Atherosclerosis 344 (2022) 71–77

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Impact of peripheral artery disease on prognosis after percutaneous coronary intervention: Outcomes from the multicenter prospective e-ULTIMASTER registry

Ofer Kobo [a], Majdi Saada [a], Peep Laanmets [b], Dimitar Karageorgiev [c], Helen Routledge [d], Jim Crowley [e], Pascual Baello [f], Javier Balague Requena [g], Fabrizio Spanó [h], Luis Perez [i], Jesus Maria Jimenez Mazuecos [j], Mamas A. Mamas [k], Ariel Roguin [a,*]

[a] Hillel Yaffe Medical Center, Israel. Rappaport Faculty of Medicine, Technion Israel Institute of Technology, Hadera, Israel
[b] Department of Cardiology, North Estonia Medical Centre, Tallinn, Estonia
[c] 2MBAL Sveta Karidad, Plovdiv, Bulgaria
[d] Worcestershire Royal Hospital, Worcester, UK
[e] Galway University Hospital, Galway, Ireland
[f] Hospital General Castellón, Castellon, Spain
[g] Hospital Universitario de Guadalajara, Guadalajara, Spain
[h] Department of Cardiology, Meander Medical Center, Amersfoort, Netherlands
[i] Guillermo Grant Benavente Hospital & University of Concepción, Concepción, Chile
[j] Hospital General de Albacete, Albacete, Spain
[k] Keele Cardiovascular Research Group, Centre for Prognosis Research, Keele University, Keele, United Kingdom

ARTICLE INFO

Keywords:
Peripheral artery disease
Drug eluting coronary stent
Percutaneous coronary intervention
Coronary artery disease
Clinical trial

ABSTRACT

Background and aims: Patients with peripheral artery disease (PAD) represent a high risk group, and have an increased risk of cardiovascular events and worse cardiovascular outcomes. Our aim was to study the impact of PAD among patients undergoing percutaneous coronary intervention (PCI) with a newer-generation thin-strut DES.

Methods: In this analysis of the e-ULTIMASTER registry, patients with and without known PAD undergoing PCI were compared. A propensity-score was used to adjust for differences between the groups. The primary outcome was target lesion failure (TLF): a composite of cardiac death, target-vessel related myocardial infarction, and/or clinically driven target lesion revascularization at 1-year follow-up.

Results: Of 33,880 patients included in the analysis, PAD was present in 2255 (6.7%). Patients with PAD were older (69.0 ± 10.0 *vs.* 63.8 ± 11.3 years) with a higher burden of comorbidities. Patients with PAD were less likely to present with STEMI (9.6% *vs.* 21%), and more likely to undergo complex PCI (left main 5.5% *vs.* 3.0% ostial lesions 10.4% *vs.* 7.0%, bifurcations 14.5% *vs.* 12.3% and calcification 26.8% *vs.* 17.8%). PAD was found to be independently associated with 41% increased risk for TLF. The risk for all cause death and for cardiac death was 75% and 103% higher, respectably. No difference was found in the rates of stent thrombosis, clinically driven target lesion revascularization, or myocardial infarction (MI).

Conclusions: Patients with PAD are at higher risk for (cardiac) death post PCI, but not target vessel or lesion repeat revascularizations. The PAD cohort represents a population with a higher risk clinical profile. Further research combining medical and device therapies is needed to further improve the outcomes in this high-risk population.

1. Introduction

Peripheral artery disease (PAD) is a common condition, with an increasing prevalence over recent decades, now estimated to occur in over 200 million people worldwide [1,2] with symptoms ranging from mild to severe. PAD shares similar risk factors as coronary artery disease (CAD), as both are a manifestation of systemic atherosclerosis. It is estimated that while half of the patients with PAD have CAD, PAD is

* Corresponding author. Hillel Yaffe Medical Center, Hadera, 3810101, Israel.

https://doi.org/10.1016/j.atherosclerosis.2022.01.007
Received 5 November 2021; Received in revised form 14 December 2021; Accepted 14 January 2022
Available online 25 January 2022

present in about 20% of the patients with CAD [3]. The presence of PAD not only indicates an increased risk for CAD, but is also associated with worse clinical outcomes in patients with myocardial infarction (MI) [4, 5] and percutaneous coronary intervention (PCI) [6]. Patients with PAD treated with PCI are more likely to develop contrast-induced nephropathy and have an increased risk of adverse cardiovascular events, bleeding, and mortality [6–11].

Most of the data that has reported on post-PCI outcomes in patients with PAD is derived from studies performed using bare metal stents (BMS) or early-generation drug eluting stents (DES). It is unknown whether the improved clinical outcomes of PCI with the newer generations DES and adjunct medical therapy in the general population [12] have translated to better outcomes in patients with PAD undergoing PCI, and whether the excess risk of patients with PAD undergoing PCI previously reported still persists.

We aimed to compare outcomes of patients with and without PAD in a large cohort of patients enrolled in the e-ULTIMASTER prospective and multinational registry study, who underwent new generation thin strut drug-eluting stent (DES) implantation.

2. Patients and methods

2.1. Study design

The large e-ULTIMASTER is an all-comer, single-arm, prospective, and multicenter registry. The study was conducted worldwide across Europe, Asia, South-America, Middle-East and Africa to further evaluate the safety and performance of the Ultimaster DES system (Terumo Corporation, Tokyo, Japan) in an all-comer clinical setting. Inclusion and exclusion criteria were described previously [13]. Briefly, patients with CAD, with reference vessel diameters between 2.5 and 3.5 mm, eligible for PCI according to local hospital practice, and who were treated using the Ultimaster stent, were enrolled in the registry. Local institutional review board approval was obtained at each institution and all patients provided written informed consent.

The present study analyzed the clinical outcomes of patients who have known PAD. Patients were grouped into (1) those with known PAD; or (2) those without known PAD. Each site applied their routine definition of PAD; there was no per-protocol definition.

2.2. Study device

The Ultimaster coronary stent system is a new-generation, open-cell, cobalt-chromium, thin-strut (80-μm) sirolimus eluting stent with an abluminal bioresorbable polymer coating (poly-D,L-lactic acid polycaprolactone). Sirolimus is released over a 3- to 4-month period, after which the polymer coating is fully degraded [14].

2.3. Outcomes and definitions

The primary outcome was target lesion failure (TLF) defined as a composite of cardiac death, target vessel–related myocardial infarction (TV-MI), and clinically driven target lesion revascularization (CD-TLR) at 1-year follow-up. Secondary outcomes included any death, cardiac death, any MI, TV-MI, any revascularization, CD-TLR, definite/probable stent thrombosis and patient-oriented composite endpoint (POCE), defined as a composite of any death, any MI, and any coronary revascularization. All primary endpoint related adverse events were reviewed and adjudicated by an independent clinical events committee.

Subcategories of death (cardiac death, and non-cardiovascular), as well as revascularizations and stent thrombosis, were adjudicated according to the Academic Research Consortium (ARC) definitions [15]. For MI, the extended historical myocardial definition was applied that primarily uses creatine kinase myocardial band (MB) as cardiac biomarker criterion but, if not measured, troponin values for the determination of a periprocedural (<48 h post PCI) reinfarction (<48 h post PCI) or spontaneous MI (>48 h post PCI) [16]. The clinicaltrial.gov identifier is NCT02188355.

2.4. Statistical analysis

Baseline characteristics were reported as percentages and numbers for categorical variables and as mean and standard deviation (SD) for continuous variables. Statistical differences between baseline characteristics were reported using *t*-test for continuous variables and chi-squared test for categorical variables. The clinical outcomes at 1-year follow up were compared using the chi-squared test.

To reduce the effect of baseline differences between the two groups, a propensity-score analysis was performed. Propensity scores were calculated using a logistic regression model, with the subgroup (PAD *vs.* No PAD) as outcome and the variables, which needed to be matched for as independent variables. The probability of belonging to one of the two groups was used as a propensity score. Variables to be entered into the model were predefined based on any possible impact on the outcomes and included: age, renal impairment, hypertension diabetes mellitus, hypercholesterolemia, STEMI, previous PCI, number of lesion identified, previous MI, previous CABG, previous smoker, LAD, left main, ostial lesions, BMI, current smoker and male gender. The inverse probability of treatment weights methodology was used to perform a matched analysis. This methodology uses the inverse of the propensity score of its own subgroup (i.e., the probability of the subject of belonging to the subgroup it is in) as a weight that can be used in the analyses. Using these weights, analyses were balanced for the covariates in the logistic regression model. The balance after matching can be tested by calculating weighted standardized difference for the inverse probability of treatment weights analysis using the calculated weights. Generally, standardized difference for all variables below 0.20 are considered well balanced, whereas standardized difference for all variables below 0.10 can be considered extremely well balanced (Supplementary Fig. 1). Weighted chi-square tests were used for binary or categorical data; weighted Wilcoxon rank-sum tests were used for continuous data.

$p < 0.05$ was considered significant. Statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC).

3. Results

Of all 37,198 patients in the e-ULTIMASTER registry, information on the PAD status was lacking for 3318 patients. The population of the present analysis therefore comprised 33,880 patients. PAD was present in 2255 patients (6.7%), while 31,625 patients (93.3%) had no known PAD (Fig. 1). Baseline demographics and clinical characteristics are reported in Table 1. Patients with PAD were older (69.0 ± 10 *vs.* 63.8 ± 11.3 years) and had a higher prevalence of comorbidities, such as diabetes (44.1% *vs.* 27.5%, insulin dependent 12.5% *vs.* 5.2% and non-insulin dependent 31.5% *vs.* 22.3%), renal impairment (18.7% *vs.* 6.4%), hypertension (81.6% *vs.* 66.2%), hyperlipidemia (73.9% *vs.* 58.5%) and history of cerebrovascular disease (14.3% *vs.* 4.7%). Of the patients with PAD 23.2% were women, and there was no difference in sex between patients with and without PAD. Patients with PAD more often had a history of previous MI (32.2% *vs.* 21.5%), PCI (37.3% *vs.* 24.8%), and CABG (11.3% *vs.* 5.0%).

The two groups differed in clinical syndrome at presentation. Patients with PAD were less likely to present with STEMI (9.6% *vs.* 21.0%) but were more likely to undergo PCI for chronic coronary syndrome (55.4% *vs.* 43.2%) (Table 1). We also observed significant procedural differences between the groups. Patients with PAD were more likely to undergo PCI via femoral access (20.8% *vs.* 17.6%), or to undergo left main coronary artery (LMCA) PCI (5.5% *vs.* 3%). The mean number of coronary lesions identified in the PAD group was higher (2.2 ± 1.2 *vs.* 1.9 ± 1.1). Small vessel PCI was more common in the PAD group (33.7% *vs.* 28.9%), as well as the complex PCI (as manifested in higher rates of ostial lesions 10.4% *vs.* 7.0%, bifurcations 14.5% *vs.* 12.3% and calcific

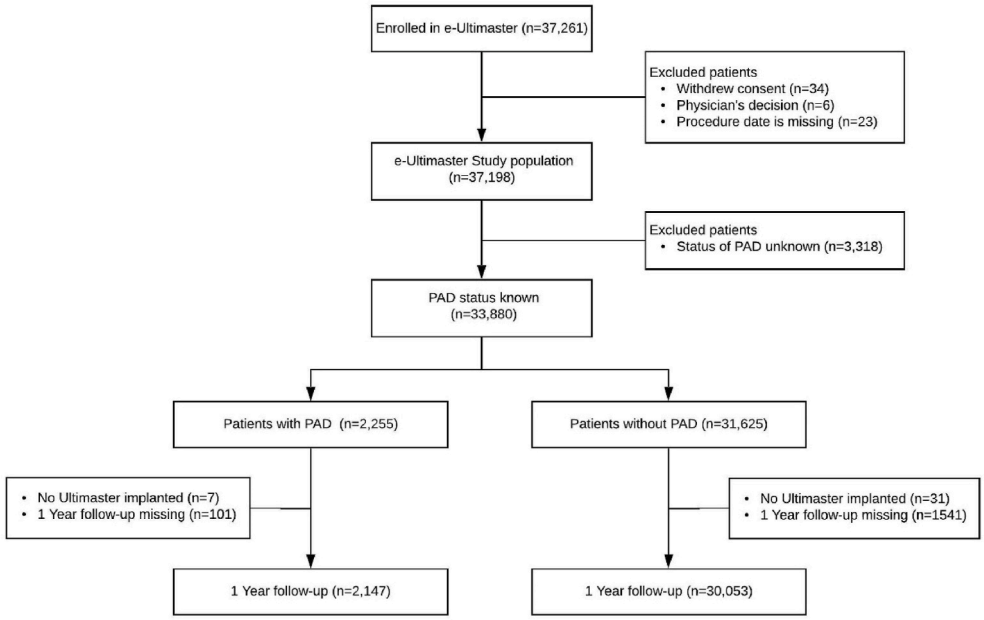

Fig. 1. Study flow chart.
PAD: peripheral artery disease.

disease 26.8% *vs*. 17.8%) (Table 1).

One-year post PCI data was available for 2147 patients (95.2%) in the PAD group, and 30,053 patients without PAD (95.0%). Table 2 presents crude clinical outcome data until 1 year after the index PCI procedure. At 1-year follow-up, the main endpoint TLF was met by 6.2% of the patients with PAD and 3.0% of the patients without PAD ($p < 0.0001$). Similarly, patients with PAD experienced higher rates of TVF (6.9% *vs.* 3.5%, $p < 0.0001$), POCE (11.0% *vs*. 6.3%, $p < 0.0001$), all-cause mortality (5.5% *vs.* 1.8%, $p < 0.0001$) and cardiac death (3.8% *vs*. 1.1%, $p < 0.001$). Clinically driven target vessel and target lesion revascularization were more common in the PAD group (3.3% *vs*. 2.3% and 2.5% *vs*. 1.7%, respectively, both $p < 0.01$). Rates of any MI and definite/probable stent thrombosis were numerically higher in the PAD group but failed to reach statistical significance. There was no difference in the number of patients on dual anti-platelet therapy at 1-year (66.4% *vs.* 70.2%, $p = 0.13$), but more patients with PAD were taking oral anticoagulants (11.1% *vs*. 5.6%, $p < 0.0001$).

After adjustment for propensity score, PAD was found to be independently associated with 41% increased risk for target lesion failure (95% CI: 18–68%, $p < 0.001$; adjusted event rate 5.9% *vs*. 4.2%, $p < 0.001$), as well as 25% increased risk for POCE (95% CI: 10–43%, $p < 0.001$; adjusted event rate 10.7% *vs*. 8.6%, $p < 0.001$), and 103% increased risk for cardiac death (95% CI: 60–158%, $p < 0.0001$; adjusted event rate 3.5% *vs*. 1.7%, $p < 0.0001$). PAD was not associated with increased risk for target vessel MI, clinically driven TV/TL revascularization or definite/probable stent thrombosis (Tables 3 and 4 and Fig. 2).

4. Discussion

This analysis of over 35,000 all-comer patients from a prospective, multicenter, large registry is to our knowledge the largest analyses of PCI outcomes in patients with PAD who underwent PCI with new-generation thin strut DES.

Among the participants in the study, 6.7% had PAD. Patients with PAD were older with higher prevalence of cardiovascular risk factors, prior stroke and ischemic heart disease and have more extensive and complex coronary disease. In addition, patients with PAD were less likely to present with STEMI, and were more likely to undergo LMCA intervention, PCI via femoral access or complex PCI. As expected, based on the higher prevalence of risk factors, and more complex coronary disease treated, patients with PAD experienced higher crude rate of the primary outcome of TLF, as well as other adverse cardiac outcome endpoints at 1-year follow-up, including cardiac and all causes mortality. The rate of stent thrombosis and target vessel MI did not differ between groups. After adjustment for differences in clinical and angiographic characteristics, patients with PAD treated with contemporary thin strut DES did not have significant higher risk of stent thrombosis, target vessel MI, or TV/TL revascularization compared to patients without PAD. However, the higher risk of TLF (47% added risk), POCE (33% added risk), all-cause death (75% added risk) and cardiac death (114% added risk) associated with PAD persisted after adjustment.

Previous studies reported PAD to be present in 5–20% of patients undergoing PCI [6,7,17]. The rate of 6.7% found in our study is within the previously reported range, however, the reported rate of PAD is relatively low. It should be noted that we included only patients with previous diagnosis of PAD. Other studies included asymptomatic PAD, which is less likely to be diagnosed, and still associated with worse clinical outcomes post PCI [18]. Patients with significant CAD and concomitant PAD had significantly more risk factors, such as older age, diabetes, hypertension, hyperlipidemia, stroke, and chronic renal disease. This observation was confirmed in our study. We found that patients with PAD were older, with a higher prevalence of cardiovascular risk factor and comorbidities. There were significant procedural differences between patients with and without PAD. Patients with PAD were more likely to undergo femoral PCI, as well as LMCA or complex PCI (ostial lesion, bifurcation, calcified lesions). Patients in the PAD group underwent PCI to more lesions, with higher rates of small vessel PCI.

Earlier studies, in patients treated by PCI with BMS, reported worse cardiovascular outcomes including higher rates of target lesion and target vessel revascularization and MI, as well as increased short- and longer-term mortality in patients with PAD [11,17]. Meta analyses of eight randomized PCI trials, found an almost 50% increased 1-year mortality risk independently associated with PAD [19]. Compared with BMS, patients with PAD treated with DES had better cardiovascular outcomes (yet still increased risk of 1-year cardiac death, MI and TVR compared to patients without PAD treated with DES) [7].

Table 1
Baseline patient vessel and lesion characteristics.

	Peripheral arterial disease	No peripheral arterial disease	*p*-value
	N = 2255	N = 31,625	
Male	76.8 (1731/2255)	76.4 (24,160/31,625)	0.69
Age, mean ± SD (N)	69.0 ± 10.0 (2255)	63.8 ± 11.3 (31,625)	<0.0001
Diabetes mellitus	44.1 (992/2251)	27.5 (8647/31,430)	<0.0001
Insulin dependent diabetes mellitus	12.5 (282/2251)	5.2 (1635/31,430)	<0.0001
Non-insulin dependent diabetes mellitus	31.5 (709/2251)	22.3 (7005/31,430)	<0.0001
Current smoking	23.1 (489/2119)	23.6 (7053/29,870)	0.57
Hypertension	81.6 (1783/2186)	66.2 (19967/30,153)	<0.0001
Hyperlipidemia	73.9 (1589/2149)	58.5 (17050/29,157)	<0.0001
Renal impairment	18.7 (419/2242)	6.4 (2005/31,420)	<0.0001
Body mass index, kg/m^2, mean ± SD (N)	27.7 ± 4.6 (1990)	27.8 ± 4.6 (26,939)	0.39
Previous cerebral disease (CVA/TIA/RIND)	14.3 (319/2228)	4.7 (1480/31,352)	<0.0001
Previous myocardial infarction	32.2 (706/2190)	21.5 (6712/31,167)	<0.0001
Previous PCI	37.3 (830/2226)	24.8 (7774/31,353)	<0.0001
Previous CABG	11.3 (251/2226)	5.0 (1564/31,272)	<0.0001
Left ventricular ejection fraction, mean ± SD (N)	53.1 ± 12.5 (1175)	53.9 ± 1.5 (13,785)	0.05
Chronic coronary syndrome	55.4 (1250/2255)	43.2 (13,656/31,625)	<0.0001
Acute coronary syndrome	44.4 (1002/2255)	56.8 (17,946/31,625)	<0.0001
Unstable angina	12.2 (275/2255)	12.1 (3831/31,625)	0.91
NSTEMI	22.6 (510/2255)	23.6 (7464/31,625)	0.29
STEMI	9.6 (217/2255)	21.0 (6651/31,625)	<0.0001
Arterial access			
Femoral	20.8 (470/2255)	17.6 (5550/31,625)	<0.0001
Radial	75.7 (1706/2255)	80.4 (25437/31,625)	<0.0001
Femoral and radial	2.4 (53/2255)	1.6 (508/31,625)	0.01
Target vessel at index procedure			
Left main	5.5 (125/2255)	3.0 (936/31,625)	<0.0001
Right coronary artery	38.2 (861/2255)	34.0 (10736/31,625)	<0.0001
Left anterior descendants	44.8 (1009/2255)	52.4 (16560/31,625)	<0.0001
Left circumflex	29.2 (658/2255)	27.9 (8832/31,625)	0.20
Graft (arterial or saphenous vein)	3.3 (74/2255)	1.1 (342/31,625)	<0.0001
Any ostial lesion	10.4 (234/2255)	7.0 (2221/31,625)	<0.0001
Any long lesion (length ≥25 mm)	26.5 (597/2255)	25.8 (8148/31,625)	0.46
Any small vessel (diameter ≤2.75 mm)	33.7 (760/2255)	28.9 (9144/31,625)	<0.0001
Any bifurcation	14.5 (326/2255)	12.3 (3894/31,625)	<0.01
Calcification (severe or moderate)	26.8 (604/2255)	17.8 (5626/31,625)	<0.0001
Number of lesions identified, mean ± SD (N)	2.2 ± 1.2 (2255)	1.9 ± 1.1 (31,607)	<0.0001
Total number of lesions treated, mean ± SD (N)	1.5 ± 0.8 (2255)	1.4 ± 0.7 (31,625)	<0.0001
Number of successfully implanted stents	1.7 ± 0.9 (2254)	1.6 ± 0.9 (31,533)	<0.0001
Total length successfully implanted stents, mean ± SD (N)	32.0 ± 21.1 (2245)	31.2 ± 19.6 (31,483)	0.55

Other data from the first-generation DES era reports conflicting outcomes. One study found no short and long term mortality difference associated with PAD [20], while others found increase post-PCI cardiovascular morbidity and up to 2-fold increased all-cause mortality in patients with PAD [7,21]. A prospective DES-registry found PAD to be an independent risk factor for all-cause mortality, MI, stent thrombosis, and clinically relevant bleeding [22].

A recently published study from the START registry reported an increased major cardiovascular and cerebrovascular event during 1-year follow up in patients with PAD [23].

A relatively large longitudinal observational study from 2 centers, based on an all-comers PCI registry, which included over 25,000 patients, confirmed the increased risk associated with PAD. However, a large proportion of patients included in this study were treated with

Table 2
Crude rate of clinical outcomes up to 1 year.

	Peripheral arterial disease	No peripheral arterial disease	*p*-value
	N = 2147	N = 30,053	
Target lesion failure	6.2 (134/2147)	3.0 (901/30,053)	<0.0001
Target vessel failure	6.9 (147/2147)	3.5 (1056/30,053)	<0.0001
POCE	11.0 (237/2147)	6.3 (1897/30,053)	<0.0001
Any death	5.5 (118/2147)	1.8 (544/30,053)	<0.0001
Cardiac death	3.8 (82/2147)	1.1 (319/30,053)	<0.0001
Any myocardial infarction	1.7 (36/2147)	1.2 (364/30,053)	0.06
Target vessel myocardial infarction	1.3 (27/2147)	0.9 (272/30,053)	0.10
Any CD TVR	3.3 (70/2147)	2.3 (679/30,053)	<0.01
Any CD TLR	2.5 (53/2147)	1.7 (495/30,053)	<0.01
Stent thrombosis (definite/probable)	1.0 (21/2147)	0.6 (191/30,053)	0.06

POCE: patient oriented composite endpoint (all death, all myocardial infarction and any revascularization); CD: clinically driven; TVR: target vessel revascularization; TVR: target vessel revascularization.

Table 3
Event rates at 1 year after inverse weighted propensity score adjustment.

	Peripheral vascular disease	No peripheral vascular disease	*p*-value
	N = 2147	N = 30,053	
Target lesion failure	5.9 (126/2147)	4.2 (1275/30,053)	<0.001
Target vessel failure	6.5 (139/2147)	4.9 (1477/30,053)	<0.01
POCE	10.7 (229/2147)	8.6 (2587/30,053)	0.001
Any death	5.1 (110/2147)	2.9 (885/30,053)	<0.0001
Cardiac death	3.5 (76/2147)	1.7 (517/30,053)	<0.0001
Any myocardial infarction	1.6 (35/2147)	1.8 (543/30,053)	0.53
Target vessel myocardial infarction	1.2 (26/2147)	1.3 (384/30,053)	0.77
Any CD TVR	3.1 (67/2147)	2.9 (879/30,053)	0.60
Any CD TLR	2.4 (51/2147)	2.1 (638/30,053)	0.44
Stent thrombosis (definite/probable)	0.9 (20/2147)	0.8 (240/30,053)	0.54

Table 4
Hazard ratio for event rates at 1 year after inverse weighted propensity score adjustment.

	HR	*p*-value
Target lesion failure	1.41 (1.18–1.68)	<0.001
Target vessel failure	1.34 (1.14–1.59)	<0.001
POCE	1.25 (1.10–1.43)	<0.001
Any death	1.75 (1.45–2.13)	<0.0001
Cardiac death	2.03 (1.60–2.58)	<0.0001
Any myocardial infarction	0.95 (0.69–1.33)	0.78
Target vessel myocardial infarction	1.03 (0.70–1.50)	0.90
Any CD TVR	1.14 (0.90–1.43)	0.29
Any CD TLR	1.18 (0.90–1.54)	0.23
Stent thrombosis (definite/probable)	1.12 (0.71–1.78)	0.62

BMS or early-generation DES [6]. According to data derived from a large analysis (>2 million) of patients with MI, PAD was found to be independently associated with worse in-hospital clinical outcomes. However, this study included patients who were treated medically [4].

The difference in the reported significance of PAD in patients undergoing PCI may be accounted for by several reasons. First, most of the reported studies have a relatively limited sample size, which also limits the number of patients with PAD included. In addition, asymptomatic undiagnosed PAD may still have considerable influence on the clinical outcomes [18].

Our study, which analyzed the 1-year clinical outcomes following PCI with contemporary new-generation thin strut DES, confirms the results of previous studies with BMS and first-generation DES. PAD independently increased the 1-year risk of several clinical endpoints such as TLF, POCE, and even cardiac and all-cause mortality. Nevertheless, it should be noted that in our study patients with PAD treated with contemporary thin struts DES did not experience higher adjusted rates of stent thrombosis, CD TL/TV revascularization, or MI.

Over the last decades, clinical outcome of PCI has gradually improved. This can be attributed to better stent platforms, wider use of intracoronary imaging and physiology, improved technical skills and more aggressive adjunct medical treatment. Regardless to this, PAD is still independently associated with increased risk of adverse clinical outcomes, including mortality. Both clinicians and patients should be aware of this increased risk and incorporate it in their decision-making process before performing non urgent procedures. The Compass trial included a relatively large proportion of patients with concomitant PAD and CAD, which benefited from a more aggressive antithrombotic therapy [24,25]. Sub analysis of the LEADER trial suggested that patients with PAD and DM may experience greater reduction in MACE following liraglutide treatment, compared to patients with DM without PAD [26]. Further studies should be performed in order to optimize both medical therapy and secondary prevention in patients with CAD and PAD. Further studies may also clarify whether other contemporary thin struts DES assist in modifying the increased risk of PAD patients undergoing PCI.

4.1. Strengths and limitations

As mentioned, our study is the largest contemporary prospective study, which examines clinical outcomes of patients with PAD undergoing PCI with new-generation, thin struts DES. Our study included over 35,000 patients with 6.7% prevalence of PAD, with pre-specified clinical outcomes and very low rate of patients lost to follow up.

Nevertheless, this study has some limitations. First, although we adjusted for numerous demographics, comorbidities, and other baseline and procedural characteristics, we cannot exclude the presence of other potential confounders. Second, this is an observational study, and the procedural techniques, as well as adjunct medical therapy, were based on operator choice, rather than randomized, as per in randomized controlled trials, or pre-defined. Third, only one type of stent was used, and our finding may not be applicable to other new generation DES. Finally, we assessed the clinical impact of PAD, as defined by the patients' medical record. We do not have ankle-brachial index. In 3318 patients, the status of PAD was not recorded, and this group was not analyzed. Accordingly, patients with asymptomatic or undiagnosed peripheral artery disease were not classified as 'patients with PAD'.

4.2. Conclusion

In this real-world analysis, we report increased cardiovascular risk profile and procedural complexity of patients with PAD and significant CAD undergoing PCI. The population of patients with both CAD and PAD is a higher risk population with an increased risk for (cardiac) mortality. However, patients with PAD treated with contemporary thin struts DES did not experience higher adjusted rates of stent thrombosis, CD TL/TV revascularization or MI. More research is needed to improve the outcomes in this high-risk patient group.

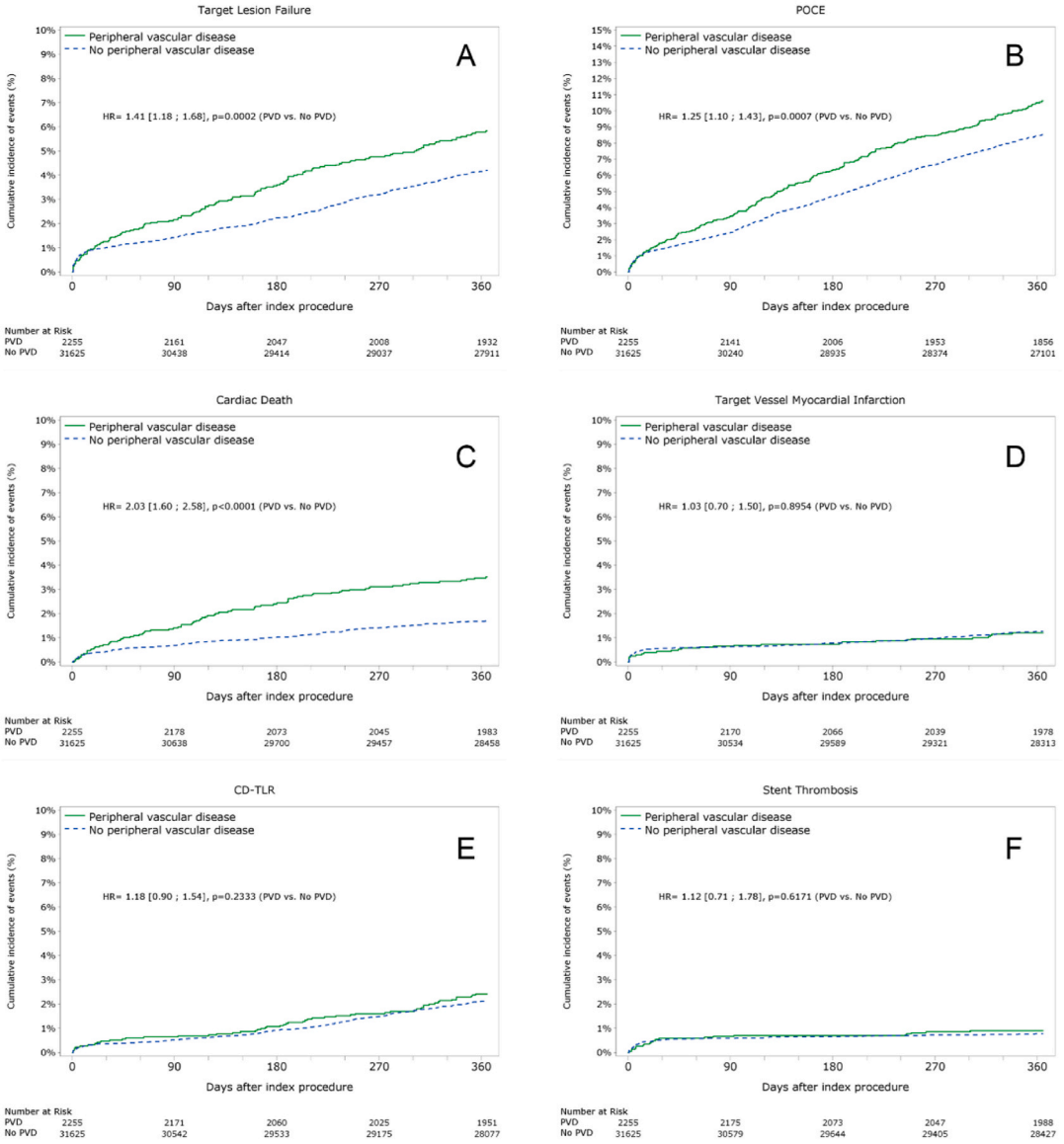

Fig. 2. Adjusted cumulative clinical outcomes after inverse weighted propensity score adjustment.
(A) Target lesion failure; (B) patient oriented composite endpoint; (C) cardiac death; (D) target vessel myocardial infarction; (E) clinically driven target lesion revascularization; (F) stent thrombosis (definite and probable).

Financial support

The e– ULTIMASTER registry was funded by Terumo Europe, Middle East & Africa (Leuven, Belgium).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Ofer Kobo: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Majdi Saada:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Peep Laanmets:** Data curation, Investigation, Writing – review & editing. **Dimitar Karageorgiev:** Data curation, Investigation, Writing – review & editing. **Helen Routledge:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Jim Crowley:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Pascual Baello:** Data curation, Investigation, Writing – review & editing. **Javier Balague Requena:** Data curation, Investigation, Writing – review & editing. **Fabrizio Spanó:** Data curation, Investigation, Methodology, Writing – review & editing. **Luis Perez:** Data curation, Investigation, Writing – review & editing. **Jesus Maria Jimenez Mazuecos:** Data curation, Investigation, Writing – review & editing. **Mamas A. Mamas:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Ariel Roguin:** Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2022.01.007.

References

[1] F.G.R. Fowkes, D. Rudan, I. Rudan, et al., Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis, Lancet (London, England) 382 (9901) (2013) 1329–1340, https://doi.org/10.1016/S0140-6736(13)61249-0.

[2] T.S. Polonsky, M.M. McDermott, Lower extremity peripheral artery disease without chronic limb-threatening ischemia: a review, JAMA 325 (21) (2021) 2188–2198, https://doi.org/10.1001/jama.2021.2126.

[3] F.G.R. Fowkes, L.-P. Low, S. Tuta, J. Kozak, Ankle-brachial index and extent of atherothrombosis in 8891 patients with or at risk of vascular disease: results of the international AGATHA study, Eur. Heart J. 27 (15) (2006) 1861–1867, https://doi.org/10.1093/eurheartj/ehl114.

[4] O. Kobo, T. Contractor, M.O. Mohamed, et al., Impact of pre-existent vascular and poly-vascular disease on acute myocardial infarction management and outcomes: an analysis of 2 million patients from the National Inpatient Sample, Int. J. Cardiol. 327 (2021) 1–8, https://doi.org/10.1016/j.ijcard.2020.11.051.

[5] E.J. Benjamin, S.S. Virani, C.W. Callaway, et al., Heart Disease and Stroke Statistics—2017 Update, vol. 135, Heart, 2017, https://doi.org/10.1161/CIR.0000000000000485.

[6] L. Perl, T. Bental, H. Vaknin-Assa, et al., Independent impact of peripheral artery disease on percutaneous coronary intervention, J. Am. Heart Assoc. 9 (24) (2020), e017655, https://doi.org/10.1161/JAHA.120.017655.

[7] J. Ramzy, N. Andrianopoulos, L. Roberts, et al., Outcomes in patients with peripheral vascular disease following percutaneous coronary intervention, Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv 94 (4) (2019) 588–597, https://doi.org/10.1002/ccd.28145.

[8] T. Ishihara, K. Yamaji, O. Iida, et al., Impact of peripheral artery disease on short-term outcomes after percutaneous coronary intervention: a report from Japanese nationwide registry, PLoS One 15 (10) (2020), e0240095, https://doi.org/10.1371/journal.pone.0240095.

[9] T. Nakahashi, H. Tada, K. Sakata, et al., Impact of decreased ankle-brachial index on 30-day bleeding complications and long-term mortality in patients with acute coronary syndrome after percutaneous coronary intervention, J. Cardiol. 74 (2) (2019) 116–122, https://doi.org/10.1016/j.jjcc.2019.01.008.

[10] T. Nakahashi, H. Tada, K. Sakata, et al., Impact of concomitant peripheral artery disease on contrast-induced acute kidney injury and mortality in patients with acute coronary syndrome after percutaneous coronary intervention, Heart Ves. 35 (10) (2020) 1360–1367, https://doi.org/10.1007/s00380-020-01614-z.

[11] M. Singh, R.J. Lennon, D. Darbar, B.J. Gersh, D.R.J. Holmes, C.S. Rihal, Effect of peripheral arterial disease in patients undergoing percutaneous coronary intervention with intracoronary stents, Mayo Clin. Proc. 79 (9) (2004) 1113–1118, https://doi.org/10.4065/79.9.1113.

[12] O. Kobo, M. Saada, S.R. Meisel, et al., Modern stents: where are we going? Rambam Maimonides Med J 11 (2) (2020) https://doi.org/10.5041/RMMJ.10403.

[13] M.O. Mohamed, J. Polad, D. Hildick-Smith, et al., Impact of coronary lesion complexity in percutaneous coronary intervention: one-year outcomes from the large, multicentre e-Ultimaster registry, *EuroIntervention J Eur Collab with Work Gr Interv Cardiol Eur Soc Cardiol*. June (2020), https://doi.org/10.4244/EIJ-D-20-00361.

[14] A. Chisari, A.M. Pistritto, R. Piccolo, A. La Manna, G.B. Danzi, The ultimaster biodegradable-polymer sirolimus-eluting stent: an updated review of clinical evidence, Int. J. Mol. Sci. 17 (9) (2016), https://doi.org/10.3390/ijms17091490.

[15] D.E. Cutlip, S. Windecker, R. Mehran, et al., Clinical end points in coronary stent trials: a case for standardized definitions, Circulation 115 (17) (2007) 2344–2351, https://doi.org/10.1161/CIRCULATIONAHA.106.685313.

[16] P. Vranckx, D.E. Cutlip, R. Mehran, et al., Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies, EuroIntervention J Eur Collab with Work Gr Interv Cardiol Eur Soc Cardiol 5 (7) (2010) 871–874, https://doi.org/10.4244/eijv5i7a146.

[17] E. Nikolsky, R. Mehran, G.S. Mintz, et al., Impact of symptomatic peripheral arterial disease on 1-year mortality in patients undergoing percutaneous coronary interventions, J Endovasc Ther an Off J Int Soc Endovasc Spec 11 (1) (2004) 60–70, https://doi.org/10.1177/152660280401100108.

[18] S. Nakata, Y. Yokoi, R. Matsumoto, et al., Long-term cardiovascular outcomes following ischemic heart disease in patients with and without peripheral vascular disease, Osaka City Med. J. 54 (1) (2008) 21–30.

[19] J. Saw, D.L. Bhatt, D.J. Moliterno, et al., The influence of peripheral arterial disease on outcomes: a pooled analysis of mortality in eight large randomized percutaneous coronary intervention trials, J. Am. Coll. Cardiol. 48 (8) (2006) 1567–1572, https://doi.org/10.1016/j.jacc.2006.03.067.

[20] S. Midwall, R.V. Swaminathan, K. Charitakis, et al., Impact of peripheral vascular disease on short- and long-term outcomes in patients undergoing non-emergent percutaneous coronary intervention in the drug-eluting stent era, J. Invasive Cardiol. 25 (3) (2013) 132–136.

[21] I. Al-Zakwani, E. Al Siyabi, N. Alrawahi, et al., Association between peripheral artery disease and major adverse cardiovascular events in patients with acute coronary syndrome: findings from the gulf COAST registry, Med Princ Pract Int J Kuwait Univ Heal Sci Cent 28 (5) (2019) 410–417, https://doi.org/10.1159/000497790.

[22] R. Gupta, A.J. Kirtane, M.O. Ozan, et al., Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents in subjects with peripheral arterial disease: analysis from the ADAPT-DES study (assessment of dual antiplatelet therapy with drug-eluting stents), Circ Cardiovasc Interv 10 (3) (2017), https://doi.org/10.1161/CIRCINTERVENTIONS.116.004904.

[23] P. Gresele, G. Guglielmini, M. Del Pinto, et al., Peripheral arterial disease has a strong impact on cardiovascular outcome in patients with acute coronary syndromes: from the START Antiplatelet registry, Int. J. Cardiol. 327 (2021) 176–182, https://doi.org/10.1016/j.ijcard.2020.10.079.

[24] J.W. Eikelboom, S.J. Connolly, J. Bosch, et al., Rivaroxaban with or without aspirin in stable cardiovascular disease, N. Engl. J. Med. 377 (14) (2017) 1319–1330, https://doi.org/10.1056/NEJMoa1709118.

[25] S.S. Anand, J.W. Eikelboom, L. Dyal, et al., Rivaroxaban plus aspirin versus aspirin in relation to vascular risk in the COMPASS trial, J. Am. Coll. Cardiol. 73 (25) (2019) 3271–3280, https://doi.org/10.1016/j.jacc.2019.02.079.

[26] S. Verma, D.L. Bhatt, S.C. Bain, et al., Effect of liraglutide on cardiovascular events in patients with type 2 diabetes mellitus and polyvascular disease: results of the LEADER trial, Circulation 137 (20) (2018) 2179–2183, https://doi.org/10.1161/CIRCULATIONAHA.118.033898.