



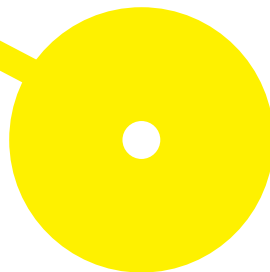
MESTRADO

EMMAH -EUROASIAN MASTER IN MEDICAL TECHNOLOGY AND HEALTHCARE BUSINESS

Third generation biodegradable polymer versus polymer free drug-eluting stents : a Systematic Review

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**Third generation biodegradable polymer versus polymer-free drug-eluting stents for
percutaneous coronary intervention: a systematic review**

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Resumo

Introdução: A 3ª geração de *stents* com libertação de fármacos (DES), usados em intervenção coronária percutânea (PCI), foram desenvolvidos para minimizar problemas importantes que surgiram no *follow-up* de doentes com DES de gerações anteriores, de que são exemplo a trombose tardia do stent, cicatrização tardia e inflamação, causadas por polímeros permanentes. Entre os *stents* de 3ª geração, estão os de polímero biodegradável (BD-DES) e os sem polímero (PF-DES).

Objetivo: Analisar os resultados publicados recentemente de *outcomes* clínicos dos BD-DES em comparação com os PF-DES, em pacientes submetidos a PCI.

Métodos: Esta revisão sistemática qualitativa seguiu as orientações da *checklist* PRISMA 2020. Os critérios de inclusão foram data de publicação entre 01-01-2014 e 31-12-2023, acesso aberto, PCI com PF-DES ou BD-DES, e pelo menos um dos seguintes *outcomes*: mortalidade cardíaca, mortalidade total/todas as causas de morte, revascularização do vaso alvo, revascularização da lesão alvo (TLR), falha da lesão alvo, falha do vaso alvo, perda tardia de lúmen (LLL), enfarte do miocárdio e trombose do stent.

Resultados: De um total de 701 artigos, 5 foram incluídos, publicados entre 2017-2023, com diferentes desenhos de estudo. Dois estudos não encontraram diferenças significativas entre BP-DES e PF-DES, numa amostra global. Um estudo relatou que os BP-DES foram superiores aos PF-DES na TLR, numa amostra global. Um estudo relatou que a segurança e eficácia foram melhores nos PF-DES do que nos BP-DES, apenas no grupo de diabéticos. O último estudo encontrou, nos grupos com calcificação coronária moderada a severa, diferenças apenas na LLL observadas aos 9 meses nos dois grupos, mas completamente atenuadas aos 10 anos. Uma meta-análise não foi realizada devido à heterogeneidade dos estudos, mas a avaliação do risco de viés foi globalmente baixa.

Conclusões: Na maioria dos estudos não foram encontradas diferenças significativas entre os perfis de segurança dos BP-DES e dos PF-DES, para amostras globais, o que está de acordo com estudos anteriores. Estudos futuros devem focar-se em períodos de *follow-up* mais longos, bem como investigar a potencial superioridade de PF-DES sobre BP-DES em pacientes com diabetes.

Palavras-chave: Intervenção coronária percutânea, stent com libertação de fármacos de polímero biodegradável, BD-DES, stent com libertação de fármacos sem polímero, PF-DES.

Abstract

Background: Third generation drug eluting stents (DES) for percutaneous coronary intervention (PCI) were developed to minimize major outcome problems that previous DES caused during the follow-up, mainly very late stent thrombosis, delayed healing, and inflammation, caused by durable polymer. Among this last generation stent were the biodegradable polymer (BD-DES) and the polymer-free (PF-DES) stents.

Aim: To analyze the most recent results published in studies addressing clinical outcomes of BD-DES compared with PF-DES in patients undergoing PCI.

Methods: This qualitative systematic review was performed following the PRISMA 2020 checklist. The inclusion criteria were publication date between 01-01-2014 and 31-12-2023, open access, PCI with PF-DES or BD-DES, and at least one of these outcomes: cardiac mortality, total mortality/all causes of death, target vessel revascularization, target lesion revascularization, target lesion failure, target vessel failure, late lumen loss, myocardial infarction, stent thrombosis.

Results: After screening a total of 701 articles 5 articles were included 2017–2023. Study design differed across studies. Two studies found no significant differences between BP-DES and PF-DES in an all-comers population. One study reported that BP-DES was superior to PF-DES in TLR rates in an all-comers population. One study reported that safety and efficacy profiles were better for PF-DES than the BP-DES only for diabetic patients. The last study found that in patients with moderate to severe coronary artery calcification, the differences in LLL observed at 9 months between the two groups were fully attenuated at 10 years, and no other outcome differed significantly at this point. A meta-analysis was not performed due to the heterogeneity of the studies, but the evaluation of risk of bias was globally low.

Conclusions: This review found no significant differences in safety profiles between BP-DES and PF-DES in an all-comers population, aligning with previous findings. However, most studies reported comparable efficacy profiles between the two stent types. Future studies should focus on longer follow-up periods and investigate the potential superiority of PF-DES over BP-DES in patients with diabetes mellitus..

Keywords: Percutaneous coronary intervention, biodegradable polymer drug eluting stent, BD-DES, polymer free drug eluting stent, PF-DES.

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List of Abbreviations

Abbreviation	Full term
ST	Stent thrombosis
DES	Drug-eluting stents
BMS	Bare metal stents
PCI	Percutaneous coronary intervention
PF	Polymer free
BP	Biodegradable polymer
DP	Durable polymer
CAD	Coronary artery disease
MI	Myocardial infarction
TVR	Target vessel revascularization
TLR	Target lesion revascularization
LLL	Late lumen loss
CM	Cardiac mortality
TLF	Target lesion failure
TVF	Target vessel failure
TM	Total mortality
CEST	Central European Summer Time
JBI	Joanna Brigs Institute
DM	Diabetes mellitus
CAC	Coronary artery calcification
QCA	Quantitative coronary angiography
SS	Statistically significant

1. Introduction

First generation drug-eluting stents (DES) were introduced in 2002(1) in an attempt to overcome in-stent restenosis and stent thrombosis (ST) events due to neointimal hyperplasia (e.g. proliferation of neointimal tissue in the stented segment) associated with bare metal stents (BMS).(2) The first DES included a polymer coating carrying an antiproliferative and/or immunosuppressant drug in addition to the stent platform(3). Although these stents decreased the rates of in-stent restenosis and repeat revascularizations when compared to BMS, they were later discovered to be at higher risk of late and very late stent thrombosis. Possible reasons for this were identified as delayed endothelialization caused by the eluted drugs or delayed hypersensitivity reactions to the polymer in the DES. Therefore, thinner stent struts, new polymers and novel antiproliferative agents were introduced with the second generation DES in 2004 (4) (5). These were shown to perform better when compared to the first generation devices, with reduced rates of death and myocardial infarction as well as stent thrombosis(6). Second generation DES became the gold standard of stents for PCI, but complications such as late thrombosis, very late stent thrombosis, delayed healing, and inflammation remained. The permanent polymer coating that stays even after drug-elution completion was associated with chronic inflammation and could be related to the aforementioned issues(7) (8). In order to exclude the complications associated with the durable polymer, a third generation of DES was introduced including two different kinds of stents. On the one hand, the polymer-free (PF) DES avoid the need for a polymer coating altogether by presenting drug reservoirs all over their surface that allow drug delivery. On the other hand, the biodegradable-polymer (BP) DES are coated with polymers that degrade once drug-elution is completed. (8) Several studies have shown that PF-DES have comparable safety and efficacy profiles to those of durable-polymer (DP) DES(9) (10), whereas others point out that BP-DES have similar and even better outcomes than second generation stents(11) (12). Published in 2018, the work of Nogic et al. (13) stated to be the only systematic review and meta-analysis comparing BP-DES and PF-DES at the time. This study analyzed these two kinds of DES in patients afflicted with coronary artery disease (CAD) both in terms of safety outcomes, namely all-cause death, myocardial infarction (MI) and stent thrombosis (ST) as well as efficacy outcomes, including target vessel revascularization (TVR), target lesion revascularization (TLR) and angiographic in-stent late lumen loss (LLL). Results from this analysis indicate that the BP-DES were associated with significantly reduced rates of TVR, TLR and in stent LLL rates when compared to PF-DES. In addition, an equal frequency of MI, ST, and

all-cause death was reported. These findings suggest that BP-DES might have an equal safety and an even better efficacy profile than PF-DES. In the last five years, long-term data of previous studies as well as new studies comparing BP-DES and PF-DES have been published. Moreover, additional outcomes such as target lesion failure (TLF) and target vessel failure (TVF) can be used to study these stents. Therefore, this systematic review intends to analyze the most recent studies comparing intervention with BP-DES versus PF-DES in patients undergoing PCI in terms of cardiac mortality (CM), target vessel revascularization (TVR), target lesion revascularization (TLR), late lumen loss (LLL), myocardial infarction (MI), stent thrombosis (ST), target lesion failure (TLF), target vessel failure (TVF) and total mortality/all cause death (TM). This work aims to provide useful insights on the safety and efficacy of third generation DES that could guide interventional cardiologists in their everyday practice.

2. Methods

This qualitative systematic review was conducted by two independent researchers and reported based on the PRISMA 2020 statement: an updated guideline for reporting systematic reviews (14). Preliminary research on this topic was done with scientific guidance of an interventional cardiology expert.

2.1. Eligibility criteria

Articles that met the following inclusion criteria were included in this review: they were published in scientific journals between January 1st 2014 and December 31st 2023, they were open access, they focused on patients undergoing PCI, they compared the intervention with BP-DES and PF-DES. The measure of at least one among the following patient-centered outcomes was also an inclusion criteria : cardiac mortality (CM), target vessel revascularization (TVR), target lesion revascularization (TLR), late lumen loss (LLL), myocardial infarction (MI), stent thrombosis (ST), target lesion failure (TLF), target vessel failure (TVF) and total mortality/all cause death (TM). The articles were excluded if they did not fit the previous inclusion criteria, if they missed full text, if they were non-human studies or if they consisted in surveys, questionnaires, reviews or other systematic reviews.

2.2. Data sources and search strategy

The literature research was conducted on three free access electronic databases : Pubmed, Web of Science and EBSCO. Within the three databases, the Boolean sentence search was the following : ((Biodegradable stent) OR (biodegradable-polymer)) AND ((percutaneous coronary intervention) OR (PCI)) AND ((cardiovascular mortality) OR (CM) OR (target vessel revascularization) OR (TVR) OR (target lesion revascularization) OR (TLR) OR (late lumen loss) OR (LLL) OR (myocardial infarction) OR (MI) OR (Stent thrombosis) OR (ST) OR (TLF) OR (Target lesion failure) OR (Target vessel failure) OR (TVF) OR (Total mortality) OR (TM)). The research was performed on June 2nd 2024 at 12:08 pm CEST, on June 2nd 2024 at 12:39 pm, and on June 3rd 2024 at 6:30 pm within Pubmed, Web of Science and EBSCO respectively. For the Pubmed research, the filters "Clinical Trial", "Randomized Controlled Trial", "Free full text", "Full text", "Publication date : 2014-2023" were selected, whereas the filters "Open access" and "Publication date : 2014-2023" were chosen for the EBSCO research. The publication date range was set

between 2014 and 2023 within the Web of Science database as well. The research of the three databases was supervised by a librarian expert.

2.3. Data collection and extraction

For each database, the articles resulting from the Boolean sentence research were imported in Rayyain.ai(15). Duplicates were automatically identified and then manually checked. Both reviewers screened title and abstract of each article independently. The importation and the full-text screening of the possibly relevant articles was performed by both researchers independently. The data extraction from included articles was performed by one of the researchers and covered the following information : 1) Study type 2) Population 3) Percentage of the population afflicted with diabetes 4) Follow-up period 5) BP-DES type (Intervention) 6) PF-DES type (Comparison) 7) Population subgroups (if applicable) 8) Measure of outcomes (LLL, ST, TLR, TVR, TLF, TVF, MI, CM, all cause death) 9) Other treatments 10) Main findings. The aforementioned outcomes were defined according to the Academic Research Consortium-2 Consensus Document(16). However, not all studies provided such definition of the outcomes. The choice was made to retrieve all included articles independently of the outcome definition as long as falling under the same name. The extracted data was discussed and reviewed by the two researchers. In this phase, the supervision of the librarian expert was also fundamental. The authors agreed not to perform a meta-analysis due to the heterogeneity between studies, including methodological differences (not all studies are RCTs) and the incertitude about the outcomes definition. Risk of bias was assessed using the JBI critical appraisal tools(17) for randomized controlled trials and for cohort studies with the help of an expert.

3. Results

After database research, 701 articles were imported on Rayyain.ai. The PRISMA 2020 flow diagram(13) of the whole review process is shown in Figure 1.

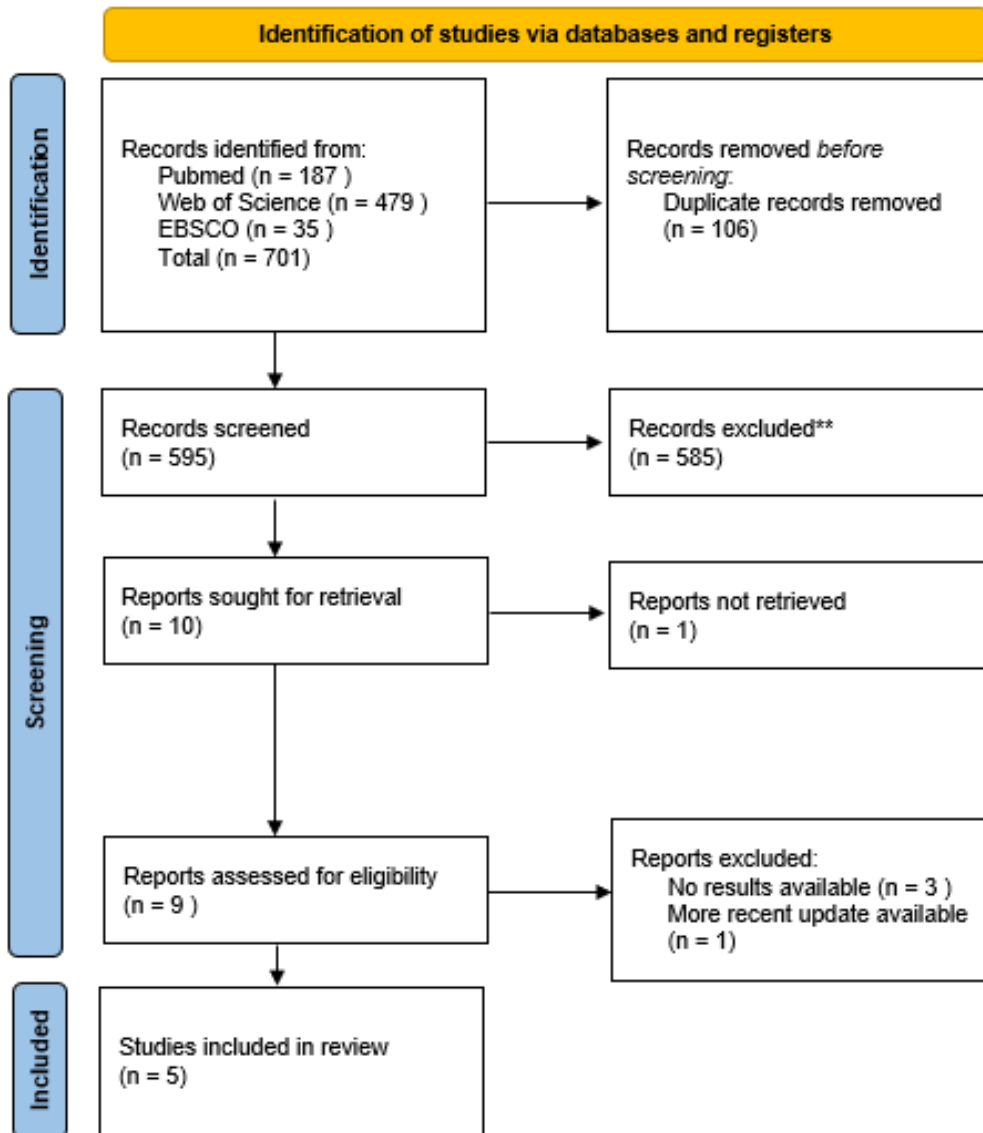


Figure 1: PRISMA 2020 flow diagram of the review process

A total of 106 duplicates was automatically detected, manually checked and excluded. The remaining 595 were screened by title and abstract, which allowed to exclude 585 of them for not meeting the inclusion criteria. One article was excluded for missing full text, while the other 9 were full text-screened. Of these, 4 were excluded (3 missing results for the outcomes, 1 more recent update available). Therefore, a total of 5 articles was included in this systematic review.

3.1. Studies' baseline characteristics

The baseline characteristics of each included study can be found in Table 1.

Study	Study type	Total patients	Patients subgroups (n° of patients)	BP stent type, eluted drug (n° of patients)	PF stent type, eluted drug (n° of patients)	Measured Outcomes	Total Follow up
Gregersen et al. 2022 (18)	Multicenter RTC (SORT OUT IX)	3151	None	ORSIRO®, sirolimus (1579)	BIOFREEDOM®, sirolimus (1572)	ST, TLR, TVR, TLF, TVF, MI, CM, all cause death	2 years
Viswanathan et al. 2018 (19)	Single-center RTC (CTRI/2013/03/0045 12)	205	None	BP YUKON CHOICE®, sirolimus (113)	PF YUKON CHOICE®, sirolimus (91)	Cardiac death, ST	1 year
Godino et al. 2017 (20)	Analysis of 2 multicenter observational registries (ASTUTE, INSPIRE-1)	1330	Non DM patients (850)	NOBORI®, biolimus (425)	Cre8®, amphiliimus (425)	ST, TLR, TVR, TLF, TVF, MI, CM, all cause death	1 year
			DM patients (480)	NOBORI®, biolimus (240)	Cre8®, amphiliimus (240)		
Tao L, Li Z, Yin Z et al. 2021 (21)	Multicenter RTC (RECOVERY, NCT02542007)	440	None	COMBO®, sirolimus (220)	NANO®, sirolimus (220)	LLL, ST, TLR, TVR, TLF, MI, CM, all cause death	2 years (QCA at 9 months)
Rheude et al. 2023 (22)	Pooled analysis of individual patient data from two RTC (ISAR TEST 4, ISAR TEST 5)	4953	Moderate to Severe CAC (1672)	BP YUKON CHOICE®, sirolimus (304)	COROFLEX®, probucutol (755)	LLL, ST, TLR, MI, all cause death	10 years (QCA at 6-8 months)

Table 1: Baseline characteristics of all included studies. RTC : Randomized Controlled Trial ; DM: Diabetes Mellitus ; QCA: Quantitative Coronary Angiograph

All studies were published between 2017 and 2023 ; amongst them, three were randomized controlled trials (RTC), one was an analysis of two multicenter observational registries and the last one consisted in a pooled analysis of individual patient data from two different RTCs.

The total study population in the work of Godino et al.(20) was 1776 patients reduced to 1330 after propensity score matching. It was divided into two sub-cohorts of patients according to the presence or absence of diabetes. Both sub-cohorts were treated with either the BP biolimus-eluting NOBORI® stent or the PF amphiliimus-eluting Cre8® stent.

In the study of Rheude et al. (22), patients were divided into four subgroups depending on their degree of coronary artery calcification (CAC): no, mild CAC, moderate CAC or severe CAC. All patients then underwent intervention with either a BP-DES, a PF-DES or a permanent polymer (PP) DES regardless of their degree of CAC. The analysis of the outcomes based on the polymer coating strategy was limited to the 1672 patients afflicted with moderate to severe CAC. For the

scope of this systematic review, only the 304 patients treated with the BP sirolimus eluting YUKON CHOICE ® stent as well as the 755 patients treated with the PF probucutol eluting COROFLEX ® stent were taken into consideration.

The follow up was limited to clinical for all the studies except the one of Tao L, Li Z, Yin Z et al.(21) and the work of Rheude et al. (22), in which quantitative coronary angiography (QCA) was performed after 9 months and 6 to 8 months, respectively.

3.2. Patients' baseline characteristics

For the BP and the PF group of each study, major patient baseline characteristics including mean age, number of male participants, diabetic patients, current smokers, patients with hypertension, dyslipidemia previous MI and previous PCI can be consulted in Table 2 and Table 3. Statistically significant differences are underlined.

Study	Mean age, years	Men, n (%)	Diabetes mellitus, n (%)	Current smoker, n (%)
Gregersen et al. 2022 (18)	66,1 BP ORSIRO ® 66,4 PF BIOFREEDOM ® p = 0,35	1221 (77,3) BP ORSIRO ® 1219 (77,5) PF BIOFREEDOM ® p = 0,88	303 (19,2) BP ORSIRO ® 304 (19,3) PF BIOFREEDOM ® p = 0,91	437 (29,3) BP ORSIRO ® 443 (29,8) PF BIOFREEDOM ® p = 0,78
Viswanathan et al. 2018 (19)	56,9 BP YUKON CHOICE ® 55,8 PF YUKON CHOICE ® p = 0,39	83 (73,45) BP YUKON CHOICE ® 80 (87,91) PF YUKON CHOICE ® p = 0,64	50 (44,24) BP YUKON CHOICE ® 45 (49,45) PF YUKON CHOICE ® p = 0,45	Not reported
Godino et al. 2017 (20)	Non DM 65,37 BP NOBORI ® 66 PF Cre8 ® p = 0,339	Non DM 348 (82) BP NOBORI ® 348 (82) PF Cre8 ® p = 1,000	Non diabetic patients	Non DM 238 (56) BP NOBORI ® 210 (490) PF Cre8 ® p = 0,054
	DM 67,39 BP NOBORI ® 67,71 PF Cre8 ® p = 0,711	DM 195 (81) BP NOBORI ® 197 (82) PF Cre8 ® p = 0,831	Diabetic patients	DM 135 (56) BP NOBORI ® 121 (50) PF Cre8 ® p = 0,200
Tao L, Li Z, Yin Z et al 2021 (21)	58,3 BP COMBO ® 59,3 PF NANO ® p = 0,26	147 (68,1) BP COMBO ® 137 (63,4) PF NANO ® p = 0,31	43 (19,9) BP COMBO ® 46 (21,3) PF NANO ® P = 0,81	97 (44,9) BP COMBO ® 93 (43.1) PF NANO ® p = 0,59
Rheude et al. 2023 (22)	68,7 BP 69,1 PF p = 0,518	229 (75,3) BP 590 (78,1) PF p = 0,585	110 (36,2) BP 243 (32,2) PF p = 0,416	44 (14,5) BP 130 (17,2) PF p = 0,112

Table 2 : Patient baseline characteristics for each study including mean patients' age, number of male participants, number of diabetic patients, number of current smokers.

No statistically significant differences in patients' baseline characteristics between the BP and the PF group were reported in three(18) (19) (21) out of five studies. In the Godino et al.(20) study, patient baseline characteristics in the diabetic sub-cohort did not differ significantly between the two intervention groups. On the contrary, in the non-diabetic propensity matched sub-cohort

patients receiving the BP stent showed significantly higher levels of dyslipidemia. Regarding the study by Rheude et al. (22), the baseline characteristics reported in in Table 2 and Table 3 did not differ between the two groups. However, patients in the BP group had significantly lower acute myocardial infarction rates as well as higher unstable angina rates than the patients in the PF group. Patients in the BP group also had a lower mean number of lesions than patients in the PF group.

Study	Hypertension, n (%)	Previous MI, n (%)	Previous PCI, n (%)	Dyslipidemia
Gregersen et al. 2022 (18)	850 (56,0) ORSIRO ® 893 (59,0) BIOFREEDOM ® p = 0,21	234 (15,2) ORSIRO ® 224 (14,7) BIOFREEDOM ® p = 0,53	311 (20,9) ORSIRO ® 322 (20,9) BIOFREEDOM ® p = 0,59	Not reported
Viswanathan et al. 2018 (19)	45 (49,45) BP YUKON CHOICE ® 58 (51,33) PF YUKON CHOICE ® p = 0,79	Not reported	Not reported	Not reported
Godino et al. 2017 (20)	Non DM 288 (68) BP NOBORI ® 299 (70) PF Cre8 ® p = 0,573	Non DM 75 (31) BP NOBORI ® 82 (34) PF Cre8 ® p = 0,496	Non DM 117 (49) BP NOBORI ® 98 (41) PF Cre8 ® p = 0,111	Non DM 268 (63) BP NOBORI ® 233 (55) PF Cre8 ® p = 0,111
	DM 193 (80) BP NOBORI ® 188 (78) PF Cre8 ® p = 0,573	DM 106 (42) BP NOBORI ® 185 (45) PF Cre8 ® p = 0,414	DM 88 (34,5) BP NOBORI ® 118 (29) PF Cre8 ® p = 0,106	DM 152 (63) BP NOBORI ® 161 (67) PF Cre8 ® p = 0,388
Tao L, Li Z, Yin Z et al 2021 (21)	116 (53,7) COMBO ® 130 (60,2) PF NANO ® p = 0,17	Not reported	21 (9,7) BP COMBO ® 20 (9,3) PF NANO ® p = 0,87	Not reported
Rheude et al. 2023 (22)	222 (73,0) BP 532 (70,5) PF p = 0,669	80 (26,3) BP 216 (28,6) PF p = 0,669	Not reported	Not reported

Table 3: Patient baseline characteristics for each study including number of patients with hypertension, number of patients with dyslipidemia, number of patients that had a previous MI, number of patients that underwent a previous PCI.

3.3. Studies' major findings

For each study, major findings by analyzed outcome are summarized in Table 4 and Table 5. Concerning LLL, the only two studies that analyzed this outcome were those of Tao L, Li Z, Yin Z et al. (21) and Rheude et al. (22), but only the latter found a significant lower mean LLL in the patients treated with the BP stent (YUKON CHOICE ®). In two studies (19) (21), no ST events were registered whereas in the Godino et al.(20) analysis a significantly higher ST rate was measured for diabetic patients with BP stents (NOBORI ®). Gregersen et al. (18) found significantly higher TLR events in the PF (BIOFREEDOM ®) group than in the BP (ORSIRO ®) group. On the contrary, Godino et al.(20) found TLR as well as TVR rates to be significantly lower for in the diabetic sub-cohort with PF stents.

Study	LLL	ST	TLR	TVR
Gregersen et al. 2022 (18)	/	No SS difference in (Definite, Probable, Definite or Probable, Possible) ST between the two groups at 2 years	Significantly higher TLR for PF group at 2 years (2,6% ORSIRO ® vs 5,1% BIOFREEDOM ® p= 0,0004)	No SS difference in TVR between the two groups at 2 years
Viswanathan et al. 2018 (19)	/	No instances of ST at 1 year follow up	/	/
Godino et al. 2017 (20)	/	No SS difference in definite ST nor definite/probable ST in NON-DM patients	No SS difference in TLR in NON-DM patients	Significantly higher TVR for BP group in NON-DM patients (25 NOBORI ® vs 12 Cre8 ® p= 0,029)
	/	Significantly higher definite/probable ST for BP group in DM patients (7 NOBORI ® vs 1 Cre8 ® p= 0,032)	Significantly higher TLR for BP in DM patients (21 NOBORI ® vs 9 Cre8 ® p= 0,019)	No SS difference in TVR in DM patients
Tao L, Li Z, Yin Z et al 2021 (21)	No SS difference In-segment LLL at 9 months (0.29 +/- 0.46 mm COMBO ® vs 0.31 +/- 0.44 mm NANO ® with p= 0,57)	No definite/ probable ST at 24 months in both groups	No SS difference of ischemia driven TLR at 24 months (6,2% COMBO ® and 3,8% NANO ® p=0,26)	No SS difference of ischemia driven TVR at 24 months (7,1% COMBO ® and 4,2% NANO ® p=0,20)
Rheude et al. 2023 (22)	Mean LLL lower with BP at 6-8 months (0,26+/- 0,62 mm BP group vs 0,37 +/-0,65 mm PF group p= 0,034)	No SS difference in definite/probable ST between the two groups (2,0 % BP group vs 1,8% PF group p=0,76)	No SS difference in definite/probable TLR between the two groups at 10 years (25,0 % BP group vs 26,1% PF group p=0,29)	/

Table 4 : Key findings by analyzed outcome including late lumen loss (LLL), stent thrombosis (ST), target vessel revascularization (TVR), target lesion revascularization (TLR), statistically significant (SS)

No study found statistically significant differences in terms of TLF, TVF, MI or CM between the two intervention groups, except for the Godino et al.(20) one that showed significantly higher rates for all of these outcomes in the diabetic subgroup that had received the BP stent. In the same study, all cause death was significantly more frequent in the non-diabetic patients with a PF stent.

Study	TLF	TVF	MI	CM	All cause death
Gregersen et al. 2022 (18)	No SS difference in TLF between the two groups at 2 years	No SS difference in TVR between the two groups at 2 years	No SS difference in MI between the two groups at 2 years	No SS difference in CM between the two groups at 2 years	No SS difference in all cause death between the two groups at 2 years
Viswanathan et al. 2018 (19)	/	/	/	No SS difference in all cause death at 1 year 2,04% PF Yukon Choice ® vs 1,17% BP Yukon Choice ® p=0,65	/
Godino et al. 2017 (20)	No SS difference in TLF in NON-DM patients	No SS difference in TLF in NON-DM patients	No SS difference in any MI in NON-DM patients	No SS difference in CM in NON-DM patients	Significantly higher all cause death for PF in DM patients (5 NOBORI ® vs 16 Cre8 ® p= 0,018)

	<u>Significantly higher TLF for BP in DM patients (31 NOBORI ® vs 12 Cre8 ® p= 0,002)</u>	<u>Significantly higher TVR for BP in DM patients (35 NOBORI ® vs 18 Cre8 ® p= 0,013)</u>	<u>Significantly higher MI (any) for BP in DM patients (10 NOBORI ® vs 3 Cre8 ® p= 0,047)</u>	<u>Significantly higher CM for BP in DM patients (11 NOBORI ® vs 3 Cre8 ® p= 0,029)</u>	No SS difference in all cause death in DM patients
Tao L, Li Z, Yin Z et al. 2021 (21)	No SS difference of TLF at 24 months (9,4% COMBO ® and 8,0% NANO ® p=0,62)	/	No SS difference of target vessel MI at 24 months (3,3% COMBO ® and 5,2% NANO ® p=0,34)	No SS difference of CM at 24 months (0,5% COMBO ® and 0% NANO ® p=1,00)	No SS difference of all cause death at 24 months (1,4% COMBO ® and 0% NANO ® p=0,25)
Rheude et al. 2023 (22)	/	/	No SS difference in definite/probable MI between the two groups at 10 years (8,7% BP group vs 6,5% PF group p=0,05)	/	No SS difference in all-cause mortality between the two groups at 10 years (41,6% BP group vs 43,5% PF group p=0,82)

Table 5: Key findings by analyzed outcomes including target lesion failure (TLF), target vessel failure (TVF), myocardial infarction (MI), cardiac mortality (CM), all cause death, statistically significant (SS)

3.4. Studies' key conclusions

As shown in Table 6, two (18) (20) studies out of five concluded that no significant differences were found between the BP and the PF stent analyzed in an all-comers population.

Study	Conclusions
Gregersen et al. 2022 (18)	<u>At two years after PCI, the PF BIOFREEDOM ® stent showed an increased risk of TLR compared to the BP ORSIRO ® stent.</u>
Viswanathan et al. 2018 (19)	No difference between BP YUKON CHOICE ® and PF YUKON CHOICE ® was found at 1 year after PCI in terms of ST and CM.
Godino et al. 2017 (20)	At 1 year follow up, there were no differences safety and efficacy profile between PF CRE8 ® stent and BP NOBORI ® stent the non-diabetes group.
	<u>At 1 year follow up, PF CRE8 ® stent showed better safety and efficacy profile than BP NOBORI ® stent in patients with diabetes mellitus.</u>
Tao L, Li Z, Yin Z et al. 2021 (21)	At 24 months follow up, the BP COMBO ® stent proved to be non-inferior to PF NANO ® stent in terms of LLL, ST, TLR, TVR, TLF, MI, CM and all-cause death.
Rheude et al. 2023 (22)	In patients with severe or moderate CAC, there was no significant difference in adverse clinical event rates at 10 years between BP YUKON CHOICE ® and PF COROFLEX ® stents for LLL, ST, TLR, MI, all cause death.

Table 6: Key conclusions for each included study. Percutaneous coronary intervention (PCI), Biodegradable polymer (BP), Polymer-free (PF), Target lesion revascularization (TLR), Stent thrombosis (ST), Cardiac Mortality (CM), Late lumen loss (LLL), Target vessel revascularization (TVR), Target lesion failure, Myocardial infarction (MI), Coronary artery calcification (CAC)

One study(18) pointed out that the BP stent (BP YUKON CHOICE ®) was superior to the PF stent (BIOFREEDOM ®) at least in terms of TLR rates in an all comers population. The fourth study(20) reported the safety and efficacy profiles to be better for the PF stent (Cre8) than the BP one (NOBORI ®) for diabetic patients, but not statistically different between the two stents for non-diabetic subjects. The last study(22) concluded that, in patients with moderate to severe CAC, the differences in LLL observed at 9 months between the two stent types were fully attenuated at 10 years, as no other outcome differed significantly at this point.

3.5. Risk of bias assessment

The risk of bias assessment for each article was completed using the JBI appraisal tool and it can be found in the Annex of this review. The JBI checklist for cohort studies was applied to the Godino et al. (19) work, whereas the one for randomized controlled trials was employed for the other articles(17) (18) (20) (21). No study was excluded following the assessment.

According to our analysis, the study of Gregersen et al. (17) did not present any possible risk of bias except for the fact that those delivering the treatment (either the BP-or the PF-DES) were not blind to treatment assignment (question 5 of the checklist).

The assessment of the work by Viswanathan et al. (18) raised some points of vigilance regarding risk of bias (question 4,5,7,10 and 12). First of all, it consisted in a deliberately open label study, therefore both participants and treatment deliverers were not blind to treatment assignment. It remains unclear whether or not outcome assessors were blind to treatment assignment, because it was not specified if a blind committee reviewed outcome results. Concerning follow-up, in both groups, only one third of symptomatic patients were willing to undergo a check angiogram. Of the asymptomatic patients, 33% of patients in the PF group and roughly 50% of patients in the BP group did not consent for stress testing. This was reported in the study limitations. In addition, the appropriate statistical analysis failed to be used for the "(cardiac) death" outcome, as the authors applied the Chi-square test even if the cell values were inferior to five.

Concerning Godino et al. (19), only one potential risk of bias source was individuated (question 8). Although follow up was complete, the authors report the relatively short follow up time as a study limitation.

As for Tao L, Li Z, Yin Z et al. (20), both participants and treatment deliverers were not blind to treatment assignment because the study was open labeled (question 4,5). Moreover, although

the outcome assessors were blind in the case of LLL, it is unclear if they were for ST and TLF as well (question 7).

The outcome analysis of different coating strategies (BP vs PF-DES) in patients with moderate and severe CAC, was the only pertinent part of Rheude et al.(21)'s work for the scope of this systematic review. Therefore, the assessment of this study was performed considering only that component and some possible bias sources were found (question 3,6, 7). First of all, some of the patients' baseline characteristics differed significantly between the BP and PF subgroups. Patients in the BP group had significantly lower acute myocardial infarction rates as well as higher unstable angina rates than the patients in the PF group. Patients in the BP group also had a lower number of lesions than patients in the PF group. In addition, some procedural characteristics differed significantly between the two subgroup : both number of stents and total stent length were higher in the PF group. Lastly, it is not specified whether or not outcome assessors were blind to treatment assignment.

4. Discussion

This systematic review on third generation stents was meant to compare the BP-DES and PF-DES in terms of patient-centered outcomes previously described.

Only one study(17) found a BP-DES stent to perform better than a PF-DES in an all-comers population. In the SORT OUT IX trial, Gregersen et al. (17) showed the BP-stent (ORSIRO ®) to be more efficient in terms of TLR when compared to the PF-stent (BIOFREEDOM ®) at two years follow-up. Nonetheless, other efficiency (TVR), safety (ST, MI, CM and all-cause death), as well as composite outcomes (TVF and TLF) did not differ significantly between the two stents. This is partially in line with the results of Nogic et al.(12), that associated BP-DES stents with significantly lower LLL, TVR and TLR rates (efficiency outcomes), but not significantly different MI, ST and all-cause death rates (safety outcome). As Gregersen et al. (17) suggest in their study limitations, a longer follow up might be necessary to assess the benefits of the biodegradable polymer even after polymer degradation (12-24 months). For this reason, they set a goal to evaluate the safety and efficacy of the stents included in SORT OUT IX trial five years after implantation. The mean follow up in the studies included in the Nogic et al. (12) review was limited to 14±5 months. Nevertheless, following the results of the SORT OUT IX trial at five years follow up could ultimately confirm whether or not Gregersen et al. (17) findings' match those of Nogic et al (12).

Two studies(18) (20) found no significant differences between BP-DES and PF-DES in an all-comers population, and one(21) suggests the same in patients with moderate to severe CAC.

According to Viswanathan et al. (18), there was no significant difference in the rates of ST and CM between BP YUKON CHOICE ® and PF YUKON CHOICE ® at 1 year after implantation. More precisely, no occurrences of ST were observed in either of the two groups. However, these results should be considered taking into account the study limitations. Firstly, in both groups, only one third of symptomatic patients were willing to undergo a check angiogram. Of the asymptomatic patients, 33% of patients in the PF group and roughly 50% of patients in the BP group did not consent for stress testing. As angiography is accounted among the imaging methods to detect ST(23), it might be possible that ST events failed to be found in both groups because some of the patients did not consent for this test. In addition, the appropriate statistical analysis was not used for the "cardiac death" (CM) outcome, as the authors applied the Chi-square test even if the cell values were inferior to five. Therefore, this particular result might be evaluated again after using another statistical analysis tool such as Fisher's exact test.

The 2021 article by Tao L, Li Z, Yin Z et al. (20) included in this review compared the 9 months rates of LLL as well as the two years rates of ST, TLR, TVR, TLF, MI, CM and all-cause death between the BP COMBO® and the PF NANO® in the RECOVERY trial. No significant differences were found across these outcomes between the intervention and the comparison. Nogic et al. (12) stated to have included an article of Tao et al. dated 2017 and covering the same results of the RECOVERY trial but at 1 year follow up. Unfortunately, the authors of the present review did not manage to retrieve and therefore properly cite nor analyze this article. Thus, it is not possible to argue whether there were changes in ST, TLR, TVR, TLF, MI, CM rates in the additional follow-up year or not.

As for Rheude et al.(21), no significant difference in terms of LLL, ST, TLR, MI, all cause death rates at ten years follow-up between the BP YUKON CHOICE® and the PF COROFLEX® stents in patients with moderate to severe CAC. These results should be considered accounting the several study limitations, that include differences in both procedural and patient baseline characteristics between the two stent types. Moreover, an analysis of the outcomes according to polymer coating strategy in patients with no or mild CAC could have possibly provided more understanding of the BP versus PF stents' performance the whole spectrum of calcified coronary conditions.

As previously mentioned, Godino et al. (19) compared the rates of ST, TLR, TVR, TLF, TVF, MI, CM and all-cause death between the BP NOBORI® and the PF Cre8® stents at one year follow up in two patients subgroups according to the presence or absence of diabetes mellitus. In the non-diabetic patients, no significant differences were found between the two stents types. Interestingly, this was not true for diabetic patients, who experienced higher rates of ST, TLR, TLF, MI and CM with the BP stent than with the PF stent. It is important to notice that the two stents did not only differ by polymer coating, but also for strut thickness and eluted drugs. As the authors of the study itself report, these factors could all partially contribute to superiority of PF-DES compared to BP-DES. On the one hand, the absence of the polymer and the thinner strut could of PF-DES possibly be beneficial that in the pro-inflammatory state of diabetic patients. On the other hand, the eluted drug by this particular PF-DES, amphillimus, could also contribute to their better performance. A recent systematic review and meta-analysis(24) showed the superiority of amphillimus-eluting PF-DES at least in TLF rates when compared to zotarolimus eluting DP-DES in patients with diabetes at one year follow-up. As these authors suggest, and might be applicable to the Godino et al. analysis(19), is that a longer-term follow up should be considered.

This systematic review had several limitations. First of all, the limited number of the included studies as well as their heterogeneity brought the authors to choose not to perform a meta-analysis. As a matter of fact, not all studies specified or agreed to outcome definition Academic Research Consortium-2 Consensus Document(15). Moreover, both biodegradable polymer and polymer-free stents differed across the studies. Therefore, only a qualitative analysis of the included articles was possible.

5. Conclusion

Overall, no study included in this review identified any significant differences between the safety profiles of BP-DES and PF-DES in an all-comers population , confirming what previously demonstrated by Nagic et al. (12). On the contrary, most of the included studies also reported BP-DES and PF-DES to be comparable in terms of efficacy outcomes in an all-comers population. Therefore, the authors suggest that future research should focus on longer follow-up periods to assess the potential benefits of the biodegradable polymer, which might not have been disclosed due to the relatively short follow up time of most studies (1-2 years). In addition to this, further scientific investigation might be devoted to clarify whether or not PF-DES are superior to BP-DES in patients with diabetes mellitus.

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Annex

This Annex reports the risk of bias analysis through the JBI appraisal tools performed for each study included in the review.

Assessor: Emanuela Basile & Pedro Amorim	Date of Appraisal: 9.10.2024	Record Number: DOI:10.4244/EIJ-D-21-00874
Study Author: Julia Ellert-Gregersen	Study Title: Polymer-free biolimus-coated (...)	Study Year: 2022

Internal Validity		Choice - Comments/Justification	Yes	No	Unclear	N/A
Bias related to selection and allocation						
1	Was true randomization used for assignment of participants to treatment groups?	1:1	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Was allocation to treatment groups concealed?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Were treatment groups similar at the baseline?	Table 1	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bias related to administration of intervention/exposure						
4	Were participants blind to treatment assignment?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	Were those delivering the treatment blind to treatment assignment?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6	Were treatment groups treated identically other than the intervention of interest?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bias related to assessment, detection and measurement of the outcome						
7	Were outcome assessors blind to treatment assignment?		Yes	No	Unclear	N/A
	Outcome 1 - TLF	An independent event committee, blinded to study stent type assignment during the adjudication process, reviewed all endpoints	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2 - MI		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3 - TLR		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4 - TVR		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 5 - CM		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 6 - ST		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 7 - All death		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8	Were outcomes measured in the same way for treatment groups?		Yes	No	Unclear	N/A
	Outcome 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 5		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 6		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 7		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9	Were outcomes measured in a reliable way		Yes	No	Unclear	N/A

Outcome 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Outcome 2		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Outcome 3		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Outcome 4		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Outcome 5		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Outcome 6		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Outcome 7		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Bias related to participant retention

10	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?					
	Outcome 1		Yes	No	Unclear	N/A
	Result 1	no patients were lost to follow-up.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 5		Yes	No	Unclear	N/A

Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Outcome 6		Yes	No	Unclear	N/A
Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Outcome 7		Yes	No	Unclear	N/A
Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Statistical Conclusion Validity

11	Were participants analysed in the groups to which they were randomized?					
	Outcome 1		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 5		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 6		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 7		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

12	Was appropriate statistical analysis used?		Yes	No	Unclear	N/A
	Outcome 1		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 5		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 6		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 7		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

			Yes	No	Unclear	N/A
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13	Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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Overall appraisal: Include: Exclude: Seek Further Info:

Comments:

Annex 1: Risk of bias assessment for the study of Gregersen et al. (2022) (17)

Assessor: Emanuela Basile & Pedro Amorim	Date of Appraisal: 09/10/2024	Record Number: 10.1016/j.jhj.2018.08.015
Study Author: Viswanathan et al.	Study Title: Open-labelled randomized (...)	Study Year: 2018

Internal Validity	Choice - Comments/Justification	Yes	No	Unclear	N/A	
Bias related to selection and allocation						
1	Was true randomization used for assignment of participants to treatment groups?	Block randomization into groups of four	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Was allocation to treatment groups concealed?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Were treatment groups similar at the baseline?	No significant difference in patient baseline (Table 2)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bias related to administration of intervention/exposure						
4	Were participants blind to treatment assignment?	Open-label study	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	Were those delivering the treatment blind to treatment assignment?	Open-label study	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

6	Were treatment groups treated identically other than the intervention of interest?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bias related to assessment, detection and measurement of the outcome						
7	Were outcome assessors blind to treatment assignment?	Not specified	Yes	No	Unclear	N/A
	Outcome 1 - MACE		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	Outcome 2 - Cardiac death		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	Outcome 3 - urgent TVR		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	Outcome 4 - ACS		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	Outcome 5 - Stroke		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	Outcome 6 - Stent thrombosis		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
8	Were outcomes measured in the same way for treatment groups?		Yes	No	Unclear	N/A
	Outcome 1 - MACE		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2 - Cardiac death		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3 - urgent TVR		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4 - ACS		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 5 - Stroke		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 6 - Stent thrombosis		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9	Were outcomes measured in a reliable way	Direct follow-up at the center 1 year after the procedure was the follow-up of choice. If this was not possible, a telephonic follow-up was performed.	Yes	No	Unclear	N/A
	Outcome 1 - MACE		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2 - Cardiac death		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3 - urgent TVR		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4 - ACS		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 5 - Stroke		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 6 - Stent thrombosis		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bias related to participant retention						
10	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?		Yes	No	Unclear	N/A
	Outcome 1 - MACE	Fig 1 patient flowchart	Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2 - Cardiac death	Fig 1 patient flowchart	Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3 - urgent TVR	Fig 1 patient flowchart	Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4 - ACS	Fig 1 patient flowchart	Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 5 - Stroke	Fig 1 patient flowchart	Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 6 - Stent thrombosis	In both groups, only one third of symptomatic patients were willing to undergo a check angiogram. Of the asymptomatic patients, 33% of patients in the PF group and roughly 50% of patients in the BP group did not consent for stress testing.	Yes	No	Unclear	N/A
	Result 1		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Statistical Conclusion Validity

11	Were participants analysed in the groups to which they were randomized?	Table 5				
	Outcome 1 - MACE		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2 - Cardiac death		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3 - urgent TVR		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4 - ACS		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 5 - Stroke		Yes	No	Unclear	N/A
Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Outcome 6 - Stent thrombosis		Yes	No	Unclear	N/A	
Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
12	Was appropriate statistical analysis used?					
	Outcome 1 - MACE	Chi-square test with frequency < 5	Yes	No	Unclear	N/A
	Result 1		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2 - Cardiac death	Chi-square test with frequency < 5	Yes	No	Unclear	N/A
	Result 1		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3 - urgent TVR	No TVR occurrence	Yes	No	Unclear	N/A
	Result 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
	Outcome 4 - ACS	Chi-square test with frequency < 5	Yes	No	Unclear	N/A
	Result 1		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 5 - Stroke	Chi-square test with frequency < 5	Yes	No	Unclear	N/A
Result 1		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Outcome 6 - Stent thrombosis	No ST occurrence	Yes	No	Unclear	N/A	
Result 1		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
			Yes	No	Unclear	N/A
13	Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Overall appraisal:			Include: <input checked="" type="checkbox"/>	Exclude: <input type="checkbox"/>	Seek Further Info: <input type="checkbox"/>	

Annex 2: Risk of bias assessment for the study of Viswanathan et al. (18)

Reviewer: Emanuela Basile & Pedro Amorim Date: 10/10/2024
 Author: Godino et al. Year: 2017 Record Number DOI: 10.1016/j.ijcard.2017.06.028

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Was the exposure measured in a valid and reliable way?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Were confounding factors identified?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Were strategies to deal with confounding factors stated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

7. Were the outcomes measured in a valid and reliable way?
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?
10. Were strategies to address incomplete follow up utilized?
11. Was appropriate statistical analysis used?

Overall appraisal: Include Exclude Seek further info

Annex 3: Risk of bias assessment for the study of Godino et al. (2017) (19)

Assessor: Emanuela Basile & Pedro Amorim	Date of Appraisal: 9.10.2024	Record Number: DOI: 10.1002/ccd.29553
Study Author: Tao L, Li Z, Yin Z et al.	Study Title: Nine-month angiographic (...)	Study Year: 2021

Internal Validity	Choice - Comments/Justification	Yes	No	Unclear	N/A	
Bias related to selection and allocation						
1	Was true randomization used for assignment of participants to treatment groups?	1:1	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Was allocation to treatment groups concealed?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Were treatment groups similar at the baseline?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bias related to administration of intervention/exposure						
4	Were participants blind to treatment assignment?	Open-label study	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	Were those delivering the treatment blind to treatment assignment?	Open-label study	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6	Were treatment groups treated identically other than the intervention of interest?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bias related to assessment, detection and measurement of the outcome						
7	Were outcome assessors blind to treatment assignment?		Yes	No	Unclear	N/A
	Outcome 1 – LLL		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2 – TLF, PoCE and ST		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
8	Were outcomes measured in the same way for treatment groups?		Yes	No	Unclear	N/A
	Outcome 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9	Were outcomes measured in a reliable way		Yes	No	Unclear	N/A
	Outcome 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bias related to participant retention						
10	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?		Yes	No	Unclear	N/A
	Outcome 1		Yes	No	Unclear	N/A
	Result 1	Patient flowchart	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2		Yes	No	Unclear	N/A
	Result 1	Patient flowchart	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Statistical Conclusion Validity

11	Were participants analysed in the groups to which they were randomized?					
	Outcome 1		Yes	No	Unclear	N/A
	Result 1	Table 3	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2		Yes	No	Unclear	N/A
	Result 1	Table 4	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12	Was appropriate statistical analysis used?					
	Outcome 1		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13	Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	No deviations	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	Overall appraisal:	Include: <input checked="" type="checkbox"/> Exclude: <input type="checkbox"/>	Seek Further Info: <input type="checkbox"/>			
Comments: The authors assume that the RCT is open-label. Questions marked "unclear" are not determinative.						

Annex 4 : Risk of bias assessment for the study of Tao L, Li Z, Yin Z et al. (2021)

Assessor: Emanuela Basile & Pedro Amorim	Date of Appraisal: 10/10/2024	Record Number:
Study Author: Rheude et al.	Study Title: Ten year clinical outcomes (...)	Study Year: 2023

Internal Validity	Choice - Comments/Justification	Yes	No	Unclear	N/A	
Bias related to selection and allocation						
1	Was true randomization used for assignment of participants to treatment groups?	2:1:1 (ISAR TEST 4), 2:1 (ISAR TEST 5)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Was allocation to treatment groups concealed?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Were treatment groups similar at the baseline?	Pooled analysis of individual patient data from two RTCs Supplementary table 1	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bias related to administration of intervention/exposure						
4	Were participants blind to treatment assignment?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	Were those delivering the treatment blind to treatment assignment?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
6	Were treatment groups treated identically other than the intervention of interest?	Supplementary table 2	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bias related to assessment, detection and measurement of the outcome						
7	Were outcome assessors blind to treatment assignment?	Not specified	Yes	No	Unclear	N/A
	All-cause mortality		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	Target lesion revascularization		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	Myocardial infarction		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	Definite/probable stent thrombosis		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
8	Were outcomes measured in the same way for treatment groups?	Patients were systematically evaluated at 1 and 12 months and annually up to 10 years after the index PCI. Extended follow-up was performed in the setting of routine care by either telephone calls or visits at the outpatient clinic of the participating centres. In both trials, follow-up angiography was performed systematically at 6-8 months.	Yes	No	Unclear	N/A
	Outcome 1 - All-cause mortality		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2 - Target lesion revascularization		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3 - Myocardial infarction		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Outcome 4 - Definite/probable stent thrombosis		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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9	Were outcomes measured in a reliable way		Yes	No	Unclear	N/A
	Outcome 1 - All-cause mortality		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2 - Target lesion revascularization		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3 - Myocardial infarction		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4 - Definite/probable stent thrombosis		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Bias related to participant retention

10	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	Ten-year follow-up was complete in all but 793 patients (16.0%), with no difference among the degrees of calcification (p=0.39). In patients without complete follow-up to 10 years, the median follow-up interval was 5.3 (4.1-6.9) years().Angiographic follow-up at 6-8 months was available in 76.8% of all patients				
	Outcome 1 - All-cause mortality		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2 - Target lesion revascularization		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3 - Myocardial infarction		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4 - Definite/probable stent thrombosis		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Statistical Conclusion Validity

11	Were participants analysed in the groups to which they were randomized?					
	Outcome 1		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2 - TLR		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3 - MI		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 4 - Definite/probable ST		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

12	Was appropriate statistical analysis used?	Paragraph on Statistical Analysis				
	Outcome 1 - All cause mortality		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 2 - TLR		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Outcome 3 - Myocardial infarction		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Outcome 4 - Definite/probable stent thrombosis		Yes	No	Unclear	N/A
	Result 1		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

13	Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Pooled analysis of two RCTs, accounted for in the Limitations section	Yes	No	Unclear	N/A
			<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Overall appraisal: Include: Exclude: Seek Further Info:

Comments:

Annex 5 : Risk of bias assessment for the study of Rheude et al. (2023)