total: 16.5% vs 16.7%, *P*=0.52; major 7.3% vs 7.6%, *P*=0.51; minor 7.9% vs 10.6%, *P*=0.18). Five DES and four BMS patients suffered fatal intracranial bleeds. Fifteen major bleeding events occurred during the index hospitalization (related to femoral access in 45% of cases). Early bleeding was more common in BMS patients, (within 30 days of procedure 38% vs 17%, p <0.0001). Bleeding tended to occur later in DES patients treated with TT (median 40 [range 1-201] days post procedure vs. 25 [range 1-40] days post procedure in BMS patients (*P*=0.01).

Kaplan–Meier survival curves demonstrated a similar incidence of total and major bleeding events at 1-year follow-up, regardless of stent type (Figures 1A, 1B). Multivariate analysis after adjustment for confounding variables demonstrated that DES use was not associated with the incidence of total or major bleeding (Table 3).

Drug-eluting stents and major adverse cardiac events

Throughout follow-up, all-cause mortality and rates of MACE and stent thrombosis were similar in BMS and DES patients (Table 2). Twenty four patients (2.20%) suffered definite or probable stent thrombosis (DES 2.20% vs BMS 2.30%, *P=0.54*). Early stent thrombosis occurred in 6 patients (3 of each stent type) and late stent thrombosis in a further 18 (BMS n=8, DES n=10 [paclitaxel-eluting stent n=6,

third generation DES n=4]). No patient suffered very late stent thrombosis. However the incidence of TVR was lower in DES patients (5.3% vs 8.5%, adjusted HR.0.52; 95% CI: 0.29-0.92, *P*=0.02).

Kaplan-Meier survival curves demonstrated a similar incidence of MACE and all-cause of mortality at 1-year follow-up, regardless of stent type (Figures 1C and 1D, respectively). Multivariate analysis after adjustment for confounding variables demonstrated that DES use was not associated with MACE or all-cause mortality (Table 3).

Additional data concerning outcome predictors identified using multivariate analysis are shown in Supplementary Table 2. After adjusting for confounder variables, the use of DES was not associated to any adverse outcomes analyzed total and major bleeding, MACE or any cause of death.

Secondary analysis. Safety of DES in patients at high risk of bleeding

Several subgroup analyses were performed. After adjustment, the association of DES with risk of 1-year total or major bleeding was similar between older (≥75 years) versus younger patients, men versus women, renal failure vs normal renal function, femoral access vs radial access (p for interaction >0. 05 f or al l). Figure 2.

Propensity score analysis

Stent type had no significant effect on outcome in the 368 propensity matched pairs (Table 2). Logistic regression identified several variables as independent 'risk factors' for adverse outcomes (Table 3): female sex, age, stroke, diabetes, smoking, hypertension, hypercholesterolemia, previous PCI, previous CABG, previous MI, acute coronary syndromes, femoral access, number of vessels, total stent length, number of stents and antithrombotic therapy. Multivariable analysis after adjustment for

confounding variables demonstrated that DES use was not significantly associated with adverse outcomes (total or major bleeding, MACE or all-cause mortality, Table 3).

DISCUSSION

We found that DES use was not associated with a higher rate of bleeding when compared with BMS, despite longer duration of combined antithrombotic treatment, thereby reinforcing the notion that DES use is safe in patients who require long-term OAC. In addition, DES patients demonstrated similar rates of MACE and stent thrombosis. However, TVR and restenosis rates were lower in this group (despite higher prevalence of diabetes, previous PCI-S, CABG, and complex lesions)[7,8]. Finally, DES use was not significantly associated with adverse outcomes in the propensity matched analysis.

This prospective cohort of patients requiring long-term OAC reflects everyday clinical practice in OAC patients receiving DES. Importantly, this was not a randomised controlled trial and the similar rates of bleeding and ischemic events in DES and BMS patients may be readily explained by the good clinical judgement of the PCI operators concerning the choice of stent (DES vs BMS) and antithrombotic regime (TT vs DAT) in individual patients.

The major concern of clinicians is the incidence of bleeding events in patients on OAC undergoing PCI-S. However, a short use of DAPT or DAT in this population recommended in the updated ESC guidelines could decrease these outcomes. The newer generation of DES has provided the use of shorter antithrombotic regimen in this scenario.

Consistent with our findings, other authors found no significant difference between DES and BMS patients in the rates of major bleeding and thrombotic

complications[14,15,17]. Conversely, other authors concluded that routine DES use was inappropriate in this population due to increased risk of bleeding[13,19], even though longer regimes of TT in patients receiving first generation DES may have contributed to this difference.

In addition, in our study the incidence of major bleeding events (BARC≥3) was a little lower than in a recent randomized trial-LEADERS-FREE study- (5.9% vs 6.0% compared to 7.2% vs 7.3% in the later study) [20]. Remarkably, in our study, 51% of patients were on TT with a mean duration of 6.2±3 in DES compared to BMS. 1.5±0.5 months. In contrast, the ZEUS trial, which only included 12.% of patients on OAC, showed a surprisingly lower incidence of bleeding events (BARC≥3 was <1%)[21].

Bleeding rates peaked in our study in the second month of treatment, in contrast with previous studies when bleeding events were most common during the first 30 days following PCI-S (and particularly during the index admission, perhaps as a result of more frequent use of femoral access). Higher rates of radial access (57.8%) in our study [12-14] may also explain this disparity. Furthermore, we tested for interactions among multiple subgroups and found no evidence of any of DES with bleeding events.

Consistent with previous reports, the use of TT in DES patients was low in our series, although similar to other series -for both DES and BMS- which may have resulted in a lower than expected incidence of major bleeding[12-16,23-25]. Moreover, although there is evidence to support a strategy of OAC combined with clopidogrel in this seting[26,27], this regime was infrequent in our series with a high number of ACS as an index event. This was probably due to concerns that omission of DAPT could result in a higher incidence of early and late stent thrombosis. The number of patients

receiving this treatment combination was too insufficient to allow definitive conclusions.

Our study confirms that restricted duration of TT in DES patients with AF is not associated with higher rates of stent thrombosis. Indeed, stent thrombosis seems to be rare in patients requiring OAC in real-world practice[12]. Moreover, risks of stent thrombosis are even lower with contemporary third generation and polymer-free DES[28], and shorter durations of combination antithrombotic therapy might soon become routine clinical practice[29].

To this respect, our data is similar to that shown in the LEADERS-FREE trial where drug coated stents were used [29]. Hence, in LEADERS FREE, stent thrombosis rate was 2.0% in patients with DES compared to 2.2% in those with BMS, while in our study this rate was 2.2% compared to 2.3% in BMS, despite including patients treated with first-generation stents. However, in the ZEUS trial the incidence of definite or probable stent thrombosis was lower than in our series (1.0% compared to 2.0% in patients with BMS), showing the role of hydrophilic polymer based stent, although patients on only OAC were 12.0% of the sample size[30].

On the other hand, DES reduces the rate of TVR compared with BMS[7,8] and in our series the TVR rate was significantly lower in patients treated with DES, with similar rates shown in LEADERS-FREE (5.4% vs 8.4% compared with 10.3% vs 5.6% in the later study) [29].

Furthermore, other antihrombotic options could be considered. AF is known to induce P-selectin levels, and thereby, platelet activation during AF. This might be of particular in AF patients undergoing PCI [31]. In addition, FXa is known to influence

cardiac cells via PAR1/PAR2 activation. Thus, FXa inhibition by inhibitors or PAR1 inhibition by Vorapaxar might be effective in this clinical setting [32].

Strengths and limitations

Our series included a large study population of 1,002 patients across the wide demographic and socio-economic spectrum with access to medical care.

Although the PS allows adjustment for differences in baseline characteristics and risk-based decision-making regarding treatment strategy, unmeasured confounders may compromise these comparisons. Furthermore, changes in antithrombotic regimens may have occurred during follow-up in relation to thrombotic or hemorrhagic complications. Reflecting on real world clinical practice, full information concerning the adequacy of anticoagulant control was unavailable which may have impacted on the risk of stroke and major hemorrhage. The use of DOACs was limited during this study, and we cannot draw conclusions. In our study none patient received Edoxaban, and we are waiting for the results of ENTRUST AF-PCI study that it is on going (NCT02866175). Finally, decisions concerning the choice of stent type and therapeutic regime at discharge were made at the discretion of the attending interventional cardiologist or clinician.

Conclusions

Our results suggest that DES use in patients requiring OAC is safe and reduces the incidence of ischaemic events in patients at high risk of restenosis. Until more randomized trial data is available on this population, selection of stent type should be based on assessment of individual patient characteristics, balancing the risks of bleeding and thromboembolism against the likelihood of stent thrombosis and restenosis.

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DISCLOSURES

The authors have no competing interests to declare in relation to this paper.

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Legends

Figure 1. Kaplan–Meier survival curves relating to the use of drug-eluting stents (DES) and bare metal stents (BMS) in patients receiving triple therapy (TT). Number of patients followed up: BMS n=316; DES n=198. A. Total bleeding events; B. Major bleeding events; C. Major adverse cardiac events; D. All-cause mortality

Table 1. Baseline clinical and procedural characteristics of the study population

	BMS (N=613)	DES (N=389)	Difference (BMS vs DES)	p value
Women, n (%)	143 (23.3)	94 (24.1)	1.53	0.76
Mean (SD), age (years)	72.3 (9.8)	71.5 (9.6)	-8.25	0.22
Medical history				
Indication for OAC, n (%)				
Atrial fibrillation	526 (81.2)	316 (85.3)	-20.2	0.01
Mechanical valve prosthesis	35 (5.7)	32 (8.2)		
pulmonary embolism	18 (4.9)	8 (2.0)		
*Other	33 (5.4)	12 (3.0)		
Smoking, n (%)	309 (50.4)	191 (49.1)	-2.12	0.68
Hypertension, n (%)	447 (72.9)	279 (71.7)	-2.18	0.67
Diabetes, n (%)	193 (31.4)	166 (42.6)	18.87	<0.0001
Hypercholesterolaemia, n (%)	322 (52.5)	211 (54.2)	2.78	0.59
History of heart failure, n (%)	128 (21.2)	90 (23.4)	4.29	0.42
History of stroke, n (%)	92 (15.0)	37 (9.5)	-14.21	0.01
Renal failure, n (%)	88 (14.3)	53 (13.6)	-1.66	0.74
Peripheral arterial disease, n (%)	71 (11.5)	49 (12.6)	2.74	0.63

Previous PCI, n (%)	153 (24.9)	137 (35.2)	18.16	<0.0001
Previous CABG, n (%)	60 (9.8)	47 (12.1)	5.93	0.24
Previous MI, n (%)	176 (28.7)	150 (38.5)	16.83	0.001
HAS-BLED score ≥3, n (%)	424 (69.1)	249 (64.0)	-8.78	0.09
CHA_2DS_2-VASc score ≥ 2, n (%)	393 (64.2)	269 (69.4)	6.7	0.07
ACS index event, n (%)	457 (77.2)	234 (65.4)	21.27	<0.0001
Procedural characteristics				
Femoral access	326 (53.3)	165 (42.4)	20.56	0.001
Mean (SD) total nº stents,	1.48 (0.8)	1.72 (0.9)	26.47	<0.0001
Mean (SD) stent diameter, (mm)	3.5 (0.4)	3.2 (0.5)	-1.91	0.05
Mean (SD) stent length, (mm)	18 (23.0)	27 (14.0)	13.27	<0.0001
Antithrombotic therapy				
Triple therapy, n (%)	316 (51.5)	198 (50.9)	-0.98	0.52
Dual antiplatelet therapy, n (%)	254 (41.4)	170 (43.7)	3.79	
Acenocumarol + clopidogrel, n (%)	43 (7.0)	21 (5.4)	-5.35	
Mean (SD), duration of triple therapy, (months)	1.5 (1.0)	6.2 (3.0)	-5.2	0.0001
Mean (SD), duration of dual antiplatelet, (months)	1.6 (1.5)	7.3 (4.6)	-4.2	0.0001
Mean (SD), duration of acenocumarol + clopidogrel, (months)	1.6 (1.0)	6.9 (2.2)	-4.9	0.0001

Footnotes: MI: myocardial infarction; PCI: percutaneous coronary intervention; HAS-BLED score: hypertension, renal/liver failure, stroke, bleeding history of predisposition, INR lability, age > 65 years, concomitant drugs or alcohol; ACS: acute coronary syndrome as the indicator for PCI. *Other indications for OAC: left ventricular thrombus, mitral stenosis, ventricular dysfunction, or antiphospholipid syndrome

Table 2. Comparison of outcomes between stent groups before and after propensity score matching over 1-year follow-up

	Before propensity score			After propensity score		
	BMS (N=613)	**DES** (N=389)	**P value**	**BMS** (N=368)	**DES** (N=368)	**p value**
Total bleeding (%)	82 (13.4)	56 (14.4)	0.64	42 (11.4)	54 (14.6)	0.18
Major bleeding (%)	37 (6.0)	23 (5.9)	0.93	19 (5.1)	23 (6.2)	0.52
Minor bleeding (%)	38 (6.2)	32 (8.2)	0.22	23 (6.2)	30 (8.1)	0.31
MACE (%)	114 (18.6)	59 (15.2)	0.09	67 (18.3)	67 (18.2)	0.46
All-cause mortality (%)	71 (11.5)	42 (10.8)	0.70	37 (10.0)	41 (11.1)	0.63
Cardiovascular mortality (%)	49 (7.9)	26 (6.6)	0.44	26 (7.0)	25 (6.7)	0.88
Target vessel revascularization	52 (8.5)	21 (5.4)	0.02	32 (8.7)	25 (6.7)	0.33
Stent thrombosis (%)	11 (1.8)	7 (1.8)	0.98	7 (1.9)	8 (2.1)	0.85
MAE (%)	166 (27.0)	107 (27.5)	0.88	97 (26.3)	104 (28.2)	0.56

Footnotes: MACE: major adverse cardiac events (death, myocardial infarction, target vessel failure or stent thrombosis), MAE: major adverse events (MACE, any thromboembolic or major bleeding event).

Table 3. Cumulative incidence of outcome events for the whole population and by stent type, and association between DES and outcome events

	Cumulative incidence			HR (95% CI)					
						*Cox regression			
	BMS N=613	DES N=389	P	Unadjusted N=1002	P	Adjusted N=1002	P	**PS paired N=750	P
Total bleeding (model 1)	82 (13.4)	56 (14.4)	0.64	0.82 (0.58-1.14)	0.82	0.82 (0.58-1.17)	0.37	1.17 (0.75-1.85)	0.47
Major bleeding (model 2)	37 (6.0)	23 (5.9)	0.93	0.94 (0.56-1.59)	0.84	1.22 (0.71-2.09)	0.46	0.86 (0.41-1.81)	0.69

MACE	97 (15.8)	52 (13.3)	0.28	0.82 (0.58-1.14)	0.25	0.82 (0.57-1.17)	0.28	0.79 (0.52-1.18)	0.26
(model 3)									
All-cause death	42 (10.8)	71 (11.5)	0.70	0.92 (0.63-1.35)	0.99	1.09 (0.71-1.65)	0.94	1.02 (0.88-1.19)	0.67
(model 4)									

Footnotes: *Model 1: adjusted for: age, stroke, CABG, antithrombotic therapy, HAS-BLED score.

*Model 2: adjusted for: sex, age, stroke, HAS-BLED score, acute coronary syndrome, antithrombotic therapy.

*Model 3: adjusted for: sex, age, smoking, hypertension, CABG, heart failure, acute coronary syndrome, number of vessels, antithrombotic therapy.

*Model 4: adjusted for: age, smoking, hypertension, diabetes, CABG, heart failure, acute coronary syndrome, number of vessels, antithrombotic therapy.

**PS: sex, age, stroke, diabetes, smoking, hypertension, hypercholesterolemia, previous PCI, previous CABG, previous MI, acute coronary syndrome, number of vessels, number of stents, antithrombotic therapy.

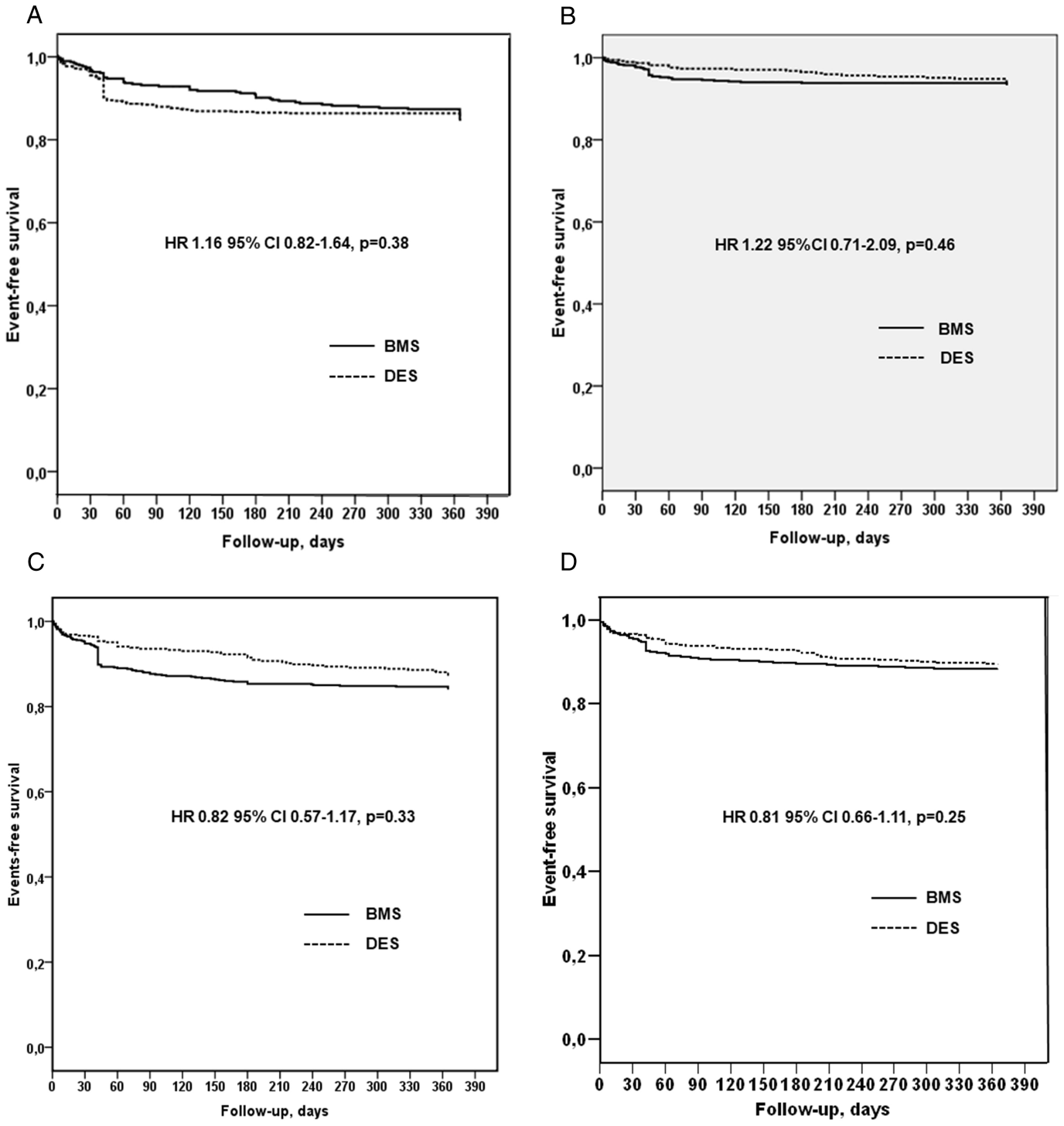
A
Event-free survival
1,0
0,8
0,6
0,4
0,2
0,0
HR 1.16 95% CI 0.82-1.64, p=0.38
BMS
DES
0 30 60 90 120 150 180 210 240 270 300 330 360 390
Follow-up, days
B
Event-free survival
HR 1.22 95%CI 0.71-2.09, p=0.46
BMS
DES
Follow-up, days
C
Events-free survival
HR 0.82 95% CI 0.57-1.17, p=0.33
BMS
DES
Follow-up, days
D
Event-free survival
HR 0.81 95% CI 0.66-1.11, p=0.25
BMS
DES
Follow-up, days

Figure 1

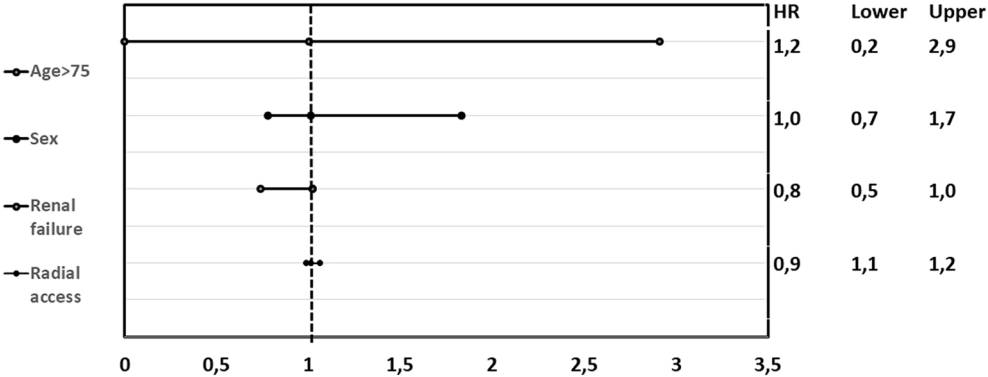
HR
Lower
Upper
Age>75
1,2
0,2
2,9
Sex
1,0
0,7
1,7
Renal failure
0,8
0,5
1,0
Radial access
0,9
1,1
1,2
0
0,5
1
1,5
2
2,5
3
3,5

Figure 2