

# Paclitaxel-coated balloons for femoropopliteal peripheral arterial disease: final five-year results of the IN.PACT Global Study

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## KEYWORDS

- calcified stenosis
- drug-eluting balloon
- femoropopliteal disease
- in-stent restenosis
- total occlusion

## Abstract

**Background:** Numerous randomised controlled trials (RCTs) have demonstrated the superiority of paclitaxel drug-coated balloons (DCBs) over non-coated angioplasty balloons for treatment of femoropopliteal peripheral arterial disease (PAD). There is a paucity of clinical evidence in more complex patients who are often excluded from RCTs and long-term data up to 5 years are very limited in PAD revascularisation studies.

**Aims:** This is a report of the 5-year outcomes from the prospective, single-arm, international IN.PACT Global Study. The IN.PACT Admiral DCB was evaluated for femoropopliteal atherosclerotic disease treatment in a real-world patient population.

**Methods:** In total, 1,535 patients were enrolled at 64 international sites. The prespecified clinical cohort included 1,406 patients with claudication or rest pain. Patients were evaluated up to 5 years for the occurrence of adverse events and clinically driven target lesion revascularisations (CD-TLR).

**Results:** The mean lesion length was 12.1±9.5 cm in 1,774 lesions, 18.0% had in-stent restenosis, 35.5% were total occlusions and 68.7% were calcified. Per independent clinical events committee adjudication, the Kaplan-Meier estimate of freedom from CD-TLR up to 5 years was 69.4%, and the restricted mean survival time to first CD-TLR was 1,470.1 days. Outcomes were similar for males and females; freedom from CD-TLR was 69.1% in females and 69.6% in males (p=0.602). The cumulative incidence of major adverse events for the clinical cohort was 45.9% and freedom from all-cause mortality with the vital status update was 78.9% up to 5 years.

**Conclusions:** The IN.PACT Admiral DCB demonstrated safe and durable outcomes in real-world participants with complex femoropopliteal disease. ClinicalTrials.gov: NCT01609296

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## Abbreviations

<b>ABI</b>	ankle-brachial index
<b>ASA</b>	acetylsalicylic acid (aspirin)
<b>BMI</b>	body mass index
<b>CD-TLR</b>	clinically driven target lesion revascularisation
<b>CD-TVR</b>	clinically driven target vessel revascularisation
<b>CEC</b>	clinical events committee
<b>CI</b>	confidence interval
<b>DAPT</b>	dual antiplatelet therapy
<b>DCB</b>	drug-coated balloon
<b>EQ-5D</b>	EuroQol 5 dimensions
<b>HR</b>	hazard ratio
<b>ISR</b>	in-stent restenosis
<b>KM</b>	Kaplan-Meier
<b>MAE</b>	major adverse event
<b>PAD</b>	peripheral arterial disease
<b>PTA</b>	percutaneous transluminal angioplasty
<b>RCC</b>	Rutherford clinical category
<b>RCT</b>	randomised controlled trial
<b>RMST</b>	restricted mean survival time
<b>RVD</b>	reference vessel diameter
<b>SFA</b>	superficial femoral artery
<b>TLR</b>	target lesion revascularisation

## Introduction

The treatment of peripheral arterial disease (PAD) in patients with multiple comorbidities is challenging and remains a global health concern, impacting approximately 236 million people worldwide<sup>1</sup>. Drug-coated balloons (DCB) emerged as a novel endovascular treatment option a decade ago.

Numerous randomised controlled trials (RCTs)<sup>2-6</sup> and a meta-analysis<sup>7</sup> have demonstrated the superiority of DCB over uncoated percutaneous transluminal angioplasty (PTA) for the treatment of PAD in the femoropopliteal segment. Patients with more complex lesions, such as in-stent restenosis (ISR), lesions longer than 18 cm, and lesions with significant calcification, are usually excluded from RCTs, thus there are limited data on real-world patients. There are also few prospective studies on endovascular treatments for PAD with long-term ( $\geq 5$  years) evidence<sup>2,8-11</sup>.

The IN.PACT Global Study was a large prospective study that assessed the IN.PACT Admiral DCB (Medtronic) for the treatment of atherosclerotic disease of the superficial femoral artery (SFA) and/or the popliteal artery in a real-world patient population. The study was designed with very broad selection criteria, allowing for the inclusion of a complex patient population. This article reports on the final 5-year outcomes of the full clinical cohort.

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## Methods

The IN.PACT Global Study was a prospective, international, single-arm study. It evaluated the safety and effectiveness of the IN.PACT Admiral DCB for the treatment of obstructive disease in femoropopliteal (including the entire popliteal artery) arteries caused by

atherosclerosis. Details on the trial design and outcomes up to 3 years have been reported previously<sup>12-14</sup>. Briefly, the inclusion criteria included Rutherford clinical category (RCC) 2-4 (claudication and/or ischaemic rest pain). *De novo* and restenotic lesions (including ISR) were permitted if they were severely stenosed or occluded and  $\geq 2$  cm in length. Relevant exclusion criteria included aneurysmatic and acute thrombotic lesions. The primary effectiveness endpoint was freedom from clinically driven target lesion revascularisation (CD-TLR) within 12 months. CD-TLR was defined as any reintervention of the target lesion(s) because of symptoms or a drop in the ankle-brachial index (ABI) of  $\geq 20\%$  or  $>0.15$  when compared with the post-index procedure ABI. The primary safety composite endpoint was freedom from device- and procedure-related death up to 30 days, and freedom from major target limb amputation and clinically driven target vessel revascularisation (CD-TVR) within 12 months. A major adverse event (MAE) was defined as all-cause mortality, major target limb amputation, CD-TVR, or thrombosis at the target lesion site up to 5 years. Results from the 1-, 2-, and 3-year follow-up periods have been reported<sup>12-14</sup>.

Dual antiplatelet therapy (DAPT) was required consistent with standard clinical practice, including aspirin (ASA) indefinitely and DAPT for 1 month (3 months for stented patients). Participants were followed up at discharge, 30 days, 6 months, 12 months and then annually up to 5 years. Follow-up evaluations, including medication compliance, were conducted via clinical visits up to 3 years. At years 4 and 5, follow-up was conducted over the phone to evaluate the incidence of adverse events, including revascularisations. To improve ascertainment of mortality, investigational sites were also asked to obtain vital status from study participants who withdrew or were lost to follow-up to verify safety information obtained as part of the original study design. Vital status results are specifically labelled as such when these additional data have been included.

An independent Clinical Events Committee (CEC; Syntactx) adjudicated all MAEs including death, major target limb amputation, CD-TVR, CD-TLR, and thrombosis at the target lesion site. The statistical methods were designed by the study sponsor and documented prospectively in the clinical trial protocol.

The study was conducted in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki and all applicable country laws. The institutional review board or ethics committee at each participating site approved the study protocol, and informed consent was obtained from all participants prior to enrolment.

## STATISTICS

Baseline characteristics and outcomes are summarised descriptively using percentages and frequencies for categorical variables and the mean, standard deviation, and number of observations for continuous variables. Time-to-event outcomes are summarised using the Kaplan-Meier (KM) method. Participants were censored at the time of withdrawal, loss to follow-up, or death. Confidence intervals (95% CI) were derived for time-to-event outcomes using the log-log transformation. Outcomes are also summarised using the

restricted mean survival time (RMST) and 95% CI with a time horizon of 1,800 days. The RMST is the average time to an event within a fixed time period and corresponds to the area under the survival curve from the start of follow-up to the fixed time point. Baseline demographics, clinical characteristics, and outcomes are reported or analysed on a patient basis and lesion characteristics are reported on a lesion basis. Data were analysed according to the study protocol. A patient was included in the analysis if the study DCB was introduced into the sheath and after the guidewire had successfully passed through the target lesion. Annual cut-offs for the statistical analysis used 360 days per year (e.g., 1,800 days for the 5-year cut-off). The denominator for binary endpoints used the sum of those with an event and those with follow-up of at least 1,740 days. A pre-specified subgroup analysis by gender is also presented.

An exploratory analysis of the association between baseline characteristics and the time to CD-TLR and MAE was computed using a Cox proportional hazards model for the full clinical cohort and each gender subgroup separately. Univariate models were computed first followed by a multivariable model that was derived using stepwise regression. The entry and stay criteria for the stepwise regression were 0.2 and 0.1, respectively, starting with the set of variables that had a p-value <0.2 in the univariate models. Single imputation stratified by gender was performed for missing data in the multivariable analysis for variables with less than 15% missingness, using the mean for continuous variables and the mode for categorical and binary variables. DAPT was included as a time-varying variable to allow for potential changes in use between discharge and 30 days.

No adjustment was made for multiple comparisons, and the level of statistical significance was set at 0.05. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

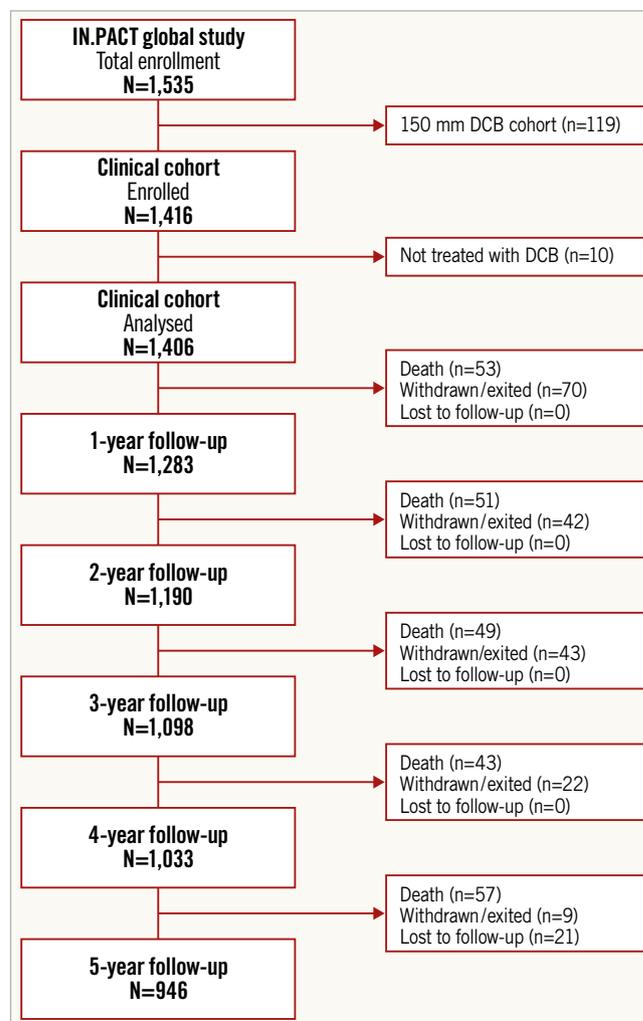
## Results

From May 2012 to March 2014, 1,535 patients were enrolled at 64 global centres. This report includes outcomes on 1,406 participants who were treated with the DCB. Patients from the 150 mm DCB cohort were enrolled non-consecutively and were excluded from the current analysis. The participant flow chart up to 5 years is shown in **Figure 1**. By the end of the 5-year follow-up window (1,885 days), 253 participants died, 186 withdrew or exited the study, 21 were lost to follow-up, and 28 did not have follow-up completed by the close of the study. Five-year data on 97.0% of the 946 eligible participants were obtained.

Baseline demographics and lesion characteristics have been previously reported<sup>12-14</sup> and are shown in **Table 1**. Medication compliance was collected up to 3 years; data are provided in **Supplementary Table 1**.

### EFFECTIVENESS AND SAFETY OUTCOMES

The KM estimate of freedom from CD-TLR up to 5 years was 69.4% (95% CI: 66.7%-72.0%) (**Central illustration, Figure 2A**). The RMST to first CD-TLR up to 5 years was 1,470.1 days (95% CI: 1,439.2-1,501.0 days).



**Figure 1.** IN.PACT Global study patient flowchart up to 5 years. Follow-up windows were 365 days per year with windows of  $\pm 60$  days. N represents the number of participants eligible for evaluation at each timepoint. DCB: drug-coated balloon

The cumulative incidence of MAEs based on the KM estimate up to 5 years was 45.9% (95% CI: 43.2%-48.7%) including the following: arterial thrombosis 5.7% (95% CI: 4.6%-7.1%), major target limb amputation 1.7% (95% CI: 1.1%-2.6%), CD-TVR 31.9% (95% CI: 29.3%-34.6%) and all-cause death 19.5% (95% CI: 17.4%-21.8%).

In total, 19 participants underwent major target limb amputation. The mean time to amputation was 27.5 $\pm$ 19.1 months. Details on the 12 amputations occurring within 3 years post-procedure have been previously reported<sup>13</sup>. Seven amputations occurred >3 years post-procedure; of these, all had 2 or more risk factors or concomitant atherosclerotic disease manifestations including diabetes mellitus (n=5), hypertension (n=5), hyperlipidaemia (n=6), coronary artery disease (n=4), renal insufficiency (n=2), currently smoking (n=2) and below-the-knee disease on the target limb (n=4). Four were classified as RCC 3 at baseline, 1 was RCC 4, and 2 were RCC 5. Five had a CD-TLR prior to amputation, and

**Table 1. Baseline and procedural characteristics.**

Patient characteristics		Clinical cohort (N=1,406 patients) (N=1,774 lesions)
Age (years)		68.6±10.1
Male		67.8% (953/1,406)
Obesity (BMI ≥30 kg/m <sup>2</sup> )		20.5% (285/1,391)
Hypertension		83.4% (1,169/1,401)
Hyperlipidaemia		70.5% (960/1,362)
Diabetes mellitus		39.9% (560/1,402)
Insulin-dependent diabetes mellitus		17.8% (249/1,402)
Coronary artery disease		40.5% (540/1,332)
Carotid artery disease		20.2% (241/1,196)
Current smoker		31.8% (447/1,406)
Renal insufficiency*		11.2% (136/1,216)
On dialysis		2.7% (38/1,396)
Previous peripheral revascularisation		52.4% (737/1,406)
Rutherford clinical category	1 <sup>†</sup>	0.1% (1/1,403)
	2	31.1% (436/1,403)
	3	57.7% (810/1,403)
	4	8.6% (120/1,403)
	5 <sup>†</sup>	2.6% (36/1,403)
ABI (mmHg ratio)		0.7±0.2
<b>Lesion characteristics</b>		
Lesion length (cm)		12.1±9.5
Diameter stenosis (%)		88.8±12.3
Occluded		35.5% (630/1,774)
Lesion type	<i>De novo</i>	74.3% (1,318/1,774)
	Restenotic (non-stented)	7.7% (136/1,774)
	In-stent restenosis	18.0% (320/1,774)
Reference vessel diameter (mm)		5.2±0.7
Calcification		68.7% (1,217/1,772)
Severe		10.2% (181/1,772)
Lesion location <sup>‡</sup>	Superficial femoral artery	87.6% (1,554/1,774)
	Proximal popliteal artery	27.3% (484/1,774)
<b>Procedural characteristics</b>		
Predilatation		78.0% (1,097/1,406)
Post-dilatation		35.1% (491/1,397)
Provisional stenting		21.2% (373/1,762)
Dissections	0	56.7% (1,006/1,773)
	A-C	35.4% (628/1,773)
	D-F	7.8% (139/1,773)

Data are % (n/N) or mean±standard deviation. \*Baseline serum creatinine ≥1.5 mg/dl. †Protocol deviations, patients enrolled and included in analyses. ‡Multiple lesion locations are reported in a single target limb, the total lesion locations could be more than the total number of target limbs. ABI: ankle-brachial index; BMI: body mass index

5 died within the duration of the study, ranging from 8 days to 386 days post-amputation.

There were 253 deaths reported within the 5-year follow-up window (1,885 days). Deaths occurring within 3 years of the index procedure and the causes of those deaths have been previously

reported<sup>13</sup>. Ninety-seven deaths were reported between 3 years and 5 years (1,800 days) post-procedure, and 9 deaths occurred after the cut-off of 1,800 days, but within the end of the 5-year follow-up window of 1,885 days. Per CEC adjudication, none of the deaths occurring within the 3-5 year window were procedure-related. One death was classified as device-related; the cause of death was right limb infection and sepsis, and the patient died 1,516 days post-procedure. CEC adjudicated outcomes are shown in **Table 2**.

**Table 2. CEC adjudicated outcomes through 5 years\*\*†.**

Outcome	Rate
CD-TLR	30.6% (366)
Any TLR	31.3% (374)
Safety composite <sup>‡</sup>	67.4% (392)
Major adverse event composite	45.9% (589)
Death (all-cause)	19.5% (244)
CD-TVR	31.9% (381)
Major target limb amputation	1.7% (19)
Thrombosis	5.7% (73)

\*Up to 1,800 days post-procedure. †Per Kaplan-Meier estimate (number of patients with an event). ‡Defined as freedom from device- and procedure-related death through 30 days, major target limb amputation and CD-TVR within 5 years, per KM analysis. CD-TLR: clinically driven target lesion revascularisation; CD-TVR: clinically driven target vessel revascularisation; CEC: clinical events committee; TLR: target lesion revascularisation

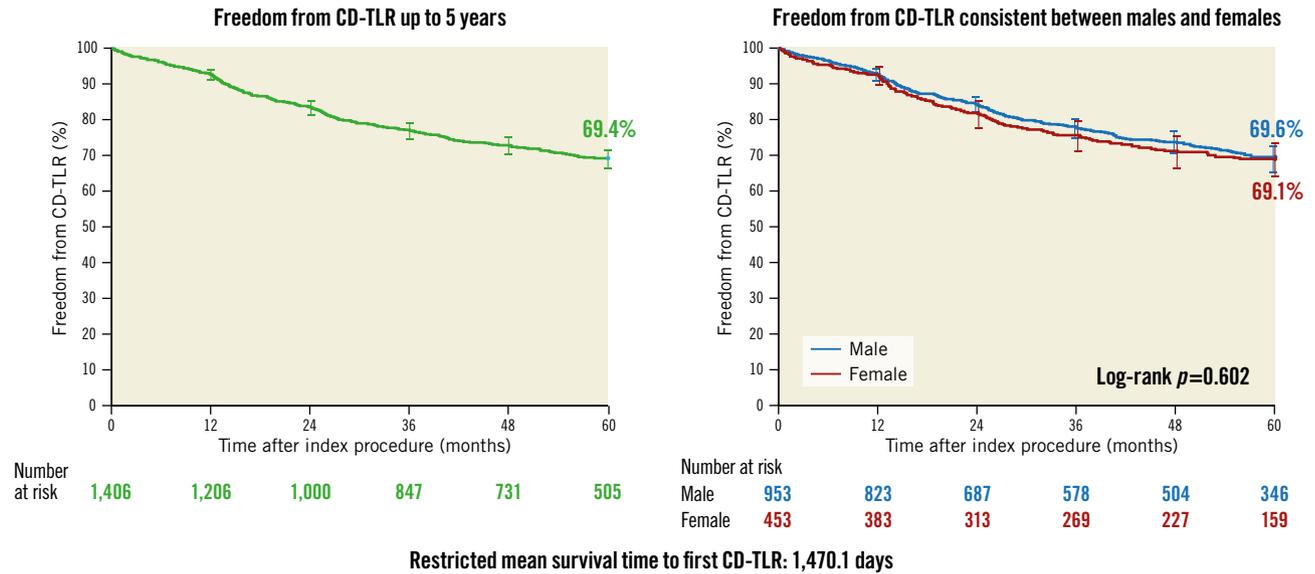
After the vital status update, 96.4% (1,355/1,406) of the participants had vital status information, which resulted in 78.9% (95% CI: 76.7%-81.0%) freedom from all-cause mortality per the KM estimate (**Figure 2B**). Deaths found through the vital status data collection were not adjudicated by the CEC due to lack of adequate source documentation availability.

A summary of safety and effectiveness outcomes for the IN.PACT Global Study up to 5 years is reported in **Table 3**.

### MULTIVARIABLE ANALYSES

Exploratory multivariable Cox proportional hazards analyses (MVA) were employed to identify the predictors of CD-TLR, MAE, and all-cause mortality. Statistically significant key factors are listed below. All variables selected for the final model are shown in **Supplementary Figure 1-Supplementary Figure 3**. Univariate analysis outcomes are included in **Supplementary Table 2-Supplementary Table 4**. Variables associated with an increased risk of CD-TLR included ISR, moderate-to-severe target lesion calcification, longer lesion length, and higher post-procedure residual diameter restenosis. A larger reference vessel diameter (RVD) and having a target lesion confined to the SFA (vs extending into the popliteal) were associated with a reduced risk of CD-TLR. Variables associated with an increased risk of MAE included RCC ≥4, carotid artery disease, and coronary artery disease. Having a lesion confined to the SFA (vs extending into the popliteal) or a higher EQ-5D (EuroQol 5 dimensions) index score at baseline were associated with a reduced risk

**CENTRAL ILLUSTRATION** Key outcomes up to 5 years from the IN.PACT Global Study.



**Safety composite: 67.4%**

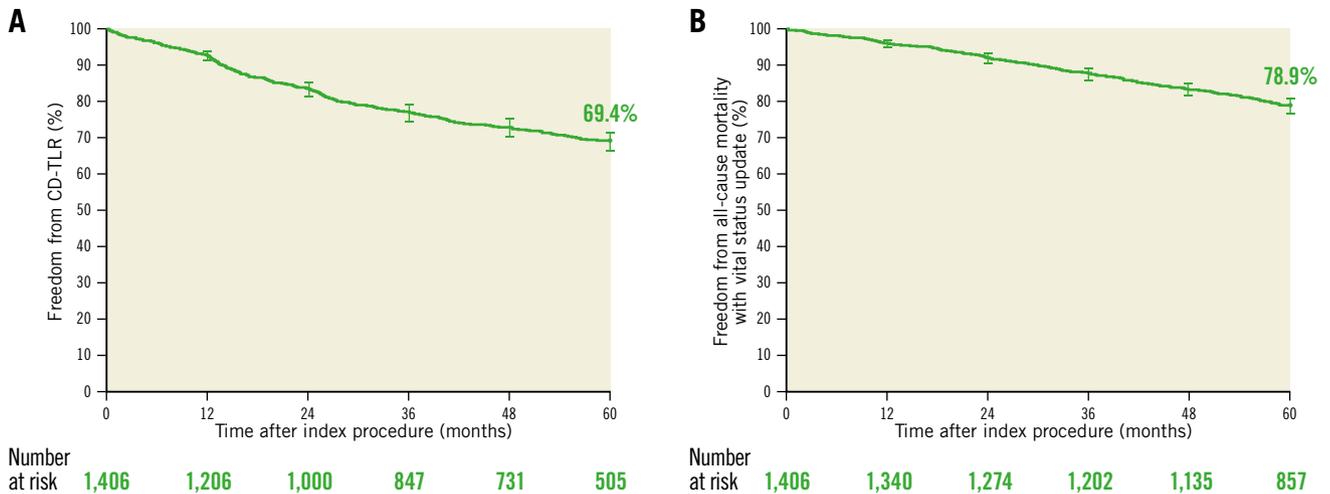
Safety composite defined as freedom from device- and procedure-related mortality within 30 days and freedom from major target limb amputation and clinically driven TVR within 60 months.

**Major adverse event rates through 5 years**

**Death (all-cause)** 19.5%  
**Major target limb amputation** 1.7%  
**Clinically driven TVR** 31.9%  
**Thrombosis** 5.7%

Major adverse events (MAE) defined as a composite of death, major target limb amputation, clinically driven TVR, and thrombosis.

CD-TLR: clinically driven target lesion revascularisation; TVR: target vessel revascularisation



**Figure 2.** Freedom from CD-TLR and all-cause mortality: Kaplan-Meier curve up to 5 years. Bars represent 95% CI. A) Freedom from CD-TLR. B) All-cause mortality that includes additional vital status follow-up data. CD-TLR: clinically driven target lesion revascularisation; CI: confidence interval

**Table 3. Summary of annual outcomes through 5 years.**

Key outcomes					
Kaplan-Meier estimates	1 year	2 years	3 years	4 years	5 years
Freedom from all-cause death with vital status <sup>*†</sup>	96.1%	92.2%	87.8%	83.5%	78.9%
Freedom from CD-TLR <sup>*‡</sup>	92.8%	83.5%	77.1%	73.0%	69.4%
Proportion rates, % (n/N) <sup>§</sup>	1 year <sup>14</sup>	2 years <sup>12‡</sup>	3 years <sup>13</sup>	4 years	5 years
CD-TLR	7.5% (98/1,311)	16.8% (214/1,276)	22.9% (289/1,262)	26.1% (330/1,266)	30.1% (366/1,215)
Major adverse events	12.0% (157/1,311)	25.5% (325/1,276)	34.8% (439/1,262)	40.7% (515/1,266)	48.5% (589/1,215)
All-cause death	3.5% (46/1,311)	7.9% (101/1,276)	11.6% (147/1,262)	15.5% (196/1,266)	20.1% (244/1,215)
CD-TVR	8.1% (106/1,311)	17.6% (224/1,276)	23.7% (299/1,262)	26.9% (341/1,266)	31.4% (381/1,215)
Major target limb amputation	0.2% (3/1,311)	0.7% (9/1,276)	1.0% (12/1,262)	1.1% (14/1,266)	1.6% (19/1,215)
Thrombosis	2.9% (38/1,311)	4.5% (57/1,276)	5.6% (71/1,262)	5.6% (71/1,266)	6.0% (73/1,215)

<sup>\*</sup>Kaplan-Meier estimates based on final locked database. <sup>†</sup>Vital status not CEC adjudicated. <sup>‡</sup>Results updated since the original publication. <sup>§</sup>Data derived from different snapshots from the database; site monitoring and collection of additional data between follow-up timepoints impacted the sample size at each time point. CD-TLR: clinically driven target lesion revascularisation; CD-TVR: clinically driven target vessel revascularisation

of MAE. Variables associated with an increased risk of all-cause mortality (with vital status update) included having previous target limb amputation, diabetes and older age.

### GENDER ANALYSIS

Prespecified analyses were performed to compare outcomes in males and females for CD-TLR and MAEs. Freedom from CD-TLR per KM estimate (**Figure 3A**) up to 5 years was not different between males and females (log-rank  $p=0.602$ ). The RMST to CD-TLR up to 5 years was 1,480.9 (95% CI: 1,444.1-1,517.7) days in males and 1,446.9 (95% CI: 1,390.3-1,503.6) days in females ( $p=0.325$ ).

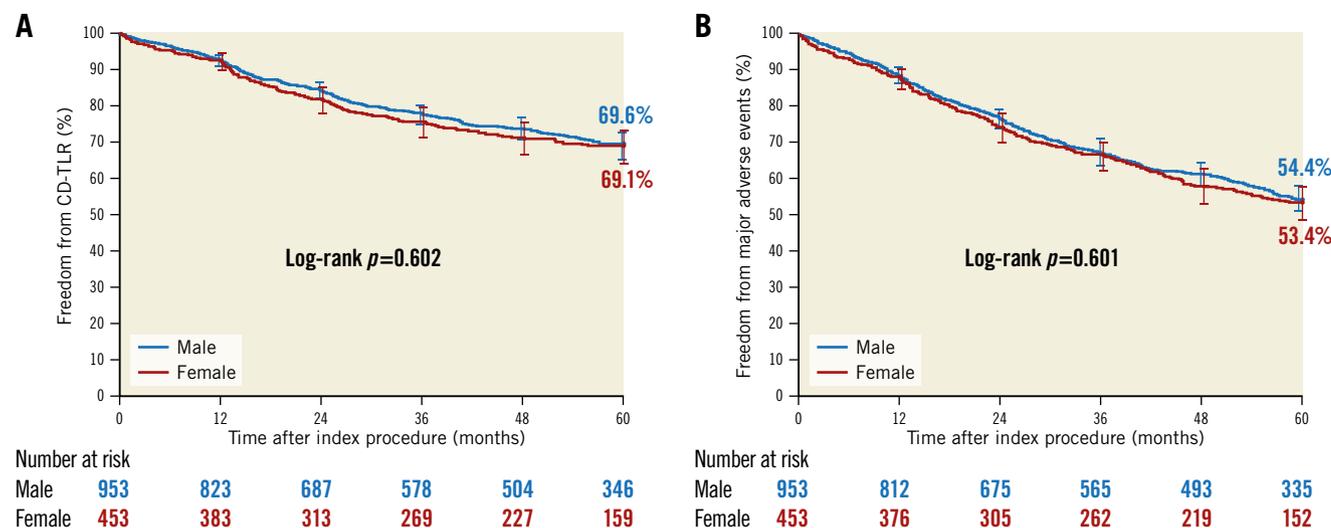
Freedom from MAE per the KM estimate (**Figure 3B**) was not different between males and females (log-rank  $p=0.601$ ). Females experienced a significantly greater number of thrombotic events (cumulative incidence based on KM of 7.5% vs 4.9%; log-rank

$p=0.045$ ); other components of the endpoint were numerically similar and statistically non-significant.

In univariate analyses, gender was not significantly associated with CD-TLR (**Supplementary Table 2**) or MAE (**Supplementary Table 3**). A non-significant trend toward lower all-cause mortality including vital status data was observed in male patients versus female patients (HR 0.81, 95% CI: 0.63-1.03;  $p=0.08$ ) (**Supplementary Table 4**) in the univariate analysis. However, gender was not selected in the final MVA model for all-cause mortality including vital status data. Exploratory MVAs show factors in the subgroup of males and females associated with risk of CD-TLR (**Supplementary Figure 4**) and MAEs (**Supplementary Figure 5**).

### Discussion

The research and development of DCBs has been progressing steadily for the last 2 decades. Recently, DCBs achieved the



**Figure 3.** Subgroup analysis of freedom from CD-TLR and MAE up to 5 years. A) Freedom from CD-TLR in males and females not numerically or statistically different (log-rank  $p=0.602$ ); B) Freedom from an MAE was not numerically or statistically different in males and females, (log-rank  $p=0.601$ ). CD-TLR: clinically driven target lesion revascularisation

highest level of recommendation (Class 1) per the Society for Cardiovascular Angiography and Interventions guidelines<sup>15</sup>. The data presented here add valuable evidence on the use of DCBs in a more complex patient population with 5-year follow-up and rigorous study conduct. The IN.PACT Global Study is the largest independently adjudicated real-world study of endovascular interventions to treat PAD to date. The uniquely broad selection criteria resulted in the inclusion of complex lesions and patients with known risk factors that contribute to disease progression. Additionally, follow-up up to 5 years is uncommon in this space, and high follow-up compliance was achieved through vigilant study management and oversight by each participating centre.

The 5-year freedom from CD-TLR rate observed in this study was 69.4%, which is lower than the 74.5% rate observed in the DCB arm and higher than the 65.3% rate observed in the PTA arm of the IN.PACT SFA randomised trial<sup>8,16</sup>. However, the randomised trial had tighter selection criteria and enrolled fewer complex lesions. As compared to the IN.PACT Global Study, the DCB arm of IN.PACT SFA had a shorter mean lesion length (8.9 cm vs 12.1 cm), fewer total occlusions (25.8% vs 35.5%), less calcification (59.3% vs 68.7%), and no ISR lesions as they were excluded, whereas 18.0% of lesions in IN.PACT Global Study were ISR<sup>16</sup>. The randomised THUNDER trial reported a 5-year cumulative TLR rate of 20.8% in the DCB cohort versus 55.6% in the PTA cohort, again in a patient cohort characterised by shorter lesion lengths (7.5 cm), fewer total occlusions (27%), and less calcification (50%) than observed in the IN.PACT Global Study<sup>11,17</sup>.

As observed by an exploratory MVA in this study and others, ISR, calcification, a smaller RVD, and a longer lesion length are consistently associated with an increased risk for CD-TLR. The high prevalence of these challenging characteristics allowed for a critical assessment of this DCB's efficacy beyond the initial tightly controlled randomised trials.

The use of adjunctive atherectomy or vessel preparation devices was not permitted in this study, in order to limit bias. However, vessel preparation may have further improved outcomes in lesions with a heavier plaque burden or with more calcification. It was hypothesised that the removal of plaque may increase the homogeneity of the drug application onto the vessel wall and increase diffusion into the vessel wall layers. The DEFINITIVE AR pilot study<sup>18</sup>, which also enrolled more complex lesions, tested this theory. A *post hoc* analysis showed a numerically higher 1-year patency rate observed in lesions where  $\leq 30\%$  residual stenosis was obtained following directional atherectomy prior to DCB treatment, as compared to lesions that had more than 30% stenosis remaining in the vessel before the DCB was delivered (84.2% vs 77.8%). Only 1 patient (5.3%) enrolled in the severe calcification arm required a stent, and no stents were needed in the randomised directional atherectomy plus DCB arm. The provisional stenting rate per lesion in the IN.PACT Global Study was 21.2%, suggesting directional atherectomy should be considered when stent avoidance is a priority<sup>18</sup>.

The efficacy of DCBs in women has not been consistently demonstrated, and very little long-term outcomes data have been reported. In the LEVANT 2 trial, women had lower 1-year patency rates in the DCB arm versus the control arm (56.4% DCB vs 61.4% PTA), but superior patency was observed in men treated with a DCB over PTA (70.6% DCB vs 48.4% PTA)<sup>19</sup>. In the DCB arm of the THUNDER trial, women had a higher rate of TLR at 5 years (38% vs 17% in men), but women treated with DCB had a lower cumulative rate of TLR as compared to women treated with PTA (38% vs 52%)<sup>11</sup>.

A recently published *post hoc* analysis of freedom from CD-TLR in the IN.PACT SFA trial showed women treated with DCBs had better outcomes than women in the PTA arm up to 5 years (67.4% for DCB, 52.9% for PTA;  $p=0.049$ )<sup>8</sup>. The gender subgroup analysis conducted in the IN.PACT Global Study showed no difference in freedom from CD-TLR between males and females (69.6% in men and 69.1% in women; log-rank  $p$ -value=0.602). This is consistent with the *post hoc* analysis on sex differences conducted in the IN.PACT SFA randomised trial up to 3 years<sup>20</sup>. Kohi et al reported freedom from CD-TLR in participants treated with the IN.PACT Admiral was 81.1% in women and 86.4% in men ( $p=0.285$ ) at 3 years. The predictors in the MVAs were different in the subgroup analyses of males and females. Significant predictors of CD-TLR up to 3 years for women treated with DCBs were severe calcification, previous ipsilateral revascularisation, absence of hyperlipidaemia, and insulin-dependent diabetes. For men, predictors of increased CD-TLR consisted of a smaller RVD and a higher BMI<sup>20</sup>. In the current study, anticoagulant use at discharge was associated with an increased risk of CD-TLR and MAE in male patients. This association is not likely causal and may be related to underlying comorbidities.

The all-cause mortality rate observed in this study was 20.1%. A review paper that calculated 5-year mortality rates in the same manner reported similar rates in the more restrictively enrolled DCB arms of RCTs, including 15.8% in IN.PACT SFA, 20.3% in LEVANT 2, and 28.1% in the drug-eluting stent arm of the Zilver PTX trial<sup>21</sup>. Causes of death up to 3 years have been previously reported for IN.PACT Global Study but were not captured beyond 3 years<sup>13</sup>. Of note, as compared to the IN.PACT SFA randomised trial<sup>8</sup>, the IN.PACT Global Study enrolled patients with more comorbidities and more complex baseline lesion characteristics. Given the broader selection criteria and inclusion of critical limb ischaemia patients in the IN.PACT Global Study, putting the data into context with epidemiological studies is warranted. As expected, this population is associated with significant mortality, and individual trial rates will vary greatly depending on comorbidities and severity of PAD. Mueller et al reported the 5-year mortality rates of PAD patients  $\geq 75$  years old: 52% in those with diabetes and 38% in those without diabetes<sup>22</sup>. Heikkila et al reported a wide range of 5-year mortality rates when stratified by the type of intervention (open or endovascular) and severity level of PAD. The lowest rate was 24.7% in patients with claudication

treated endovascularly and was highest, at 55.2%, in patients with severe limb ischaemia including tissue loss<sup>23</sup>.

Multivariable predictors of all-cause mortality up to 5 years observed in the IN.PACT Global Study included hyperlipidaemia as having a protective effect, but anticoagulation use was not significant. These results are counterintuitive and may be due to underlying comorbidities of patients prescribed anticoagulation medications. Likewise, having a hyperlipidaemia diagnosis would result in statin use, which has been shown to reduce the risk of mortality<sup>24</sup>.

## Limitations

This was a single-arm study that did not include a control group. The results cannot be directly compared to other study or treatment outcomes. Assessments at years 4 and 5 were limited to CD-TLR, MAEs and mortality and did not include functional outcomes or medication compliance. While this study cohort represents a real-world patient population, the study follow-up requirements may have resulted in a higher medication compliance than might be seen in everyday clinical practice. Finally, the impact of provisional stenting on outcomes requires additional analyses that will be addressed in a future publication.

## Conclusions

These long-term results from this large, international, real-world study add to the growing body of evidence that demonstrates the safety, effectiveness, consistency, and durability of the IN.PACT Admiral DCB for the treatment of femoropopliteal lesions.

### Impact on daily practice

This study provides the first 5-year data on the use of the IN.PACT Admiral drug-coated balloon in real-world participants with complex femoropopliteal disease. Per independent CEC adjudication, the Kaplan-Meier estimate of freedom from CD-TLR up to 5 years was 69.4%. The data observed here validate the previously conducted RCT outcomes in a broader patient population. In-stent restenosis and severe calcification were identified as strong predictors of CD-TLR within 5 years; in these patients, vessel preparation may improve outcomes.

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## Conflict of interest statement

T. Zeller has received honoraria/consulting fees from Abbott Vascular, BIBA Medical, Shockwave, Biotronik, Cook Medical, Eformoral, Philips-Spectranetics, CSI, Intact Vascular, and Bayer; received grants or contracts from Bard, Biotronik, Veryan, Cook, Gore & Associates, Medtronic, Philips, Terumo, Trireme, Shockwave, MedAlliance, B. Braun, Intact Vascular, Boston Scientific, University of Jena, Pluristem, PQ Bypass, Reflow Medical, Ablative Solutions, and Surmodics; participated on a Data Safety Monitoring Board or Advisory Board for Medtronic, Boston Scientific, Gore, Veryan, Vesper Medical, and VentureMed. He also holds stock/stock options in QT Medical. M. Brodmann has received speaker honoraria from Bard Peripheral Vascular, Biotronik, Medtronic Spectranetics, and VIVA Physicians; and is a consultant for Bard Peripheral Vascular, Biotronik, Medtronic, and Spectranetics. G. Ansel received consulting fees from Medtronic, Boston Scientific, Veryan Medical, and Cook Medical; received royalties from Surmodics; honoraria from Cook Medical, and Medtronic; participated on a Data Safety Monitoring Board or Advisory Board for Syntactx, and Hart Clinical Consultants; and has stock/stock options in Reflow Medical. D. Scheinert has received consulting fees and/or speaker honoraria from Abbott, Acotec, Alvimedica, Bayer, Boston Scientific, Cook Medical, Cardionovum, CR Baird, IVascular, Gardia Medical/Allium, Medtronic, Philips, and Upstream Peripheral Technologies; and received payment for participation on a Data Safety Monitoring Board or Advisory Board for Boston Scientific. G. Tepe has received study support from BARD, BSC, Gore, Medtronic, CSI, Philips, and Shockwave; grants or contracts from B Braun, Biotronik, Bayer, Verian, Gore, Shockwave and Philips; is on the Global Advisory Board of Medtronic, BSC, B Braun, and Philips; received payment or honoraria for presentations from BSC, Biotronik, B Braun, Verian, Gore and Shockwave; and has a leadership or fiduciary role in CX London. J. Menk is an employee of Medtronic and holds stock. A. Micari is on the advisory board for Medtronic; is a consultant for Boston Scientific, and Terumo; has received support for attending meetings from Medtronic, Boston and Terumo. The other author has no conflicts of interest to declare.

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## Supplementary data

**Supplementary Table 1.** Medication compliance.

**Supplementary Table 2.** Univariate analysis – CD-TLR up to 5 years.

**Supplementary Table 3.** Univariate analysis – MAE up to 5 years.

**Supplementary Table 4.** Univariate analysis – all-cause mortality up to 1,800 days.

**Supplementary Figure 1.** Predictors of CD-TLR per multivariable Cox proportional hazard regression analysis outcomes.

**Supplementary Figure 2.** Predictors of MAE per multivariable Cox proportional hazard regression analysis outcomes.

**Supplementary Figure 3.** Predictors of all-cause mortality per multivariable Cox proportional hazard regression analysis outcomes.

**Supplementary Figure 4.** Subgroup analysis of predictors of CD-TLR per multivariable Cox proportional hazard regression analysis.

**Supplementary Figure 5.** Subgroup analysis of predictors of MAE per multivariable Cox proportional hazard regression analysis.

The supplementary data are published online at:

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## Supplementary data

**Supplementary Table 1: Medication compliance**

	<b>Dual Anti-platelet Therapy*</b>	<b>Anti-coagulant Therapy†</b>	<b>Statins</b>
Discharge	91.1% (1277/1402)	5.6% (78/1402)	71.6% (1004/1402)
30 days	78.1% (1049/1343)	6.0% (80/1343)	70.5% (947/1343)
6 Months	40.3% (495/1225)	7.5% (92/1228)	71.4% (877/1228)
12 Months	33.4% (391/1170)	7.9% (93/1170)	71.0% (831/1170)
24 Months	25.5% (260/1021)	8.4% (86/1021)	70.3% (718/1021)
36 Months	24.4% (226/928)	8.7% (81/928)	70.4% (653/928)

\*Aspirin plus clopidogrel/ticlopidine/prasugrel

† Includes vitamin K antagonists, direct thrombin inhibitors, and other oral anti-coagulants and other (i.e Warfarin, apixaban , betrixaban, dabigatran, edoxaban and rivaroxaban.)

**Supplementary Table 2. Univariate analysis – CD-TLR up to 5 years**

<b>Predictors of CD-TLR up to 5 years</b>		<b>Standard</b>	<b>Hazard Ratio</b>	
<b>Simple Cox proportional hazards regression</b>	<b>Coefficient</b>	<b>Error</b>	<b>[95%CI]</b>	<b>P-Value</b>
Total Lesion Length (cm)	0.030	0.005	1.030 [1.020,1.041]	<.001
Pre-procedure RVD (mm)	-0.390	0.080	0.677 [0.580,0.792]	<.001
Target Lesion type - ISR vs. non-ISR	0.525	0.115	1.691 [1.349,2.119]	<.001
Target Lesion type - de novo vs. restenotic	-0.453	0.111	0.635 [0.511,0.790]	<.001
Previous Peripheral revascularization on target limb (Y/N)	0.427	0.107	1.532 [1.241,1.891]	<.001
Target Lesion Location – SFA only (Y/N)	-0.397	0.107	0.672 [0.545,0.830]	<.001
Target Limb (unilateral vs bilateral)	-0.545	0.158	0.580 [0.426,0.790]	<.001
Coronary artery disease (Y/N)	0.305	0.105	1.356 [1.103,1.667]	0.004
Anticoagulant at Discharge	0.551	0.197	1.735 [1.180,2.551]	0.005
Baseline Rutherford Assessment (≥ 4 vs. <4)	0.424	0.155	1.528 [1.128,2.070]	0.006
CTO (%DS=100% and Occluded length ≥ 50mm, Y/N)	0.296	0.109	1.344 [1.086,1.663]	0.007
Post-procedure %DS	0.010	0.004	1.010 [1.002,1.018]	0.011
Target Limb Posterior Tibial Artery Pulse (Present vs Absent)	-0.307	0.123	0.736 [0.578,0.937]	0.013
Carotid artery disease (Y/N)	0.299	0.130	1.348 [1.046,1.738]	0.021
Previous Peripheral Revascularization on BTK (Y vs. N)	0.366	0.166	1.441 [1.042,1.995]	0.027
Age (years)	-0.011	0.005	0.989 [0.979,0.999]	0.030
Pre-procedure %DS	0.011	0.005	1.012 [1.001,1.022]	0.031
Total occlusion (%DS=100%, Y/N)	0.218	0.105	1.244 [1.013,1.528]	0.037
Target Lesion Calcification – moderate severe and severe (3&4, Y/N)	0.238	0.118	1.269 [1.008,1.599]	0.043
Target Limb Dorsalis Pedis Artery Pulse (Present vs Absent)	-0.206	0.117	0.814 [0.648,1.023]	0.077
Target Lesion Treated (single vs. multiple)	-0.207	0.121	0.813 [0.641,1.032]	0.089
Provisional Stent Use (Y/N)	0.154	0.117	1.166 [0.927,1.466]	0.189
Signs of Micro-emboli on Target Limb (Y/N)	-0.204	0.164	0.815 [0.591,1.124]	0.213
Insulin Dependent (Y/N)	0.162	0.134	1.176 [0.905,1.529]	0.225
Renal Insufficiency (Baseline Creatinine ≥ 1.5 mg/dL)	-0.241	0.203	0.786 [0.527,1.171]	0.236
Diabetes Mellitus (Y/N)	0.123	0.106	1.131 [0.918,1.392]	0.248
Hyperlipidemia (Y/N)	0.133	0.119	1.142 [0.904,1.442]	0.266
Target Lesion Calcification - (Y/N)	0.130	0.118	1.139 [0.903,1.435]	0.272
Baseline Target Limb ABI/TBI (mmHg ratio)	-0.284	0.261	0.753 [0.451,1.255]	0.276
Hypertension (Y/N)	-0.146	0.134	0.864 [0.664,1.125]	0.278
Baseline EQ-5D Index	-0.187	0.176	0.830 [0.588,1.171]	0.288
Pre-procedure ASA use (Y/N)	0.136	0.131	1.146 [0.887,1.481]	0.298
Time-Varing DAPT	0.108	0.106	1.114 [0.905,1.371]	0.310
BTK disease (Y/N)	0.096	0.105	1.100 [0.896,1.351]	0.360
Previous limb amputation on target limb (Y/N)	0.304	0.382	1.355 [0.641,2.862]	0.426
Target Lesion Calcification - Severe (4, Y/N)	0.125	0.158	1.134 [0.832,1.544]	0.427
Pre-dilatation (Y/N)	0.098	0.131	1.103 [0.853,1.425]	0.455
Previous Non-target limb amputation (Y/N)	-0.324	0.450	0.723 [0.299,1.747]	0.471
Obesity(BMI ≥ 30 kg/m <sup>2</sup> )	0.090	0.126	1.094 [0.854,1.402]	0.476
Lesion access (antegrade vs. retrograde)	0.059	0.105	1.061 [0.864,1.303]	0.573
Gender (Male vs Female)	-0.058	0.111	0.944 [0.759,1.174]	0.602
Statin at Discharge	0.061	0.118	1.063 [0.843,1.341]	0.607

<b>Predictors of CD-TLR up to 5 years Simple Cox proportional hazards regression</b>	<b>Coefficient</b>	<b>Standard Error</b>	<b>Hazard Ratio [95% CI]</b>	<b>P-Value</b>
Outflow Impaired (Y vs. N)	0.052	0.107	1.053 [0.854,1.299]	0.629
Final Dissection Grade $\geq$ D (Y vs. N)	-0.064	0.180	0.938 [0.659,1.335]	0.721
Target Lesion Thrombus (Y/N)	0.169	0.503	1.184 [0.442,3.171]	0.737
BMI (per kg/m <sup>2</sup> )	0.004	0.012	1.004 [0.980,1.028]	0.757
Inflow Impaired (Y vs. N)	-0.107	0.358	0.899 [0.446,1.811]	0.766
On Dialysis (Y/N)	0.087	0.338	1.091 [0.563,2.114]	0.797
Baseline Serum Creatinine ( $\mu$ mol/L)	0.000	0.001	1.000 [0.999,1.001]	0.808
Pre-procedure ASA + Clopidogrel/Prasugrel/Ticlopidine (Y/N)	-0.013	0.115	0.987 [0.787,1.237]	0.908
Target Lesion Location – Popliteal Artery only (Y/N)	0.023	0.203	1.023 [0.686,1.524]	0.912
Previous/Current Smoker vs Never	-0.009	0.117	0.991 [0.788,1.245]	0.937
Pre-procedure AntiPlatelet use (Clopidogrel,Prasugrel, or Ticlopidine, Y/N)	0.001	0.108	1.001 [0.810,1.237]	0.993

ASA: acetylsalicylic acid (aspirin); BMI: body mass index; BTK: below-the-knee; CD-TLR: clinically driven target lesion revascularization; CTO: chronic total occlusion; DAPT: dual anti-platelet therapy; DS: diameter stenosis; EQ-5D: Euroqol 5 dimensions; ISR: in-stent restenosis; RVD: reference vessel diameter; SFA: superficial femoral artery

**Supplementary Table 3: Univariate analysis - MAE up to 5 years**

<b>Predictors of MAE to 5 years</b>	<b>Coefficient</b>	<b>Standard Error</b>	<b>Hazard Ratio [95%CI]</b>	<b>P-Value</b>
Baseline Rutherford Assessment ( $\geq 4$ vs. $<4$ )	0.649	0.114	1.914 [1.532,2.391]	<.001
Total Lesion Length (cm)	0.023	0.004	1.023 [1.015,1.031]	<.001
Target Lesion Location – SFA only (Y/N)	-0.394	0.085	0.675 [0.571,0.797]	<.001
Pre-procedure RVD (mm)	-0.283	0.063	0.754 [0.666,0.853]	<.001
Coronary artery disease (Y/N)	0.351	0.083	1.421 [1.208,1.672]	<.001
Previous Peripheral revascularization on target limb (Y/N)	0.341	0.084	1.407 [1.193,1.658]	<.001
Anticoagulant at Discharge	0.608	0.154	1.836 [1.359,2.482]	<.001
Baseline EQ-5D Index	-0.483	0.132	0.617 [0.476,0.799]	<.001
Target Lesion type - ISR vs. non-ISR	0.318	0.096	1.374 [1.139,1.657]	<.001
Previous Peripheral Revascularization on BTK (Y vs. N)	0.417	0.128	1.518 [1.181,1.952]	0.001
On Dialysis (Y/N)	0.652	0.208	1.920 [1.276,2.889]	0.002
Baseline Serum Creatinine ( $\mu\text{mol/L}$ )	0.001	0.000	1.001 [1.000,1.002]	0.002
Carotid artery disease (Y/N)	0.310	0.102	1.363 [1.116,1.665]	0.002
Target Limb Posterior Tibial Artery Pulse (Present vs Absent)	-0.288	0.096	0.750 [0.621,0.906]	0.003
Baseline Target Limb ABI/TBI (mmHg ratio)	-0.581	0.209	0.559 [0.371,0.843]	0.005
Insulin Dependent (Y/N)	0.280	0.102	1.323 [1.083,1.616]	0.006
Target Lesion type - de novo vs. restenotic	-0.249	0.091	0.779 [0.651,0.932]	0.006
Previous limb amputation on target limb (Y/N)	0.668	0.254	1.949 [1.186,3.204]	0.008
Diabetes Mellitus (Y/N)	0.216	0.083	1.241 [1.055,1.461]	0.009
Target Lesion Calcification – moderate severe and severe (3&4, Y/N)	0.234	0.093	1.263 [1.052,1.517]	0.012
Target Lesion Treated (single vs. multiple)	-0.235	0.095	0.791 [0.656,0.953]	0.014
Target Limb Dorsalis Pedis Artery Pulse (Present vs Absent)	-0.201	0.092	0.818 [0.684,0.979]	0.028
Renal Insufficiency (Baseline Creatinine $\geq 1.5$ mg/dL)	0.285	0.130	1.329 [1.031,1.714]	0.028
Target Limb (unilateral vs bilateral)	-0.295	0.137	0.744 [0.569,0.974]	0.031
Previous Non-target limb amputation (Y/N)	0.503	0.239	1.653 [1.034,2.644]	0.036
BTK disease (Y/N)	0.173	0.082	1.188 [1.011,1.397]	0.036
Target Lesion Calcification - (Y/N)	0.192	0.094	1.212 [1.008,1.458]	0.041
Post-procedure %DS	0.007	0.003	1.007 [1.000,1.013]	0.046
CTO (%DS=100% and Occluded length $\geq 50$ mm, Y/N)	0.174	0.087	1.191 [1.003,1.413]	0.046
Outflow Impaired (Y vs. N)	0.171	0.086	1.186 [1.003,1.403]	0.046
Total occlusion (%DS=100%, Y/N)	0.151	0.083	1.163 [0.989,1.367]	0.069
Previous/Current Smoker vs Never	-0.138	0.090	0.871 [0.730,1.038]	0.122
Inflow Impaired (Y vs. N)	-0.500	0.336	0.607 [0.314,1.172]	0.137
Age (years)	0.006	0.004	1.006 [0.998,1.015]	0.148
Provisional Stent Use (Y/N)	0.130	0.093	1.139 [0.949,1.367]	0.162
Target Lesion Calcification - Severe (4, Y/N)	0.167	0.124	1.182[0.928,1.506]	0.176
Final Dissection Grade $\geq D$ (Y vs. N)	-0.184	0.148	0.832 [0.623,1.112]	0.213
Pre-procedure %DS	0.005	0.004	1.005 [0.997,1.012]	0.256
Pre-procedure ASA use (Y/N)	-0.108	0.097	0.898 [0.743,1.085]	0.263
BMI (per $\text{kg/m}^2$ )	-0.008	0.010	0.992 [0.973,1.011]	0.391
Statin at Discharge	-0.078	0.091	0.925 [0.774,1.106]	0.391
Lesion access (antegrade vs. retrograde)	0.068	0.083	1.070 [0.910,1.259]	0.410

<b>Predictors of MAE to 5 years Simple Cox proportional hazards regression</b>	<b>Coefficient</b>	<b>Standard Error</b>	<b>Hazard Ratio [95%CI]</b>	<b>P-Value</b>
Target Lesion Location – Popliteal Artery only (Y/N)	0.124	0.154	1.132 [0.838,1.529]	0.420
Gender (Male vs Female)	-0.046	0.088	0.955 [0.803,1.134]	0.598
Hypertension (Y/N)	0.041	0.113	1.042 [0.835,1.300]	0.715
Pre-procedure ASA + Clopidogrel/Prasugrel/Ticlopidine (Y/N)	-0.030	0.091	0.970 [0.812,1.160]	0.740
Time-Varing DAPT	-0.026	0.079	0.974 [0.834,1.138]	0.740
Pre-procedure AntiPlatelet use (Clopidogrel,Prasugrel, or Ticlopidine, Y/N)	0.026	0.085	1.027 [0.870,1.212]	0.755
Target Lesion Thrombus (Y/N)	-0.116	0.449	0.891 [0.369,2.148]	0.797
Signs of Micro-emboli on Target Limb(Y/N)	0.028	0.120	1.029 [0.814,1.300]	0.814
Hyperlipidemia (Y/N)	0.021	0.092	1.022 [0.854,1.222]	0.816
Pre-dilatation (Y/N)	0.023	0.101	1.023 [0.840,1.246]	0.823
Obesity (BMI $\geq$ 30 kg/m <sup>2</sup> )	0.013	0.102	1.013 [0.830,1.238]	0.895

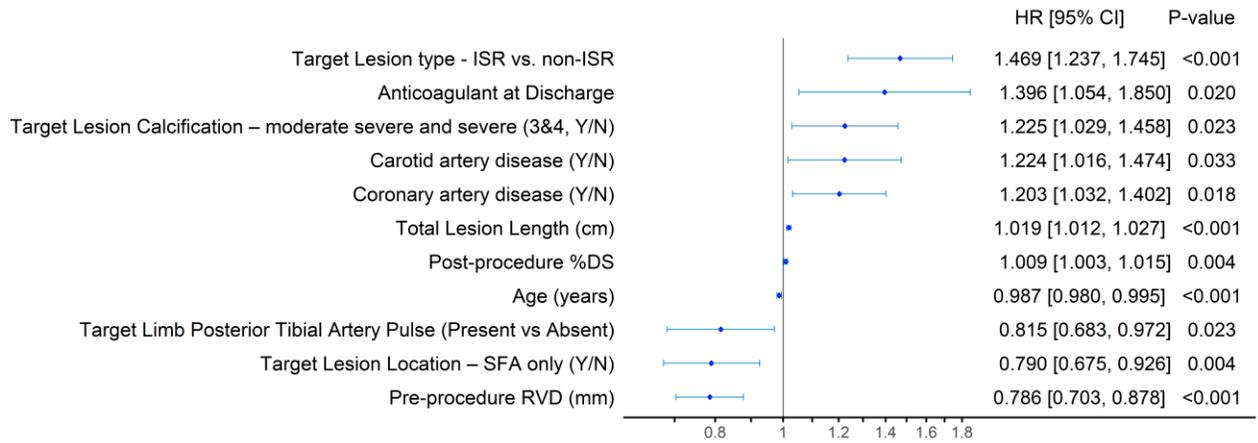
ABI/TBI: ankle brachial index/ toe brachial index; ASA: acetylsalicylic acid (aspirin); BMI: body mass index; BTK: below-the-knee; CTO: chronic total occlusion; DAPT: dual anti-platelet therapy; DS: diameter stenosis; EQ-5D: Euroqol 5 dimensions; ISR: in-stent restenosis; RVD: reference vessel diameter; SFA: superficial femoral artery

**Supplementary Table 4: Univariate analysis – all-cause mortality up to 1,800 days**

<b>Predictors of all-cause mortality based on vital update to 1,800 days</b>	<b>Coefficient</b>	<b>Standard Error</b>	<b>Hazard Ratio [95%CI]</b>	<b>P-Value</b>
Target Lesion Thrombus (Y/N)	3.011	1.033	20.298 [2.682,153.650]	0.004
Signs of Micro-emboli on Target Limb(Y/N)	0.484	0.170	1.623 [1.163,2.264]	0.004
BTK disease (Y/N)	0.303	0.119	1.354 [1.073,1.709]	0.011
Baseline Target Limb ABI/TBI (mmHg ratio)	0.633	0.247	1.883 [1.159,3.058]	0.011
Age (years)	0.014	0.007	1.014 [1.001,1.027]	0.032
Baseline Serum Creatinine (μmol/L)	0.001	0.000	1.001 [1.000,1.002]	0.035
Outflow Impaired (Y vs. N)	0.267	0.128	1.305 [1.015,1.678]	0.038
Target Lesion type - ISR vs. non-ISR	-0.307	0.154	0.736 [0.545,0.994]	0.046
Previous/Current Smoker vs Never	-0.233	0.123	0.792 [0.622,1.009]	0.059
Time-Varing DAPT	-0.187	0.107	0.830 [0.673,1.022]	0.080
Gender (Male vs Female)	-0.216	0.124	0.805 [0.631,1.028]	0.082
Previous limb amputation on target limb (Y/N)	0.501	0.295	1.651 [0.926,2.946]	0.090
CTO (%DS=100% and Occluded length ≥ 50mm, Y/N)	-0.213	0.129	0.808 [0.628,1.040]	0.098
Hyperlipidemia (Y/N)	-0.195	0.126	0.823 [0.643,1.053]	0.122
Post-procedure %DS	0.007	0.005	1.007 [0.998,1.016]	0.148
Diabetes Mellitus (Y/N)	0.161	0.118	1.175 [0.932,1.481]	0.173
Statin at Discharge	-0.165	0.126	0.848 [0.663,1.085]	0.190
Target Lesion type - de novo vs. restenotic	0.186	0.143	1.205 [0.911,1.593]	0.192
Pre-procedure ASA use (Y/N)	-0.164	0.130	0.849 [0.658,1.096]	0.209
Target Limb Posterior Tibial Artery Pulse (Present vs Absent)	0.171	0.140	1.187 [0.903,1.560]	0.220
On Dialysis (Y/N)	0.257	0.218	1.293 [0.844,1.981]	0.237
Inflow Impaired (Y vs. N)	-1.010	1.002	0.364 [0.051,2.595]	0.313
Insulin Dependent (Y/N)	0.136	0.135	1.146 [0.879,1.493]	0.314
Carotid artery disease (Y/N)	0.146	0.146	1.157 [0.869,1.541]	0.318
Target Lesion Calcification - Severe (4, Y/N)	0.167	0.168	1.182 [0.851,1.642]	0.319
Pre-procedure RVD (mm)	0.079	0.083	1.082 [0.919,1.274]	0.345
Coronary artery disease (Y/N)	-0.104	0.118	0.901 [0.715,1.136]	0.377
Previous Peripheral Revascularization on BTK (Y vs. N)	0.138	0.174	1.147 [0.816,1.614]	0.430
Target Limb Dorsalis Pedis Artery Pulse (Present vs Absent)	0.094	0.132	1.099 [0.848,1.423]	0.476
Renal Insufficiency (Baseline Creatinine ≥ 1.5 mg/dL)	0.105	0.148	1.111 [0.831,1.485]	0.477
Baseline Rutherford Assessment (≥ 4 vs. <4)	0.103	0.145	1.108 [0.834,1.473]	0.479
BMI (per kg/m <sup>2</sup> )	-0.009	0.013	0.991 [0.965,1.017]	0.485
Target Lesion Calcification – moderate severe and severe (3&4, Y/N)	0.088	0.129	1.092 [0.847,1.407]	0.497
Anticoagulant at Discharge	0.133	0.199	1.142 [0.772,1.687]	0.506
Pre-procedure AntiPlatelet use (Clopidogrel,Prasugrel, or Ticlopidine, Y/N)	-0.069	0.121	0.934 [0.736,1.185]	0.572

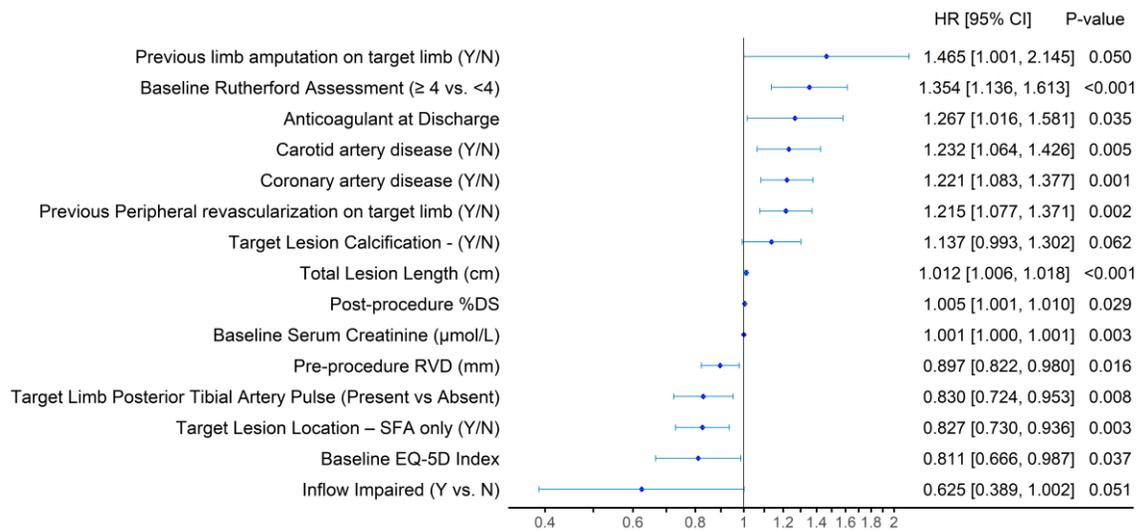
<b>Predictors of all-cause mortality based on vital update to 1,800 days</b>				
<b>Simple Cox proportional hazards regression</b>	<b>Coefficient</b>	<b>Standard Error</b>	<b>Hazard Ratio [95%CI]</b>	<b>P-Value</b>
Total Lesion Length (cm)	0.004	0.006	1.004 [0.991,1.016]	0.573
Pre-procedure %DS	-0.002	0.005	0.998 [0.988,1.008]	0.651
Lesion access (antegrade vs. retrograde)	-0.050	0.119	0.952 [0.754,1.201]	0.676
Previous Peripheral revascularization on target limb (Y/N)	-0.047	0.119	0.954 [0.756,1.204]	0.693
Baseline EQ-5D Index	0.064	0.167	1.067 [0.769,1.478]	0.699
Target Lesion Location – Popliteal Artery only (Y/N)	0.071	0.196	1.074 [0.731,1.576]	0.717
Target Limb (unilateral vs bilateral)	-0.085	0.244	0.919 [0.570,1.481]	0.728
Target Lesion Location – SFA only (Y/N)	-0.039	0.121	0.962 [0.759,1.219]	0.748
Pre-procedure ASA + Clopidogrel/Prasugrel/Ticlopidine (Y/N)	-0.041	0.131	0.960 [0.742,1.240]	0.752
Target Lesion Treated (single vs. multiple)	0.044	0.139	1.045 [0.795,1.373]	0.753
Total occlusion (%DS=100%, Y/N)	-0.026	0.119	0.975 [0.772,1.230]	0.829
Target Lesion Calcification - (Y/N)	0.027	0.137	1.028 [0.785,1.345]	0.843
Previous Non-target limb amputation (Y/N)	0.046	0.250	1.047 [0.641,1.711]	0.853
Provisional Stent Use (Y/N)	0.025	0.136	1.025 [0.785,1.338]	0.857
Pre-dilatation (Y/N)	-0.017	0.137	0.983 [0.751,1.286]	0.899
Hypertension (Y/N)	0.021	0.178	1.021 [0.720,1.447]	0.908
Final Dissection Grade $\geq$ D (Y vs. N)	0.015	0.227	1.015 [0.651,1.583]	0.947
Obesity (BMI $\geq$ 30 kg/m <sup>2</sup> )	-0.003	0.152	0.997 [0.740,1.343]	0.984

ABI/TBI: ankle brachial index/ toe brachial index; ASA: acetylsalicylic acid (aspirin); BMI: body mass index; BTK: below-the-knee; CTO: chronic total occlusion; DAPT: dual antiplatelet therapy; DS: diameter stenosis; EQ-5D: Euroqol 5 dimensions; ISR: in-stent restenosis; RVD: reference vessel diameter



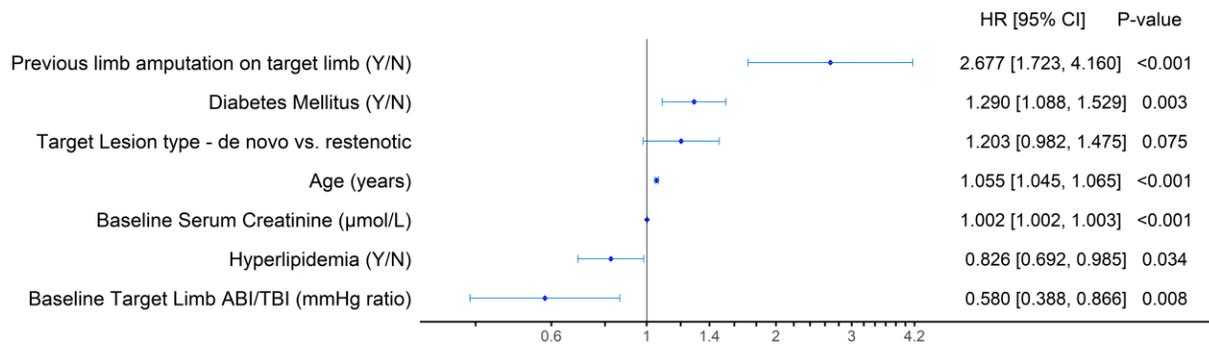
**Supplementary Figure 1.** Predictors of CD-TLR per multivariable Cox proportional hazard regression analysis outcomes.

CI: confidence interval; CD-TLR: clinically driven target lesion revascularization; DS: diameter stenosis; HR: hazard ratio; ISR: in-stent restenosis; RVD: reference vessel diameter; SFA: superficial femoral artery



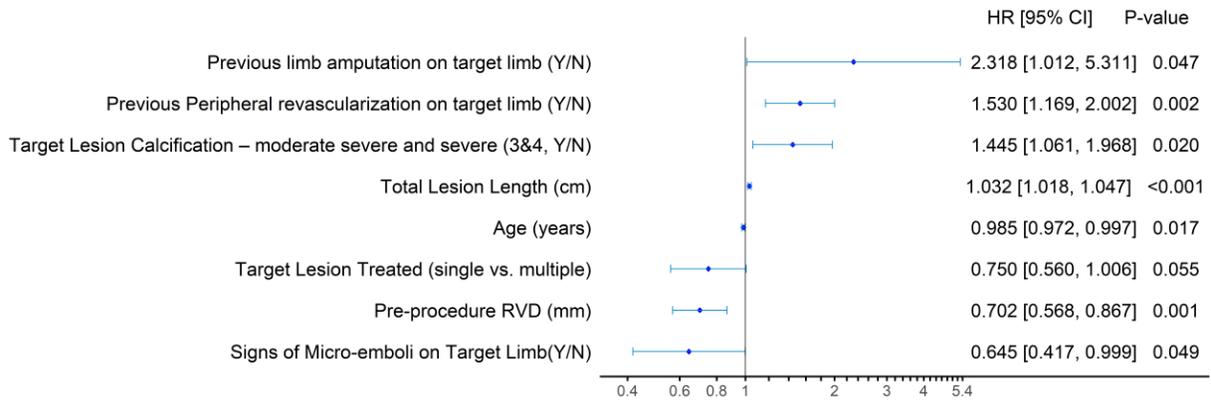
**Supplementary Figure 2.** Predictors of an MAE per multivariable Cox proportional hazard regression analysis outcomes.

DS: diameter stenosis; EQ-5D: Euroqol 5 dimensions; MAE: major adverse event; RVD: reference vessel diameter; SFA: superficial femoral artery

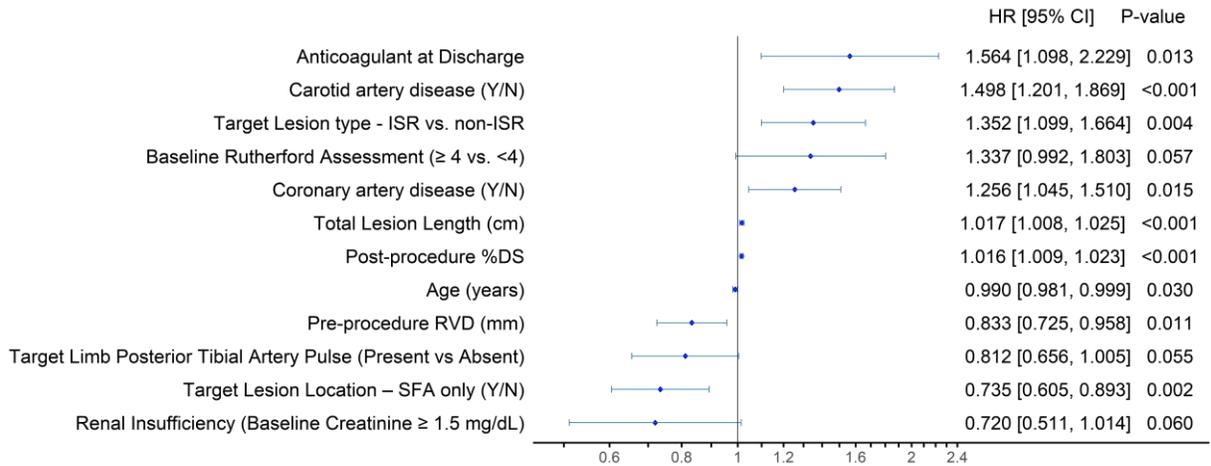


**Supplementary Figure 3.** Predictors of all-cause mortality with vital status update per multivariable Cox proportional hazard regression analysis outcomes.

ABI/TBI: ankle brachial index/ toe brachial index



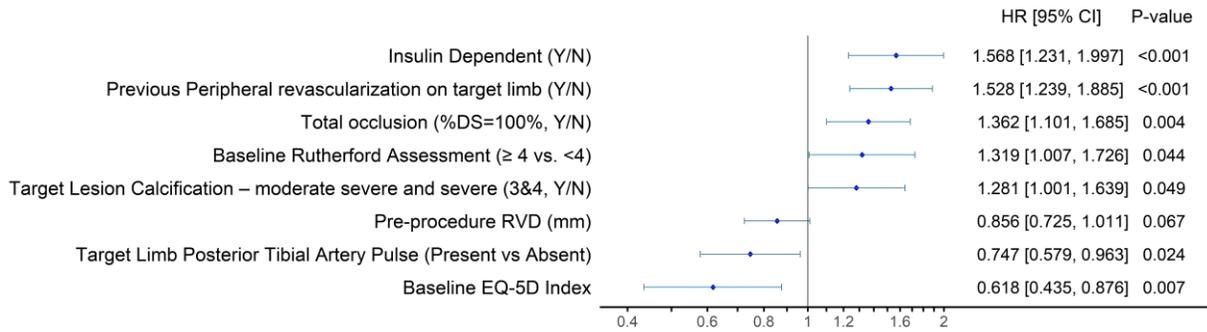
### a. Females



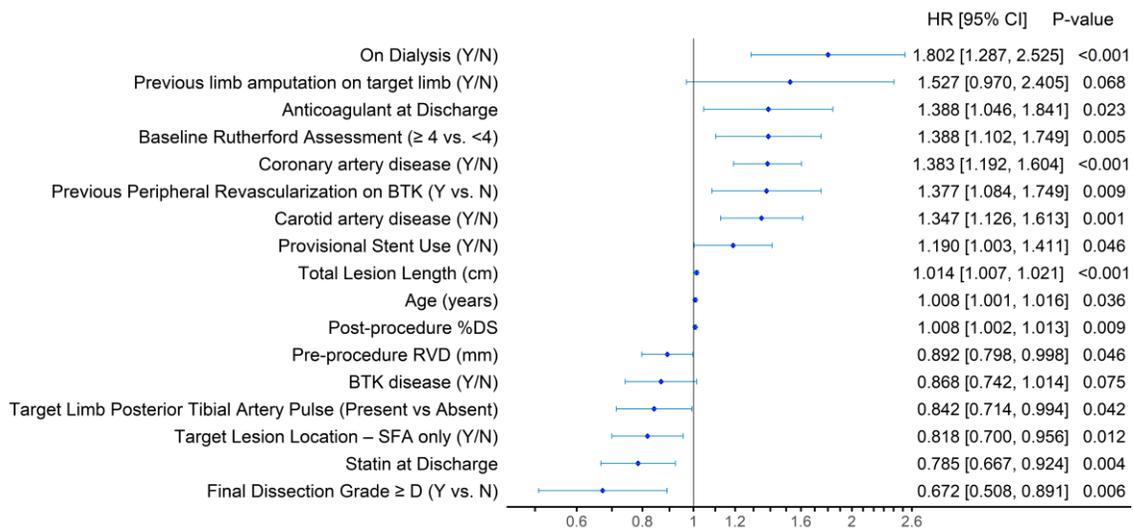
### b. Males

**Supplementary Figure 4:** Subgroup analysis of predictors of CD-TLR per multivariable Cox proportional hazard regression analysis. a) Outcomes in females and b) outcomes in males

DS: diameter stenosis; ISR: in-stent restenosis; RVD: reference vessel diameter; SFA: superficial femoral artery



### a. Females



### b. Males

**Supplementary Figure 5:** Subgroup analysis of predictors of MAE per multivariable Cox proportional hazard regression analysis. a) Outcomes in females and b) outcomes in males

BTK: below the knee; DS: diameter stenosis; EQ-5D: Euroqol 5 dimensions; RVD: reference vessel diameter; SFA: superficial femoral artery