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The efficacy and safety of the intracoronary stents at patients with acute stemi: a meta-analysis and systematic review

Učinkovitost i sigurnost intrakoronarnih stentova u bolesnika s akutnim stemi: meta-analiza i sustavni pregled

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Summary

Introduction: This meta-analysis investigates and reevaluates the efficacy and safety of various intracoronary stents after acute ST-elevation myocardial infarction (STEMI).

Methods: PubMed/ScienceDirect databases were systematically searched for Randomized Controlled Trials (RCTs) w[2]ith outcomes after acute STEMI in relation to stent type. During follow-up, the efficacy outcomes were target lesion revascularization (TLR) and target vessel revascularization (TVR), while the safety outcomes were overall death, cardiac death, myocardial infarction, total in-stent thrombosis (IST) and major adverse cardiovascular events/target vessel failure (MACE/TVF) (the composite of overall/cardiac death, myocardial infarction, TLR and TVR). Stents were classified as bare-metal stent (BMS), drug-eluting stent of the first (DES^{1st}) and second-generation (DES^{2nd}), and biodegradable polymer DES (BP-DES).

Results: We included 31 RCTs, with 17,010 participants (74.6% males), with an average age of 61.2 years. During the average 35-month follow-up, DES are preferred over BMS in reducing the risk of TLR (odds ratio (OR) = 0.47, confidence interval (CI) [0.41-0.54]), TVR (OR = 0.54, CI [0.47-0.61]), overall death (OR = 0.85, CI [0.74-0.99]) and MACE/TVF (OR = 0.61, CI [0.55-0.68]); DES^{2nd} are preferred over DES^{1st} in reducing the risk of myocardial infarction (OR = 0.61, CI [0.39-0.96]), IST (OR = 0.41, CI [0.22-0.73]) and MACE/TVF (OR = 0.70, CI [0.54-0.90]); and, BP-DES are preferred over DES^{2nd} in reducing the risk of TLR (OR = 0.55, CI [0.35-0.86]) and IST (OR = 0.56, CI [0.33-0.96]) (for all P<0.05).

Conclusion: After acute STEMI, DES are superior to BMS in efficacy and safety, DES^{2nd} to DES^{1st} in safety, and BP-DES to DES^{2nd} in efficacy and safety.

Keywords: stents; acute ST-elevation myocardial infarction; outcomes.

Sažetak

Uvod: Ova meta-analiza istražuje i reevaluira učinkovitost i sigurnost različitih intrakoronarnih stentova nakon akutnog infarkta miokarda sa ST-elevacijom (STEMI).

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Metode: Sustavno su pretražene baze podataka PubMed/ScienceDirect za randomizirana kontrolirana ispitivanja (RCT) s ishodima nakon akutnog STEMI u odnosu na vrstu stenta. Tijekom praćenja, ishodi učinkovitosti bili su revaskularizacija ciljne lezije (TLR) i revaskularizacija ciljne žile (TVR), dok su sigurnosni ishodi bili ukupna smrt, srčana smrt, infarkt miokarda, ukupna tromboza u stentu (IST) i glavni štetni kardiovaskularni događaji/zatajenje ciljne žile (MACE/TVF) (kompozit ukupne/srčane smrti, infarkta miokarda, TLR i TVR). Stentovi su klasificirani kao metalni stent (BMS), stent s lijekom prve (DES^{1gen}) i druge generacije (DES^{2gen}) te biorazgradivi polimerni DES (BP-DES).

Rezultati: Uključili smo 31 RCT sa 17.010 sudionika (74,6% muškaraca), prosječne starosti 61,2 godine. Tijekom prosječnog 35-mjesečnog praćenja, DES ima prednost u odnosu na BMS u smanjenju rizika od TLR (omjer izgleda (OR) = 0,47, interval pouzdanosti (CI) [0,41-0,54]), TVR (OR = 0,54, CI [0,47-0,61]), ukupne smrti (OR = 0,85, CI [0,74-0,99]) i MACE/TVF (OR = 0,61, CI [0,55-0,68]); DES^{2gen} imaju prednost u odnosu na DES^{1gen} u smanjenju rizika od infarkta miokarda (OR = 0,61, CI [0,39-0,96]), IST (OR = 0.41, CI [0.22-0.73]) i MACE/TVF (OR = 0.70, CI [0.54-0.90]), dok BP-DES imaju prednost u odnosu na DES^{2gen} u smanjenju rizika od TLR (OR = 0,55, CI [0,35-0,86]) i IST (OR = 0,56, CI [0,33-0,96]) (za sve $P<0,05$).

Zaključak: Nakon akutnog STEMI-a, DES je superiorniji od BMS-a u djelotvornosti i sigurnosti, DES^{2gen} od DES^{1gen} u sigurnosti, a BP-DES od DES^{2gen} u djelotvornosti i sigurnosti.

Ključne riječi: stentovi; akutni infarkt miokarda sa ST-elevacijom; ishodi.

Introduction

Primary percutaneous coronary intervention (PCI) is the treatment of choice in patients with acute ST-segment elevation myocardial infarction (STEMI).[1] In contrast to subjects with chronic coronary or non-ST-elevation acute coronary syndrome, patients presenting with STEMI carry the highest risk of early and late adverse events after PCI due to heightened platelet activation and the presence of thrombus.[2-4] Due to plaque vulnerability, high clot burden, and persistent inflammation, STEMI patients are predisposed to delayed healing and positive vessel remodeling, which results in high rates of uncovered stent struts and stent malapposition.[5] As a consequence, the risk of stent thrombosis in STEMI patients is the highest among coronary artery disease patients.[2,6]

Compared to angioplasty, bare-metal stents (BMS) have shown the benefit in reducing the risk of reocclusion of the ischemia-related artery and the need for repeated revascularization.[7] But, the main limitation of these devices is in-stent thrombosis (IST), which is present in more than 20% of subjects with STEMI.[8]

According to the current guidelines, a new generation of drug-eluting stents (DES) are preferred over BMS (Class of Recommendation I, Level of Evidence: A).[1] A new DES generation, with more biocompatible durable polymers or biodegradable polymers, were developed to reduce the increased risk of stent thrombosis observed with first-generation DES (DES^{1st}).

In the STEMI population, biolimus biodegradable polymer DES (BP-DES) has shown improved clinical outcomes compared with BMS and DES^{1st}.[9,10] The high lipophilicity of biolimus may facilitate rapid drug distribution and potentiate local drug effects in lipidic lesions in patients with STEMI.[11]

Conversely, the safety of BP-DES compared with durable polymer DES has been questioned in several meta-analyses.[12,13]

This meta-analysis aimed to investigate and reevaluate the safety and efficacy of different generations of stents in patients with acute STEMI treated with primary PCI.

Methods

Data sources

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) statement.[13]

PubMed and ScienceDirect databases were systematically searched for studies (Randomized Controlled Trials, RCTs) that reported adverse outcomes in relation to stent type in patients with acute STEMI. Multiple queries using the following keywords were performed: drug-eluting stent or bare-metal stent or biodegradable stent or bioresorbable stent or durable stent or uncoated stent or everolimus eluting stent or zotarolimus-eluting stent or sirolimus eluting stent or paclitaxel eluting stent and ST segment elevation myocardial infarction or ST segment elevation acute coronary syndrome or STEMI and primary PCI.

Eligibility criteria

Studies fulfilling the eligibility criteria were included in the analysis. The selection process was performed according to the PRISMA statement

(Figure 1).[14]

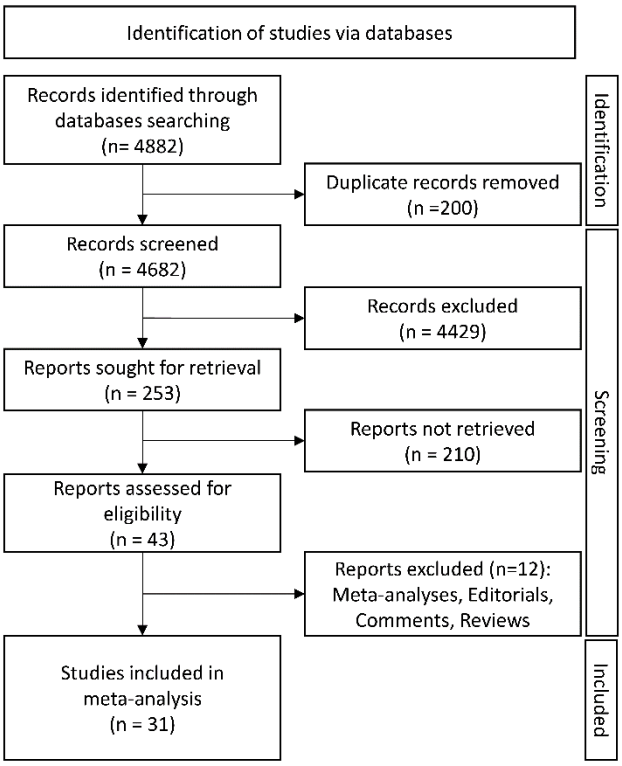

Figure 1 Flow diagram of the study (according to the PRISMA* statement).
Slika 1. Dijagram toka studije (prema izjavi PRISMA).*
PRISMA, Preferirane stavke izvještavanja za sustavne preglede i meta-analize.

In brief, eligible studies had to meet the following criteria: (1) RCTs; (2) included only patients with acute STEMI; (3) related to the association between stents type and outcomes; (4) minimum 6-month follow-up; (5) published in English or other language which can be translated for the purpose of sufficient data extraction. The range of time for the years of the included studies was not limited. Studies were excluded if they were abstracts, editorials, comments, other meta-analyses, or literature reviews. The titles and abstracts of the retrieved studies were screened independently according to the above criteria by two researchers. The full texts of the potentially relevant studies were then obtained and strictly assessed. Disagreements were resolved by discussion with the other researchers.

Data extraction and synthesis

Data extraction was conducted by two researchers separately. Discrepancies were resolved by discussion with the other researchers. The following data were extracted from each eligible study: the first author or the name of the RCT, the enrollment period, the study population, stent type, symptom-to-balloon time, dual antiplatelet treatment (DAPT) duration, GP IIb/IIIa treatment, and follow-up maximum duration. During follow-up, the efficacy outcomes were target lesion revascularization (TLR) and target vessel revascularization (TVR), while the safety outcomes included overall death, cardiac death, myocardial infarction, total IST (probable/definite) and major adverse cardiovascular events/target vessel failure (MACE/TVF) (the composite of overall/cardiac death, myocardial infarction, TLR, and TVR). Stents were classified as follows:

a) BMS;
b) DES^{1st} (sirolimus/paclitaxel (SES/PES)) and second-generation (DES^{2nd}) (everolimus/zotarolimus (EES/ZES)); and,
c) BP-DES.

Statistical analysis

A meta-analysis was performed to calculate the odds ratio (OR) and associated 95% confidence interval [CI]. The I-squared statistic test was used to test for the heterogeneity across studies. If no evidence of heterogeneity was presented (I-squared<50%, P>0.05), a fixed effect model was used. Otherwise, a random effect model was adopted. The publication bias was evaluated by funnel plots and the Egger's linear regression test, which was considered positive in case of P<0.05. For comparison between the groups, we used a chi-squared test with values presented as the absolute number and percentage. The probability value P<0.05 was considered statistically significant. All statistical analyses were performed using MedCalc software (12.7.0.0. for Windows).

Results

Study characteristics

We identified 4,882 studies through the Pubmed and ScienceDirect databases (Figure 1); after screening and exclusion, this meta-analysis finally included 31 studies (RCTs)[15-45] enrolled in the period 2002-2018 (10 single-center), with 17,010 participants (74.6% males), average aged 61.2 years; 21 studies investigated various relationships between DES and BMS, four studies among DES^{1st} generation, six studies between DES^{2nd} and DES^{1st}, and two studies between BP-DES and DES devices. Other RCTs characteristics are presented in Table 1. The average follow-up duration was 35 months.

Table 1 The list of RCT's* which evaluate the efficacy and safety according to stent type during 35-month follow-up after acute STEMI (31 studies, 17,010 patients)
Tablica 1. Popis RCT-ova koji procjenjuju učinkovitost i sigurnost prema vrsti stenta tijekom 35-mjesečnog praćenja nakon akutnog STEMI-a (31 studija, 17.010 bolesnika)*

Author/Trial *Autor/Pokus*	Enrollment period *Razdoblje upisa*	Design *Dizajn*	Patients *Bolesnici*	Age (years) *Starost*	Males (%) *Muškarci*	Stents *Stentovi*	Symptom-to-balloon *Simptom do balona*	DAPT (months) *mjeseci*	GP IIb/IIIa (%)	Efficacy and safety outcomes of the interest# *Ishodi učinkovitosti i sigurnosti od interesa#*	Follow-up (months) *Pregled (mjeseci)*
BASKET [15], 2009	2002-2003	Single-center, RCT, superiority *Jednocentrično, RCT, superiornost*	210	62.1	80.0	DES[1st] (SES, PES) *vrs* BMS	-	6	-	IST, death, myocardial infarction *IST, smrt, infarkt miokarda*	36
BIOSTEMI [16], 2023	2016-2018	Multicenter, RCT, superiority *Multicentrično, RCT, superiornost*	1300	62.7	76.0	BP-DES *vrs* DES[2nd] (EES)	-	≥12	-	TVF (the composite of cardiac death, myocardial infarction, TVR), overall/cardiac death, myocardial infarction, TLR, TVR, IST *TVF (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST*	60
COMFORTABLE-AMI [17], 2019	2009-2011	Multicenter, RCT, superiority *Multicentrično, RCT, superiornost*	1157	60.6	79.4	BP-DES *vrs* BMS	<12h	≥12	48.0 *vrs* 45.7	MACE (the composite of cardiac death, myocardial infarction and TLR), overall/cardiac death, myocardial infarction, TLR, TVR, IST *MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST*	60
COMPARE [18], *USPOREDBA* 2012	2007-2008	Single-center, RCT, superiority *Jednocentrično,*	452	-	-	DES[2nd] (EES) *vrs*	-	12	-	MACE (the composite of overall death, myocardial infarction and TVR),	24

Author/Trial *Autor/Pokus*	Enrollment period *Razdoblje upisa*	Design *Dizajn*	Patients *Bolesnici*	Age (years) *Starost*	Males (%) *Muškarci*	Stents *Stentovi*	Symptom-to-balloon *Simptom do balona*	DAPT (months) *mjeseci*	GP IIb/IIIa (%)	Efficacy and safety outcomes of the interest# *Ishodi učinkovitosti i sigurnosti od interesa#*	Follow-up (months) *Pregled (mjeseci)*
		RCT, superiornost				DES[1st] (PES)				overall/cardiac death, myocardial infarction, TLR, TVR, IST *MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST*	
DEBATER [19], 2012 *DEBATAR*	2006-2008	Single-center, RCT, superiority *Jednocentrično, RCT, superiornost*	907	60.5	76.5	DES[1st] (SES) *vrs* BMS	<12h	≥1 for BMS and ≥6-12 for DES	54 *vrs* 55	MACE (the composite of death, myocardial infarction, stroke, repeat revascularization, and bleeding), overall death, TVR, IST *MACE (kombinacija smrti, infarkta miokarda, moždanog udara, ponovljene revaskularizacije i krvarenja), ukupna smrt, TVR, IST*	12
DEDICATION [20], 2013 *POSVETA*	2005-2006	Multicenter, RCT, superiority *Multicentrično, RCT, superiornost*	626	62.5	73.5	DES[1st] (SES, PES) and DES[2nd] (ZES) *vrs* BMS	<12h	12	97 *vrs* 96	MACE (the composite of cardiac death, myocardial infarction and TLR), overall/cardiac death, myocardial infarction, TLR, TVR, IST *MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST*	60
Diaz et al. [21], 2007	2004-2006	Single-center, RCT, superiority *Jednocentrično,*	114	64.5	79.2	DES[1st] (SES) *vrs*	<12h	≥1 for BMS and ≥9 for	100 *vrs* 100	MACE (the composite of cardiac death, myocardial infarction and TLR), cardiac	12

Author/Trial *Autor/Pokus*	Enrollment period *Razdoblje upisa*	Design *Dizajn*	Patients *Bolesnici*	Age (years) *Starost*	Males (%) *Muškarci*	Stents *Stentovi*	Symptom-to-balloon *Simptom do balona*	DAPT (months) *mjeseci*	GP IIb/IIIa (%)	Efficacy and safety outcomes of the interest# *Ishodi učinkovitosti i sigurnosti od interesa#*	Follow-up (months) *Pregled (mjeseci)*
		RCT, superiornost				BMS		DES		death, IST, TLR *MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda i TLR-a), srčana smrt, IST, TLR*	
EXAMINATION-EXTEND [22], 2021 *PRODUŽETAK ISPITIVANJA*	2008-2010	Multicenter, RCT, superiority *Multicentrično, RCT, superiornost*	1498	61.2	82.6	DES[2nd] (EES) *vrs* BMS	<1 2h	12	53.3 *vrs* 51.5	MACE (the composite of all-cause death, myocardial infarction, revascularization), overall/cardiac death, myocardial infarction, TLR, TVR, IST *MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST*	120
Gao et al. [23], 2007	January 2005-December 2005	Single-center, RCT, superiority *Jednocentrično, RCT, superiornost*	156	58.8	80.8	DES[1st] (SES) *vrs* BMS	-	9-12	-	MACE (the composite of overall death, myocardial infarction, TLR, TVR, IST), overall death, TVR *MACE (kompozitni pokazatelj ukupne smrti, infarkta miokarda, TLR-a, TVR-a, IST-a), ukupna smrt, TVR*	6
HORIZONS-AMI [24], 2010	2005-2007	Multicenter, RCT, superiority *Multicentrično, RCT, superiornost*	3006	59.6	76.5	DES[1st] (PES) *vrs* BMS	<12h	≥6	52.0 *vrs* 51.5	MACE (the composite of death, myocardial infarction, stroke, IST), overall/cardiac death, myocardial infarction, TLR, TVR, IST *MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt*	24

Author/Trial *Autor/Pokus*	Enrollment period *Razdoblje upisa*	Design *Dizajn*	Patients *Bolesnici*	Age (years) *Starost*	Males (%) *Muškarci*	Stents *Stentovi*	Symptom-to-balloon *Simptom do balona*	DAPT (months) *mjeseci*	GP IIb/IIIa (%)	Efficacy and safety outcomes of the interest# *Ishodi učinkovitosti i sigurnosti od interesa#*	Follow-up (months) *Pregled (mjeseci)*
										miokarda, TLR, TVR, IST	
Juwana et al. [25], 2009	2005-2007	Single-center, RCT, superiority *Jednocentrično, RCT, superiornost*	397	61.0	72.0	DES^{1st} (PES) *vrs* DES^{1st} (SES)	-	≥6	33 vrs 28	MACE (the composite of overall death, myocardial infarction, TVR), overall death, myocardial infarction, TVR, IST *MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST*	12
KOMER-AMI [26], 2011	2006-2008	Multicenter, RCT, superiority *Multicentrično, RCT, superiornost*	611	59.8	78.9	DES^{1st} (PES) *vrs* DES^{1st} (SES) *vrs* DES^{2nd} (ZES)	-	12	-	MACE (the composite of cardiac death, myocardial infarction and TLR), IST *MACE (kombinacija srčane smrti, infarkta miokarda i TLR-a), IST*	18
MASTER [27], 2019	2013-2015	Multicenter, RCT, superiority *Multicentrično, RCT, superiornost*	500	61.0	80.6	DES^{1st} (SES) *vrs* BMS	<12h	-	26.1 *vrs* 18.2	TVF (the composite of cardiac death, myocardial infarction, and TVR), all-cause/cardiac death, myocardial infarction, TLR, TVR, IST *TVF (kompozit srčane smrti, infarkta miokarda i TVR-a), smrt od svih uzroka/srčana smrt, infarkt miokarda, TLR, TVR, IST*	12
MISSION [28], 2012	2004-2006	Single-center, RCT, superiority *Jednocentrično,*	310	59.2	77.8	DES^{1st} (SES) *vrs*	<12h	12	100 *vrs* 100	TVF (the composite of cardiac death, myocardial infarction, TVR), overall/cardiac death,	60

Author/Trial *Autor/Pokus*	Enrollment period *Razdoblje upisa*	Design *Dizajn*	Patients *Bolesnici*	Age (years) *Starost*	Males (%) *Muškarci*	Stents *Stentovi*	Symptom-to-balloon *Simptom do balona*	DAPT (months) *mjeseci*	GP IIb/IIIa (%)	Efficacy and safety outcomes of the interest# *Ishodi učinkovitosti i sigurnosti od interesa#*	Follow-up (months) *Pregled (mjeseci)*
		RCT, superiornost				BMS				myocardial infarction, TLR, TVR, IST *TVF (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST*	
MULTI-STRATEGY [29,30], 2008/2013	2004-2007	Multicenter, RCT, superiority *Multicentrično, RCT, superiornost*	744/736	63.9	75.9	DES[1st] (SES) *vrs* BMS	<12h	≥3	100 *vrs* 100	MACE (the composite of overall death, myocardial infarction and TVR), overall death, myocardial infarction, TLR, TVR, IST *MACE (kompozitni pokazatelj ukupne smrti, infarkta miokarda i TVR-a), ukupna smrt, infarkt miokarda, TLR, TVR, IST*	36
PASEO [31], 2009	2003-2005	Single-center, RCT, superiority *Jednocentrično, RCT, superiornost*	270	62.3	70.4	DES[1st] (SES) *vrs* DES[1st] (PES) *vrs* BMS	<12h	6	100 *vrs* 100 *vrs* 100	MACE (the composite of death, myocardial infarction and TLR), myocardial infarction, TLR, IST, cardiac death *MACE (kompozit smrti, infarkta miokarda i TLR-a), infarkt miokarda, TLR, IST, srčana smrt*	24
PASSION [32,33], 2006/2011	2003-2004	Multicenter, RCT, superiority *Multicentrično, RCT, superiornost*	619	61.0	76.0	DES[1st] (PES) *vrs* BMS	<12h	≥6	73.2 *vrs* 74.4	MACE (the composite of cardiac death, myocardial infarction,TLR), overall/cardiac death, myocardial infarction, IST, TLR *MACE (kompozit smrti,*	60

Author/Trial *Autor/Pokus*	Enrollment period *Razdoblje upisa*	Design *Dizajn*	Patients *Bolesnici*	Age (years) *Starost*	Males (%) *Muškarci*	Stents *Stentovi*	Symptom-to-balloon *Simptom do balona*	DAPT (months) *mjeseci*	GP IIb/IIIa (%)	Efficacy and safety outcomes of the interest# *Ishodi učinkovitosti i sigurnosti od interesa#*	Follow-up (months) *Pregled (mjeseci)*
										infarkta miokarda i TLR-), ukupna smrt, infarkt miokarda, IST, TLR, TVR	
RACES-MI [34], 2016	2007-2009	Single-center, RCT, superiority *Jednocentrično, RCT, superiornost*	500	59.0	64.8	DES^{2nd} (EES) *vrs* DES^{1st} (SES)		≥12	54.4 *vrs* 42.4	MACE (the composite cardiac death, myocardial infarction, IST, TVR), cardiac death, myocardial infarction, TVR, IST *MACE (kompozit smrti, infarkta miokarda i TLR), ukupna smrt, infarkt miokarda, IST, TLR, TVR*	84
RESOLVE [35], 2014	2005-2010	Multicenter, RCT, superiority *Multicentrično, RCT, superiornost*	1,271	64.0	79.1	BP-DES *vrs* DES^{1st} (SES)	<12h	≥12	76.0 *vrs* 74.0	MACE (the composite of all-cause death, myocardial infarction, TLR), overall/cardiac death, myocardial infarction, TLR, IST *MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST*	12
SELECTION [36], 2007	2004-2005	Multicenter, RCT, superiority *Multicentrično, RCT, superiornost*	80	60.7	82.5	DES^{1st} (PES) *vrs* BMS	<12h	9	100 *vrs* 100	MACE (the composite of death, myocardial infarction and TLR), overall death, myocardial infarction, IST, TLR, TVR *MACE (kompozit smrti, infarkta miokarda i TLR-a), ukupna smrt, infarkt miokarda, IST, TLR, TVR*	7

Author/Trial *Autor/Pokus*	Enrollment period *Razdoblje upisa*	Design *Dizajn*	Patients *Bolesnici*	Age (years) *Starost*	Males (%) *Muškarci*	Stents *Stentovi*	Symptom-to-balloon *Simptom do balona*	DAPT (months) *mjeseci*	GP IIb/IIIa (%)	Efficacy and safety outcomes of the interest# *Ishodi učinkovitosti i sigurnosti od interesa#*	Follow-up (months) *Pregled (mjeseci)*
SESAMI [37], 2010	2003-2006	Single-center, RCT, superiority *Jednocentrično, RCT, superiornost*	320	62.5	80.0	DES[1st] (SES) *vrs* BMS	<12h	-	77.4 *vrs* 73.7	MACE (the composite of death, myocardial infarction, CABG, and TLR), death, TLR, TVR and TVF (the composite of TVR, myocardial infarction and cardiac death), IST *MACE (kompozit smrti, infarkta miokarda, CABG-a i TLR-a), smrt, TLR, TVR i TVF (kompozit TVR-a, infarkta miokarda i srčane smrti), IST*	36
SEZE [38], 2012	2007-2009	Multicenter, RCT, superiority *Multicentrično, RCT, superiornost*	122	60.9	80.9	DES[2nd] (ZES) *vrs* DES[1st] (SES)	<12h	≥12	11.7 *vrs* 13.1	MACE (the composite of cardiac death, myocardial infarction, TVR), overall/cardiac death, myocardial infarction, TLR, TVR, IST *MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST*	12
STRATEGY [39-41], 2005/2007/2009	2003-2004	Multicenter, RCT, superiority *Multicentrično, RCT, superiornost*	175	62.5	73	DES[1st] (SES) *vrs* BMS	-	≥3	100 *vrs* 100	MACE (the composite of death, myocardial infarction, stroke and TLR), death, myocardial infarction, TLR, TVR, IST *MACE (kompozit smrti, infarkta miokarda, moždanog udara i TLR smrt, infarkt miokarda, TLR, TVR, IST*	60
TYPHOON [42,43],	2003-2005	Multicenter,	712	59.3	78.4	DES[1st]	<12h	≥6	69.3	TVF (the composite of cardiac	48

Author/Trial *Autor/Pokus*	Enrollment period *Razdoblje upisa*	Design *Dizajn*	Patients *Bolesnici*	Age (years) *Starost*	Males (%) *Muškarci*	Stents *Stentovi*	Symptom-to-balloon *Simptom do balona*	DAPT (months) *mjeseci*	GP IIb/IIIa (%)	Efficacy and safety outcomes of the interest# *Ishodi učinkovitosti i sigurnosti od interesa#*	Follow-up (months) *Pregled (mjeseci)*
2006/2011		RCT, superiority *Multicentrično, RCT, superiornost*				(SES) *vrs* BMS			*vrs* 73.7	death, myocardial infarction, TVR), overall/cardiac death, myocardial infarction, IST, TLR, TVR *TVF (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST*	
XAMI [44], 2012	2008-2009	Multicenter, RCT, superiority *Multicentrično, RCT, superiornost*	625	61.6	74.1	DES^{2nd} (EES) *vrs* DES^{1st} (SES)	<12h	≥12	74.5 *vrs* 77.8	MACE (the composite of cardiac death, myocardial infarction, TVR), overall/cardiac death, myocardial infarction, TLR, TVR, IST *MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST*	12
ZEST-AMI [45], 2009	2006-2007	Multicenter, RCT, superiority *Multicentrično, RCT, superiornost*	328	59.6	82.3	DES^{2nd} (ZES) *vrs* DES^{1st} (SES) *vrs* DES^{1st} (PES)	<12h	≥12	18.5 *vrs* 20.9 *vrs* 20.0	MACE (the composite of overall death, myocardial infarction and TVR), overall/cardiac death, TVR, IST *MACE (kompozitni pokazatelj ukupne smrti, infarkta miokarda i TVR-a), ukupna/srčana smrt, TVR, IST*	12

*Abbreviations: BMS, bare-metal stent; BP-DES, biodegradable polymer drug-eluting stent; EES, everolimus-eluting stent; IST, in-stent thrombosis; MACE, major adverse cardiovascular events; PES, paclitaxel-eluting stent; RCT, randomized controlled trial; SES, sirolimus-eluting stent; STEMI, ST-elevation myocardial infarction; TLF, target lesion failure; TLR, target lesion revascularization; TVF, Target vessel failure; TVR, target vessel revascularization; ZES, zotarolimus-eluting stent. Kratice: BMS, stent od golog metala; BP-DES, biorazgradivi polimerni stent koji otpušta lijek; EES, stent koji otpušta everolimus; IST, tromboza u stentu; MACE, veći štetni kardiovaskularni događaji; PES, stent koji otpušta paklitaksel; RCT, randomizirano kontrolirano ispitivanje; SES, stent koji otpušta sirolimus; STEMI, infarkt miokarda s elevacijom ST linije; TLF, neuspjeh ciljne lezije; TLR, revaskularizacija ciljne lezije; TVF, neuspjeh ciljne žile; TVR, revaskularizacija ciljne žile; ZES, stent koji otpušta zotarolimus #Efficacy parameters: TLR and TVR. Safety parameters: myocardial infarction, IST, overall death, cardiac death, MACE/TVF. #Parametri učinkovitosti: TLR i TVR. Parametri sigurnosti: infarkt miokarda, IST, ukupna smrt, smrt od srčanih bolesti, MACE/TVF.

Study results

a) Myocardial infarction: DES were not superior to BMS (14 studies, no publication bias, fixed OR=0.88, CI [0.74-1.05], *P*=0.162); DES^{2nd} were superior to DES^{1st} due to EES (3 studies, publication bias, fixed OR=0.61, CI [0.39-0.96], *P*=0.033); and, BP-DES were not superior do DES^{2nd} (2 studies, publication bias, fixed OR=0.89, CI [0.60-1.32], *P*=0.554) (Table 2, Fig. 2). There were no significant differences among DES^{1st} generation of stents (PES/SES) (2 studies, publication bias, fixed OR=0.90, CI [0.39-2.08], *P*=0.806);
b) TLR: DES were superior to BMS (14 studies, publication bias), mainly due to SES (fixed OR=0.39, CI [0.30-0.51], *P*=0.000); DES^{2nd} were not superior to DES^{1st} (4 studies, no publication bias, random OR=1.05, CI [0.29-3.80], *P*=0.939); and, BP-DES were superior to DES^{2nd} (2 studies, publication bias, fixed OR=0.55, CI [0.35-0.86], *P*=0.000) (Table 2, Fig. 2). There were no significant differences among DES^{1st} generation of stents (PES/SES) (2 studies, publication bias, fixed OR=1.64, CI [0.52-5.11], *P*=0.398);
c) TVR: DES were superior to BMS (13 studies, publication bias), mainly due to SES (fixed OR=0.45, CI [0.36-0.56], *P*=0.000); and, DES^{2nd} were superior to DES^{1st} due to EES (3 studies, no publication bias, random OR=0.52, CI [0.33-0.80], *P*=0.003) (Table 2, Fig.2). There was only one study for comparison between the BP-DES and DES^{2nd}, and the meta-analysis was not possible. There were no significant differences among DES^{1st} generation of stents (PES/SES) (2 studies, publication bias, fixed OR=1.25, CI [0.63-2.45], *P*=0.634);
d) IST: DES were not superior to BMS (17 studies, no publication bias, fixed OR=0.86, CI [0.71-1.05], *P*=0.133); DES^{2nd} were superior to DES^{1st} due to EES (2 studies, publication bias, fixed OR=0.34, CI [0.17-0.71], *P*=0.004); and, BP-DES were superior to DES^{2nd} (2 studies, publication bias, fixed OR=0.50, CI [0.27-0.92], *P*=0.027) (Table 2, Fig. 2). There were no significant differences among DES^{1st} generation of stents (PES/SES) (4 studies, no publication bias, fixed OR=0.90, CI [0.37-2.19], *P*=0.822);
e) Overall death: DES were superior to BMS (13 studies, no publication bias), mainly due to EES (fixed OR=0.77, CI [0.60-0.98], *P*=0.048); DES^{2nd} were not superior to DES^{1st} (4 studies, no publication bias, fixed OR=0.74, CI [0.39-1.38], *P*=0.340); and, BP-DES were not superior to DES^{2nd} (2 studies, publication bias, fixed OR=0.96, CI [0.71-1.29], *P*=0.771) (Table 2, Fig. 2). There were no significant differences among DES^{1st} generation of stents (PES/SES) (2 studies, publication bias, fixed OR=0.46, CI [0.16-1.29], *P*=0.139);
f) Cardiac death: DES were not superior to BMS (12 studies, no publication bias, fixed OR=0.94, CI [0.79-1.13], *P*=0.512); DES^{2nd} were not superior to DES^{1st} (5 studies, no publication bias, fixed OR=0.70, CI [0.44-1.11], *P*=0.125); and, BP-DES were not superior to DES^{2nd} (2 studies, publication bias, fixed OR=0.91, CI [0.65-1.26], *P*=0.562) (Table 2, Fig. 2). There were no significant differences among DES^{1st} generation of stents (PES/SES) (2 studies, publication bias, fixed OR=0.86, CI [0.29-2.53], *P*=0.784); and,
g) MACE/TVF: DES were superior to BMS (15 studies, publication bias), mainly due to SES (fixed OR=0.53, CI [0.45-0.63], *P*=0.000); DES^{2nd} were superior to DES^{1st} due to EES (3 studies, no publication bias, fixed OR=0.55, CI [0.41-0.74], *P*=0.000); BP-DES were not superior to DES^{2nd} (2 studies, publication bias, fixed OR=0.81, CI [0.63-1.03], *P*=0.078) (Table 2, Fig. 2). There were no significant differences among DES^{1st} generation of stents (PES/SES) (4 studies, no publication bias, fixed OR=1.15, CI [0.77-1.71], *P*=0.509).

Discussion

This meta-analysis brings updated data about the influence of various stents on outcomes after acute STEMI treated with primary PCI. According to our results, DES are preferred over BMS in reducing the risk of TLR, TVR, overall death, and MACE/TVF, mainly due to SES and EES; DES^{2nd} over DES^{1st} in reducing the risk of myocardial infarction, IST, and MACE/TVF due to EES; and BP-DES over DES^{2nd} in reducing the risk of TLR and IST.

In the previous meta-analysis, DES were superior to BMS concerning long-term efficacy, while second-generation DES were superior to first-generation DES in reducing IST.[46] Other meta-analyses revealed improvements in outcomes with the evolution from BMS to first-generation and second-generation DES, with the most favorable safety and efficacy was with DES-EES.[47,48] DES versus BMS was associated with a substantial decrease in the risk of TVR without compromising safety; DES-EES had the added advantage of a substantial reduction in the risk of IST when compared with first-generation DES and BMS with no increase in very late IST.[49]

Table 2 Differences between stents in outcomes during 35-month follow-up after acute STEMI* (31 studies, 17,010 patients)

Tablica 2. Razlike između stentova u ishodima tijekom 35-mjesečnog praćenja nakon akutnog STEMI (31 studija, 17.010 bolesnika)*

OUTCOMES# ***ISHODI***	***Myocardial infarction*** ***OR [CI]***	***TLR*** ***OR [CI]***	***TVR*** ***OR [CI]***	***IST*** ***OR [CI]***	***Overall death*** ***OR [CI]***	***Cardiac death*** ***OR [CI]***	***MACE/TVF*** ***OR [CI]***
DES/BMS	*0.88 [0.74-1.05]*	***0.47 [0.41-0.54]***	***0.54 [0.47-0.61]***	*0.86 [0.71-1.05]*	***0.85 [0.74-0.99]***	*0.94 [0.79-1.13]*	***0.61 [0.55-0.68]***
SES/BMS	*0.82 [0.58-1.15]*	***0.39 [0.30-0.51]***	***0.45 [0.36-0.56]***	*0.76 [0.46-1.25]*	*0.83 [0.62-1.11]*	*0.77 [0.53-1.12]*	***0.53 [0.45-0.63]***
PES/BMS	*1.23 [0.37-4.10]*	***0.54 [0.43-0.67]***	***0.50 [0.25-0.99]***	*1.00 [0.69-1.44]*	*0.76 [0.55-1.06]*	*0.77 [0.55-1.08]*	*0.40 [0.16-1.02]*
EES/BMS	*0.88 [0.57-1.36]*	***0.62 [0.42-0.93]***	*0.73 [0.53-1.02]*	*0.72 [0.40-1.31]*	***0.77 [0.60-0.98]***	*1.06 [0.77-1.47]*	***0.77 [0.62-0.95]***
BP-DES/BMS	*0.67 [0.44-1.04]*	***0.44 [0.28-0.69]***	***0.55 [0.37-0.83]***	*0.67 [0.39-1.16]*	*0.95 [0.63-1.43]*	*0.88 [0.52-1.49]*	***0.54 [0.37-0.79]***
DES1st/DES1st (PES/SES)	*0.90 [0.39-2.08]*	*1.64 [0.52-5.11]*	*1.25 [0.63-2.45]*	*0.90 [0.37-2.19]*	*0.46 [0.16-1.29]*	*0.86 [0.29-2.53]*	*1.15 [0.77-1.71]*
DES2nd/DES1st	***0.61 [0.39-0.96]***	*1.05 [0.29-3.80]*	*0.72 [0.38-1.37]*	***0.41 [0.22-0.73]***	*0.74 [0.39-1.38]*	*0.70 [0.40-1.21]*	***0.70 [0.54-0.90]***
ZES/DES1st	*-*	*2.22 [0.89-5.50]*	*1.56 [0.85-2.87]*	*0.54 [0.20-1.48]*	*1.09 [0.31-3.87]*	*0.28 [0.03-2.39]*	*1.25 [0.79-1.98]*
EES/DES1st	***0.61 [0.39-0.96]***	*0.50 [0.08-2.94]*	***0.52 [0.33-0.80]***	***0.34 [0.17-0.71]***	*0.65 [0.32-1.33]*	*0.76 [0.43-1.36]*	***0.55 [0.41-0.74]***
BP-DES/DES2nd	*0.89 [0.60-1.32]*	***0.55 [0.35-0.86]***	***-***	***0.50 [0.27-0.92]***	*0.96 [0.71-1.29]*	*0.91 [0.65-1.26]*	*0.81 [0.63-1.03]*

*Abbreviations: BMS, bare-metal stent; BP-DES, biodegradable polymer drug-eluting stent; CI, confidence interval; EES, everolimus-eluting stent; IST, in-stent thrombosis; MACE/TVF, major adverse cardiovascular events/target vessel failure; OR, odds ratio; PES, paclitaxel-eluting stent; RCT, randomized controlled trial; SES, sirolimus-eluting stent; STEMI, ST-elevation myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; ZES, zotarolimus-eluting stent.

Kratice: BMS, metalni stent; BP-DES, biorazgradivi polimerni stent koji otpušta lijek; CI, interval pouzdanosti; EES, stent koji otpušta everolimus; IST, tromboza u stentu; MACE/TVF, glavni štetni kardiovaskularni događaji/zatajenje ciljne žile; OR, omjer šansi; PES, stent koji otpušta paklitaksel; RCT, randomizirano kontrolirano ispitivanje; SES, stent koji otpušta sirolimus; STEMI, infarkt miokarda sa ST-elevacijom; TLR, revaskularizacija ciljne lezije; TVR, revaskularizacija ciljne žile; ZES, stent koji otpušta zotarolimus

#Efficacy parameters: TLR and TVR. Safety parameters: myocardial infarction, IST, overall death, cardiac death, MACE/TVF.

Parametri učinkovitosti: TLR i TVR. Parametri sigurnosti: infarkt miokarda, IST, ukupna smrt, srčana smrt, MACE/TVF.

Significant values are marked in bold (P<0.05).

Značajne vrijednosti označene su podebljano (P<0,05).

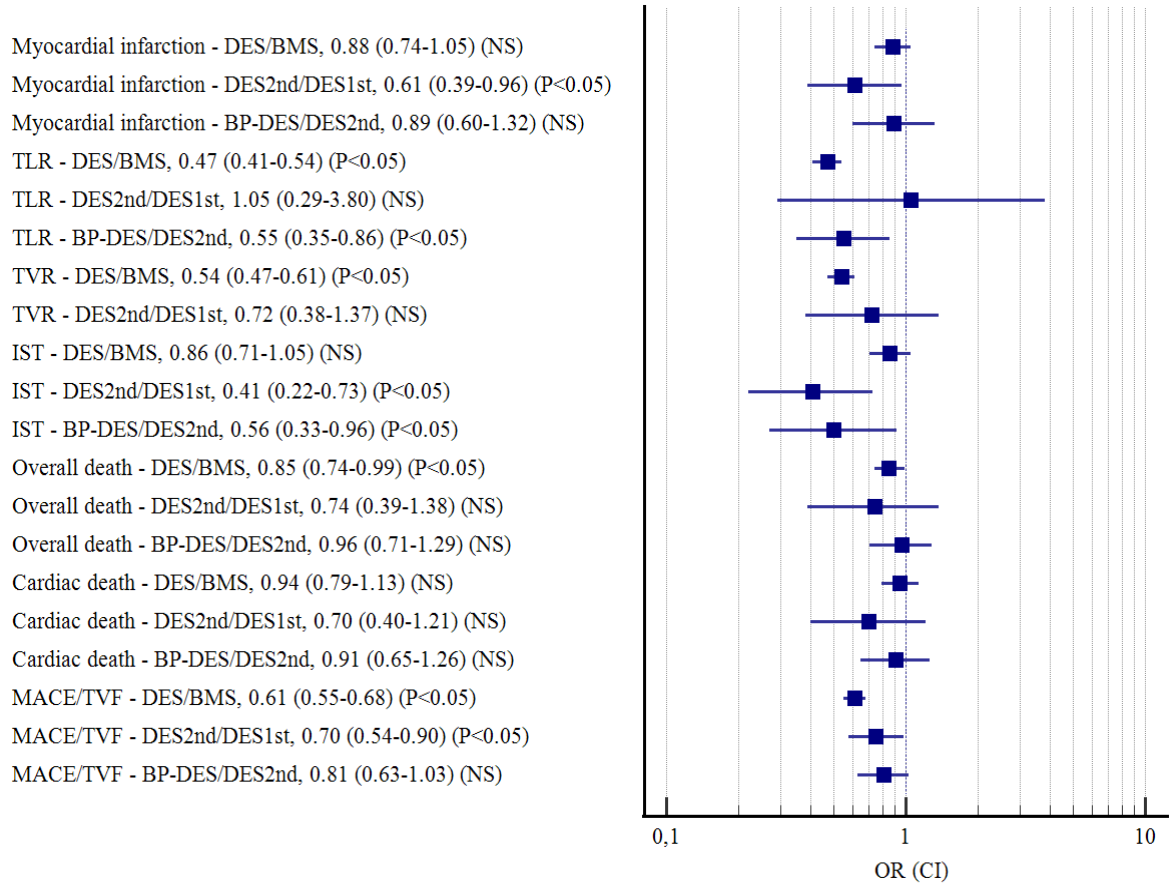

Figure 2 Forest plot with differences between stents in outcomes during 35-month follow-up after acute STEMI* (31 studies, 17,010 patients)

*Abbreviations: BMS, bare-metal stent; BP-DES, biodegradable polymer drug-eluting stent; CI, confidence interval; EES, everolimus-eluting stent; IST, in-stent thrombosis; MACE/TVF, major adverse cardiovascular events/target vessel failure; NS, non-significant; OR, odds ratio; PES, paclitaxel-eluting stent; RCT, randomized controlled trial; SES, sirolimus-eluting stent; STEMI, ST-elevation myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization, ZES, zotarolimus-eluting stent.

#Efficacy parameters: TLR and TVR. Safety parameters: myocardial infarction, IST, overall death, cardiac death, MACE/TVF.

Significant values with $P<0.05$.

DES or BMS in STEMI patients

In most RCTs, the implantation of DES (including BP-DES) resulted in more favorable short and long-term outcomes, with the lower rates of MACE, reduction of repeat revascularization (TVR/TLR) and low incidence of acute/subacute IST; DES demonstrated confirmed superiority in combined patient and device-oriented composite endpoints compared with BMS, with no safety concerns.[17,19,21-24,27,29-31,36,37,39-43] Some RCTs reported an increased rate of late IST and a trend to more related clinical events (cardiac mortality) in patients treated with DES, while in the other trials, no significant difference in MACE was observed.[15,20,28,32,33] Taken together, our meta-analysis of these RCTs revealed efficacy and safety of DES over BMS, mainly due to EES and SES.

BMS is a small, tubular, wire-mesh device that is pre-loaded in a collapsed form onto a catheter balloon, threaded to the narrowed section of the artery, and expanded within the vessel. Once expanded, the BMS acts as a mechanical scaffold, reducing elastic recoil and maintaining post-treatment vessel patency. BMS generally results in extremely favourable initial clinical results; however, re-narrowing of the treated artery is commonly observed in 20–30% of patients. This re-narrowing of the treated artery is due to in-stent restenosis (ISR).[50] To deal with this ISR, a repeat procedure of angiography needs to be performed, and despite extensive research, no therapy consistently prevents this difficult problem. With antiproliferative drugs released slowly, the use of DES interrupts the smooth

muscle cell cycle and thus their proliferation and can significantly reduce ISR.

First or second-generation DES in STEMI patients

DES-EES are superior to DES-PES and DES-SES in terms of safety and efficacy.[18,34] DES-EES are noninferior to DES-SES, and superiority for MACE was suggested.[44] According to the other trials, the use of DES-ZES had similar rates of MACE, cardiac death, and recurrent MI at long-term follow-up as compared with DES-PES and DES-SES.[26] Also, compared to DES-SES, DES-ZES was associated with significantly higher in-stent late lumen loss at 9-month angiographic follow-up, although there was no significant difference in 1-year clinical outcomes.[38] In the ZEST-AMI trial, the efficacy and safety of the three different DESs (ZES, SES, and PES) showed similar, acceptable results in the treatment of STEMI.[45] Finally, DES-SES results in less late luminal loss compared with DES-PES. However, these benefits did not translate into a significant decrease in major adverse cardiac events at 1-year follow-up.[25] Taken together, our meta-analysis of these RCTs revealed the safety of DES^{2nd} over DES^{1st} due to EES. First-generation DES, such as SES and PES, have improved coronary intervention results by improving early results and reducing the risk of restenosis. But, there is presently debate on the safety of first-generation DES regarding late IST, especially after discontinuing dual antiplatelet therapy.[50] Thus, second-generation DES such as ZES and EES have been introduced with promising anti-restenotic efficacy as well as long-term safety. They differ from the first-generation stents concerning the antiproliferative agent, the polymer layer, and the stent frame.

BP-DES or DES in STEMI patients

BP-DES was proven superior to DES-EES concerning target lesion failure at 5 years of follow-up. The difference was driven by a numerically lower risk for ischaemia-driven TLR.[16] In the RESOLVE trial, the use of BP-DES was associated with noninferior 1-year rates of MACE compared with DES-SES.[35] In our meta-analysis of these studies, BP-DES is superior to DES^{2nd} in efficacy and safety.

Recent refinements of newer generation DES involve the reduction of strut thickness of the metallic stent platform and using biodegradable polymers as a carrier for the antiproliferative substance. These improvements in stent design mitigate arterial injury, inflammation, and thrombogenicity, facilitate endothelialization, and reduce neointimal hyperplasia.[16,50]

Study limitations

The main limitation of this study was the small number of studies that evaluate the influence of biodegradable stents on outcomes and consequent publication bias, so further investigations will be necessary. The second limitation is the usage of GPIIb/IIIa inhibitors and duration of DAPT, which varies across the trials. Third, as with any meta-analysis, our report shares the limitations of the original RCTs. Fourth, follow-up data for some studies are limited to 6 months, while for others, they are limited to 120 months. Therefore, whether the observed differences would remain constant, increase, or diminish with more extended follow-up is unknown. Finally, some endpoints (e.g., MACE, TVF, overall/cardiac death) were based on study-specific definitions, which were not uniform across trials, a limitation inherent in most cardiovascular meta-analyses.

Conclusion

In conclusion, DES devices are superior to BMS, as well as BP-DES to the older generation of DES, in terms of efficacy and safety, and should be preferred in everyday clinical practice according to the judgment of an interventional cardiologist.

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