Circulation

ORIGINAL RESEARCH ARTICLE

Efficacy of a Drug-Eluting Stent Versus Bare Metal Stents for Symptomatic Femoropopliteal Peripheral Artery Disease: Primary Results of the EMINENT Randomized Trial

Yann Gouëffic, MD, PhD; Giovanni Torsello, MD; Thomas Zeller, MD; Giovanni Esposito, MD; Frank Vermassen, MD; Klaus Armin Hausegger, MD; Gunnar Tepe, MD; Marcus Thieme, MD; Michael Gschwandtner, MD; Andrea Kahlberg, MD; Marc Schindewolf, MD; Marc Sapoval, MD; Juan Diaz-Cartelle, MD; Konstantinos Stavroulakis, MD; on behalf of the EMINENT Investigators

BACKGROUND: A clear patency benefit of a drug-eluting stent (DES) over a bare metal stent (BMS) for treating peripheral artery disease of the femoropopliteal segment has not been definitively demonstrated. The EMINENT study (Trial Comparing Eluvia Versus Bare Metal Stent in Treatment of Superficial Femoral and/or Proximal Popliteal Artery) was designed to evaluate the patency of the Eluvia DES (Boston Scientific, Marlborough, MA), a polymer-coated paclitaxel-eluting stent, compared with BMS for the treatment of femoropopliteal artery lesions.

METHODS: EMINENT is a prospective, randomized, controlled, multicenter European study with blinded participants and outcome assessment. Patients with symptomatic peripheral artery disease (Rutherford category 2, 3, or 4) of the native superficial femoral artery or proximal popliteal artery with stenosis ≥70%, vessel diameter of 4 to 6 mm, and total lesion length of 30 to 210 mm were randomly assigned 2:1 to treatment with DES or BMS. The primary effectiveness outcome was primary patency at 12 months, defined as independent core laboratory–assessed duplex ultrasound peak systolic velocity ratio ≤2.4 in the absence of clinically driven target lesion revascularization or surgical bypass of the target lesion. Primary sustained clinical improvement was a secondary outcome defined as a decrease in Rutherford classification of ≥1 categories compared with baseline without a repeat velocity ratio ≤2.4 in the absence of clinically driven target lesion revascularization. Health-related quality of life and walking function were assessed.

RESULTS: A total of 775 patients were randomly assigned to treatment with DES (n=508) or commercially available BMS (n=267). Baseline clinical, demographic, and lesion characteristics were similar between the study groups. Mean lesion length was 75.6±50.3 and 72.2±47.0 mm in the DES and BMS groups, respectively. The 12-month incidence of primary patency for DES treatment (83.2% [337 of 405]) was significantly greater than for BMS (74.3% [165 of 222]; $P<0.01$). Incidence of primary sustained clinical improvement was greater among patients treated with the DES than among those who received a BMS (83.0% versus 76.6%; $P=0.045$). The health-related quality of life dimensions of mobility and pain/discomfort improved for the majority of patients in both groups (for 66.4% and 53.6% of DES-treated and for 64.2% and 58.1% of BMS-treated patients, respectively) but did not differ significantly. At 12 months, no statistical difference was observed in all-cause mortality between patients treated with the DES or BMS (2.7% [13 of 474] versus 1.1% [3 of 263]; relative risk, 2.4 [95% CI, 0.69–8.36]; $P=0.15$).

Correspondence to: Yann Gouëffic, MD, PhD, Groupe Hospitalier Paris St. Joseph, Department of Vascular and Endovascular Surgery, 185 Rue Raymond Losserand, Paris, 75014-France. Email ygoueffic@ghpsj.fr

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.122.059606.

For Sources of Funding and Disclosures, see page XXX

Circulation is available at www.ahajournals.org/journal/circ

ORIGINAL RESEARCH ARTICLE

CONCLUSIONS: By demonstrating superior 1-year primary patency, the results of the EMINENT randomized study support the benefit of using a polymer-based paclitaxel-eluting stent as a first-line stent-based intervention for patients with symptomatic peripheral artery disease attributable to femoropopliteal disease.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02921230.

Key Words: drug-eluting stents ■ endovascular procedures ■ paclitaxel ■ peripheral arterial disease

Editorial, see p XXX

Clinical Perspective

What Is New?

- With 775 patients, EMINENT (Trial Comparing Eluvia Versus Bare Metal Stent in Treatment of Superficial Femoral and/or Proximal Popliteal Artery) is the largest randomized trial of drug-eluting stent treatment for symptomatic femoropopliteal arterial disease to report patency results to date.
- Primary effectiveness analysis from the EMINENT randomized study demonstrated superior 1-year primary patency for the paclitaxel-eluting polymer-based Eluvia drug-eluting stent versus bare metal stents (83.2% versus 74.3%; $P<0.01$), and drug-eluting stent treatment was associated with a greater incidence of Rutherford classification improvement without the need for reintervention. Functional parameters demonstrated improvements in both groups.
- No statistical difference was observed in 1-year mortality between patients treated with the paclitaxel-eluting stent and those treated with bare metal stents.

What Are the Clinical Implications?

- High-level evidence supports the 1-year benefit of polymer-based paclitaxel elution over bare metal stents to treat superficial femoral artery or proximal popliteal artery lesions.

Nonstandard Abbreviations and Acronyms

BATTLE	Bare Metal Stent vs. Paclitaxel Eluting Stent in the Setting of Primary Stenting of Intermediate-Length Femoropopliteal Lesions
BMS	bare metal stent
CD-TLR	clinically driven target lesion revascularization
COVID-19	coronavirus disease 2019
DES	drug-eluting stent
EMINENT	Trial Comparing Eluvia Versus Bare Metal Stent in Treatment of Superficial Femoral and/or Proximal Popliteal Artery
IMPERIAL	ELUVIA™ Drug-eluting Stent Versus Zilver® PTX® Stent
MAE	major adverse event
SFA	superficial femoral artery
TLR	target lesion revascularization

Endovascular therapies such as percutaneous transluminal angioplasty and stent implantation are common methods for the treatment of symptomatic femoropopliteal artery disease in cases in which lifestyle modification, exercise, and pharmacological risk factor management yield an inadequate response.[1,2]

Randomized controlled trials have shown the benefit of paclitaxel-based devices in decreasing the need for repeat procedures, but the majority used percutaneous transluminal angioplasty with an uncoated (ie, plain, not drug coated) balloon as the control group,[3–5] which is currently not considered the standard of care for most femoropopliteal artery lesions. Bare metal stent (BMS) implantation, however, remains a routine treatment for femoropopliteal artery lesions because the patency benefit of drug-eluting stents (DESs) over BMSs has not yet been definitively shown. Two prior randomized have studies contributed to the evidence addressing this question, but 1 study did not show a significant reduction of in-stent restenosis for a polymer-free paclitaxel-coated stent versus a BMS,[6] and the other addressed the question with a secondary randomization in the provisional stenting setting.[3]

Clinical evidence for the Eluvia DES (Boston Scientific, Marlborough, MA), a polymer-based paclitaxel-eluting stent, does not currently address how performance compares with BMSs; therefore, the objective of the EMINENT study (Trial Comparing Eluvia Versus Bare Metal Stent in Treatment of Superficial Femoral and/or Proximal Popliteal Artery) was to confirm the superior effectiveness of the Eluvia DES compared with BMSs for treating superficial femoral artery (SFA) or proximal popliteal artery lesions up to 210 mm in length.

METHOD

Study Design

EMINENT is a prospective, randomized, multicenter, international study with blinded patients and outcome

assessment. Patients were randomly assigned 2:1 to treatment with the Eluvia DES or BMS. Trial personnel are listed in Tables S1 and S2).

Approval from the site-applicable Ethics Committee was required before patient enrollment (Table S1). Written informed consent was required from eligible patients before administration of any study-specific procedure. The study was performed in accordance with International Organization for Standardization 14155:2011(E) and principles of the Declaration of Helsinki. EMINENT was registered at ClinicalTrials.gov (URL: http://www.clinicaltrials.gov. Unique identifier: NCT02921230).

The first author had full access to all the data in the study and takes responsibility for its integrity and the data analysis. The data and study protocol for this clinical trial might be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy, available online.[7]

Study Population

Complete eligibility criteria for the EMINENT study are included in the Supplemental Methods and briefly summarized here. All inclusion criteria were required to be met. These included the following: presentation with Rutherford category 2, 3, or 4 symptomatology; lesions in the native SFA or proximal popliteal artery with stenosis ≥70% by visual angiographic assessment; vessel diameter of 4 to 6 mm; and total lesion length of 30 to 210 mm. Presence of any of the exclusion criteria justified exclusion. These criteria included dialysis treatment; target lesion or vessel previously treated with a drug-coated balloon within the prior 12 months or previously stented; prior SFA or proximal popliteal artery surgery in the target limb; heavy calcification; and intraprocedural use of atherectomy, laser, or other debulking devices.

Study Devices

The interventional device was the Eluvia DES, a self-expanding nitinol stent coated with a fluorinated polymer and paclitaxel at a dose density of 0.167 μg/mm^2 stent surface area. When patient enrollment began in October 2016, the DES system was available in lengths between 40 and 150 mm. In accordance with the Instructions for Use, 140-mm maximum lesion length was allowed. In November 2017, Boston Scientific initiated a voluntary removal of the 150-mm length from the market as a result of elevated complaint rates for partial stent deployment, although no deployment issues were reported in EMINENT. The 120-mm length was then the longest DES available through the study enrollment duration; the maximum lesion length was extended to 210 mm, and overlapping stents were permitted.

Control devices were BMSs, specifically self-expanding bare nitinol stents commercially available in Europe that were indicated for improving luminal diameter for the treatment of de novo or restenotic symptomatic lesions in native vascular disease of above-the-knee femoropopliteal arteries. Permitted stents were Complete SE Vascular Stent (Medtronic, Minneapolis, MN), Everflex Peripheral Self-Expanding Stent (Covidien/Medtronic, Minneapolis, MN), Innova Vascular Self-Expanding Stent (Boston Scientific, Marlborough, MA, US), Lifestent Vascular Stent (BD, Franklin Lakes, NJ), Misago Self-Expanding Peripheral Stent (Terumo, Tokyo, Japan), Pulsar-18 (Biotronik, Lake Oswego, OR), S.M.A.R.T. Flex Vascular Stent and S.M.A.R.T. CONTROL Vascular Stent (Cordis, Santa Clara, CA), and Supera Stent (Abbott, Abbott Park, IL). Stent selection among permitted BMSs was at the discretion of the treating investigator.

Procedures and Follow-Up

Investigators were expected to follow standard practices to manage cardiovascular risk factors and comorbidities for each patient. Anticoagulant therapy consistent with guidelines and hospital standards was used during stenting procedures.

Iliac artery lesions were allowed to be treated during the index procedure before target lesion treatment, provided that non–drug-eluting commercially available devices were used, the treatment resulted in residual stenosis <30%, and no clinical events such as embolization or perforation occurred.

Lower-extremity angiographic assessment was performed with standard techniques based on core laboratory guidelines. All angiographic images from the index procedure, as well as those obtained during any target vessel reinterventions, were provided to the angiographic core laboratory (coreLab Black Forest GmbH, Bad Krozingen, Germany).

Patients who met all inclusion and exclusion criteria, including angiographic eligibility criteria, were considered eligible to be randomized. Randomization to either the DES test device or BMS control device group occurred after the target lesion was successfully crossed with a guide wire. Randomization was stratified by study site and lesion length. For each site, a computer-generated list of random treatment allocations using random permuted blocks of various sizes within each stratum was used to assign subjects to treatments in a 2:1 ratio by lesion length (ie, ≤110 mm versus >110 mm).

Patients in both the DES and BMS groups were treated with 1 or 2 stents sized to adequately cover the target lesion. Sizing and procedural device use were according to the DES Instructions for Use for patients assigned to the DES group and according to the respective BMS Instructions for Use for the appropriate control stent for patients assigned to the BMS group.

Target lesions could include ≥2 tandem lesions, provided that the entire tandem lesion segment was ≤210 mm and could be covered with 1 single stent or 2 overlapping stents according to the Instructions for Use for each device. Occlusions necessitating reentry device use were required to be ≤180 mm to allow the target lesion and reentry area to be covered with 1 or 2 stents. Vessel preparation, including predilatation with optimally sized (ie, nominal artery size) balloons, was recommended. Postdilatation was performed at the investigator's discretion to ensure full stent contact with the arterial wall. Only balloons without drug coating were to be used for predilatation and postdilatation. Peristent dissections could be treated with low-pressure prolonged balloon inflation or with additional study stent implantation per standard practice. If an additional stent was required, it was to be of the same type used to treat the target lesion.

Antiplatelet medication prescription after the procedure was consistent with current local clinical practice and the Instructions for Use for each device. European guidelines[1] recommend dual antiplatelet therapy for at least 1 month after stent implantation, regardless of BMS or DES type. Per the

Instructions for Use, dual antiplatelet therapy after DES implantation is required for a minimum of 60 days.

To screen for the hypoechogenic halo ultrasound phenomenon, which has been reported in prior DES studies,[8–10] systematic B-mode transverse plane duplex ultrasound imaging optimized to identify this phenomenon with blinded core laboratory adjudication was implemented during the 1-year follow-up beginning in May 2019 (ie, after the 1-year follow-up was already underway). The ultrasound core laboratory identified hypoechogenic halo as an echolucent layer with regular well-defined borders seen adjacent to/surrounding the stented segment of artery in a transverse view with no detectable flow.

Calcification grade definitions applied by the angiographic core laboratory were as follows: mild (any readily apparent densities noted within the vascular wall at the site of stenosis), moderate (radiopacities on 1 side of the arterial wall or both sides but <1 cm of length before contrast injection or digital subtraction angiography), and severe (radiopacities noted on both sides of the arterial wall and extending >1 cm of length before contrast injection or digital subtraction angiography).

Study staff were trained to maintain patient blinding to treatment assignment through completion of all primary outcome (12-month follow-up) visits, and site personnel conducting clinical follow-up assessments were blinded to treatment assignment whenever possible. Core laboratory personnel and the Clinical Events Committee were blinded to treatment assignment.

Clinical follow-up visits were scheduled at 1 month (if standard of care), 6 months, and 12 months (primary outcome) after the index procedure and will also occur at 24 and 36 months. In addition to duplex ultrasound imaging for patency assessment, follow-up visits included assessments of clinical and hemodynamic improvement, walking function (Walking Impairment Questionnaire), and health-related quality of life (EQ-5D-5L). The 6-minute hall walk was performed at baseline and the 12-month follow up. Long-term collection of vital status, major adverse events (MAEs), and adverse device effects will occur by telephone calls, medical chart review, or public record review at 48 and 60 months.

Outcome Definitions

The primary effectiveness outcome was primary patency at 12 months, defined as duplex ultrasound peak systolic velocity ratio ≤2.4 at the 12-month visit (365±30 days), as assessed by the independent ultrasound core laboratory (VasCore, Boston, MA), in the absence of clinically driven target lesion revascularization (CD-TLR) or target lesion bypass. CD-TLR was defined as any reintervention within 5 mm proximal or distal to the original treatment segment for >50% angiographic diameter stenosis, in the presence of recurrent symptoms (ie, ≥1 increase in Rutherford class) or associated with ankle-brachial index/toe brachial index decrease of ≥20% or ≥0.15 versus baseline in the treated segment.

Secondary outcomes included primary sustained clinical improvement, defined as an improvement (decrease) in Rutherford classification by ≥1 categories compared with baseline without the need for repeat target lesion revascularization (TLR). Hemodynamic improvement was defined as an increase in ankle-brachial index to ≥0.90 or by ≥0.10 compared with before the procedure without the need for repeat TLR. The changes in Walking Impairment Questionnaire, EQ-5D-5L, and 6-minute hall walk measures from baseline to 12 months were considered secondary outcomes. The EQ-5D-5L health-related quality of life index maximum value of 1 represents full health.[11]

The MAE incidence was considered an additional outcome. MAEs were assessed in the as-treated data set and were defined as all-cause death, target limb major (ie, ankle level or above) amputation, and TLR. The independent Clinical Events Committee reviewed all deaths, TLR/target vessel revascularization, target limb amputations, and stent thrombosis as reported by site investigators and adjudicated MAEs and causes of death, which were categorized as cardiac, vascular, or noncardiovascular.

Statistical Analysis

The overall sample size was driven by the primary outcome (effectiveness). To preserve adequate statistical testing power (ie, 85% power), at least 630 evaluable patients were determined to be required at 12 months on the basis of the following assumptions: 12-month primary patency of 85% for the DES group and 75% for the BMS group (based on clinical literature), using the χ^2 test at 1-sided test significance level (α) of 2.5%, χ^2 test method, and 2-to-1 sample allocation (test versus control). Enrollment of 750 was targeted to account for 16% attrition rate.

The primary effectiveness hypothesis was that the 12-month primary patency in the DES group was superior to that of the BMS group at a 1-sided significance level of 2.5%. If 12-month primary patency was greater for DES than for BMS and χ^2 test $P<0.05$, then DES would be considered superior to BMS. The 95% CIs of the risk difference using the Wald method are also presented. The intention-to-treat population was the primary analysis set for the primary outcome. Patients with available diagnostic duplex ultrasound images were included for the analysis; those with missing duplex ultrasound data within the 12-month window were imputed as patent if a later duplex ultrasound assessment demonstrated patency, provided that they did not experience a CD-TLR before that assessment.

The Kaplan-Meier product-limit method was also used to estimate the proportion of patients with patent vessels through 1 year. The Kaplan-Meier curve for primary patency is based on duplex ultrasound measurement with core laboratory–determined peak systolic velocity ratio >2.4 (or a stent segment with reported restenosis >50% if duplex ultrasound is missing) at the 12-month clinical assessment or occurrence of CD-TLR or bypass at any time. Patients without any of these events were censored on their last study visit date or at the visit window upper limit (ie, day 396 for the 12-month visit). The time to event was compared between treatment groups with a log-rank test.

No formal hypothesis tests were planned for secondary or additional outcomes. *P* values for comparisons of secondary or additional outcomes within or between treatment groups (eg, *t* tests for continuous variables, χ^2 test or Fisher exact test for categorical variables if assumptions for χ^2 were not met) were performed for exploratory purposes, and no adjustments for multiple comparisons were used. EQ-5D-5L index values were based on the US model.[11] Statistical analyses were performed with SAS (SAS Institute Inc, Cary, NC) version 9.4 or higher.

RESULTS

Trial Conduct

Between October 2016 and March 2020, 775 patients from 58 sites in 10 European countries (Austria, Belgium, France, Germany, Ireland, Italy, Spain, Switzerland, The Netherlands, the United Kingdom) were enrolled and randomly assigned to treatment with the DES (n=508) or a BMS (n=267). A total of 453 patients in the DES group and 249 patients in the BMS group completed 12-month follow-up visits (Figure 1).

Patient and Procedural Characteristics

Baseline patient and lesion characteristics did not differ between the study groups (Table 1). The majority of study patients were male (70.1%) and White (86.2%). Mean lesion length was 75.6 mm for DES and 72.2 mm for BMS. The proportions of patients with occlusions did not differ between groups, with 42.3% of patients in the DES group and 39.9% of those in the BMS group affected. Approximately half of patients in both groups had moderate to severe calcification.

As shown in Table 2, both predilatation and postdilatation were routinely performed. A total of seventeen 150-mm-long DESs were implanted in EMINENT patients before market removal, accounting for <3% of all DESs implanted for the study. The proportions of patients treated with 1 or 2 stents were similar between groups (Table 2). The most used stent diameter in both study groups was 6 mm. Implanted stent sizes are shown in Table S3.

Primary Outcome

As shown in Table 3, the DES demonstrated superior 12-month primary patency compared with BMSs. Results from the per-protocol analysis were consistent with the intention-to-treat analysis ($P<0.01$). Sensitivity analyses showed that the conclusion was not affected by duplex ultrasound data imputation (Table S4). These binary observed results were also consistent with the Kaplan-Meier estimates that showed improved maintenance of primary patency through 1 year for patients treated with DES, with a log-rank value of $P<0.01$ (Figure S1).

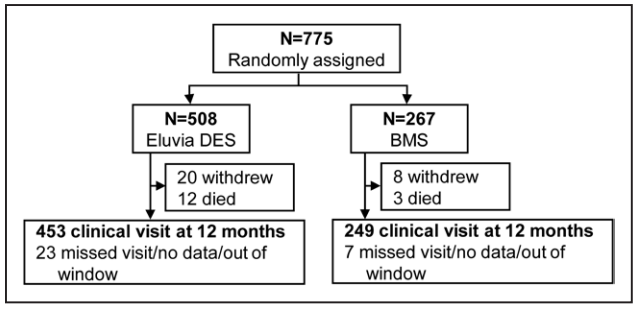

Figure 1. Patient enrollment and flow.
Deaths include those occurring up to ≤395 days with no 12-month clinical follow-up performed. One patient completed the 12-month visit and died before 395 days. BMS indicates bare metal stent; and DES, drug-eluting stent.

Safety

MAE-free incidences were not statistically different between groups through 12 months (88.2% [418 of 474] versus 88.2% [232 of 263]; $P=0.99$); the MAE and component incidences are shown in Table 3. The MAE definition included all TLRs. For 2 patients in the DES group, TLRs did not meet the criteria for clinically driven; thus the CD-TLR incidence was 8.4% (40 of 474) versus 10.6% (28 of 263; $P=0.32$). Neither of the non–CD-TLRs were for restenosis within the borders of the study stent. In the first case, the patient had a pseudoaneurysm in the distal SFA/proximal popliteal artery where the study stents were implanted that resolved with covered stent placement; the patient had no claudication symptoms, and no areas of restenosis were seen within the target lesion. The second patient had stenosis outside the study stent borders both proximally and distally; the patient underwent angioplasty proximal to and angioplasty plus stent placement distal to the study stent. One patient in the DES group underwent major amputation (below the knee). The patient was a 76-year-old man with severe dilated cardiomyopathy. The inclusion assessment at baseline was Rutherford category 4; however, the patient was admitted to the hospital 17 days after the index procedure for wound debridement on the heel of the index limb. The stented segment in the SFA/proximal popliteal artery was patent on duplex ultrasound examination, but the posterior tibial artery was occluded. The patient underwent additional debridement 11 days after the previous procedure with further evolution of the wound and exposure of the calcaneus and poor granulating tissue. At this point, the treating physician recommended a below-the-knee amputation.

No statistical difference was observed in all-cause mortality incidence between patients treated with the paclitaxel-eluting stent and those treated with BMSs (Table 3). The relative risk of death was 2.4 (95% CI, 0.69–8.36). For the DES and BMS groups, the mortality incidences in each category adjudicated by the Clinical Events Committee were 1.1% (5 of 474) versus 0.8% (2 of 263) for cardiac ($P=1.00$), 0.6% (3 of 474) versus 0% for vascular ($P=0.56$), and 1.1% (5 of 474) versus 0.4% (1 of 263) for noncardiovascular ($P=0.43$), respectively. In the noncardiovascular category, the 5 site-reported causes of death in the DES group were 2 malignancies (preexisting) and 3 infection/sepsis. These are unrelated to paclitaxel exposure.

Hypoechogenic Halo Assessment by Duplex Ultrasound

The transverse plane B-mode duplex ultrasound imaging protocol was performed on 419 patients (54% of

Table 1. Baseline Demographic, Clinical, and Lesion Characteristics of Patients Enrolled in EMINENT

Variable	Drug-eluting stent (n=508)	Bare metal stent (n=267)
Age, y	68.9±8.7	68.9±9.1
Female, % (n/N)	28.5 (145/508)	32.6 (87/267)
Race/ethnicity, % (n/N)		
White	85.4 (434/508)	87.6 (234/267)
American Indian or Alaska Native	0.2 (1/508)	0.0 (0/267)
Black of African heritage	0.2 (1/508)	0.7 (2/267)
Hispanic or Latino	0.2 (1/508)	0.4 (1/267)
Asian	0.0 (0/508)	0.4 (1/267)
Native Hawaiian or other Pacific Islander	0.0 (0/508)	0.0 (0/267)
Other	3.1 (16/508)	3.0 (8/267)
Not disclosed	10.8 (55/508)	7.9 (21/267)
Smoking history, % (n/N)		
Current	36.0 (183/508)	36.0 (96/267)
Never	17.9 (91/508)	16.5 (44/267)
Previous	39.6 (201/508)	41.6 (111/267)
Unknown	6.5 (33/508)	6.0 (16/267)
Medicallytreated diabetes, % (n/N)	31.9 (162/508)	32.6 (87/267)
Hyperlipidemia, % (n/N)	67.1 (341/508)	68.2 (182/267)
Hypertension, % (n/N)	78.1 (397/508)	76.0 (203/267)
Chronic obstructive pulmonary disease, % (n/N)	12.8 (65/508)	12.4 (33/267)
Coronary artery disease, % (n/N)	31.3 (159/508)	36.0 (96/267)
History of myocardial infarction, % (n/N)	14.8 (75/508)	15.4 (41/267)
History of congestive heart failure, % (n/N)	6.9 (35/508)	4.9 (13/267)
History of renal insufficiency, % (n/N)	11.6 (59/508)	8.2 (22/267)
Rutherford class, % (n/N)		
1	0.2 (1/507)	0.0 (0/267)
2	29.6 (150/507)	35.2 (94/267)
3	66.3 (336/507)	62.2 (166/267)
4	3.6 (18/507)	2.6 (7/267)
5	0.4 (2/507)	0.0 (0/267)
Ankle brachial index	0.7±0.2	0.7±0.2
Lesion characteristics*		
Arterial segments, % (n/N)		
Ostial	0.4 (2/472)	0.4 (1/253)
Proximal superficial femoral artery	7.6 (36/472)	7.5 (19/253)
Mid superficial femoral artery	50.0 (236/472)	49.8 (126/253)
Distal superficial femoral artery	71.4 (337/472)	70.4 (178/253)
Proximal popliteal	18.0 (85/472)	19.4 (49/253)
Reference vessel diameter, mm	5.1±0.6	5.0±0.6
Percent diameter stenosis, %	86.6±15.2	85.5±15.3
Occlusion (100% stenosis), % (n/N)	42.3 (195/461)	39.9 (101/253)
Target lesion length, mm	75.6±50.3	72.2±47.0
Stented length, mm	105.8±48.4	109.2±49.8
Calcification, % (n/N)†		
None	13.0 (62/476)	12.2 (31/254)
Mild	31.1 (148/476)	28.3 (72/254)
Moderate	21.6 (103/476)	26.0 (66/254)
Severe	30.3 (144/476)	31.1 (79/254)
Unknown	4.0 (19/476)	2.4 (6/254)
Patency to foot, % (n/N)		
No infrapopliteal vessels	7.1 (34/476)	6.3 (16/254)
Anterior tibial artery	44.7 (213/476)	43.7 (111/254)
Posterior tibial artery	44.3 (211/476)	41.7 (106/254)
Peroneal artery	49.8 (237/476)	49.2 (125/254)

Data are shown as mean±SD when appropriate.

EMINENT indicates Trial Comparing Eluvia Versus Bare Metal Stent in Treatment of Superficial Femoral and/or Proximal Popliteal Artery.

*Angiographic core laboratory.

†Calcification grading: mild (any readily apparent densities noted within the vascular wall at the site of stenosis), moderate (radiopacities on 1 side of the arterial wall or both sides but <1 cm of length before contrast injection or digital subtraction angiography), severe (radiopacities noted on both sides of the arterial wall and extending >1 cm of length before contrast injection or digital subtraction angiography).

enrolled patients), and 182 had transverse plane images that were of diagnostic quality for the core laboratory. Representative examples of the halo imaging phenomenon are shown in Figure 2. With this systematic screening, hypoechogenic halo was observed in both study arms with no statistical difference in frequency (26.1% [30 of 115] for DES versus 17.9% [12 of 67] for BMS; *P*=0.21). Halo imaging characteristics were not indicative of aneurysm, and hypoechogenic halo presence was not associated with any symptoms, increased TLR incidence, or other clinical sequelae in either study group.

Clinical Outcomes

Hemodynamic improvement (ie, ankle-brachial index increase to ≥0.90 or by ≥0.10 compared with before the procedure, without the need for repeat TLR) was observed among 79.0% (331 of 419) and 76.8% (179 of 233) of patients in each treatment group, respectively (*P*=0.52).

Mean baseline EQ-5D-5L index values were 0.7±0.1 for patients in both the DES and BMS groups, improving to 0.9±0.2 for patients in the DES group and 0.9±0.1 for patients in the BMS group at 12 months. The majority of patients reported improvement in the dimensions of mobility and pain/discomfort, as shown in Table 4. No between-group differences in the

Table 2. Study Stents

Variable	Drug-eluting stent (n=508)	Bare metal stent (n=267)
Predilatation performed*	86.8 (440/507)	82.3 (219/266)
Postdeployment dilatation*	93.5 (474/507)	90.2 (240/266)
Study stents†	583	294
Innova vascular stent	NA	22.4 (66/294)
Supera stent	NA	17.3 (51/294)
Lifestent vascular stent	NA	16.0 (47/294)
Everflex peripheral self-expanding stent	NA	15.6 (46/294)
S.M.A.R.T. Flex vascular stent	NA	6.8 (20/294)
S.M.A.R.T. Control vascular stent	NA	5.8 (17/294)
Pulsar-18	NA	4.8 (14/294)
Complete SE Vascular Stent	NA	4.1 (12/294)
Misago peripheral stent	NA	0.0 (0/294)
Other	NA	7.1 (21/294)
No. of stents		
1	79.7 (392/492)	78.4 (214/273)
2	18.1 (89/492)	16.8 (46/273)
>2	2.2 (11/492)	4.8 (13/273)

Value are % (n/N). NA indicates not applicable.
*Site-reported.
†As-treated.

proportions of patients with improved dimensions were observed. Both Walking Impairment Questionnaire and 6-minute Walk Test walking function measures improved from baseline to 12 months for both groups, as shown in Tables 5 and 6.

The Rutherford category distribution shifted downward (improved) after treatment, with 84.1% (371 of 441) of patients in the DES group and 77.5% (189 of 244) of those in the BMS group presenting as category 0 or 1 at 12 months (Figure 3A). As shown in Figure 3B, incidence of Rutherford classification improvement without TLR (ie, primary sustained clinical improvement) did not differ statistically between study groups at 6 months, but improvement occurred more frequently at 12 months among patients treated with a DES than among those who received a BMS (83.0% versus 76.6%, *P*=0.045; relative risk, 1.08 [95% CI, 1.00–1.17]).

Antiplatelet Medications

Antiplatelet therapy was reported by all patients at 12 months with acetylsalicylic acid the most common, reported for 80.0% (335 of 419) and 82.8% (192 of 232) of the DES group and BMS group, respectively, at 12 months (*P*=0.38). Clopidogrel, which is recommended as a first-line treatment in European guidelines,[1] was reported for 48.2% (202 of 419) and 43.5% (101 of 232), respectively, at 12 months (*P*=0.25). Dual antiplatelet therapy was reported by 85.7% (397 of 463) and 85.0% (216 of 254) at 1 month (*P*=0.80) and 38.4% (161of 419) and 35.3% (82 of 232), respectively, at 12 months (*P*=0.44).

DISCUSSION

EMINENT is the largest randomized trial of DES treatment for symptomatic artery disease in the femoropopliteal artery circulation to report efficacy outcomes to date. This prospective randomized controlled trial provides quality evidence in a powered primary analysis to show that polymer-based DES treatment yielded superior 1-year primary patency compared with BMS. DES treatment was also associated with a clinical benefit without the need for reintervention. One-year mortality incidences were not statistically different between the paclitaxel-treated and BMS groups, and the hypoechogenic halo imaging finding was observed in both study arms with no statistical difference in frequency or apparent effect on safety.

EMINENT adds to the body of clinical evidence for polymer-based DES efficacy relative to other contemporary endovascular options. EMINENT met its primary outcome of 12-month primary patency, yielding robust conclusions across the primary intention-to-treat analysis, as well as the per-protocol and Kaplan-Meier analyses and sensitivity analyses for imputation. EMINENT results add to the consistently high 1-year incidence of

Table 3. The 12-Month Efficacy and Safety

	Drug-eluting stent (n=508), % (n/N)	Bare metal stent (n=267), % (n/N)	Difference (95% CI), %	*P* value
Primary patency*	83.2 (337/405)	74.3 (165/222)	8.9 (2.1 to 15.7)	<0.01
Major adverse event†	11.8 (56/474)	11.8 (31/263)	0.0 (−4.8 to 4.9)	0.99
All-cause death‡	2.7 (13/474)	1.1 (3/263)	1.6 (−0.3 to 3.6)	0.15
Target limb major amputation	0.2 (1/474)	0.0 (0/263)	0.2 (−0.2 to 0.6)	>0.99
Target lesion revascularization	8.9 (42/474)	10.6 (28/263)	−1.8 (−6.3 to 2.7)	0.43

*Intention-to-treat data set. Defined as peak systolic velocity ratio ≤2.4 at the 12-month visit in the absence of clinically driven target lesion revascularization or bypass of the target lesion.
†As-treated data set. Includes events occurring through the upper limit of the visit window (day 395); patients with an event or who reached the lower limit for the visit window (day 335) are included in the denominator.

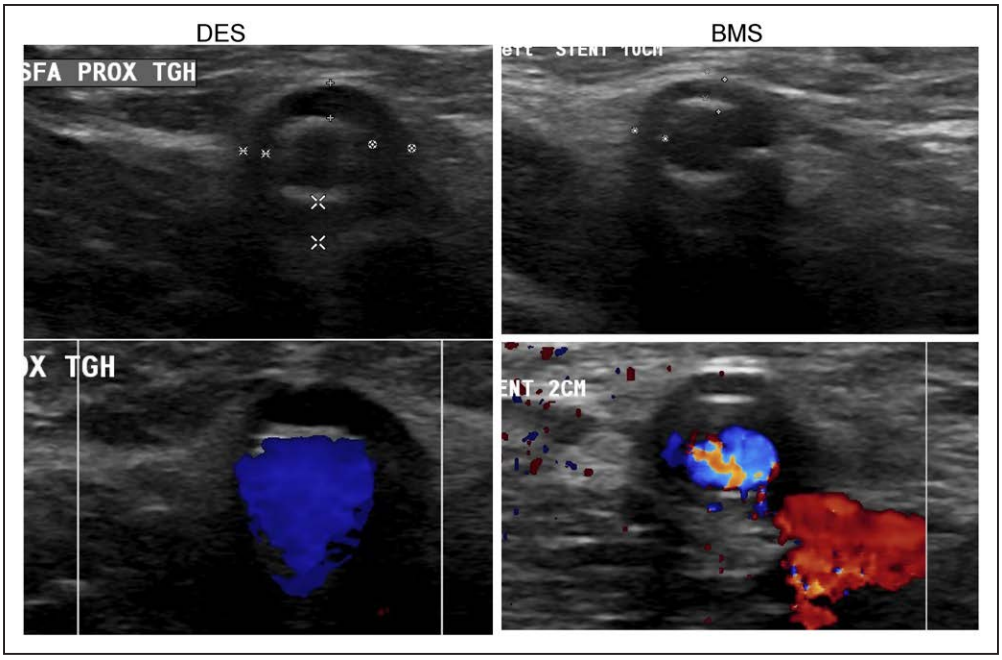

Figure 2. Hypoechogenic halo.
B-mode, transverse plane duplex ultrasound images obtained at the 12-month visit showing hypoechogenic halo in vessels treated with drug-eluting stent (DES) or bare metal stent (BMS).

primary patency the polymer-based DES has demonstrated across clinical studies.[12–14]

The prior BATTLE trial (Bare Metal Stent vs. Paclitaxel Eluting Stent in the Setting of Primary Stenting of Intermediate-Length Femoropopliteal Lesions)[6] and Zilver PTX randomized trial[3] provide context for EMINENT results but with important caveats. In a primary analysis from the randomized BATTLE trial,[6] the paclitaxel-coated polymer-free stent failed to show a significant in-stent restenosis reduction at 1 year compared with a BMS. The Zilver PTX randomized trial[3] compared the paclitaxel-coated polymer-free stent with percutaneous transluminal angioplasty with an uncoated balloon in the primary randomization and with BMS in a secondary randomization for provisional stenting. In this study, the paclitaxel-coated stent showed a significant and sustained primary patency versus percutaneous transluminal angioplasty with an uncoated balloon and greater 1-year primary patency versus BMS in the provisional setting, but the study was not designed to conclusively compare groups in this secondary randomization arm.

In the IMPERIAL randomized study (ELUVIA™ Drug-eluting Stent Versus Zilver® PTX® Stent), the durable polymer-coated Eluvia DES showed a superior incidence of primary patency at 1 year versus the paclitaxel-coated polymer-free stent.[12] The DES platform, the coating composition, and the amount of drug loaded on the stent differ from that of the paclitaxel-coated polymer-free stent. A lower drug concentration is loaded on the Eluvia DES (0.167 µg versus 3 µg paclitaxel per 1 mm^2 stent surface area); the polymer coating controls its sustained release over time,[15] whereas the polymer-free Zilver PTX delivers most of its drug within a short time frame.[16]

Although comparisons across studies are inherently limited, the eligibility criteria and mean lesion length represented in EMINENT are similar to those of the BATTLE,[6] IMPERIAL,[12] and Zilver PTX randomized controlled trials[3] (ie, Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease

Table 4. EQ-5D-5L Improvement at 12 Months

Variable	Drug-eluting stent (n=508), % (n/N)	Bare metal stent (n=267), % (n/N)	Difference (95% CI), %	*P* value
Mobility	66.4 (295/444)	64.2 (158/246)	2.2 (–5.2 to 9.6)	0.56
Self-care	8.8 (39/445)	7.7 (19/246)	1.0 (–3.2 to 5.3)	0.64
Usual activities	38.0 (169/445)	37.0 (91/246)	1.0 (–6.5 to 8.5)	0.80
Pain/discomfort	53.6 (238/444)	58.1 (143/246)	–4.5 (–12.2 to 3.2)	0.25
Anxiety/depression	22.5 (100/444)	20.0 (49/245)	2.5 (–3.8 to 8.9)	0.44

Percentage of patients with improved scores at 12 months.
EQ-5D-5L indicates XXXXX.

Table 5. Walking Impairment Questionnaire Score 12-Month Improvement

Variable	Drug-eluting stent (n=508), % (n/N)	Bare metal stent (n=267), % (n/N)	Difference (95% CI)	*P* value
Peripheral artery disease–specific question*	79.5 (360/453)	73.9 (184/249)	5.6 (–1.0 to 12.2)	0.09
Distance	82.1 (372/453)	81.9 (204/249)	0.2 (–5.7 to 6.1)	0.95
Speed	70.9 (321/453)	69.5 (173/249)	1.4 (–5.7 to 8.5)	0.70
Stair climbing	66.2 (300/453)	63.9 (159/249)	2.4 (–5.0 to 9.8)	0.53

Percentage of patients with improved scores at 12 months.
*Pain, aching, or cramps in calves or buttocks.

A/B, range of mean length, 66.4–86.5 mm across studies). The EMINENT efficacy conclusions for DES versus BMS differ from what was found in BATTLE.[6] In that study (N=186), the drug-coated polymer-free stent failed to demonstrate superiority in preventing in-stent restenosis compared with a BMS, although it had demonstrated greater 1-year primary patency versus BMS in the secondary randomization arm (ie, provisional stenting) from the earlier Zilver PTX randomized trial.[3] The BATTLE authors postulated that the lack of superiority of the paclitaxel-coated stent over BMS could be caused by the polymer-free stent coating, which does not sustain drug release over the 1-year period in which in-stent restenosis mainly occurs.[6,16,17]

The 1-year incidence of TLR did not differ statistically between EMINENT treatment groups, but the study was not designed with adequate power to assess this secondary outcome. The TLR incidence was also similar to those reported for both BATTLE study arms[6] and IMPERIAL.[12] Although incidence was similar to that in prior studies, it is possible that health care resource limitations or reluctance for patients to access health care during the coronavirus disease 2019 (COVID-19) pandemic dampened reintervention rates.

Table 6. The 6-Minute Walk Test

Variable	Baseline	At 12 mo	*P* value
Drug-eluting stent			
Total walk time (range), min	4.7±1.9 (0.2–16.6)	5.6±2.4 (0.9–45.0)	<0.01
No.	461	382	
Total distance, m	258.4±153.4	392.4±286.0	<0.01
No.	468	386	
Speed, m/min	55.5±26.0	68.7±22.7	<0.01
No.	461	382	
Bare metal stent			
Total walk time (range), min	4.5±1.9 (0.3–10.2)	5.3±1.4 (1.0–10.0)	<0.01
No.	246	219	
Total distance, m	239.1±150.0	361.9±176.2	<0.01
No.	251	221	
Speed, m/min	52.8±21.1	65.9±27.7	<0.01
No.	246	219	

Data are shown as mean±SD. Patients who did not complete the assessment or who had entered 0 for distance or time were excluded from the analysis. Total time >6 minutes is attributable to inclusion of rest time at some sites.

The proportion of patients with Rutherford category improvement without TLR (ie, primary sustained clinical improvement) was greater in the DES arm of EMINENT. No difference in this measure was observed between arms in BATTLE.[6] This difference at 12 months, along with the difference in primary patency (driven by the duplex ultrasound restenosis component), may preview a differential need for future reintervention assuming a delayed relationship between restenosis and TLR. A distinguishing effect of sustained drug release may also become more apparent beyond the 1-year mark; indeed the between-group difference in TLR became more pronounced in favor of the polymer-based DES over 2 years in IMPERIAL.[9] Longer-term follow-up is ongoing for EMINENT, and reintervention rates will be further assessed at future time points. Although the primary sustained clinical improvement result was greater for the DES arm at 12 months, health-related quality of life and walking function measures did not show a differential improvement between study arms overall. However, the primary sustained clinical improvement measure accounts for potential TLR-based effects on Rutherford category improvement, whereas the other functional outcome measures did not (ie, patients were included in the outcome assessment regardless of whether they had undergone TLR). Moreover, stronger conclusions based on the 6-minute walk test are limited because of inconsistent adherence to the time limit. Functional and health-related quality of life outcomes did improve in both groups, demonstrating functional benefits of stenting among patients with claudication. Proportions of patients with EQ-5D dimension improvements were similar to those reported after stenting in the IMPERIAL trial.[12]

Incidence of all-cause mortality observed in EMINENT at 1 year was not statistically different between the paclitaxel-eluting and uncoated stent study arms and in the range expected for patients with intermittent claudication.[18] The specific causes of death reported (ie, noncardiovascular-adjudicated preexisting malignancies and infection/sepsis) do not suggest a link to paclitaxel or the DES. Although the 1-year time frame is insufficient to evaluate differential mortality in this cohort and

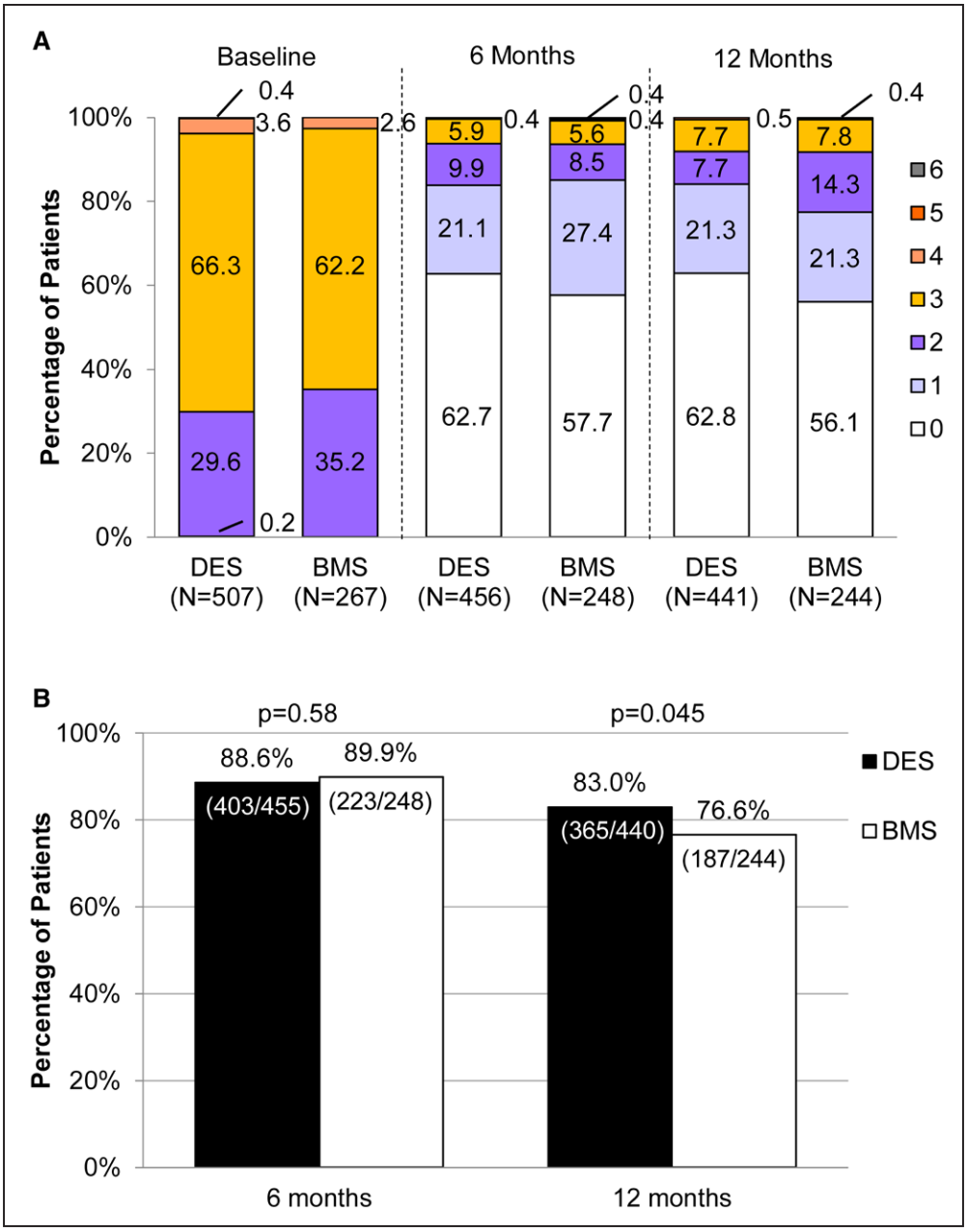

Figure 3. Rutherford category distribution (A) and primary sustained clinical improvement (B).
BMS indicates bare metal stent; and DES, drug-eluting stent.

vital status follow-up is scheduled through 5 years, these results add to the numerous efforts undertaken to more thoroughly analyze the relationship between paclitaxel devices and mortality. Evidence is accumulating that provides important and reassuring information reinforcing the safety profile of paclitaxel-containing devices.[18–24]

Incidence of duplex ultrasound hypoechogenic halo detection was not statistically different for the DES and BMS study arms, challenging any suggestion of a putative link to paclitaxel or the DES polymer. Halo imaging characteristics were not suggestive of aneurysm, and similar imaging findings have previously been reported after non–drug-coated stent implantation in the SFA,[25,26] in a case of nitinol allergy with a bare stent,[27] and in vasculitis,[28] which supports the possibility of a localized inflammatory reaction attributable to the presence of a metallic implant for which some patients may have a higher sensitivity. Halo prevalence among DES-treated patients at 1 year (26.1%) was similar to that observed for patients in IMPERIAL treated with DES (33.7%) and polymer-free paclitaxel-coated stent (21.4%) at 2 years (ie, systematic screening was implemented at the 2-year follow-up in IMPERIAL).[9] Consistent with the reports by Stavroulakis et al[8] and Iida et al,[10] the imaging finding was not associated with increased TLR risk among EMINENT patients. Halo was not assessed in all EMINENT

patients at 1 year because of the implementation timing of the transverse plane imaging protocol. The evolution of the phenomenon over time is not known, but transverse plane duplex ultrasound imaging will be repeated at 2 and 3 years.

Like many other European-based paclitaxel device studies for femoropopliteal artery treatment, the EMINENT sample was predominantly White with fewer than one-third women. Lesion characteristics in EMINENT patients were comparable to those represented in other randomized trials of DES,[3,6,12] with moderate length and more than half with moderate to severe calcification. Occlusion prevalence was greater in EMINENT at ≈41% compared with 30% to 38% in the noted prior studies.[3,6,12] Current shortcomings related to representativeness of patient populations and lesion complexity in DES trials may be addressed with future analyses of data from the ELEGANCE Registry (Drug-Eluting Registry: Real-World Treatment of Lesions in the Peripheral Vasculature; URL: http://www.clinicaltrials.gov. Unique identifier: NCT04674969), which is intended to yield real-world data from diverse patient populations.

Limitations of the study include the poor representation of women and populations that are not White despite multinational study sites. With inclusion eligibility confined to Rutherford category 2 to 4, the study sample is representative of patients with peripheral artery disease and intermittent claudication or rest pain but not with chronic limb-threatening ischemia with tissue loss. The study reflects common practice in a limited geographic region (Western Europe). Average lesion length was shorter than anticipated given the long lesion length allowances. Thus, results are applicable to moderate-length lesions, but the study is not conclusive for long Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease II C/D lesion types. In addition, adjunctive debulking devices were not allowed in the study procedures. These might typically be used for the moderate to severe lesion calcification observed in approximately half of the study patients. Because device costs differ between DESs and BMSs, longer term follow up—which is ongoing—and dedicated cost-effectiveness analyses are needed to evaluate the impact of preserving patency on TLR rates and associated economic benefits. Bias in procedural follow-up in this trial setting (eg, closer follow-up) is another potential limitation: Although patients and assessors were blinded to the study arm, the treating investigator was not.

Analytical limitations are inherent in the pooled comparator group design. The study was designed to compare the Eluvia DES group with the pooled BMS group, and BMS use was distributed across multiple different devices. This design is valid for comparison with the BMS class, but comparisons between DES and any 1 small BMS subgroup could not be considered purely randomized and would likely be insufficiently powered to demonstrate statistical superiority.

Last, follow-up occurred during the COVID-19 pandemic, which affected clinical trial conduct generally.[29,30] Pandemic-related circumstances could have affected follow-up procedures and increased the threshold for patients to seek symptom-driven care, thereby potentially reducing reintervention rates. Patients might also be more likely to delay or miss study follow-up visits, which (along with nondiagnostic imaging) contributes to missing duplex ultrasound data for the primary end point patency evaluation. Attrition in EMINENT remained within the initially anticipated levels, and 1-year visit compliance was in the expected range, but imputation was used in the primary effectiveness analysis with the intention of minimizing missing data resulting from patients being unable to complete their duplex ultrasound assessments within the specified visit window. Sensitivity analyses performed to assess the influence of imputation yielded conclusions consistent with the primary analysis.

Conclusions

Eluvia is the first DES to demonstrate superior 1-year primary patency compared with any globally marketed BMS in an adequately designed randomized trial. The EMINENT and IMPERIAL randomized trials together support the benefit of a polymer-based paclitaxel-eluting stent for treating SFA or proximal popliteal artery lesions of intermediate length.

ARTICLE INFORMATION

Received February 10, 2022; accepted August 30, 2022.

Affiliations

Groupe Hospitalier Paris St. Joseph, Department of Vascular and Endovascular Surgery, Paris, France (Y.G.). St. Franziskus-Hospital Münster, Münster, Germany (G.T.). Universitäts-Herzzentrum Freiburg-Bad Krozingen, Bad Krozingen, Germany (T.Z.). Department of Advanced Biomedical Sciences, University of Naples Federico II, Italy (G.E.). Gent University Hospital, Belgium (F.V.). Klinikum Klagenfurt am Wörthersee, Austria (K.A.H.). Klinikum Rosenheim, Germany (G.T.). REGIOMED Vascular Center Sonneberg, Germany (M.T.). Jena University Hospital, Clinic for Internal Medicine I, Germany (M.T.). Medizinische Universität Wien, Vienna, Austria (M.G.). Vita-Salute University, San Raffaele Scientific Institute, Milan, Italy (A.K.). Division of Angiology, Swiss Cardiovascular Center, Inselspital, Bern (M. Schindewolf). University Hospital, University of Bern, Switzerland (M. Schindewolf). Hôpital Européen Georges-Pompidou, Paris, France (M. Sapoval). Boston Scientific Corp, Marlborough, MA (J.D.-C.). Ludwig-Maximilian University, Munich, Germany (K.S.).

Acknowledgments

The authors thank the core laboratory staff at VasCore and coreLab Black Forest GmbH for their contributions to the imaging analyses. They thank the following Boston Scientific employees for their assistance: Andrew Campbell and Janiece Rutherford, RN, MBA (clinical trial management); Samantha Ryan, MSc, and Lei Zhang, ScM (statistical analysis management); and Elizabeth J. Davis, PhD (medical writing). Results from EMINENT were presented at VIVA 2021, October 6, 2021, Las Vegas, NV.

Sources of Funding

The study was funded and sponsored by Boston Scientific Corp, Marlborough MA.

Disclosures

Dr Gouëffic has received research funding from Abbott, Boston Scientific, General Electric, Veryan, and WL Gore, as well as personal fees and grants from Abbott, Bard, Biotronik, Boston Scientific, Cook, General Electric, Medtronic, Penumbra, Terumo, Veryan, and WL Gore. Dr Torsello has received research funding and honoraria from Boston Scientific, WL Gore, Cook, and Medtronic. Dr Zeller reports receiving honoraria from Abbott Vascular, Veryan, Biotronik, Boston Scientific Corp, Cook Medical, Gore & Associates, Medtronic, Philips-Spectranetics, TriReme, Veryan, Shockwave, Biotronik, B. Braun, and Efemoral; consulting for Boston Scientific Corp, Cook Medical, Gore & Associates, Medtronic, Spectranetics, Veryan, Intact Vascular, and Veryan; and holding common stock in QT Medical. Dr Vermassen reports receiving research grants, consultancy, or speaking fees from Boston Scientific, Medtronic, and Philips. Dr Tepe has received research funding from B. Braun, Biotronic, BSC, BARD, Gore, Philips, and Veryan. Dr Kahlberg has received research grants, consultancy, or speaking fees from Alvimedica/CID, Boston Scientific, Cordis, Getinge, Medtronic, and Terumo. Dr Schindewolf reports receiving speaker fees from Abbott, Aspen, Boston Scientific, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, and Sanofi; travel grants from Bard, Bayer, Bristol-Myers Squibb, Medtronic, and Terumo; research grants from Cook, Daiichi Sankyo, and Terumo; and consulting fees from Bayer, Bristol-Myers Squibb, Daiichi Sankyo, and Sanofi. Dr Sapoval has received research funding and honoraria from Boston Scientific. Dr Diaz-Cartelle is an employee of and owns stock in Boston Scientific. Dr Stavroulakis is a consultant for Phillips, Shockwave, Terumo, and Boston Scientific and received honoraria from Medtronic, Boston Scientific, Bentley, Abbott, and Biotronik.

Supplemental Material

Supplemental Methods

Tables S1–S4

Figure S1

REFERENCES

1. Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. *Eur Heart J.* 2018;39:763–816. doi: 10.1093/eurheartj/ehx095
2. Bailey SR, Beckman JA, Dao TD, Misra S, Sobieszczyk PS, White CJ, Wann LS, Bailey SR, Dao T, Aronow HD, et al. ACC/AHA/SCAI/SIR/SVM 2018 appropriate use criteria for peripheral artery intervention: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Heart Association, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, and Society for Vascular Medicine. *J Am Coll Cardiol.* 2019;73:214–237. doi: 10.1016/j.jacc.2018.10.002
3. Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, Zeller T, Roubin GS, Burket MW, Khatib Y, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. *Circ Cardiovasc Interv.* 2011;4:495–504. doi: 10.1161/CIRCINTERVENTIONS.111.962324
4. Caradu C, Lakhlifi E, Colacchio EC, Midy D, Berard X, Poirier M, Ducasse E. Systematic review and updated meta-analysis of the use of drug-coated balloon angioplasty versus plain old balloon angioplasty for femoropopliteal arterial disease. *J Vasc Surg.* 2019;70:981–995.e10. doi: 10.1016/j.jvs.2019.01.080
5. Zhou Y, Zhang Z, Lin S, Xiao J, Ai W, Wang J, Li Y, Li Q. Comparative efficacy and safety of endovascular treatment modalities for femoropopliteal artery lesions: a network meta-analysis of randomized controlled trials. *Cardiovasc Intervent Radiol.* 2020;43:204–214. doi: 10.1007/s00270-019-02332-4
6. Gouëffic Y, Sauguet A, Desgranges P, Feugier P, Rosset E, Ducasse E, Kaladji A, Salomon du Mont L, Pernes JM, Commeau P, et al. A polymer-free paclitaxel-eluting stent versus a bare-metal stent for de novo femoropopliteal lesions: the BATTLE trial. *JACC Cardiovasc Interv.* 2020;13:447–457. doi: 10.1016/j.jcin.2019.12.028
7. Boston Scientific. Data sharing requests. Accessed xxxx. https://www.bostonscientific.com/en-US/data-sharing-requests.html
8. Stavroulakis K, Torsello G, Bosiers M, Argyriou A, Tsilimparis N, Bisdas T. 2-Year outcomes of the Eluvia drug-eluting stent for the treatment of complex femoropopliteal lesions. *JACC Cardiovasc Interv.* 2021;14:692–701. doi: 10.1016/j.jcin.2021.01.026
9. Müller-Hülsbeck S, Benko A, Soga Y, Fujihara M, Iida O, Babaev A, O'Connor D, Zeller T, Dulas DD, Diaz-Cartelle J, et al. Two-year efficacy and safety results from the IMPERIAL randomized study of the Eluvia polymer-coated drug-eluting stent and the Zilver PTX polymer-free drug-coated stent. *Cardiovasc Intervent Radiol.* 2021;44:368–375. doi: 10.1007/s00270-020-02693-1
10. Iida O, Takahara M, Soga Y, Yamaoka T, Fujihara M, Kawasaki D, Ichihashi S, Kozuki A, Nanto S, Sakata Y, et al. 1-Year outcomes of fluoropolymer-based drug-eluting stent in femoropopliteal practice: predictors of restenosis and aneurysmal degeneration. *JACC Cardiovasc Interv.* 2022;15:630–638. doi: 10.1016/j.jcin.2022.01.019
11. EuroQol Research Foundation. EQ-5D-5L User Guide. 2019.
12. Gray WA, Keirse K, Soga Y, Benko A, Babaev A, Yokoi Y, Schroeder H, Prem JT, Holden A, Popma J, et al. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. *Lancet.* 2018;392:1541–1551. doi: 10.1016/S0140-6736(18)32262-1
13. Müller-Hülsbeck S, Keirse K, Zeller T, Schroe H, Diaz-Cartelle J. Twelve month results from the MAJESTIC trial of the Eluvia paclitaxel-eluting stent for treatment of obstructive femoropopliteal disease. *J Endovasc Ther.* 2016;23:701–707. doi: 10.1177/1526602816650206
14. Golzar J, Soga Y, Babaev A, Iida O, Kawasaki D, Bachinsky W, Park J, Prem JT, Vermassen F, Diaz-Cartelle J, et al. Effectiveness and safety of a paclitaxel-eluting stent for superficial femoral artery lesions up to 190 mm: one-year outcomes of the single-arm IMPERIAL Long Lesion Substudy of the Eluvia drug-eluting stent. *J Endovasc Ther.* 2020;27:296–303. doi: 10.1177/1526602820901723
15. Hou D, Huibregtse BA, Eppihimer M, Stoffregen W, Kocur G, Hitzman C, Stejskal E, Heil J, Dawkins KD. Fluorocopolymer-coated nitinol self-expanding paclitaxel-eluting stent: pharmacokinetics and vascular biology responses in a porcine iliofemoral model. *EuroIntervention.* 2016;12:790–797. doi: 10.4244/EIJV12I6A128
16. Dake MD, Van Alstine WG, Zhou Q, Ragheb AO. Polymer-free paclitaxel-coated Zilver PTX stents: evaluation of pharmacokinetics and comparative safety in porcine arteries. *J Vasc Interv Radiol.* 2011;22:603–610. doi: 10.1016/j.jvir.2010.12.027
17. Iida O, Uematsu M, Soga Y, Hirano K, Suzuki K, Yokoi H, Muramatsu T, Inoue N, Nanto S, Nagata S. Timing of the restenosis following nitinol stenting in the superficial femoral artery and the factors associated with early and late restenoses. *Catheter Cardiovasc Interv.* 2011;78:611–617. doi: 10.1002/ccd.23064
18. Nordanstig J, James S, Andersson M, Andersson M, Danielsson P, Gillgren P, Delle M, Engstrom J, Fransson T, Hamoud M. et al. Mortality with paclitaxel-coated devices in peripheral artery disease. *N Engl J Med.* 2020;383:2538–2546. doi: 10.1056/NEJMoa2005206
19. Schneider PA, Varcoe RL, Secemsky E, Schermerhorn M, Holden A. Update on paclitaxel for femoral-popliteal occlusive disease in the 15 months following a summary level meta-analysis demonstrated increased risk of late mortality and dose response to paclitaxel. *J Vasc Surg.* 2021;73:311–322. doi: 10.1016/j.jvs.2020.07.093
20. Dinh K, Limmer AM, Chen AZL, Thomas SD, Holden A, Schneider PA, Varcoe RL. Mortality rates after paclitaxel-coated device use in patients with occlusive femoropopliteal disease: an updated systematic review and meta-analysis of randomized controlled trials. *J Endovasc Ther.* 2021;28:755–777. doi: 10.1177/15266028211023505
21. Gouëffic Y, Postaire B, Leclere B. Fragility of the signal. *J Endovasc Ther.* 2020;27:871–872. doi: 10.1177/1526602820941800
22. Behrendt CA, Sedrakyan A, Peters F, Kreutzburg T, Schermerhorn M, Bertges DJ, Larena-Avellaneda A, L'Hoest H, Kolbel T, Debus ES. Long term survival after femoropopliteal artery revascularisation with paclitaxel coated devices: a propensity score matched cohort analysis. *Eur J Vasc Endovasc Surg.* 2020;59:587–596. doi: 10.1016/j.ejvs.2019.12.034
23. Bertges DJ, Sedrakyan A, Sun T, Eslami MH, Schermerhorn M, Goodney PP, Beck AW, Cronenwett JL, Eldrup-Jorgensen J. Mortality after paclitaxel coated balloon angioplasty and stenting of superficial femoral and popliteal artery in the Vascular Quality Initiative. *Circ Cardiovasc Interv.* 2020;13:e008528. doi: 10.1161/CIRCINTERVENTIONS.119.008528
24. Freisinger E, Koeppe J, Gerss J, Goerlich D, Malyar NM, Marschall U, Faldum A, Reinecke H. Mortality after use of paclitaxel-based devices in peripheral arteries: a real-world safety analysis. *Eur Heart J.* 2020;41:3732–3739. doi: 10.1093/eurheartj/ehz698

25. Muller-Hulsbeck S, Link J, Schwarzenberg H, Steffens JC, Brossmann J, Hulsbeck A, Heller M. MR imaging signal-intensity abnormalities after placement of arterial endoprostheses. *AJR Am J Roentgenol.* 1997;169:743–748. doi: 10.2214/ajr.169.3.9275890
26. Soga Y, Ando K. "Low echoic area" around stent after bare and drug-coated stenting or stent graft placement for superficial femoral artery disease. *SAGE Open Med Case Rep.* 2021;9:2050313X211014519. doi: 10.1177/2050313X211014519
27. D'Arrigo G, Giaquinta A, Virgilio C, Davi A, Pierfrancesco V, Veroux M. Nickel allergy in a patient with a nitinol stent in the superficial femoral artery. *J Vasc Interv Radiol.* 2014;25:1304–1306. doi: 10.1016/j.jvir.2014.03.026
28. Tato F, Hoffmann U. Clinical presentation and vascular imaging in giant cell arteritis of the femoropopliteal and tibioperoneal arteries: analysis of four cases. *J Vasc Surg.* 2006;44:176–182. doi: 10.1016/j.jvs.2006.02.054
29. European Medicines Agency. Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic: version 4. 2021. Accessed December 9, 2021. https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf
30. US Food and Drug Administration. Conduct of clinical trials of medical products during the COVID-19 public health emergency: guidance for industry, investigators, and institutional review boards. 2021. Accessed December 9, 2021. https://www.fda.gov/media/136238/download