Research Article

Comparing Polymer-Free and Polymer-Coated Drug-Eluting Stents in Coronary Artery Disease: An Updated Meta-Analysis

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Abstract

Transfemoral (TF) access is the safest and the most preferred option for Transcatheter Aortic Valve Implantation (TAVI). However, femoral access is often difficult in a significant number of patients due to inadequate vessel diameter, iliofemoral tortuosity or calcification. Other access routes for TAVI include transapical, transaortic, subclavian, axillary, carotid and transcaval. Choice of vascular access requires both extensive preoperative work-up and adaptive intraprocedural planning by the heart team. Here, we present a challenging case of TAVI in an elderly patient with peripheral artery disease, which required a change in the vascular access site from femoral to carotid artery, midway during procedure, as a strategy to prevent untoward vascular complications. This case also highlights the limitations of current hardware and technologies in negotiating tricky situations.

Key-words: transfemoral access; multiple co-morbidities; iliofemoral tortuosity or calcification; carotid approach

1. Introduction

The field of percutaneous coronary interventions (PCI) for patients with coronary artery disease (CAD) has undergone several advancements over the years, from bare-metal stents to polymer-coated drug-eluting stents (PC-DES) and now polymer-free drug eluting stents (PF-DES). The second type is known to consist of either permanent polymer (PP-DES) or bioresorbable polymer (BP-DES). [1] However, these polymers have been associated with stent-related complications and higher inflammatory and thrombogenic responses. [2,3] PF-DES have been developed for their advantage of drug-release control in the absence of a polymer. [2-4] PF-DES releases its, where the drug was released through micropores instead of a polymer. Intravascular imaging has demonstrated that this method allows for early endothelization and neointimal coverage within one month after implantation. [2-4] The recently published guidelines for coronary artery revascularization from American College of Cardiology (ACC), American Heart Association (AHA), and Society for Cardiovascular Angiography and Interventions (SCAI) indicated that patients undergoing PCI should receive DES as compared to bare metal stents (Class of Recommendation 1, Level of evidence A). [5] However, no mention of PC-DES, PP-DES, BP-DES, or PF-DES was made in the guidelines. Therefore, to delineate the difference between the different DES we conducted an updated meta-analysis to compare PC-DES versus PF-DES in patients with CAD receiving PCI. We also performed new additional analyses to evaluate the effect based on the follow-up period and the specific difference between PF-DES and PP-DES and BP-DES.

2. Materials and Methods

We conducted a comprehensive search of the electronic databases of PUBMED, EMBASE, and COCHRANE from inception to December 2021 for relevant studies. The inclusion criteria consisted of: (1) a prospective double-arm study or arandomized controlled trial (RCT), (2) comparison PF-DES versus a type or both of PC-DES, (3) patients with CAD, (4) reported either efficacy or safety outcomes, and (5) human subjects. Exclusion criteria were the following: (1) ongoing or irretrievable data, (2) single-arm study, (3) retrospective study, (4) use of bare-metal stents or COMBO stents, (5) use of animals, and (6) no clinical outcome endpoint. This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and registered on the International Prospective Register of Systematic Reviews (PROSPERO).

The search included the following keywords: "polymer", "free", "drugeluting stent", ""randomized trial", "meta-analysis", and "mortality". Two authors (RMP and SB) independently reviewed the search results, extracted potential articles, and assessed their eligibility. The Cochrane Collaboration risk-of-bias tool was used by two different authors (RMP and SB) to assess the quality of the included studies.

The primary outcome of this meta-analysis was all-cause mortality. Secondary outcomes included cardiac death, recurrent target vessel myocardial infarction (TV-MI), target lesion revascularization (TLR), and stent thrombosis. Stent thrombosis was defined as definite and

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probable thrombosis as per the Academic Research Consortium-2. [6] For each outcome, subgroup analyses were performed to analyze the data based on follow-up duration. Short-term follow-up was defined as less than 1 year, mid-term was 2-5 years, and long-term was greater than 5 years. An additional analysis was conducted for the primary outcome of all-cause mortality to specifically compare PF-DES vs the different types of PC-DES (PP-DES or BP-DES). We also collected baseline characteristics of the included studies and patients.

Statistical analysis was conducted using Review Manager (RevMan), version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark).

The Mantel-Haenszel random-effects models were used to estimate the odds ratios, 95% confidence intervals, and p-values. Two-sided p values of <0.05 were considered statistically significant. I2 statistics were used to assess statistical heterogeneity. A rule-one-out analysis will be conducted for the results with high heterogeneity values.

3. Results

Seventeen RCTs were included with a total of 15,098 patients and a median-weighted follow-up of 3.23 years (Figure 1).

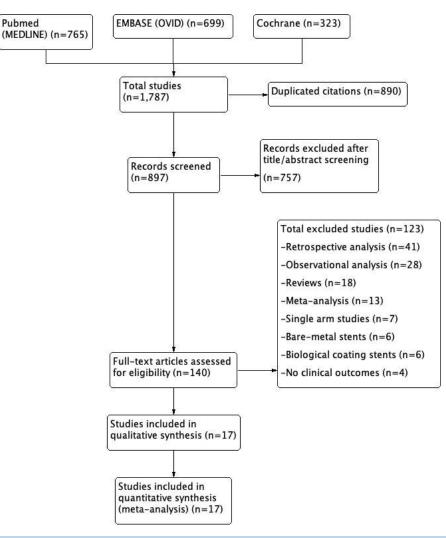


Figure 1: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

(6-23) of the included studies, the exact PF-DES varied per the study, but the common stents were Sirolimus-eluting, Paclitaxel-eluting, Sirolimusand Probucol-eluting, as well as Amphilimus- and Sirolimus-eluting. (Table 1) As for the control group of PC-DES, the majority of the trials used PP-DES, but two trials used BP-DES [9,23] and two trials used a combination of PP-DES and BP-DES [12,16] The average age of the included patients was 66.3 years, 73.9% were males, 27% were smokers. In regards to the patient's medical history, 39.5% had diabetes mellitus, 70.2% had hypertension, 58.1% had dyslipidemia, 20.6% had a previous myocardial infarction, and 18.8% had a previous percutaneous coronary intervention. (Table 2)

Study name	First Autho r	Publi cation year	Study Population	PF-DES	PC-DES	DAPT Strategy	Total patien ts (n)	Follow-up period (y)
ISAR- TEST-2	Byrne	2009	Older than 18 years, coronary ischemic symptoms, evidence of MI, and greater than 50% de novo stenosis in native coronary artery, informed consent	Dual Rapamycin- and Probucol- eluting stent (Dual DES)	PP Sirolimus- eluting stent (Cypher) PP Zotarolimus- eluting stent (Endeavor)	Clopidogrel (for over 6 months) + Aspirin (indefinitely)	1007	1
ISAR- TEST-3	Byrne	2009	Older than 18 years, coronary ischemic symptoms, evidence of MI, greater than 50% de novo stenosis in native coronary artery, informed consent	Rapamycin-eluting stent	PP Rapamycin- eluting stent (Cypher) BP Rapamycin- eluting stent	Clopidogrel (for 12 months) + Aspirin (indefinitely)	605	2
ISAR- TEST	King	2012	Older than 18 years, angina or evidence of coronary ischemia, and 50% de-novo stenosis in a native coronary artery	Sirolimus-eluting stent (Yukon, Translumina, Hechingen, Germany)	PP Paclitaxel- eluting stent (Taxus, Boston Scientific, Natick, MA, USA)	Clopidogrel + Aspirin	450	5
DKPLUS -Wave 1	Chen	2012	Older than 18 years, coronary ischemic symptoms, evidence of MI, greater than 70% de novo stenosis in native coronary artery	Dual Sirolimus- and Probucol- eluting stent (Dual DES)	BP Sirolimus- eluting stent (Excel, Jiwei/Biosensor, Shangdong, China)	Clopidogrel (For 6 months) + Aspirin (indefinitely)	346	1
_	Dang	2012	Acute STEMI with primary PCI within 12 hrs of symptoms	Paclitaxel-eluting stent (Yinyi, Liaoning Biomedical Materials R&D Center Co., Ltd, Dalian, Liaoning, China)	PP Siroliumus- eluting stent (Partner, Lepu Medical, Beijing, China)	Clopidogrel + Aspirin	105	1
		2015	Older than 18 years, stable or unstable angina, acute MI requiring PCI, same type of randomly assigned stent implanted in each of multiple lesions and in a single lesion needing more than 2	Paclitaxel-eluting stent (Yinyi, Liaoning Biomedical Materials R&D Center Co., Ltd, Dalian, Liaoning,	PP Siroliumus- eluting stent (Partner, Lepu Medical, Beijing, China) BP Sirolimus- eluting stent (Excel, Jiwei/Biosensor,	Clopidogrel		
-	Zhang	2013	stents	China)	Shangdong, China)	+Aspirin	989	3

	gy and Caro			Paclitaxel-eluting		Copy rights @		
-	Shirato ri	2014	Older than 18 years, stable or unstable angina, NSTEMI, silent MI, and atherosclerotic CAD	stent (Axxion, Biosensors International, Kampong, Singapore)	PP Paclitaxel- eluting stent (Taxus Express, Boston Scientific, Natick, MA, USA)	Clopidogrel + Aspirin for over 6 months	164	2
Nano	Zhang	2014	Older than 18 years, maximum two de novo coronary artery lesions, greater than 70% stenosis in native coronary artery	Sirolimus-eluting stent (Nano)	PP Siroliumus- eluting stent (Partner, Lepu Medical, Beijing, China)	Clopidogrel + Aspirin for over 12 months	291	2
LIPSIA Yukon	Stierm aier	2014	Older than 18 years, DM, coronary ischemic symptoms, evidence of MI, greater than 50% de novo stenosis in native coronary artery	Sirolimus-eluting stent (Yukon Choice, Translumina, Hechingen, Germany)	PP Paclitaxel- eluting stent (Taxus Liberte, Boston Scientific, Natick, MA, USA)	Clopidogrel (for 12 months) + Aspirin (indefinitely)	236	5
RESERV OIR	Romag uera	2016	DM, silent ischemia, stable or unstable angina, NSTEMI, single or two-vessel disease treated with a single stent or additional stents if suboptimal results	Amphilimus- and Sirolimus-eluting stent (Cre8, Alvimedica, Istanbul, Turkey)	PP Everolimus- eluting stent (Xience Prime or Xience Expedition, Abbott Vascular, Abbott Park, IL, USA)	Clopidorel, Prasugrel, or Ticagrelor + Aspirin	112	1
Biofreedo m FIM	Costa	2016	Older than 18 years, stable/unstable angina or presence of MI, single de novo target lesion (stenosis of 50- 99%, length of 14 mm, 2.5-3.0 mm in diameter), candidate for CABG; and agreed to protocol follow-up	Biolimus-coated stents (Biofreedom, Biosensors Europe SA, Morges, Switzerland) Standard dose and Low dose of Biofreedom	PP Paclitaxel- eluting stent (Taxus Liberte, Boston Scientific, Natick, MA, USA)	Clopidorel, Prasugrel, or Ticagrelor + Aspirin for over 6 months	182	5
ONYX ONE	Winde cker	2020	CAD, clinical indication for PCI, and high bleeding risk or candidate for short- term prophylaxis for stent thrombosis	Umirolimus-coated stent (Biofreedom, Biosensors Interventional Technologies)	PP Zotarolimus- eluting stent (Resolute Onyx, Medtronic, Minneapolis, MN, USA)	Clopidogrel + Aspirin for 1 month, then Aspirin or Clopidogrel	1996	1
ISAR-			Older than 18 years, coronary ischemic symptoms, evidence of MI, greater than 50% de novo stenosis in native coronary artery, informed	Dual Sirolimus- and Probucol- eluting stent (ISAR VIVO, Translumina Therapeutics, Dehradoon, India / Hechingen,	PP Zotarolimus- eluting stent (Resolute, Medtronic Cardiovascular, Santa Rosa, CA,	Clopidogrel +		

	gy and Card	llovascula	r Interventions	[[Copy rights@	Ronan Ma	aonu Prasao
				Coroflex ISAR, B. Braun Melsungen, Berlin, Germany)				
SORT OUT IX	Jensen	2020	Older than 18 years, CAD with greater than 50% diameter stenosis requiring treatment with a drug- eluting stent	Biolimus A9- coated stent (BioFreedom, Biosensors, Morges, Switzerland)	BP ultrathin strut Sirolimus-eluting stent (Orsiro, Biotronik, Bulach, Switzerland)	Clopidogrel, Prasugrel, or Ticagrelor + Aspirin If stable angina (for 6 months) versus if unstable angina (12 months)	3151	1
NEXT	Carrie	2020	Stable/unstable angina or silent ischemia, single de novo lesions (length of 20mm) or maximum 2 coronary arteries (diameter of 3-3.75mm)	Amphilimus- and Sirolimus-eluting stent (Cre8, CID S.p.A, Alvimedica, Salugia, Italy)	PP Paclitaxel- eluting stent (Taxus Liberte, Boston Scientific, Natick, MA, USA)	Clopidorel, Prasugrel, or Ticagrelor (for over 6 months) + Aspirin (indefinitely)	323	5
SUGAR	Romag uera	2021	Older than 18 years, CAD, silent ischemia, greater than 50% stenosis requiring PCI, DM	Amphilimus- and Sirolimus-eluting stent (Cre8, CID S.p.A, Alvimedica, Salugia, Italy)	PP Zotarolimus- eluting stent (Resolute Onyx, Medtronic, Minneapolis, MN, USA)	Clopidorel, Prasugrel, or Ticagrelor + Aspirin	1175	1
ReCre8	van Hemer t	2021	Older than 18 years, clinical ischemic symptoms, coronary stenosis requring PCI	Amphilimus- and Sirolimus-eluting stent (Cre8, CID S.p.A, Alvimedica, Salugia, Italy)	PP Zotarolimus- eluting stent (Resolute Integrity, Medtronic Vascular, Minneapolis, MN, USA)	Clopidogrel, Prasugrel, or Ticagrelor + Aspirin If troponin negative (for 1 month) versus if troponin positive (for 12 months)	1433	3

Abbreviations: BP, bioresorbable polymer; CABG, coronary artery bypass graft; CAD, coronary artery disease; DM, diabetes mellitus; MI, myocardial infarction; mm, millimeter; NSTEMI, non-ST elevation myocardial infarction; PC, polymer coated; PCI, percutaneous coronary intervention; PF, polymer free; PP, permanent polymer; STEMI, ST elevation myocardial infarction

			Table	Charact	ensues of m	cluded studio	es				
Study	Patients in PF-DES arm (n)	Patients in PC-DES arm (n)	Age (y)	Males	Smokers	Diabetes mellitus	Hypert ension	Dyslipi demia	Previo us Stroke	Previo us MI	Previo us PCI
		PP									
		Sirolimus									
		335									
ISAR-		PP									
TEST-2		Zotarolimu	$67.0 \pm$	772	185	276	672	662		134	89
2009	333	s 339	11.1	(76.7)	(18.4)	(27.4)	(66.7)	(65.7)	NR	(13.3)	(8.8)

 Table 1: Characteristics of included studies

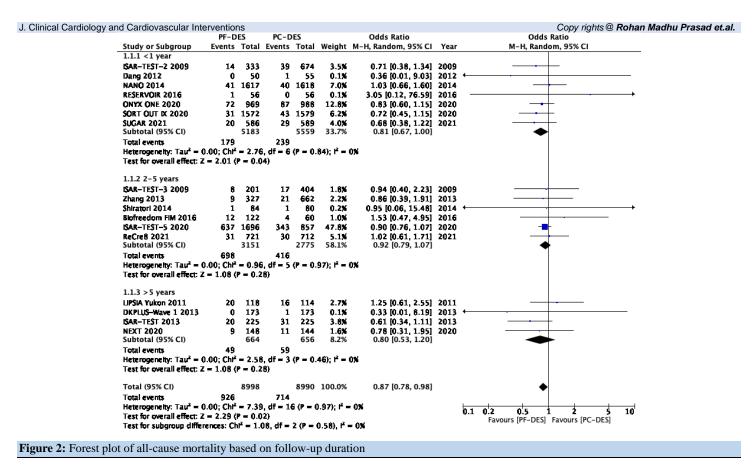
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TEST-3 2009	201	PP 202 BP 202	66.1 ± 10.7	480 (79.0)	99 (16.4)	166 (27.4)	410 (67.8)	416 (68.8)	NR	199 (32.9)	69 (11.4)
ISAR-TEST 2012	225	225	66.7 ± 10.4	346 (76.9)	82 (18.2)	131 (29.1)	297 (66.0)	335 (74.4)	NR	143 (31.8)	50 (11.1)
DKPLUS- Wave 1 2012	173	173	63.8 ± 10.9	271 (78.3)	96 (27.8)	96 (27.8)	237 (68.5)	106 (30.6)	NR	52 (15.3)	67 (19.4)
Dang 2012	50	55	66.2 ± 13.2	73 (69.5)	67 (63.8)	27 (25.7)	46 (43.8)	23 (21.9)	8 (7.6)	6 (5.7)	2 (1.9)
Zhang 2013	327	PP 321 BP 341	66.2 ± 10.5	670 (67.7)	410 (41.5)	282 (28.5)	652 (65.9)	425 (42.9)	NR	51 (5.0)	94 (9.5)
Shiratori 2014	80	84	65.6 ± 9.3	119 (72.6)	31 (19)	53 (32.3)	120 (73.2)	101 (61.6)	NR	51 (31.1)	47 (28.7)
Nano 2014	143	148	57.4 ± 10.3	223 (76.6)	150 (51.5)	49 (16.8)	156 (53.6)	90 (30.9)	NR	88 (30.2)	40 (13.8)
LIPSIA Yukon 2014	120	116	67.2 ± 9.3	162 (68.6)	59 (0.3)	236 (100)	230 (97.5)	NR	NR	52 (22.0)	71 (30.0)
RESERVOI R 2016	56	56	67.0 ± 9.3	84 (75.0)	65 (58.0)	112 (100)	95 (85.0)	92 (82.1)	14 (12.5)	30 (27.0)	41 (36.6)
Biofreedom FIM 2016	122	60	67.2 ± 8.8	127 (69.7)	29 (15.9)	50 (27.5)	155 (85.0)	131 (71.9)	NR	36 (19.7)	73 (40.1)
ONYX ONE 2020	1003	993	74.1 ± 9.7	1330 (66.6)	201 (10.1)	770 (38.6)	1603 (80.3)	1262 (63.2)	259 (13.0)	513 (25.7)	467 (23.4)
ISAR- TEST-5 2020	2002	1000	67.9 ± 11.0	2295 (76.4)	523 (17.4)	870 (29)	2002 (66.7)	1907 (63.5)	NR	885 (29.5)	284 (9.5)
SORT OUT IX 2020	1572	1579	66.3 ± 10.9	2440 (77.4)	880 (27.9)	607 (19.3)	1743 (55.3)	1607 (51.0)	NR	458 (14.5)	633 (20.1)
NEXT 2020	162	161	64.7 ± 10.3	233 (72.1)	79 (24.5)	87 (26.9)	208 (64.4)	200 (61.9)	NR	29 (9.0)	49 (15.0)
SUGAR 2021	586	589	67.9 ± 10.2	888 (75.6)	255 (21.7)	1122 (95.5)	981 (83.5)	956 (81.4)	102 (8.7)	200 (17.0)	258 (22.0)
ReCre8 2021	721	712	NR	1094 (73.4)	NR	284 (19.0)	NR	NR	NR	NR	NR

Abbreviations: BP, bioresorbable polymer; MI, myocardial infarction; n, number; NR, not reported; PC, polymer coated; PCI, percutaneous coronary intervention; PF, polymer free; PP, permanent polymer; y, years

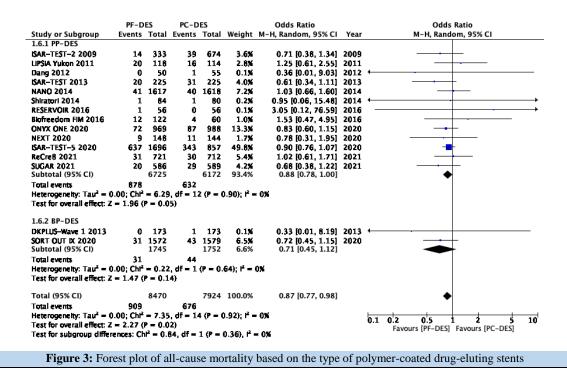
Table 2: Baseline characteristics of included patients

In regards to the primary outcome of all-cause mortality, the statistical analysis showed that it was significantly decreased in the PF-DES group (PF-DES 10.3% vs PC-DES 7.9%, p=0.02, I2=0) (Figure 2). The subgroup analysis based on follow-up duration illustrated that the significance of all-cause mortality was specifically seen in the short-term

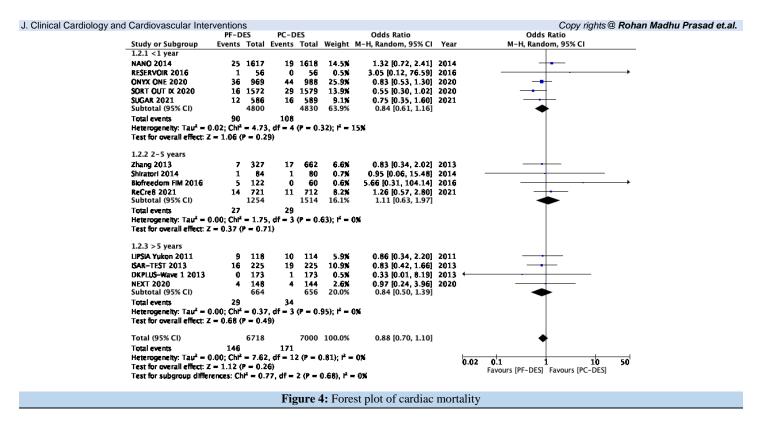
(PF-DES 3.5% vs PC-DES 4.3%, p=0.04, I2=0) (Figure 2). The results insignificantly favored PF-DES in the mid-term (PF-DES 22.2% vs PC-DES 15.0%, p=0.28, I2=0) and long-term (PF-DES 7.4% vs PC-DES 9.0%, p=0.28, I2=0) setting (Figure 2).



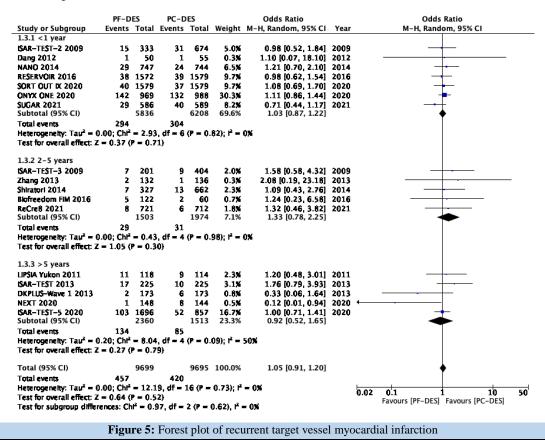
An additional analysis was done to compare all-cause mortality in PF-DES vs PC-DES when separating PC-DES into PP-DES or BP-DES. Interestingly, all-cause mortality favored PF-DES in this analysis – Significantly when compared to PP-DES (PF-DES 13.1% vs PC-DES 10.2%, p=0.05, I2=0) and insignificantly when compared to BP-DES (PF-DES 1.8% vs 2.5%, p=0.14, I2=0) (Figure 3).



There was no difference in cardiac death between the two groups (PF-DES 2.2% vs PC-DES 2.4%, p=0.26, I2=0) (Figure 4).



Furthermore, there was no difference in the recurrent TV-MI (PF-DES 4.7% vs PC-DES 4.3%, p=0.52, I2=0) and the subgroups based on follow-up duration had similar results (Figure 5).



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Overall TLR had similar rates (PF-DES 11.7% vs PC-DES 8.7%, p=0.33, I2=67) (Figure 6). Finally, there was no difference in stent thrombosis overall (PF-DES 1.3% vs PC-DES 1.2%, p=0.82, I2=0) or in any of the subgroups (Figure 7).

	PF-D		PC-D			Odds Ratio			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Random, 95% CI	
1.4.1 <1 year										
SAR-TEST-2 2009	26	333		674	7.6%	0.63 [0.40, 1.00]				
Dang 2012	5	50	4	55	2.4%	1.42 [0.36, 5.60]				
NANO 2014	22	747		744	6.3%	1.10 [0.59, 2.03]				
RESERVOIR 2016		1572		1579	7.1%	0.36 [0.21, 0.60]				
ONYX ONE 2020	39	969	28	966	7.3%	1.44 [0.88, 2.36]				
SORT OUT IX 2020		1579		1579	7.1%	0.36 [0.21, 0.60]				
SUGAR 2021	14		23	589	5.8%	0.60 [0.31, 1.18]	2021			
Subtotal (95% CI)		5836		6208	43.8%	0.69 [0.44, 1.08]				
Total events	146	• •	265	.		3				
Heterogeneity: Tau ² = (Test for overall effect: 2				6 (P = 1).0004);	r = 75%				
1.4.2 2-5 years										
ISAR-TEST-3 2009	27	201	36	404	7.1%	1.49 [0.88, 2.53]	2009		+	
Zhang 2013	6	132	7	136	3.6%	1.19 [0.42, 3.38]	2013			
Shiratori 2014	7	327	19	662	4.5%	0.74 [0.31, 1.78]	2014			
Biofreedom FIM 2016	14	122		60	3.6%	1.17 [0.42, 3.21]	2016			
ReCreß 2021 Subtotal (95% CI)	22	721 1503	23	712 1974	6.5% 25.4%	0.94 [0.52, 1.71] 1.13 [0.82, 1.56]	2021			
Total events	78		93							
Heterogeneity: Tau ² = (Test for overall effect: Z				(P = 0.	67); ř =	0%				
1.4.3 > 5 years										
LIPSIA Yukon 2011	16	116	16	114	5.6%	0.96 [0.47, 1.95]	2011			
DKPLUS-Wave 1 2013	16	173			2.8%	5.77 [1.65, 20.20]				
SAR-TEST 2013	34	225			7.1%	1.04 [0.62, 1.74]				
NEXT 2020	13	148		144	5.3%	0.63 [0.30, 1.34]				
SAR-TEST-5 2020		1696	415	857	10.0%	1.01 [0.86, 1.19]			_ _	
Subtotal (95% CI)		2360		1513	30.8%	1.07 [0.73, 1.55]			-	
Total events	907		466						T	
Heterogeneity: Tau ² = ().09; Chl ²	= 9.00), df = 4	$(\mathbf{P}=0)$	06); i ² =	56%				
Test for overall effect: 2	= 0.33 (P = 0.7	4)							
Total (95% CI)		9699		9695	100.0%	0.89 [0.69, 1.13]			•	
Total events	1131		846							
Heterogeneity: Tau ² = (16 (P <	0.0001)	i ^r = 67%		0 1	0.2 0.5 1 2	5 1
Test for overall effect: 2								V .1	Favours [PF-DES] Favours [PC-I	
Test for subgroup differ	rences: Ch	1 ² = 3.	35, df =	2 (P = I	0.19), i ² -	= 40.4%				

Figure 6: Forest plot of target lesion revascularization

			Surc o	• 1 01	est pio	t of target lesion it	vuse	ululization
	PF-D		PC-D			Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M–H, Random, 95% CI
1.5.1 <1 year								
ISAR-TEST-2 2009	3	333	6	674	4.0%	0.76 [0.20, 2.87]	2009	
Dang 2012	1	50	1	55	0.9%	1.10 [0.07, 18.10]	2012	
NANO 2014	9	747	6	744	6.5X	1.50 [0.53, 4.24]	2014	
RESERVOIR 2016	17	1572	16	1579	15.0%	1.07 [0.54, 2.12]	2016	_ _
ONYX ONE 2020	20	969	13	988	14.2%	1.58 [0.78, 3.20]	2020	+
SORT OUT IX 2020	18	1579	16	1579	15.4%	1.13 [0.57, 2.22]	2020	
SUGAR 2021	6	586	6	589		1.01 [0.37, 2.70]	2021	
Subtotal (95% CI)		5836		6208	63.3%	1.19 [0.85, 1.66]		◆
Total events	76		66					
Heterogeneity: Tau ² = ().00; Chl ^a	= 1.49), df = 6	$(\mathbf{P}=0)$.96); i ² =	0%		
Test for overall effect: 2	: = 1.02 (P = 0.3	1)					
1.5.2 2-5 years								
ISAR-TEST-3 2009	•	201			2.2%	1 34 60 33 0 101	2000	
	2	201	3					
Zhang 2013	1	132						
Shiratori 2014	5	327	12					
ReCreß 2021 Subtotal (95% CI)	1	721 1381	1	712 1914		0.99 [0.06, 15.82]	2021	
		1201		1914	10.7%	0.89 [0.39, 2.00]		
Total events	9		16	<u> </u>	··· ·· ·2	A=/		
Heterogeneity: $Tau^2 = 0$				$(\mathbf{P}=0)$.94); =	0.5		
Test for overall effect: 2	. = 0.29 (r = 0.7	"					
1.5.3 > 5 years								
UPSIA Yukon 2011	2	118	1	114	1.2%	1.95 [0.17, 21.79]	2011	
DKPLUS-Wave 1 2013	ō		2					·
SAR-TEST 2013	i	225	3	-				
SAR-TEST-5 2020	29	1696	17					_ _
NEXT 2020	3	148						
Subtotal (95% CI)	-	2360	-		26.0%	0.77 [0.46, 1.30]		-
Total events	35		28					-
Heterogeneity: Tau ² = (= 2.16		$(\mathbf{P}=0)$	71): f ² =	0%		
Test for overall effect: Z					-/1 -			
		-						
Total (95% CI)		9577		9635	100.0%	1.03 [0.79, 1.34]		•
Total events	120		114		_			
Heterogeneity: Tau ² = (5 (P = I	0.98); 🖻 -	- 0%		0.01 0.1 1 10 100
Test for overall effect: 2								Favours [PF-DES] Favours [PC-DES]
Test for subgroup differ	rences: Ch	n ² = 2.0	02, df =	2 (P =	0.36), P	= 1.1×		
			T .*		- -		1	•

Figure 7: Forest plot of stent thrombosis

The heterogeneity for these statistics was mainly low, but overall ranged from low to moderate. The two results with elevated I2 values were TV-MI and TLR. A rule-one-out sensitivity analysis was conducted for these outcomes. After excluding the NEXT trial [21], the long-term results of TV-MI showed no difference between the two groups (PF-DES 6.0% vs PC-DES 5.6%, p=0.70, I2=20), which was consistent with the initial findings. For TLR, the DKPLUS-Wave 1 [9] and ONYX ONE [19] trials were excluded, which resulted in the following findings: overall (PF-DES 12.6% vs PC-DES 9.6%, p=0.07, I2=62), short-term (PF-DES 2.2% vs PC-DES 4.5%, p=0.007, I2=60), and long term (PF-DES 40.7% vs PC-DES 36.2%, p=0.92, I2=0). This analysis demonstrated that TLR favors PF-DES - insignificantly overall and significantly in the short-term setting. In this meta-analysis, major adverse cardiovascular events was not analyzed, but all the components were analyzed separately.

4. Discussion

Although the ACC, AHA, and ACSO have recommended DES for coronary artery revascularization, there are no recommendations as to which type of DES is preferred. [5] The PC-DES type, which compromises of PP-DES and BP-DES, has been associated with stent-related complications and higher inflammatory and thrombogenic responses. [2,3] Therefore, PF-DES have been developed in efforts to alleviate these complications. This meta-analysis was conducted with the objective of comparing PF-DES and PC-DES. The statistical analysis showed that all-cause mortality was significantly decreased in the PF-DES group, specifically when compared to PP-DES and only in the short-term follow-up.

The recently published RCT ONYX ONE by Windecker et al evaluated Umirolimus-coated PF-DES and Zotarolimus-eluting PP-DES in patients with high bleeding risk who were receiving a PCI. The study found that PF-DES was non-inferior to PP-DES in terms of a composite of all-cause mortality, TV-MI, or stent thrombosis as well as target lesion failure. [19] Additionally, Romaguera et al conducted the SUGAR trial to compare Amphilius- and sirolimus-eluting PF-DES and Zotarolimus-eluting PP-DES in patients with diabetes mellitus who were undergoing PCI. This study also showed that the rates of TLF between PF-DES and PP-DES were non-inferior. [18]

The physical difference between PP-DES, BP-DES, and PF-DES may be a source of the results seen in this meta-analysis. The polymer in PP-DES was designed to achieve drug adherence on the stent surface and control drug release. [2] However, the struts have been associated with chronic inflammation and delayed endothelization, which leads to delayed vascular healing, hypersensitivity reactions, and neoatherosclerosis. This immune response explains the higher rate of events, such as mortality and thrombosis, with when using PC-DES. [2,3,24,25]

Our results demonstrated that the effects of PF-DES were mainly seen in the short-term follow-up and when compared to PP-DES. We hypothesize this is the case because the PF-DES are endothelialized in about a month; whereas, the PP-DES are present permanently. With this hypothesis, the PF-DES should also have significant benefits in the long-term, but our meta-analysis was not able to accurately depict this outcome. Moreover, the insignificant favoring of PF-DES over BP-DES can be explained as the BP-DES have polymers that are bioresorbable, as their name indicates, and also have been associated with improved outcomes. [24,25] However, there were only two studies that directly compared PF-DES and BP-DES, so further studies are needed to confirm these findings.

In addition to the limitations inherent to a meta-analysis, we found a significant difference between the patient population. Three of the studies only included diabetic patients, [13,14,18] which is significant because diabetic patients have a higher rate of all-cause mortality and TLR [26]. Thus, these studies could've skewed our results. Additionally, within the PF-DES and PC-DES there were varying types of stents used, including drugs and PP-DES versus BP-DES. The Biofreedom FIM study had two separate groups that received a PF-DES, standard and low dose of

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Biolimus. [7] Although benefits were mainly found in all-cause mortality with PF-DES, they were not found with cardiac mortality or stent thrombosis. Thus, the mortality benefit may not actually depend on the type of stent placed. Further RCTs should be conducted to adequately compare different types of PF-DES, compare PF-DES versus BP-DES, and analyse the sub-groups of diabetics and non-diabetics. The findings from this meta-analysis is consistent with the current literature; however, ours is different then the current studies in the literature as it evaluates allcause mortality based on the type of drug-eluting stent's polymer-coating [27].

5. Conclusion

In patients who are receiving PCI with DES, the current data indicates that PF-DES has significantly favorable outcomes in all-cause mortality as compared to PC-DES in the short-term follow-up. This believed to be due to the fact that PF-DES are resorbed but PP-DES are permanently present. Further studies with longer follow-up periods and different types of PF-DES are required to confirm and expand on these results. Trials should also be conducted to compare PF-DES versus BP-DES and to compare the specific drug components of the PF-DES.

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