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Drug-Eluting Versus Bare-Metal Stents in Older Patients: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background: Despite the high prevalence of ischemic heart disease in older patients, there is a substantial lack of evidence to guide clinical decision-making in this population. Hence, we performed a meta-analysis to determine the safety and efficacy of percutaneous coronary intervention (PCI) with drug-eluting stents (DES) versus bare-metal stents (BMS).

Methods: Electronic databases were searched for randomized trials comparing DES with BMS in patients ≥70 years-old. The primary outcome was major adverse cardiovascular events (MACE). Secondary outcomes included different ischemic and bleeding events. Subgroup analyses for dual-antiplatelet therapy (DAPT) duration were conducted.

Results: We included 7 trials with a total of 5449 patients. The use of DES compared with BMS was associated with a significant reduction in MACE (odds ratio [OR]:0.76; 95% confidence interval [CI]:0.62–0.93; P = 0.007) with no increased risk of bleeding events (OR: 1.07; 95% CI: 0.89–1.27; P = 0.48). However, longer duration of DAPT (>6 months) for the DES group increased bleeding events (OR: 1.52; 95% CI: 1.05–2.20; P = 0.03). In contrast, shorter DAPT showed persistent efficacy in reducing MACE in DES-treated patients with no increased bleeding events (OR: 0.72; 95% CI: 0.60–0.87; P < 0.01 and OR: 1.01; 95% CI: 0.84–1.22; P = 0.89, respectively).

Conclusions: In older patients who had undergone PCI, DES showed superior efficacy in reducing MACE with no increased risk of bleeding compared with BMS. Persistent MACE reduction was evident with shorter DAPT durations in DES-treated patients.

Summary: This meta-analysis of randomized clinical trials demonstrated that drug-eluting stents were associated with a significant reduction in major adverse cardiovascular events with no increased risk of bleeding compared with bare-metal stents. The risk of bleeding was high with longer dual antiplatelet therapy duration for patients who underwent DES placement. However, short duration of dual antiplatelet therapy substantially reduced major adverse cardiovascular events with no increased bleeding risk.

1. Introduction

The prevalence of cardiovascular disease (CVD) increases with advanced age, and in the United States (US), approximately 46.7 million people aged ≥60 years have CVD, which accounts for >50% of the total adults with CVD [1]. Although the prevalence of ischemic heart disease (IHD) is high and the number of percutaneous coronary interventions (PCIs) in older patients has increased dramatically in the last 25 years [2–5], there is a substantial lack of evidence to guide clinical decision making in this potentially frail population [6–9].

Despite similar angiographic success rates and clinical benefits of PCI in older patients in comparison to younger patients, knowledge gaps persist [10]. The gaps have been attributed to several factors related to aging, including age-associated alterations in organ physiology, multiple comorbidities, and disabilities [9]. In addition, IHD in older patients is often advanced due to extensive coronary disease, significant calcification, and complex tortuous vascular anatomy coupled with high clinical risk profiles [11]. Furthermore, the risk of bleeding, including major and fatal bleeds from antiplatelet therapy, is higher and more sustained in older patients than in the younger population [12,13]. Therefore,

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careful inspection of the risks and benefits in this population is mandatory [10]. Hence, we performed a meta-analysis of all available evidence from randomized clinical trials (RCTs) to evaluate the safety and efficacy of drug-eluting stents (DES) versus bare-metal stents (BMS) in PCI for older patients.

2. Materials and methods

2.1. Data sources

We conducted our study in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) Statement 2015 [14]. MO and AA independently performed a systematic literature search of PubMed, Embase, the Cochrane Collaboration Central Register of Controlled Trials, and conference proceedings from inception to January 2018. BK resolved any discrepancies. We used Boolean operators for connections of the following headings: "bare-metal stent", "BMS", "drug-eluting stent", "DES", "percutaneous coronary intervention", "PCI", "elderly", "old age", "geriatrics" AND "clinical trials".

2.2. Study selection and data extraction

In this meta-analysis, we included only RCTs with the following prespecified criteria: 1. The trial was conducted in older patients (≥70). 2. The trial compared DES with BMS. 3. The trial reported sufficient clinical outcomes. 4. The trial had at least 30 days of follow-up. BK and TH extracted the data from each RCT. MO and AA resolved any discrepancies. From each clinical trial, we extracted baseline demographic, clinical, and procedural characteristics.

The primary outcome of the study was major adverse cardiovascular events (MACE). A meta-regression analysis based on the DES generation (first vs second) was performed for the primary outcome. Secondary outcomes were all-cause mortality, cardiac mortality, myocardial infarction (MI), target vessel revascularization (TVR), target lesion revascularization (TLR), stent thrombosis (according to the Academic Research Consortium criteria), major and minor bleeding, and all-bleeding events.

Subgroup analysis was performed for the dual antiplatelet therapy (DAPT) duration (short duration ≤6 months versus long duration >6 months). MACE and bleeding events were defined as per each trial's definition. The criteria used to define MACE and bleeding events are detailed in Supplemental Table S1.

2.3. Data synthesis

We calculated aggregate odds ratios (OR) and 95% confidence intervals (CIs) using the DerSimonian-Laird method for random-effects model to account for between-study heterogeneity. We examined heterogeneity with the Cochrane's Q statistic and the I^2 statistic test (<25% considered low heterogeneity and >50% considered significant heterogeneity). We measured the quality of each RCT using the Jadad score. We assessed publication bias by visual inspection of the funnel plot for the primary outcome (MACE). Sensitivity analyses were conducted by excluding the trials successively. For subgroup analyses, the aggregate OR, 95% CI, and P-value for interaction for each subgroup were calculated. All statistical analyses were performed using RevMan, version 5.3 Windows (Cochrane Collaboration, Oxford, UK).

3. Results

3.1. Study selection and trial characteristics

From a total of 4517 studies, we identified 7 RCTs that met our inclusion criteria [15–21]. The selection process of the included RCTs is detailed in Supplemental Fig. S1. There were 3 studies performed as secondary analyses [16–18] or post hoc analyses [19,20]. The included RCTs had a total of 5449 older patients (2967 in the DES group and 2482 in the BMS group). The details and designs of the included RCTs are detailed in Table 1.

Table 1
Details of the included randomized clinical trials.

Study/year	Place (sites)/study period	Age	Design	Stent		DES type	Indication for PCI	Duration of DAPT	Primary endpoint	Event rate, DES	Event rate, BMS	P-value
				DES	BMS							
SENIOR 2018	International (44) 2014–2016	≥75	1:1	596	604	EES	CAD	Stable: 1 month ACS: 6 months	All-cause mortality, MI, stroke, TLR at 1 year	12%	16%	0.02
LEADERS-FREE 2017	International (68)	≥75	1:1	789	775	BA9-coated	ACS	1 month	Cardiac death, MI, stent thrombosis at 390 days	10.7%	14.3%	0.03
NORSTENT 2016	Norway (8) 2008–2011	≥80	1:1	278	253	EES, ZES, SES, PES	CAD	9 months	All-cause death and MI at 5 years	37.4%	37.9%	HR* 0.96
BASKET-PROVE 2015	Europe (11) 2007–2008	≥75	2:1	258	147	EES, SES	CAD	12 months	Cardiac death and MI at 2 years	5%	11.6%	0.014
EXAMINATION 2015	Europe (12) 2008–2010	≥75	1:1	113	132	EES	STEMI	12 months	All-cause death, MI, any revascularization at 1 year	27.4%	22%	0.321
HORIZONS-AMI 2013	International (11) 2005–2007	≥70	3:1	534	170	PES	STEMI	6–12 months	All-cause death, stroke, reinfarction and revascularization at 3 years	18.0%	21.3%	0.07
XIMA 2013	Europe (22) 2009–2011	≥80	1:1	399	401	EES	Angina, NSTEMI	DES: 12 months BMS: 1 month	Death, MI, stroke, TVR, or major hemorrhage at 1 year	14.3%	18.7%	0.09

Abbreviations. ACS: acute coronary syndrome; BA9-coated stents: polymer-free Biolimus A9 (umirolimus)-coated stent (lipophilic sirolimus); BMS: bare-metal stents; BASKET–PROVE trial: BAsel Stent Kosten-Effektivitäts Trial–PROspective Validation Examination; CAD: coronary artery disease; DAPT: dual antiplatelet therapy; DES: drug-eluting stents; Everolimus–eluting stents; EXAMINATION trial: clinical Evaluation of the Xience-V stent in Acute Myocardial INfArcTION; HORIZONS-AMI Trial: Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; HR: hazard ratio: LEADERS FREE trial: Prospective Randomized Comparison of the BioFreedom Biolimus A9 DrugCoated Stent versus the Gazelle BareMetal Stent in Patients at High Bleeding Risk; MACE: major adverse cardiac events; MI: Myocardial Infarction; NORSTENT: Norwegian Coronary Stent Trial; NSTEMI: non-ST-elevation myocardial infarction; PES: Paclitaxel-eluting stents; SENIOR trial: SYNERGY II Everolimus elutiNg stent In patients Older than 75 years undergoing coronary Revascularization associated with a short dual antiplatelet therapy; Sirolimus-eluting stents; STEMI: ST-elevation of myocardial infarction; TLR: target-lesion revascularization; TVR: target-vessel revascularization; ZES: Zotarolimus-eluting stents; XIMA trial: Xience or Vision Stents for the Management of Angina in the Elderly.

The clinical trials included older patients as follows: ≥70 [20], ≥75 [15,16,18,19], or octogenarians ≥80 [17,21]. The indications of PCI were different among the included RCTs. Four clinical trials included PCI in older patients with stable angina [15,17,18,21]. In contrast, 2 RCTs exclusively included patients with ST-elevation myocardial infarction (STEMI) [19,20]. Most trials used everolimus-eluting stents (EES) [17–19,21], 2 RCTs used sirolimus-eluting stents (SES) [17,18], 2 RCTs used paclitaxel-eluting stents (PES) [17,20], and 1 RCT used a polymer-free Biolimus A9 (umirolimus)-coated stent (a lipophilic sirolimus) [16]. In addition, clinical trials included patients with various lesion diameters and lengths. For example, BASKET-PROVE (BAsel Stent Kosten-Effektivitäts Trial–PROspective Validation Examination) trial included patients with lesions ≥3.0 mm in diameter, whereas in the XIMA (Xience or Vision Stents for the Management of Angina in the Elderly) trial, lesions were <3.0 mm in diameter and ≥15 mm in length. However, most clinical trials specified a vessel diameter between 2.25 and 4.0 mm. Furthermore, the median number of stents per patient was 2 (range 1–3). The duration of the dual antiplatelet therapy (DAPT) also varied among the studies and ranged between 1 and 12 months. The LEADERS FREE (Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare Metal Stent in Patients at High Bleeding Risk) trial included older patients with high bleeding risk, such as patients on oral anticoagulation (in 31.4%). Furthermore, some trials included a higher number of patients on glycoprotein IIb/IIIA inhibitors (e.g., >50% in HORIZONS-AMI [Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction]). Two trials (HORIZONS-AMI and EXAMINATION [clinical Evaluation of the Xience-V stent in Acute Myocardial INfArcTION]) reported both short-term (≤1 year) and long-term (>1 year) clinical outcomes and these were included in the subgroup analyses [19,20,22]. The baseline demographic, clinical, and procedural characteristics of the 7 RCTs are detailed in Table 2. However, we were unable to extract any data from the NORSTENT (Norwegian Coronary Stent Trial) as such information was requested though not provided.

3.2. Primary outcome

The incidence of MACE was significantly reduced in the DES group in comparison with the BMS group (rate 17.3% vs 20.0%; OR: 0.76; 95% CI: 0.62–0.93; P = 0.007; I^2 48%) (Fig. 1). Meta-regression analysis did not suggest any statistically significant modifier effect based on the generation of DES used (R^2 = 27%; P = 0.16). Inspection of the funnel plot did not suggest publication bias (Supplemental Fig. S2).

3.3. Secondary outcomes

There were significant differences between both groups in MI (rate 4.9% vs 7.3%; OR: 0.63; 95% CI: 0.47–0.84; P = 0.002; I^2 17%) and TLR (rate 3.9% vs 8.1%; OR: 0.44; 95% CI: 0.27–0.72; P = 0.0009; I^2 31%). However, no significant differences were observed in TVR (rate 5.4% vs 5.9%; OR: 0.65; 95% CI: 0.33–1.27; P = 0.20; I^2 66%) or stent thrombosis (rate 1.9% vs 2.0%; OR: 0.81; 95% CI: 0.53–1.23; P = 0.32; I^2 0%) (Fig. 2A).

There was a significant reduction in cardiac mortality among older patients treated with DES (rate 4.8% vs 6.2%; OR: 0.75; 95% CI: 0.58–0.96; P = 0.02; I^2 0%). However, the rates of other events were not significantly different between both groups and include: all-cause mortality (rate 8.9% vs 9.7%; OR: 0.83; 95% CI: 0.60–1.15; P = 0.26; I^2 44%), major bleeding (rate 6.7% vs 5.1%; OR: 1.09; 95% CI: 0.81–1.47; P = 0.55; I^2 11%), minor bleeding (rate 9.3% vs 8.3%; OR: 1.02; 95% CI: 0.83–1.26; P = 0.84; I^2 0%), and all bleeding events (rate 15.1% vs 12.2%; OR: 1.07; 95% CI: 0.89–1.27; P = 0.48; I^2 0%) (Fig. 2B).

3.4. Subgroup analysis: DAPT duration

There were significant reductions in MACE favoring DES over BMS with both short (≤6 months) and long (>6 months) DAPT duration (rate 10.0% vs 14.0%; OR: 0.72; 95% CI: 0.60–0.87; P = 0.0009 and rate 23.7% vs 28.8%; OR: 0.75; 95% CI: 0.59–0.95; P = 0.02, respectively) (Supplemental Fig. S3). Although there was no significant increase in all bleeding events with short DAPT among older patients treated with DES (rate 15.1% vs 12.5%; OR: 1.01; 95% CI: 0.84–1.22; P = 0.89), there was a significant increase in all bleeding events in older patients treated with longer DAPT in the DES group versus the BMS group (rate 10.0% vs 5.4%; OR: 1.52; 95% CI: 1.05–2.20; P = 0.03) (Supplemental Fig. S4).

4. Discussion

This meta-analysis represents the first, to the best of our knowledge, to evaluate the safety and efficacy of DES compared with BMS in patients ≥70 years. In this meta-analysis of 7 RCTs, there are several notable findings. First and foremost, DES were associated with an approximately one-third reduction in MACE with no significant increase in bleeding events. The reduction in MACE was mainly driven by the significant reduction in cardiac mortality, MI, and TLR in older patients treated with DES versus BMS. The moderate heterogeneity between the studies (I^2 48%) could be explained by the different definitions of MACE across the clinical trials. However, visual inspection of the funnel plot did not suggest publication bias. Second, as expected, the longer duration of DAPT (>6 months) was associated with a significant increase in bleeding events and significant reduction of MACE in the DES group compared with BMS. In contrast, the bleeding risk was not significantly different between both groups treated with shorter DAPT duration, despite the persistent reduction of MACE in the DES group. Our results were also consistent with a previous network meta-analysis of the long-term safety of different stent types in younger patients, which showed the superiority of DES over BMS [23].

Despite the increased risk of IHD in older patients and the benefits of an invasive strategy over a conservative strategy [24–26], current guidelines for PCI in older patients remain vague and recommendations for PCI are mainly derived from younger populations. This is largely secondary to a combination of extensive and complex coronary disease, increased interventional complications, and under-representation of this challenging population in clinical trials [11,27]. Therefore, the American Heart Association, American College of Cardiology, and American Geriatrics Society have strongly recommended the inclusion of older patients in clinical trials [9]. In our study, we observed a high proportion of older patients with hypertension, multivessel coronary disease, and greater lesion length (Table 2).

Previous studies of PCI in older patients have shown better clinical outcomes and reduced mortality with DES PCI in major registries [28–30] and clinical trials [15,16,18,20,21,31]. Yet, some interventional cardiologists continue to use BMS due to the high bleeding risk associated with prolonged DAPT felt to be necessary for DES [12,32,33]. In a previous meta-analysis comparing revascularization versus initial medical therapy for non-ST elevation MI (NSTEMI) in older patients, an invasive approach reduced repeat vascularization and MI at the expense of major bleeding [34]. To improve the therapeutic risk-benefit ratio in older patients after PCI, platelet function monitoring to individualize and adjust antiplatelet therapy has been investigated. However, such a strategy in older patients showed no improvement in clinical outcomes in the ANTARCTIC (Assessment of a Normal Versus Tailored Dose of Prasugrel After Stenting in Patients Aged >75 Years to Reduce the Composite of Bleeding, Stent Thrombosis and Ischemic) trial [35].

Another strategy to reduce bleeding risk is to adopt a shorter duration of DAPT in DES-treated patients. This approach can be considered in patients with high bleeding risk according to different society guidelines where no age-specific recommendations have been stated [36–38]. However, older patients may be more likely to undergo BMS implantation [39]. The current European guidelines for DAPT no longer differentiate between the types of stents (DES or BMS) and they recommend a duration of 1–12 months according to patients' bleeding risk

Table 2
Baseline demographic, clinical, and procedural characteristics.[a]

Characteristic	SENIOR		LEADERS FREE		BASKET-PROVE		EXAMINATION		HORIZONS-AMI		XIMA	
	DES (n = 596)	BMS (n = 604)	DES (n = 789)	BMS (n = 775)	DES (n = 258)	BMS (n = 147)	DES (n = 113)	BMS (n = 132)	DES (n = 534)	BMS (n = 170)	DES (n = 399)	BMS (n = 401)
Age - yr	81.4 ± 4.3	81.4 ± 4.2	81.3 ± 4.3	81.3 ± 4.3	79.1 ± 3.4	79.1 ± 3.6	60.8 ± 12[b]	61.6 ± 13[b]	75.4 [72.6, 79.6]	75.1 [72.0, 77.7]	83.6 ± 3.2	83.4 ± 3.1
Male sex – no. (%)	368 (62%)	379 (63%)	504 (63.9%)	492 (63.5%)	130 (50.4%)	93 (63.3%)	72 (63.7%)	87 (65.9%)	322 (60.3%)	112 (65.9%)	245 (61.1%)	237 (59.1%)
Diabetes mellitus – no. (%)	158/594 (27%)	157/603 (26%)	248 (31.4%)	214 (27.6%)	41 (15.9%)	21 (14.3%)	27 (23.9%)	33 (25%)	110 (20.5%)	43 (25.3%)	102 (25.6%)	97 (24.2%)
Prior myocardial infarction – no. (%)	109/595 (18%)	80/602 (13%)	155 (19.7%)	154 (19.9%)	36 (14%)	26 (17.7%)	5 (4.4%)	10 (7.6%)	59 (11.1%)	24 (14.1%)	119 (29.8%)	86 (21.5%)
Hypertension – no. (%)	427/596 (72%)	488/604 (81%)	615 (77.9%)	618 (79.8%)	194 (75.2%)	102 (69.4%)	71 (62.8%)	94 (71.2%)	339 (63.4%)	105 (61.8%)	300 (75.1%)	311 (77.6%)
Hyperlipidemia – no. (%)	311/596 (52%)	320/604 (53%)	474 (60.1%)	458 (59.1%)	145 (56.2%)	84 (57.1%)	38 (33.6%)	43 (32.6%)	231 (43.2%)	76 (44.7%)	230 (57.6%)	212 (52.9%)
LVEF – (%)	–	–	–	–	–	–	49.36 ± 12.57	46.62 ± 10.12	EF < 40% 109 (20.4%)	EF < 40% 36 (21.0%)	EF < 40% 54 (13.5%)	EF < 40% 41 (10.1%)
Complexity of disease												
- Multivessel disease	202/593 (34%)	183/599 (31%)	503 (63.7%)	494 (63.8%)	131 (50.8%)	78 (53.1%)	18 (15.9%)	19 (14.4%)	–	–	150 (37.6%)	158 (39.4%)
- Bifurcation lesions	144/890 (16%)	119/875 (14%)	–	–	27 (10.5%)	13 (8.9%)	–	–	–	–	–	–
- Chronic total occlusion	59/890 (7%)	57/875 (7%)	–	–	9 (3.5%)	4 (2.7%)	–	–	–	–	–	–
Infarct-related artery												
- LAD	320/593 (54%)	313/599 (52%)	–	–	144 (55.8%)	82 (55.8%)	50 (44.2%)	50 (37.9%)	230 (43.1%)	83 (48.9%)	242 (60.7%)	253 (63%)
- LCx	177/593 (30%)	159/599 (27%)	–	–	59 (22.9%)	41 (27.9%)	15 (13.3%)	16 (12.1%)	–	–	126 (31.7%)	120 (30%)
- RCA	213/593 (36%)	227/599 (38%)	–	–	109 (42.3%)	58 (39.5%)	46 (40.7%)	64 (48.5%)	–	–	152 (38.1%)	142 (35.3%)
- LM	23/593 (4%)	8/599 (1%)	–	–	3 (1.2%)	3 (2%)	1 (0.9%)	1 (0.8%)	–	–	30 (7.6%)	33 (8.3%)
- Graft	7/593 (1%)	4/599 (1%)	–	–	–	–	1 (0.9%)	1 (0.8%)	–	–	14 (3.6%)	6 (1.5%)
Procedure characteristics												
- Total stent length per patient, mm	32.6 ± 20.8	30.3 ± 20.3	–	–	32.4 ± 24.6	31.0 ± 23.0	30.63 ± 16.35	28.39 ± 14.1	28 [20, 40]	24 [16, 32]	26.6 ± 14.3	24.0 ± 13.4
- Maximal stent diameter, mm	3.0 ± 0.5	3.0 ± 0.5	–	–	–	–	3.15 ± 0.41	3.10 ± 0.43	–	–	–	–
- No. of stents per patient	1.7 ± 1.0	1.6 ± 1.0	1.77 ± 1.02	1.73 ± 1.06	1.7 ± 1.1	1.8 ± 1.3	1.54 ± 0.78	1.44 ± 0.66	1.6 ± 0.9	1.5 ± 0.9	2.0 [1–3]	2.0 [1–3]
- Use of glycoprotein IIb/IIIa inhibitor	–	–	–	–	36 (14%)	27 (18.4%)	46 (40.7%)	46 (34.8%)	308 (57.6%)	91 (53.5%)	6 (1.5%)	7 (1.7%)

– indicates missing/unreported data.

Abbreviations. ACS: acute coronary syndrome; BMI: body mass index; BMS: bare-metal stents; BASKET–PROVE trial: BAsel Stent Kosten-Effektivitäts Trial–PROspective Validation Examination; DES: drug-eluting stents; EF: ejection fraction; EXAMINATION trial: clinical Evaluation of the Xience-V stent in Acute Myocardial INfArcTION; HORIZONS-AMI Trial: Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; LAD: left anterior descending artery; LCx: left circumflex; LEADERS FREE trial: Prospective Randomized Comparison of the BioFreedom Biolimus A9 DrugCoated Stent versus the Gazelle BareMetal Stent in Patients at High Bleeding Risk; LM: left main artery; LVEF: left ventricular ejection fraction; NORSTENT: Norwegian Coronary Stent Trial; NSTEMI: non-ST-elevation myocardial infarction; No.: number; PCI: percutaneous coronary intervention; RCA: right coronary artery; SENIOR trial: SYNERGY II Everolimus elutiNg stent In patients Older than 75 years undergoing coronary Revascularization associated with a short dual antiplatelet therapy; STEMI: ST-elevation of myocardial infarction; XIMA trial: Xience or Vision Stents for the Management of Angina in the Elderly.

[a] All data in: mean ± SD; median [IQR]; number (%).

[b] The mean age of older patients was missing and the reported mean age for all age groups is derived from the original paper.

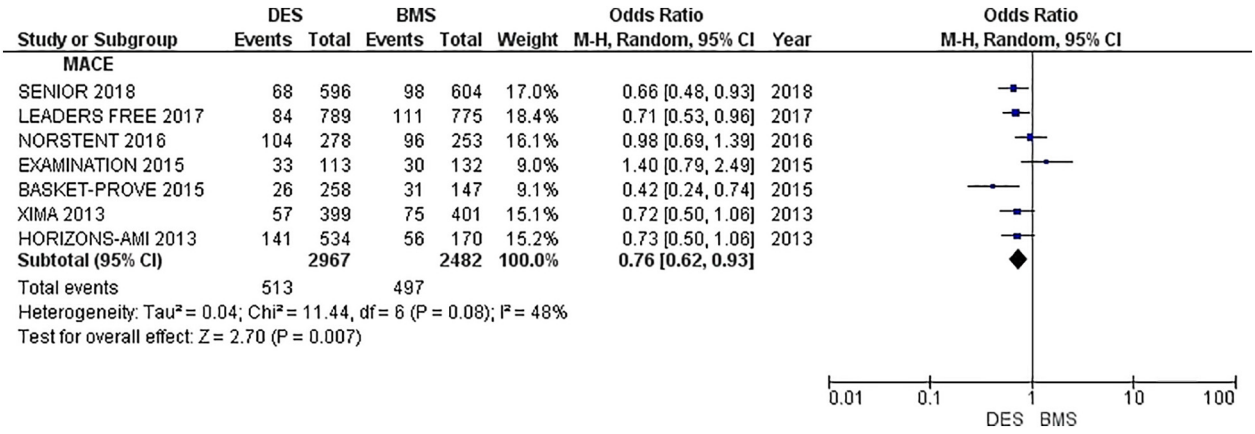

Fig. 1. Forest plot of the rate of major adverse cardiovascular events (primary outcome). Size of central markers represents each study weight. Abbreviations. BASKET–PROVE trial: BAsel Stent Kosten-Effektivitäts Trial–PROspective Validation Examination; BMS: bare-metal stent; CI: confidence interval; DES: drug-eluting stent; EXAMINATION trial: clinical Evaluation of the Xience-V stent in Acute Myocardial INfArcTION; HORIZONS-AMI Trial: Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; LEADERS FREE trial: Prospective Randomized Comparison of the BioFreedom Biolimus A9 DrugCoated Stent versus the Gazelle BareMetal Stent in Patients at High Bleeding Risk; M-H: Mantel-Haenszel method; NORSTENT: Norwegian Coronary Stent Trial; SENIOR trial: SYNERGY II Everolimus elutiNg stent In patients Older than 75 years undergoing coronary Revascularization associated with a short dual antiplatelet therapy; XIMA trial: Xience or Vision Stents for the Management of Angina in the Elderly.

and their clinical presentation, using a risk score as guidance [40]. In a recent patient-level meta-analysis among older patients, short-term DAPT after new-generation DES implantation was associated with a significant reduction in major bleeding compared with long-term DAPT, despite non-significant differences of the composite of MI, stent thrombosis, or stroke [41]. Unlike our study, their meta-analysis included randomized trials comparing DAPT duration only (3–6 months versus 12–24 months) among patients who specifically underwent DES placement. Previous trials found short duration DAPT to be safe in older patients treated with DES (≤6 months in the SENIOR [SYNERGY II Everolimus elutiNg stent In patients Older than 75 years undergoing coronary Revascularization associated with a short dual antiplatelet therapy] trial and 1 month in the LEADERS-FREE trial) [15,16] and those with uncertain bleeding risk (1 month in the ZEUS [Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates] trial) [42]. Furthermore, the benefits of DES in reducing the risk of repeat revascularization and MACE in these clinical trials were also observed, making this strategy a potentially attractive option for older patients. These results were consistent with our pooled analysis in which older patients who received longer DAPT demonstrated a high rate of bleeding events with DES compared with BMS (10.0% vs 5.4%; P = 0.03), despite their significant reduction in MACE (23.7% vs 28.8%; P = 0.02). In contrast, DES-treated patients receiving shorter DAPT duration had a persistent reduction of MACE versus BMS (10.0% vs 14.0%; P = 0.0009) but with no significant increase in bleeding events (15.1% vs 12.5%; P = 0.89).

The strengths of this meta-analysis of PCI in older patients include an extensive search of the literature for only RCTs to eliminate any likelihood of confounding biases stemming from nonrandomized studies. In addition, we performed subgroup analyses, which did not suggest any significant interactions of the treatment effect for the included subgroups. Finally, we tried to close some of the gaps in current knowledge of PCI in older patients.

There are several limitations of the included studies. There were inconsistent definitions of MACE and bleeding across different trials. Availability of data for total revascularization, TVR, and TLR varied among the trials. This may have resulted in higher heterogeneity between the studies and thus may have introduced biases in the results. In addition, the current use of BMS in this population is rare, and some of the included studies used older, first-generation DES that are no longer used today. Additionally, the indications for PCI among the trials were different. However, the vast majority included STEMI in their studied populations. Furthermore, there were various baseline risks of bleeding across the trials. For example, in the LEADERS FREE trial, 31.4% of patients were on oral anticoagulation, which made this group of patients have a higher risk of bleeding in comparison with those in other trials. The duration of DAPT also varied between DES and BMS in some but not all trials, though this reflects actual practice. Also, the prespecified inclusion criteria for lesion diameter and length were different. Likewise, the trials used different generations of DES and further studies regarding the effect of stent type on older patients are warranted. We did not have access to individual patient data, and the definition of "older" varied among the trials. Finally, most of the trials were subgroup analyses and/or post hoc analyses and were underpowered for most of the clinical outcomes.

5. Conclusions

In the present meta-analysis of 7 clinical trials in older patients undergoing PCI, DES demonstrated superior efficacy in reducing MACE, cardiac mortality, MI, and TLR compared with BMS and were as safe as BMS with regard to bleeding risks. Although the risk of bleeding was high with longer duration DAPT for patients who underwent DES placement compared with BMS, shorter DAPT duration was not associated with higher bleeding rates for DES versus BMS, yet there were still reduced rates of MACE with DES compared with BMS. These findings could support guidelines and close some of the gaps in knowledge in deciding the best PCI strategy in older patients, supporting use of DES in such patients.

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Conflict of interest

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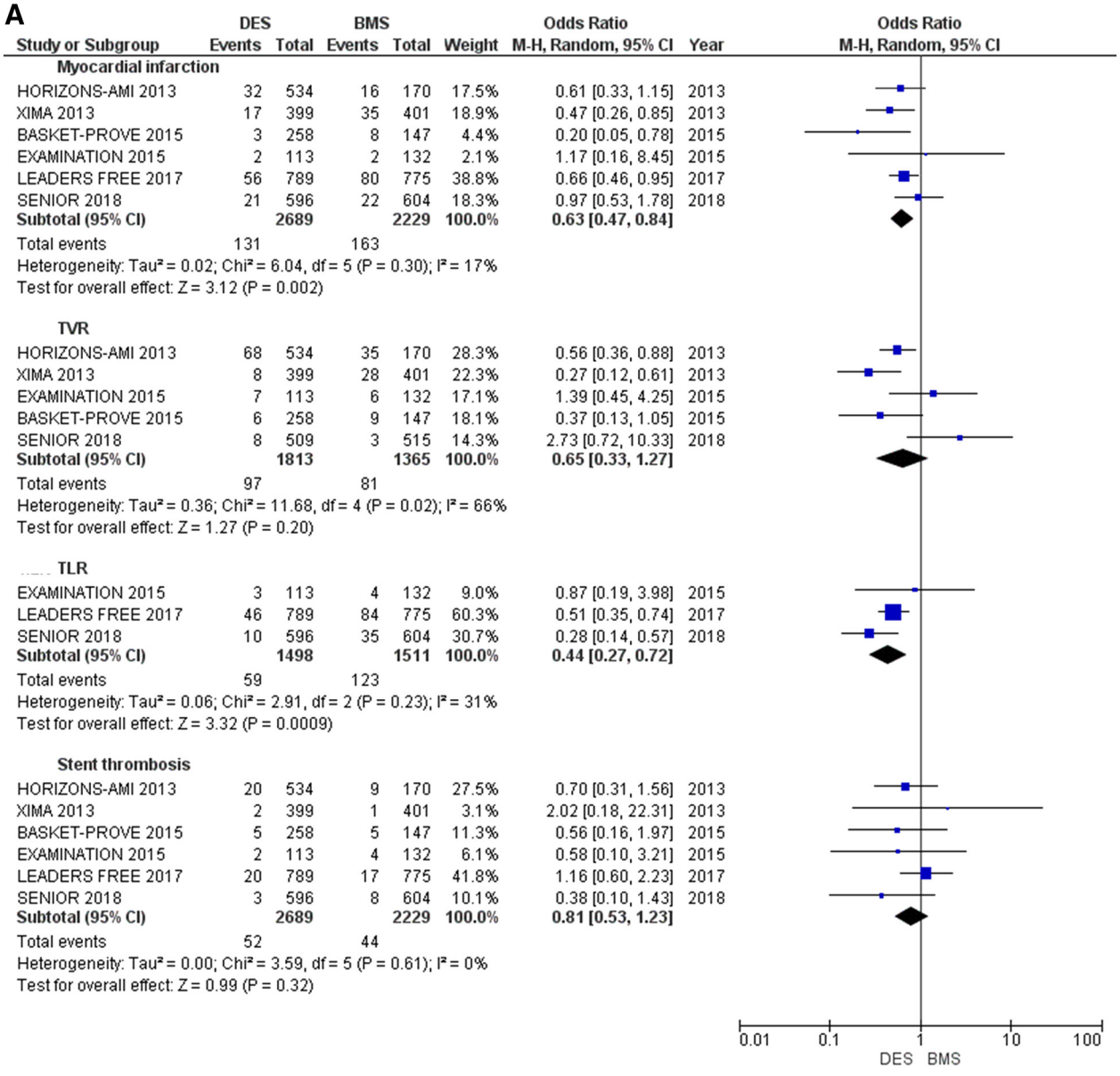

Fig. 2. Forest plots of secondary outcomes (A and B). Size of central markers represents each study weight. Abbreviations. BASKET–PROVE trial: BAsel Stent Kosten-Effektivitäts Trial–PROspective Validation Examination; BMS: bare-metal stent; CI: confidence interval; DES: drug-eluting stent; EXAMINATION trial: clinical Evaluation of the Xience-V stent in Acute Myocardial INfArcTION; HORIZONS-AMI Trial: Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; LEADERS FREE trial: Prospective Randomized Comparison of the BioFreedom Biolimus A9 DrugCoated Stent versus the Gazelle BareMetal Stent in Patients at High Bleeding Risk; M-H: Mantel-Haenszel method; NORSTENT: Norwegian Coronary Stent Trial; SENIOR trial: SYNERGY II Everolimus elutiNg stent In patients Older than 75 years undergoing coronary Revascularization associated with a short dual antiplatelet therapy; XIMA trial: Xience or Vision Stents for the Management of Angina in the Elderly.

B

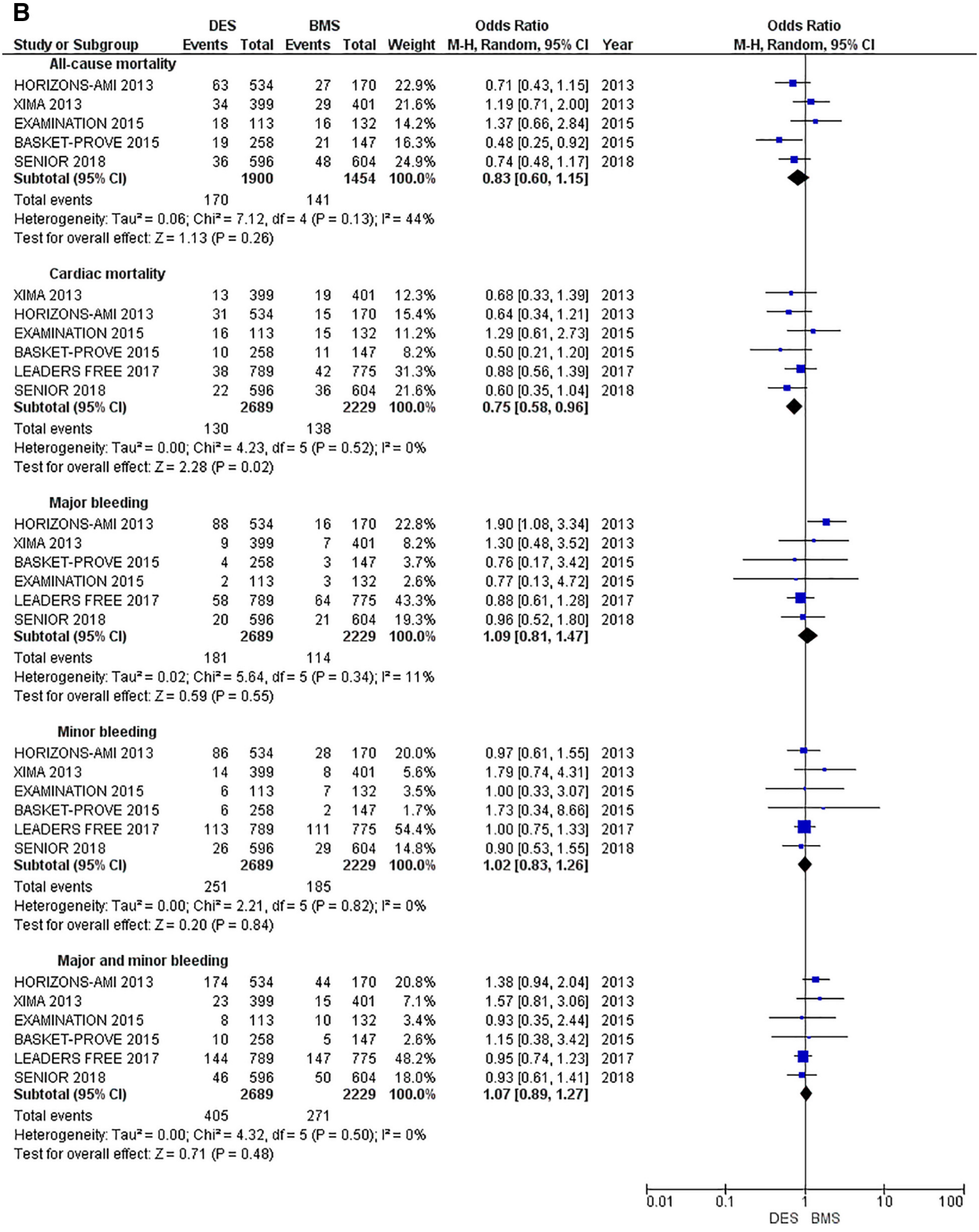

Fig. 2 (*continued*).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2018.11.005.

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