Optimal Stent Design for High Bleeding Risk Patients: Evidence From a Network Meta-Analysis

Juan G. Chiabrando, MD[1,2,3]; Giovanni M. Vescovo, MD[4]; Marco Giuseppe Del Buono, MD[5]; Marco Lombardi, MD[5]; Massimiliano Camilli, MD[5]; Krishna Ravindra, MD[1]; Rocco Antonio Montone, MD[5,6]; Giampaolo Niccoli, MD[5,6]; Giuseppe Biondi-Zoccai, MD, MStat[7,8]

Abstract

Objective. To determine the best stent design for high bleeding risk (HBR) patients. **Background.** Polymer-free (PF) drug eluting stent (DES) devices have a proven benefit over bare-metal stent (BMS) devices in previous trials. It is unknown, however, whether polymer-based (PB)-DES devices are as safe as PF-DES devices. **Methods.** A network meta-analysis including all randomized controlled trials (RCTs) that compared different stent technology in HBR patients with a 1-month course of dual-antiplatelet therapy (DAPT) was performed. The main efficacy outcome was major adverse cardiac event (MACE) rate, defined as the composite of all-cause mortality, myocardial infarction (MI), and target-lesion revascularization (TLR). Secondary efficacy events included all-cause and cardiac mortality, MI, stroke, TLR, and target-vessel revascularization (TVR). Safety outcomes included all bleeding, major bleeding, and stent thrombosis (ST). **Results.** A total of 4 RCTs with 6456 patients were included. PF-DES and PB-DES yielded a reduced rate of MACE, MI, TLR, and TVR events compared with BMS (all $P<.05$). ST events were reduced in PB-DES compared with BMS ($P=.01$). No differences were found in all-cause death, cardiac death, or stroke events in PF-DES and PB-DES compared with BMS. Furthermore, no differences were found between PF-DES and PB-DES regarding any of the outcomes. **Conclusion.** DES devices were associated with lower MACE and TVR rates compared with BMS, whereas there were no statistical differences in other efficacy endpoints. Also, PB-DES were associated with fewer ST events compared with BMS. There were no statistical differences between PB-DES and PF-DES with regard to any of the endpoints.

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Key words: drug-eluting stents, high bleeding risk, network meta-analysis

Percutaneous coronary intervention (PCI) is the preferred therapeutic approach to treat coronary artery disease (CAD) worldwide.[1] Stent placement requires the implementation of dual-antiplatelet therapy (DAPT) for a period of time, in order to reduce the risk of stent thrombosis (ST) and recurrent ischemic events.[2]

It is estimated that at least 15% of patients undergoing PCI are at high risk of bleeding events (HBR) and therefore might not be candidates for a prolonged DAPT course.[3] Due to a high risk of late ST when DAPT was prematurely suspended in first-generation drug-eluting stent (DES) devices, patients considered to be at HBR often received bare-metal stent (BMS) devices in order to shorten their DAPT duration.[4]

Recent evidence suggested that in select patients (ie, HBR patients), shorter DAPT duration may provide benefits in terms of bleeding events without a significant increase in ischemic events. In the STOPDAPT-2 (Short and Optimal Duration of Dual Anti Platelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent) trial, a 1-month DAPT course in an all-comer population reduced bleeding events without increasing cardiovascular events when compared with a 12-month DAPT course.[5]

Only recently, patients considered to be at HBR undergoing PCI were included in randomized clinical trials (RCTs) that showed better cardiovascular outcomes with DES (especially polymer-free [PF] stents) compared with BMS in a 1-month DAPT course.[6–9] Thus, the paradigm that BMS must be implanted in patients with a

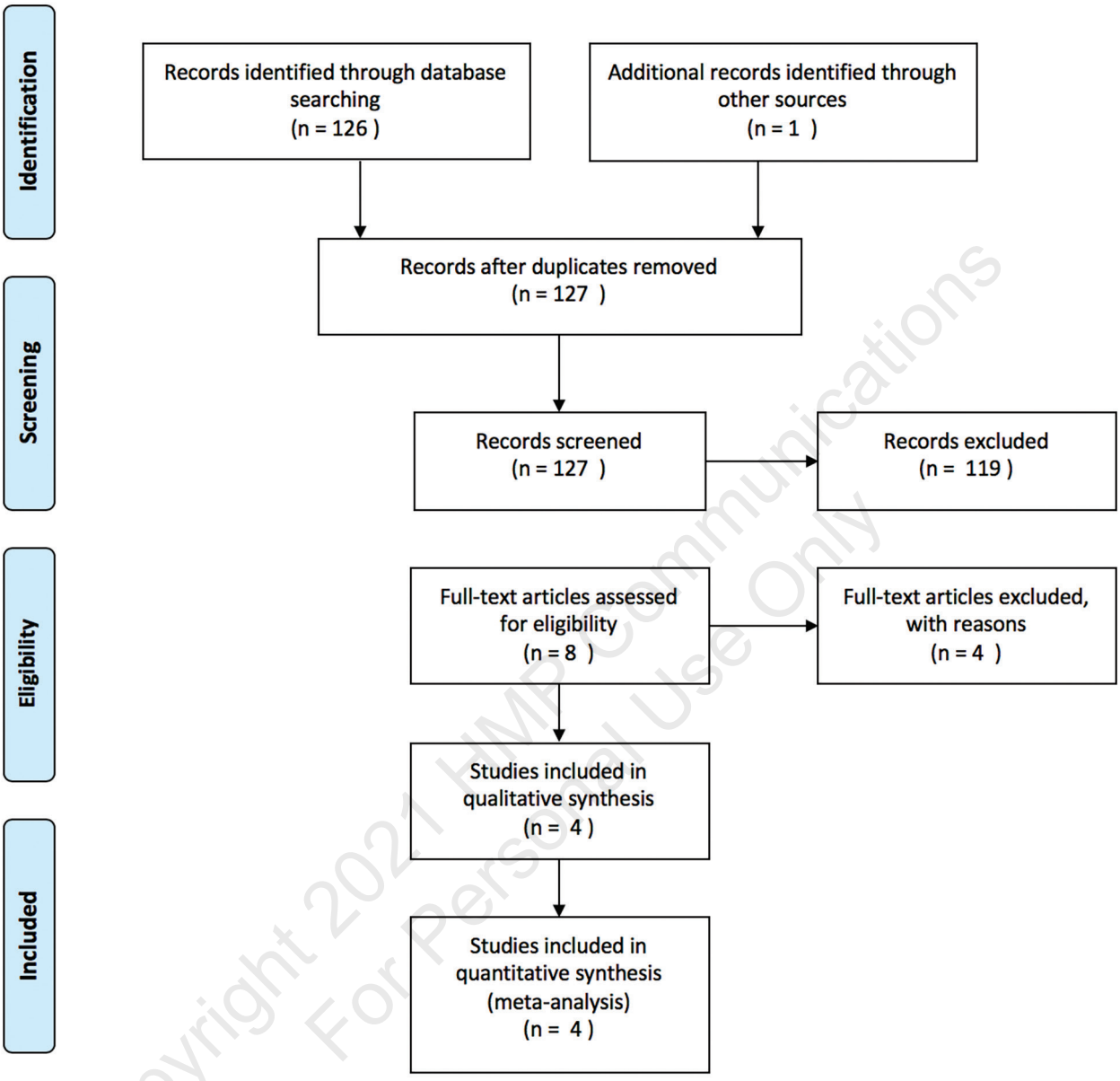

FIGURE 1. Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram.

reduced DAPT course is no longer valid. PF-DES were introduced with the aim to overcome the risks of late safety and efficacy outcomes associated with the preceding generations of stents.[6] Recently, however, a polymer-based (PB) zotarolimus-eluting stent was found to be non-inferior to PF-DES at 1 year with regard to both safety and efficacy among patients at HBR treated with 1 month of DAPT.[9]

As differences in both polymer and struts arise between stent designs, we aim to compare differences in clinical outcomes regarding stent types in HBR patients who underwent PCI with a short DAPT duration of 1 month.

Methods

This systematic review and meta-analysis is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

Data sources and searches. We conducted a systematic search of PubMed, Google Scholar, reference lists of relevant articles, and Medline. The search utilized the following terms: "drug eluting stent," "dual antiplatelet therapy," "high bleeding risk,"

and "high thrombotic risk." The search for articles compatible with our inclusion and exclusion criteria was performed from inception through March 2020 and returned a combined total of 126 articles. One additional article was included, yielding a total of 127 articles.

Study abstracts were screened for established inclusion and exclusion criteria. Studies thought to be relevant to our search were downloaded and the full manuscripts were reviewed. A thorough search of cited articles within the reviewed manuscripts was assessed for studies not previously identified from the initial database search.

Study selection. We included the articles that satisfied the following inclusion criteria: (1) RCTs comparing different stent technology in HBR patients who underwent 1 month of DAPT; (2) reported follow-up beyond 1 year of treatment; (3) reported cardiovascular outcomes; and (4) reported in English. We excluded non-randomized studies, retrospective cohorts or editorials, and articles that were not in English. The definition of HBR differed among studies, but must have met at least 1 of the following criteria: age ≥75 years; on oral anticoagulation; renal failure, liver disease; recent cancer (<3 months); anemia or transfusion; thrombocytopenia; stroke or intracranial hemorrhage; and hospitalization for bleeding. With the intent of increasing the strength to provide differences among PB-DES and PF-DES, we included bioabsorbable polymer (eg, Synergy; Boston Scientific) and durable polymer (eg, Onyx; Medtronic) as part of the same group (ie, PB-DES).

Outcomes and definitions. *Main efficacy outcomes* of interest were major adverse cardiovascular event (MACE) rate, defined as a composite of total death, myocardial infarction (MI), and target-lesion revascularization (TLR). *Secondary efficacy outcomes* were all-cause death, cardiac death, MI, stroke, TLR, and target-vessel revascularization (TVR).

Safety outcomes included all bleeding events as defined by the Bleeding Academic Research Consortium (BARC 1-5), major bleeding events (BARC 3-5), and ST. *ST* was considered definite or probable as defined by the Academic Research Consortium (ARC).[10]

Data extraction and quality assessment. Two investigators (JGC and ML) independently reviewed study titles, abstracts, and articles. Those that satisfied the inclusion criteria were retrieved for full text evaluation. Discrepancies regarding data incorporation to the database were resolved through consensus among the authors. The following data from each selected study were extracted: number of participants; demographics; procedure strategies; and cardiovascular clinical outcomes of interest. Furthermore, we appraised the studies according to the Risk of Bias Assessment Tool, version 2 (RoB 2), as recommended by the Cochrane Collaboration (Supplemental Figure S1).[11]

Data synthesis and analysis. For inferential purposes, frequentist fixed-effect network meta-analysis was used to estimate the incidence rate ratio (IRR) for incidence of cardiovascular clinical outcomes. A random-effect analysis was conducted when heterogeneity was detected among studies. Heterogeneity values are reported as a percentage in the supplemental tables and figures.[12]

Descriptive statistics on baseline characteristics of the patients in the studies are provided. Dichotomous variables were reported as counts and percentages, and continuous variables as mean ± standard deviation or as median with or without interquartile range (IQR) if the values were not normally distributed. All *P*-values reported are two-sided and all confidence intervals (CIs) are calculated at the 95% level. The network meta-analysis was performed with R statistical software (R project for statistical computing, version 3.3.3) using R package "netmeta."

Heterogeneity across studies was assessed with Cochran's Q method. I^2 testing was also performed to evaluate the magnitude of the heterogeneity between studies, which was considered substantial when it was >50%. We evaluated the probability (P) scores in order to identify the best-to-worst treatment, taking into account precision and accuracy of effect.

Results

Our initial search retrieved 127 titles, of which 4 studies were ultimately included in our systematic review and network meta-analysis, summarizing the data of 6456 patients at a median follow-up of 1 year (Figure 1). The four RCTs that met the inclusion criteria were: the ZEUS-HBR subanalysis (Zotarolimus-Eluting Versus Bare-Metal Stents in Uncertain Drug-Eluting Stent Candidates); LEADERS FREE (Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk); SENIOR (Synergy II Everolimus-Eluting Stent in Patients Older Than 75 Years Undergoing Coronary Revascularization Associated With a Short Dual-Antiplatelet Therapy) subgroup with stable ischemic disease who received 1 month of DAPT (drug-eluting stents in elderly patients with coronary artery disease); and ONYX ONE (Polymer-Based or Polymer-Free Stents in Patients at High Bleeding Risk). Baseline characteristics are presented in Table 1.[6-9] Most of the trials included elderly patients with complex coronary disease, and radial artery access was the most commonly used approach. All articles were published between 2015 and 2019.

Network meta-analysis. Statistical inconsistency and heterogeneity were not significant among the main outcomes of interest (all I^2<50% and *P*-values >.05) (Supplemental Table S2). The evidence network geometry and P-scores are shown in Supplemental Figures S2, S3, and S4).

Regarding the efficacy endpoints, in the IRR analysis (Table 2 and Figure 2), both newer-generation PB-DES and PF-DES yielded a significant reduction in MACE (IRR, 0.66; 95% CI, 0.57-0.76; *P*<.001 and IRR, 0.69; 95% CI, 0.61-0.78; *P*<.001, respectively),

TABLE 1. Demographics of the articles included.

Patients Characteristics	LEADERS FREE 2015	ZEUS-HBR 2016	SENIOR 2018	ONYX ONE 2019
Number of patients	2432 (DES 1221 / BMS 1211)	828 (DES 424 / BMS 404)	1200 (DES 596 / BMS 604)	1996 (DES 1003 / PF 993)
Stent types	PF-DES vs BMS	PB-DES vs BMS	PB-DES vs BMS	PB-DES vs PF-DES
Age	75.7 years	80.5 years	81.4 years	74.1 years
Body mass index	27.4 kg/m^2	26.0 kg/m^2	26.1 kg/m^2	27.3 kg/m^2
Male gender	1728 (71.1%)	533 (64.4%)	747 (62.3%)	666 (66.7%)
Diabetes mellitus	805 (33.1%)	254 (30.7%)	315 (26.3%)	770 (38.6%)
Hypertension	1913 (78.7%)	680 (82.1%)	915 (76.3%)	1603 (80.4%)
Hyperlipidemia	1488 (61.2%)	384 (46.4%)	631 (52.6%)	1262 (63.2%)
Smoking	NA	89 (10.7%)	81 (6.7%)	201 (10.0%)
Previous myocardial infarction	495 (20.4%)	231 (27.9%)	189 (15.8%)	513 (25.7%)
Previous percutaneous coronary intervention	570 (22.0%)	173 (20.9%)	282 (23.5%)	467 (23.4%)
Previous coronary artery bypass grafting	237 (9.7%)	77 (9.2%)	78 (6.5%)	143 (7.2%)
Previous stroke/transient ischemic attack	242 (10.0%)	66 (8.0%)	87 (6.0%)	259 (13.0%)
Atrial fibrillation	842 (34.6%)	223 (71.8%)	211 (17.6%)	644 (32.3%)
Peripheral arterial disease	380 (15.6%)	170 (20.5%)	212 (17.7%)	201 (10.1%)
Heart failure with reduced ejection fraction/congestive heart failure	325 (13.4%)	NA	76 (6.3%)	159 (11.3%)
Unstable angina/non-ST segment elevation myocardial infarction	924 (38.0%)	414 (50.0%)	417 (34.8%)	874 (23.0%)
ST-segment elevation myocardial infarction	105 (4.3%)	127 (15.3%)	127 (10.6%)	108 (27.1%)
Stable disease	1403 (57.7%)	287 (34.7%)	656 (54.7%)	729 (38.4%)
Multivessel disease	1493 (61.4%)	561 (67.8%)	385 (32.1%)	343 (17.4%)
Complex coronary disease (type 2B/C lesions)	NA	1175 (73.2%)	NA	2038 (79.8%)
Chronic kidney disease	464 (19.1%)	561 (67.8%)	203 (16.9%)	297 (14.9%)
Anemia	379 (15.6%)	68 (4.2%)	161 (13.4%)	311 (15.6%)
Radial access	1532 (60.0%)	NA	965 (80.4%)	1547 (75.1%)
Concomitant anticoagulation	879 (36.1%)	213 (13.3%)	NA	769 (38.6%)
Cancer (active or recent)	239 (9.8%)	84 (5.2%)	107 (8.5%)	156 (7.9%)

Data presented as number (percentage).
BMS = bare-metal stent; DES = drug-eluting stent; NA = not available; PB = polymer based; PF = polymer free.

TABLE 2. Incidence risk ratio between efficacy endpoints.

	BMS	PB-DES	PF-DES
Major adverse cardiovascular events			
BMS	—	1.52 (1.3-1.75); *P*<.001	1.45 (1.28-1.64); *P*<.001
PB-DES	0.66 (0.57-0.77); *P*<.001	—	0.95 (0.84-1.08); *P*=.45
PF-DES	0.69 (0.61-0.78); *P*<.001	1.05 (0.92-1.19); *P*=.45	—
Death			
BMS	—	1.07 (0.85-1.33); *P*=.57	1.18 (0.95-1.47); *P*=.14
PB-DES	0.94 (0.75-1.17); *P*<.57	—	1.11 (0.88-1.4); *P*=.39
PF-DES	0.85 (0.68-1.05); *P*<.14	0.9 (0.71-1.14); *P*=.39	—
Cardiac death			
BMS	—	1.07 (0.79-1.45); *P*=.68	1.27 (0.94-1.73); *P*=.12
PB-DES	0.94 (0.69-1.27); *P*=.68	—	1.19 (0.86-1.66); *P*=.29
PF-DES	0.78 (0.58-1.07); *P*=.12	0.84 (0.6-1.17); *P*=.29	—
Myocardial infarction			
BMS	—	1.98 (1.31-2.98); *P*<.01	1.64 (1.11-2.41); *P*=.01
PB-DES	0.51 (0.34-0.76); *P*<.01	—	0.83 (0.57-1.2); *P*=.31
PF-DES	0.61 (0.41-0.9); *P*=.01	1.21 (0.84-1.75); *P*=.03	—
Target-lesion revascularization			
BMS	—	2.39 (1.65-3.46); *P*<.001	1.86 (1.41-2.45); *P*<.001
PB-DES	0.42 (0.29-0.61); *P*<.001	—	0.78 (0.54-1.12); *P*=.18
PF-DES	0.54 (0.41-0.71); *P*<.001	1.29 (0.89-1.86); *P*=.18	—
Target-vessel revascularization			
BMS	—	2.26 (1.6-3.19); *P*<.001	1.77 (1.37-2.3); *P*<.001
PB-DES	0.44 (0.31-0.62); *P*<.001	—	0.78 (0.56-1.09); *P*=.15
PF-DES	0.56 (0.43-0.73); *P*<.001	1.27 (0.91-1.78); *P*=.15	—
Stroke			
BMS	—	1.38 (0.47-4.05); *P*=.56	1.35 (0.27-6.78); *P*=.72
PB-DES	0.73 (0.25-2.14); *P*=.56	—	0.98 (0.3-3.26); *P*=.97
PF-DES	0.74 (0.15-3.73); *P*=.72	1.02 (0.31-3.39); *P*=.97	—

Data presented as relative risk (95% confidence interval); *P*-value.
BMS = bare-metal stent; DES = drug-eluting stent; PB = polymer based; PF = polymer free.

MI (IRR, 0.51; 95% CI, 0.34-0.76; *P*<.001 and IRR, 0.61; 95% CI, 0.41-0.9; *P*<.01, respectively), TLR (IRR, 0.42; 95% CI, 0.29-0.61; *P*<.001 and IRR, 0.54; 95% CI, 0.41-0.71; *P*<.001, respectively), and TVR (IRR, 0.44; 95% CI, 0.31-0.62; *P*<.001 and IRR, 0.56; 95% CI, 0.43-0.73; *P*<.001, respectively) when compared with BMS. There were no differences among the stent technology in all-cause death, cardiac death, and stroke (all *P*>.05). Moreover, there were no statistical differences between PB-DES and PF-DES among any of the efficacy endpoints at a median of 1-year follow-up.

Regarding the safety endpoints, among the different stent technologies, there were no differences regarding bleeding (BARC 1-5) and major bleeding events (BARC 3-5). PB-DES yielded a

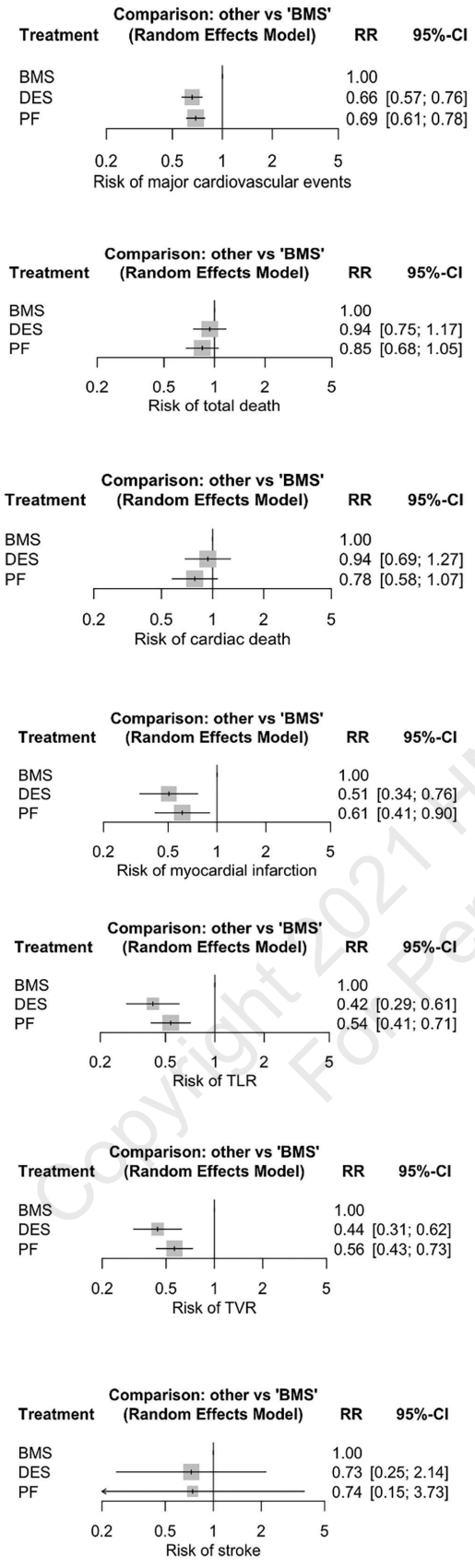

FIGURE 2. Forest plots of efficacy endpoints. Plot of relative risk (RR) of polymer-based (PB) drug-eluting stent (DES) and polymer-free (PF)-DES compared with bare-metal stent (BMS). CI = confidence interval.

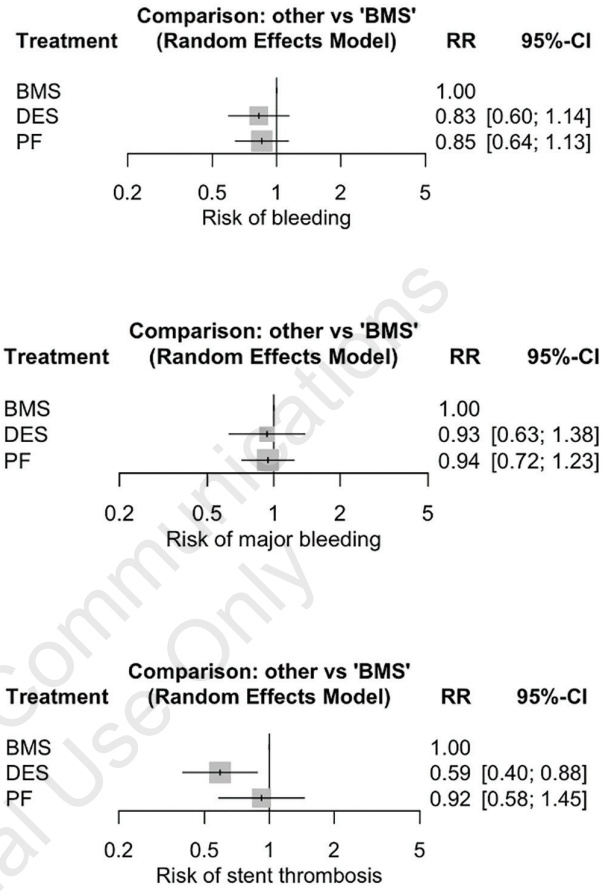

FIGURE 3. Forest plots of safety endpoints. Plot of relative risk (RR) of polymer-based (PB) drug-eluting stent (DES) and polymer-free (PF)-DES compared with bare-metal stent (BMS). CI = confidence interval.

reduction in ST events compared with BMS (IRR, 0.59; 95% CI, 0.4-0.88; *P*=.01). Moreover, there was a trend toward lower rates of ST events with PB-DES compared with PF DES; however, it did not reach statistical significance (IRR, 0.64; 95% CI, 0.39-1.05; *P*=.08) (Table 3 and Figure 3).

Discussion

Our network meta-analysis represents, to the best of our knowledge, the first network comparison between different stent technologies for the assessment of safety and efficacy in HBR patients. Of importance, our analysis demonstrated that both PB-DES and PF-DES are associated with lower MACE rates

Table 3. Incidence risk ratio between efficacy endpoints.

	BMS	PB-DES	PF-DES
Bleeding BARC 1-5			
BMS	—	1.21 (0.87-1.68); *P*=.25	1.17 (0.88-1.56); *P*=.27
PB-DES	0.83 (0.6-1.14); *P*=.25	—	0.97 (0.72-1.3); *P*=.83
PF-DES	0.85 (0.64-1.13); *P*=.27	1.03 (0.77-1.38); *P*=.83	—
Major bleeding BARC 3-5			
BMS	—	1.07 (0.72-1.59); *P*=.73	1.06 (0.81-1.39); *P*=.66
PB-DES	0.93 (0.63-1.38); *P*=.73	—	0.99 (0.7-1.41); *P*=.96
PF-DES	0.94 (0.72-1.23); *P*=.66	1.01 (0.71-1.43); *P*=.96	—
Stent thrombosis			
BMS	—	1.69 (1.14-2.52); *P*=.01	1.09 (0.69-1.72); *P*=.72
PB-DES	0.59 (0.4-0.88); *P*=.01	—	0.64 (0.39-1.05); *P*=.08
PF-DES	0.92 (0.58-1.45); *P*=.72	1.56 (0.95-2.55); *P*=.08	—

Data presented as relative risk (95% confidence interval); *P*-value.
BARC = Bleeding Academic Research Consortium; BMS = bare-metal stent; DES = drug-eluting stent; PB = polymer based; PF = polymer free.

Table 4. Differences in stent designs.

	BMS	PF-DES	Synergy	Onyx
Strut thickness	81-112 microns	120 microns	79-81 microns	81-91 microns
Polymer composition	—	polymer free	PLGA	biolinx
Polymer type	—	—	biodegradable	durable
Material	stainless steel	stainless steel	chrome platinum	cobalt nickel with platinum iridium
Drug elution time	—	30 days	4 months	6 months
Drug	—	biolimus	everolimus	zotarolimus

BMS = bare-metal stent; DES = drug-eluting stent, PF = polymer free; PLGA = DL lactide coglycolide.

(primary endpoint) and a lower TVR rate (secondary endpoint) compared with BMS in HBR patients. In particular, the lower MACE rate in the DES cohort was primarily driven by lower MI and TLR, whereas no significant differences were observed for all-cause death, cardiovascular death, or stroke between DES and BMS. There were no statistical differences between PB-DES and PF-DES among any of the efficacy endpoints. Although no differences in major and total bleeding events were found among the 3 groups, PB-DES yielded a significant reduction in ST events compared with BMS (Figure 4).

These findings are relevant due to the fact that HBR patients were generally under-represented in previous trials. In fact, HBR patients are not only at risk of bleeding, but also ischemic events. The mean pooled age of patients in our cohort was 66 years, with the following comorbid conditions: diabetes mellitus (32.2%); arterial hypertension (79.4%); previous MI (22.5%); multivessel coronary disease (44.7%); chronic kidney disease (30%); and stable coronary artery disease (46.4%). All of these factors portend a higher ischemic risk. Regarding bleeding risk, 39% had previous atrial fibrillation events, 12.2% had anemia, 29.3% were on concomitant anticoagulation, and 7.9% had a history of cancer. This is in line with previous research, in which HBR patients compared with non-HBR patients display more comorbidities, higher lesion complexity, and a higher risk of 4-year mortality.[13] Although HBR definitions varied among trials included in our analysis, we did not find heterogeneity or inconsistency in our results.

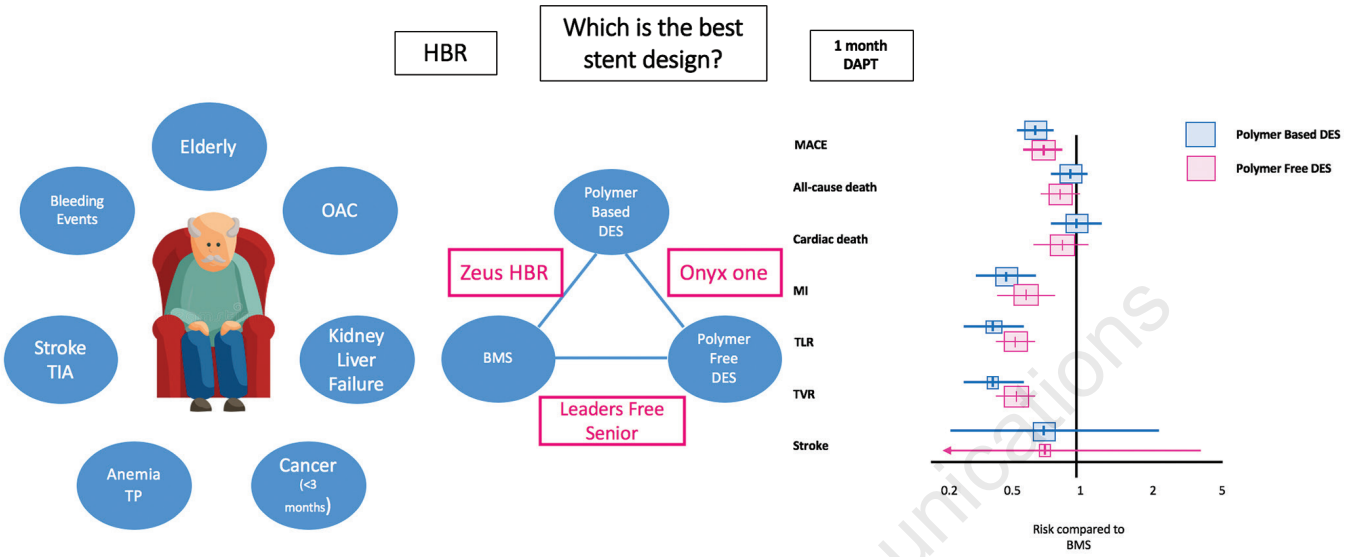

FIGURE 4. We highlight the design and results in efficacy endpoints from the network meta-analysis. BMS = bare-metal stent; DAPT = dual-antiplatelet therapy; DES = drug-eluting stent; HBR = high bleeding risk, MACE = major adverse cardiovascular events; MI = myocardial infarction; OAC = oral anticoagulation; PB = polymer based; PF = polymer free; TIA = transient ischemic attack; TLR = target-lesion revascularization; TP = thrombocytopenia; TVR = target-vessel revascularization.

We chose a 1-month DAPT therapy as the cut-off, because most trials with HBR patients included the use of 1-month DAPT as well. Furthermore, in HBR patients, extending the DAPT course may increase bleeding events without an overt benefit in reducing ischemic events. In the STOPDAPT-2 trial, the 1-month time frame provided benefit in both ischemic and bleeding events.

Few studies have compared DES with BMS for HBR patients.[14,15] Unfortunately, the included trials did not have enough power to adequately examine differences in lower-frequency secondary outcomes, such as ST, MI, and TLR. By using a network meta-analysis framework, we were able to show the benefit of DES in reducing the rate of MI and TLR compared with BMS in this population, in part because both the LEADERS FREE and ZEUS-HBR trials showed a reduction in MI and TLR with DES compared with BMS. Thus, our results confirm that routine use of BMS for HBR patients has no benefit with the availability of current-generation DES options.

Moreover, the inclusion of the BMS group in the analysis allowed us to make direct and indirect comparisons, thus providing further strength in assessing differences between PB and PF stents. Although no difference was found among PF-DES and PB-DES, a trend toward fewer ST events was found in the latter (IRR, 0.64; 95% CI, 0.39-1.05; *P*=.08). Stent composition differences might have a role in our results (Table 4 details the differences among stent designs). As polymer persistence was thought to be responsible for late restenosis events, PF-DES devices were initially introduced in order to overcome efficacy and safety issues seen in previous stent designs.[6] As a drawback, these PF stents have thicker struts (120 microns) compared with the newer, more biocompatible stent polymers (79-91 microns).[16] Also, improvements in material alloys, such as the inclusion of chrome, cobalt, and platinum, may compensate for the problems seen with previous-generation DES options.[17]

Another key element when suspending DAPT is the risk of developing ST events, due to incomplete strut coverage by early endothelialization. Previous prospective trials have shown a 78.5% strut coverage in Synergy stent deployment at 1 month.[18] Our results are in line with the recent ONYX ONE trial, which compared a zotarolimus PB-DES with a biolimus A9 PF-DES, yielding non-inferiority in the primary outcome, defined as a composite of cardiac death, MI, or ST at 1 year, between the two groups (17.1% and 16.9%, respectively).[9] We have included bioabsorbable polymer (ie, Synergy) and durable polymer (ie, Onyx) in a single group for inferential purposes. We made this decision based on previous RCTs (ie, Evolve I and II) in which Synergy stents were non-inferior to everolimus-eluting stents.[19,20] Several meta-analyses have compared bioabsorbable polymer stents with conventional DES in non-HBR patients.[21–23] Late ST occurred less often with bioabsorbable polymer stents compared with first-generation DES (odds ratio, 0.43; 95% CI, 0.24-0.79; *P*<.01), whereas the risk of late ST was similar between BP-DES and second-generation DES (odds ratio, 0.95; 95% CI, 0.30-3.02; *P*=.93). There were no significant differences between PB-DES and either first-generation or second-generation DES devices for overall death, MI, or acute/subacute ST.

Study limitations. Our analysis has several limitations. First, since this is a study-level meta-analysis, no further meta-regression analysis could be done in order to account for differences that arise among different subpopulations included in the analysis. Second, because this is an exclusive RCT network meta-analysis, our results come from only 4 RCTs, limiting the amount of comparisons made. Third, we extrapolate the results to other new-generation DES devices, although they were not included in the analysis, as we did not account for RCTs with these stent technologies. Fourth, some data from our network meta-analysis came from subgroup analyses prespecified in RCT protocols.

Conclusion

In HBR patients, PB-DES and PF-DES were both associated with lower MACE rates and lower TVR rates compared with BMS devices in patients who underwent a short course of DAPT. These findings clearly suggest that new-generation DES options should represent the gold standard for PCI in HBR patients requiring a short DAPT period. Moreover, our results show that further studies are warranted in order to ascertain the best DES technology in this challenging subset of patients.

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From the [1]VCU Pauley Heart Center, Virginia Commonwealth University, Richmond, Virginia; [2]Interventional Cardiology Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [3]Health Science Statistics Applied Laboratory (LEACS), Pharmacology, and Toxicology Department, School of Medicine, University of Buenos Aires, Buenos Aires, Argentina; [4]Department of Cardiac Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy; [5]Department of Cardiovascular and Thoracic Sciences, Catholic University of the Sacred Heart, Rome, Italy; [6]Department of Cardiovascular and Thoracic Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [7]Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy; and [8]Mediterranea-Cardiocentro, Napoli, Italy.

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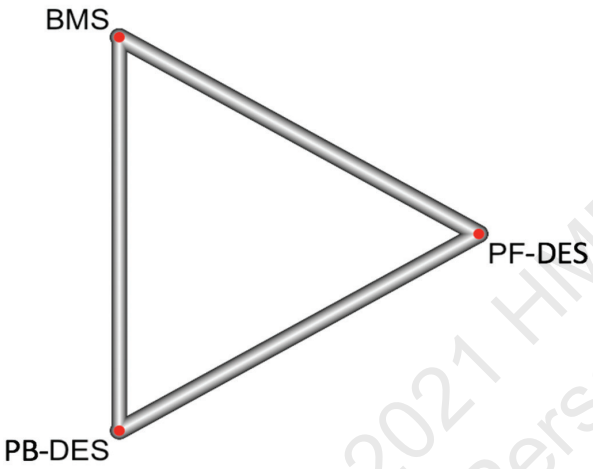
Address for correspondence: Juan Guido Chiabrando, MD, Department of Interventional Cardiology, Hospital Italiano de Buenos Aires, Peron 4190, Buenos Aires, Argentina. P.O. Box C1181ACH. Email: juan.chiabrando@hospitalitaliano.org.ar

SUPPLEMENTAL FIGURE S1. Rob2 bias assessment tool.



SUPPLEMENTAL FIGURE S2. Network geometry. We herein reference both direct and indirect comparisons among the different stent designs. In this figure, the lines represent direct comparisons between each pair of interventions. The width of the lines is proportional to the inverse standard error of the direct treatment comparison. BMS = bare-metal stent; DES = drug-eluting stent; PB = polymer based; PF = polymer free.

MACE

	P-score (fixed)	P-score (random)
DES	0.8873	0.8873
PF	0.6127	0.6127
BMS	0.0000	0.0000

Total Death

	P-score (fixed)	P-score (random)
PF	0.8686	0.8686
DES	0.4563	0.4563
BMS	0.1751	0.1751

Cardiac Death

	P-score (fixed)	P-score (random)
PF	0.8966	0.8966
DES	0.4042	0.4042
BMS	0.1992	0.1992

MI

	P-score (fixed)	P-score (random)
DES	0.9602	0.9216
PF	0.5398	0.5749
BMS	0.0001	0.0035

TLR

	P-score (fixed)	P-score (random)
DES	0.9547	0.9547
PF	0.5453	0.5453
BMS	0.0000	0.0000

TVR

	P-score (fixed)	P-score (random)
DES	0.9619	0.9619
PF	0.5381	0.5381
BMS	0.0000	0.0000

Stroke

	P-score (fixed)	P-score (random)
DES	0.6672	0.6155
PF	0.6097	0.5646
BMS	0.2230	0.3199

SUPPLEMENTAL FIGURE S3. *P*-scores to generate a rank among therapies regarding efficacy endpoints. BMS = bare-metal stent; DES = drug-eluting stent; MACE= major adverse cardiovascular events; MI = myocardial infarction; PF = polymer free; TLR = target-lesion revascularization; TVR = target-vessel revascularization.

Bleeding BARC 1-5

	P-score (fixed)	P-score (random)
DES	0.6309	0.7306
PF	0.7276	0.6391
BMS	0.1415	0.1303

Major Bleeding BARC 3-5

	P-score (fixed)	P-score (random)
DES	0.5783	0.5783
PF	0.5737	0.5737
BMS	0.3481	0.3481

Stent Thrombosis

	P-score (fixed)	P-score (random)
DES	0.9777	0.9777
PF	0.3398	0.3398
BMS	0.1825	0.1825

SUPPLEMENTAL FIGURE S4. *P*-scores to generate a rank between efficacy endpoints. BARC = Bleeding Academic Research Consortium; BMS = bare-metal stent; DES = drug-eluting stent; PF = polymer free.

SUPPLEMENTAL TABLE S1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist for reporting a systematic review involving a network meta-analysis.

Section/Topic	Item #	Reported on Page #
TITLE		1
Title	1	1
ABSTRACT		
Structured summary	2	2
INTRODUCTION		
Rationale	3	3-4
Objectives	4	3-4
METHODS		
Protocol and registration	5	4
Search	6	4
Eligibility criteria	7	4-5
Information sources	8	5
Study selection	9	5
Data collection process	10	6
Data items	11	6
Geometry of the network		
Risk of bias within individual studies	12	4S
Summary measures	13	6
Planned methods of analysis	14	6
Assessment of inconsistency		
Risk of bias across studies	15	4S
Additional analyses	16	NA
RESULTS		
Study selection	17	6-7

SUPPLEMENTAL TABLE S1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist for reporting a systematic review involving a network meta-analysis.

Section/Topic	Item #	Reported on Page #
Presentation of network structure		
Summary of network geometry		5S
Study characteristics	18	7
Risk of bias within studies	19	7
Results of individual studies	20	7
Synthesis of results	21	7-8
Exploration for inconsistency		
Risk of bias across studies	22	NA
Results of additional analyses	23	NA
DISCUSSION		
Summary of evidence	24	8-11
Limitations	25	10-11
Conclusions	26	11
ACKNOWLEDGEMENTS		
Acknowledgements	27	NA
FUNDING		
Funding	28	11
DISCLOSURE		2
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SUPPLEMENTAL TABLE S2. Heterogeneity and inconsistency analysis.

	I^2	Total *P*-Value	Heterogeneity *P*-Value	Inconsistency *P*-Value
MACE	0%	.77	.48	.89
Total Death	0%	.73	.73	.48
Cardiac Death	0%	.98	—	.98
MI	39.7%	.19	.19	.20
TLR	0%	.52	—	.52
TVR	0%	.33	—	.33
Stroke	46.9%	.17	.17	—
Bleeding BARC 1-5	35.7%	.21	.81	.08
Major bleeding BARC 3-5	0%	.32	—	.32
Stent thrombosis	0%	.64	.35	.98

BARC = Bleeding Academic Research Consortium; MACE = major adverse cardiovascular events; MI = myocardial infarction; TLR = target-lesion revascularization; TVR = target-vessel revascularization.