



HAL
open science

A Polymer-Free Paclitaxel-Eluting Stent Versus a Bare-Metal Stent for De Novo Femoropopliteal Lesions The BATTLE Trial

Yann Gouëffic, Antoine Sauguet, Pascal Desgranges, Patrick Feugier, Eugenio Rosset, Eric Ducasse, Adrien Kaladji, Lucie Salomon Du Mont, Jean Marc Pernès, Philippe Commeau, et al.

► To cite this version:

Yann Gouëffic, Antoine Sauguet, Pascal Desgranges, Patrick Feugier, Eugenio Rosset, et al.. A Polymer-Free Paclitaxel-Eluting Stent Versus a Bare-Metal Stent for De Novo Femoropopliteal Lesions The BATTLE Trial. JACC: Cardiovascular Interventions, 2020, 13, pp.447 - 457. <10.1016/j.jcin.2019.12.028>. <hal-03490054>

HAL Id: hal-03490054

<https://hal.science/hal-03490054v1>

Submitted on 22 Aug 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC 4.0 - Attribution - Non-commercial use - International License

A Polymer-free Paclitaxel-eluting Stent versus a Bare Metal Stent for De Novo Femoropopliteal Lesions: The BATTLE Trial

Yann Gouëffic, MD, PhD^{a,b}; Antoine Sauguet, MD^c; Pascal Desgranges, MD, PhD^d; Patrick Feugier, MD, PhD^e; Eugenio Rosset, MD, PhD^f; Eric Ducasse, MD, PhD^g; Adrien Kaladji, MD, PhD^h; Lucie Salomon du Mont, MD, PhDⁱ; Jean Marc Pernès, MD, PhD^j; Philippe Commeau, MD^k; Patrick Lermusiaux^l, MD; Brice Leclere^m, MD, PhD; Béatrice Guyomarc'hⁿ; Clément T. Hoffmann^o, MD; Blandine Maurel, MD, PhD^{p,b}

Affiliations:

- a. Hôpital Paris St Joseph, department of vascular and endovascular surgery, Paris, F-75014
- b. Laboratoire de Physiopathologie de la Résorption Osseuse, Inserm-UN UMR-957, Nantes, F-44000
- c. Clinique Pasteur, Toulouse, F-31076
- d. AP-HP, Hôpital Henri Mondor, service de chirurgie vasculaire, Créteil, F-94010
- e. Hôpital Edouard Herriot, service de chirurgie vasculaire, Lyon, F-69437
- f. CHU Clermont-Ferrand, Hôpital Gabriel Montpied, service de chirurgie vasculaire, Clermont-Ferrand, F-63003
- g. CHU Bordeaux, Hôpital Pellegrin, service de chirurgie vasculaire, Bordeaux, F-33076
- h. CHU Rennes, Service de chirurgie vasculaire, Rennes, F-35000
- i. CHU Besançon, Hôpital Jean Minjot, service de chirurgie vasculaire, Besançon, F-25030
- j. Hôpital privé d'Antony, Antony, F-92160
- k. Polyclinique Les Fleurs, Ollioules, F-83190
- l. Bourgoin-Jallieu, Bourgoin-Jallieu, F-38302
- m. CHU Nantes, Department of epidemiology, Nantes, F-44093
- n. CHU Nantes, institut du thorax, INSERM, CNRS, UNIV Nantes, Nantes, F-44000
- o. CHU Brest, service de médecine vasculaire, Brest, F-29200
- p. CHU de Nantes, service de chirurgie vasculaire, Institut du Thorax, Nantes, F-44000

Running title : BATTLE Randomized Clinical Trial

Address for Correspondence:

Yann Gouëffic, MD, PhD
Hôpital Paris St Joseph
Department of vascular and endovascular surgery
Paris, F-75014
Phone: +33 2 40 16 50 93
Fax: +33 2 40 16 50 81

Tweet/handle : (@GouefficYann); We suggest as tweet: BATTLE RCT: Zilver PTX vs Misago. Zilver PTX failed to show superiority for freedom from ISR at 1y for the repair of femoropopliteal lesions

Word count: 6177

Funding:

BATTLE trial was funded by Terumo Medical Corporation.

ABSTRACT

Background: No randomized studies have compared self-expanding paclitaxel eluting stents with bare metal stents in the treatment of femoropopliteal lesions.

Objectives: The primary objective of the BATTLE trial is to demonstrate the clinical superiority of the Zilver[®] PTX[®] stent over the Misago[®] stent in the treatment of femoropopliteal lesions

Methods: BATTLE is a randomised, multicenter, controlled trial in patients with symptomatic (Rutherford category 2–5) *de novo* lesions of the superficial femoral or proximal popliteal artery. The primary endpoint was freedom from in-stent restenosis at one year where restenosis was defined as a peak systolic velocity index >2.4 at the target lesion. The Kaplan–Meier method was used to evaluate time-to event data for freedom from in-stent restenosis over the two-year follow-up period.

Results: Between March 2014 and August 2016, 186 patients were enrolled; 91 were assigned to the Misago[®] arm and 90 to the Zilver[®] PTX[®] arm. Kaplan–Meier one-year estimates of freedom from ISR were 88.6% for Misago[®] and 91% for Zilver[®] PTX[®] (HR=1.2 [95% CI 0.6-2.4]; p=0.64). Comparing Misago[®] with Zilver[®] PTX[®], two-year estimates were 6.4% and 1.2% (HR=7.3 [95% CI 0.9-59.3]; p=0.0632) for mortality, 74.6% and 78.8% (HR=1.2 [95% CI 0.6-2.1]; p=0.62) for patency, and 14.4% and 12.4% (HR=1.2 [95% CI 0.5-2.8]; p=0.69) for target lesion revascularization.

Conclusions: In the treatment of symptomatic femoropopliteal lesions, the Zilver[®] PTX[®] stent failed to show superiority over the Misago[®] stent in freedom from ISR at one year.

KEY WORDS: Femoropopliteal; Zilver[®] PTX[®]; Misago[®]; paclitaxel; restenosis;

CONDENSED ABSTRACT

BATTLE is the first randomized controlled trial to compare a polymer-free paclitaxel-eluting stent (ZCONilver[®] PTX[®]) versus a bare metal stent (Zilver[®] PTX[®]; Misago[®]) for the treatment of *de novo* femoropopliteal lesions in symptomatic patients. Freedom from in-stent restenosis (ISR) was the primary endpoint. The Zilver[®] PTX[®] stent failed to show superiority over the Misago[®] stent in freedom from ISR at one year. This level 1 evidence does not support the use of paclitaxel-coated, polymer-free Zilver[®]PTX[®] instead of bare metal stents to prevent in-stent restenosis for the treatment of femoropopliteal lesions.

ABBREVIATIONS AND ACRONYMS

ABI: Ankle-Brachial Index

ACE: angiotensin-converting-enzyme

BMI: body mass index

MACE: Major adverse clinical events

PAD: peripheral artery disease

SIROCCO: SIROlimus Coated Cordis SMART Nitinol Self-expandable Stent for the treatment of Obstructive Superficial Femoral Artery Disease

TASC: Trans-Atlantic Inter-Society Consensus document II on management of peripheral arterial disease.

TECCO: traitement des lésions athéromateuses de l'artère fémorale commune par technique endovasculaire versus chirurgie ouverte

TER: Target Extremity Revascularization

TLR: Target Lesion Revascularization

INTRODUCTION

Recently, the European Society of Cardiology in collaboration with the European Society for Vascular Surgery have recommended that endovascular therapy should be the first choice treatment for femoropopliteal lesions <25 cm.¹ Restenosis continues to be the Achilles' heel of endovascular treatment of femoropopliteal lesions. Efforts to prevent restenosis first focused on stenting, to prevent elastic recoil and constrictive remodeling that follow percutaneous angioplasty (PTA). Randomized clinical trials have demonstrated that self-expanding bare metal stents (BMS) were superior to PTA, but in-stent restenosis rates remained high.³⁻⁵ In such cases, in-stent restenosis is primarily caused by intimal hyperplasia. Randomized controlled trials comparing sirolimus eluting stents to BMS demonstrated a non-statistically significant trend towards reduction in late lumen loss.^{6, 7}

In 2011, a polymer-free, paclitaxel eluting, self-expanding stent (PES) showed superior 12-month outcomes compared to PTA.⁹ Interestingly, the study was designed to randomize patients who required bailout stenting. These patients underwent a secondary random assignment to receive either provisional BMS or PES, during which a superior 12-month primary patency rate of 89.9% for PES compared with 73.0% for BMS (p=0.01) was observed. However, the study was not powered for this endpoint and no conclusion could be drawn. Currently, no studies have compared PES to BMS for the primary treatment of femoropopliteal lesions. The primary objective of the BATTLE trial (Bare metal stent versus paclitaxel-eluting stent in the trial (Bare metal stent vs. paclitaxel eluting stent in the setting of primary stenting of intermediate-length femoropopliteal lesions) was to demonstrate the clinical superiority of primary stenting using a polymer-free PES (Zilver[®] PTX[®], Cook Medical, Bloomington, IN, USA) over a latest-generation self-expanding, bare nitinol stent (Misago[®] RX, Terumo Corp., Tokyo, Japan) in the treatment of femoropopliteal lesions in symptomatic patients

METHODS

Study design:

BATTLE was a national, multicenter, prospective, randomized controlled trial conducted at 10 centres in which 186 patients with symptomatic femoropopliteal lesions were randomly assigned to receive Misago[®] or Zilver[®] PTX[®] stents. The trial was conducted in accordance with the ICH-E6, French Good Clinical Practice guidelines, and appropriate regulatory requirements. The ethical committee approved the study for France (CPP Ouest IV- Nantes #33/13). Information has been given to the patient. The trial was designed by the first author in collaboration with the department of clinical research of Nantes. This trial was registered on ClinicalTrials.gov (NCT02004951). The full protocol has been previously published.¹⁰

Patients:

Inclusion and exclusion criteria are provided in detail in the full protocol.¹⁰

Briefly, patients were eligible for enrolment if they had a history of symptomatic peripheral arterial disease (PAD) (Rutherford stage 2–5) and *de novo* atherosclerotic lesions (stenosis and/or occlusion) of the superficial femoral artery, the proximal popliteal artery, or both. Target lesion length was required to range from 2 to 14 cm (inclusive) with at least 1 patent runoff vessel (<50% diameter stenosis throughout its course) and be eligible for treatment with a maximum of two stents per lesion. The main exclusion criteria were asymptomatic lesions, restenosis, and no atheromatous disease.

Randomization and masking:

Eligible patients were randomly assigned in a 1:1 ratio to Misago[®] or Zilver[®] PTX[®] stent implantation. Simple randomization was performed with the use of a web-based system before the procedure. Randomization was stratified according to investigational site to ensure proportional assignment. Because of the nature of the interventions, treating physicians were aware of study-group assignments. Patients remained blinded to the assigned

and received treatment until the primary endpoint analysis. The clinical events committee, site personnel who conducted clinical follow-up assessments (except when conducted by the implanting investigator), core laboratory personnel (who assessed duplex ultrasonography and radiographs), and individuals involved in the data analysis were also blinded to treatment assignment until the primary endpoint analysis. An independent data reviewer, blinded to treatment assignment, monitored aggregate safety data. The sponsor did not have access to treatment assignment.

The Misago[®] RX, a self-expanding nitinol stent with a rapid exchange catheter, was compared to the Zilver[®] PTX[®], a polymer-free PES with an over-the-wire system. During the trial, available maximum lengths for Misago[®] RX and Zilver[®] PTX[®] were 15 and 10 cm, respectively. Interventions and follow-up information is given in detail in the full protocol. Briefly, clinical follow-up visits were scheduled to take place at 30 days, 12 and 24 months. All patients underwent a duplex scan at 30 days, 12 and 24 months post-procedure. Biplane X-rays were recorded at one, 12, and 24 months for evaluation of stent fractures. An intravenous bolus of 50 IU/kg heparin and aspirin (dose left to the discretion of the interventionalist) were administered. In both arms, post procedure medical treatment included aspirin 75 mg daily (for a minimum duration of two months) and clopidogrel 75 mg daily throughout the length of the study (two years). In case of contraindication to clopidogrel, ticlopidine was given at a dose according to standard hospital practice. Aspirin was the only antiplatelet agent added for patients who were receiving oral anti-coagulant treatment. Initiation and discontinuation of antiplatelet medications were documented

Outcomes:

The primary outcome was the rate of freedom from in-stent restenosis at one year after the procedure. Restenosis was defined as a peak systolic velocity index >2.4 at the target lesion.

The secondary endpoints and their definitions are provided in detail in the full protocol.¹⁰ Briefly, primary sustained clinical improvement at 1, 12 and 24 months post procedure was defined as a sustained upward shift of 1 category of the Rutherford classification for claudicants and by wound healing and rest pain resolution for patients in critical limb ischemia, without the need for repeated target lesion revascularization (TLR) in surviving patients. Secondary sustained clinical improvement at 1, 12 and 24 months post procedure was defined as primary sustained clinical improvement including the need for repeated TLR. A cost effectiveness analysis was performed using the incremental cost-effectiveness ratio based on quality of life for cost-utility analysis and on freedom from in-stent restenosis for cost-effectiveness. These data will be released in a separate manuscript

Statistical analysis:

We calculated that a sample of 186 patients, randomly assigned in a 1:1 ratio, would be required to provide the study with an 80% power to detect a between-group difference of 19.3% in the rate of freedom from in-restenosis (86.2% in the PES group and 66.9% in the bare metal stent group), at a two-sided alpha level of 0.05 and 10% dropout. These estimates were based on the findings of the Zilver[®] PTX[®] randomized controlled study at one year for the PES group.⁹ For the bare metal stent group, estimates were based on a mean of the restenosis rates in previously published studies.³⁻⁵ Data on freedom from in-stent restenosis for the Misago[®] stent were not available.

Continuous data are presented as the means \pm standard deviation, or as medians with interquartile ranges for non-normal distributions or censored data sets. Categorical data are given as count and percentage. Continuous data were compared with the use of the Student's t-test. Chi-squared or Fisher's exact tests were used for comparison of categorical data. A modified intention-to-treat analysis was performed to include only patients who had undergone randomization and met the major inclusion criteria. The per-protocol analysis

included only randomized patients who received the assigned treatment. All patients were analyzed according to their initial study group assignment. The Kaplan–Meier method was used to evaluate time-to-event data for all-cause mortality, patency, freedom from restenosis, freedom from thrombosis, TLR target extremities revascularization (TER) and sustained clinical improvement over the two-year follow-up period. Differences between groups were assessed using the log-rank test and a hazard ratio (HR) with a 95% confidence interval (CI) in the Cox model. All p values are two-sided; $p < 0.05$ indicated a statistically significant difference and no correction was made for multiple comparisons. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Role of the funding source:

The sponsor of the study had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

RESULTS

Between March 2014 and August 2016, we enrolled 186 patients (figure 1). Of these, five patients were not randomized and were withdrawn from the analysis. Three of these cases were twice included, one patient had a contraindication to antiplatelet treatment, and one patient was not eligible due to lesion characteristics. Consequently, these 5 patients were not treated and not followed up. Ninety-one patients were assigned to Misago[®] and 84 underwent the assigned intervention (2 ineligible lesions; 1 chronic renal failure; 1 failure to cross the lesion; 1 randomization error; 2 non-authorized stents). Ninety patients were assigned to Zilver[®] PTX[®] and 85 received the assigned intervention (3 ineligible lesions; 1 failure to cross the lesion; 1 non-authorized stent). The characteristics of the patients in the modified intention-to-treat population were well balanced between groups, with the exception of diabetes mellitus rates (table 1). Based on symptoms, interventions were performed on 70 limbs (82%) in the Misago[®] group and 68 limbs (79%) in the Zilver[®] PTX[®] group. The

mean lesion length was 7.6 ± 4.1 cm in the Misago[®] group versus 6.9 ± 3.5 cm in the Zilver[®] PTX[®] group. Procedural characteristics and target lesions at baseline are described in table 2. Technical success defined as residual angiographic stenosis of no greater than 30% were 100% in each group. One-hundred-and-two stents were implanted in the Misago[®] group and 117 in the Zilver[®] PTX[®] group. Overall, the most commonly used stent diameters were 6 mm (73.9%).

The mean stent length per patient in Misago[®] and Zilver[®] PTX[®] groups was 9 ± 4 and 7 ± 3 cm, respectively. Concomitant interventions among Misago[®] and Zilver[®] PTX[®] groups occurred in 16 of 85 and 19 of 86 patients, respectively ($p=0.60$). Additional angioplasty or stenting were performed for the iliac arteries (Misago[®]: $n=9$ and Zilver[®] PTX[®]: $n=4$), the femoropopliteal arteries (Misago[®]: $n=10$ and Zilver[®] PTX[®]: $n=16$) and the below-the-knee arteries (Misago[®]: $n=1$ and Zilver[®] PTX[®]: $n=2$). No debulking therapy was performed. The median follow-up was 24 months (interquartile range, 24–26). Follow-up data at one year and two years, respectively, were available for 80 and 68 patients with Misago[®], and 83 and 76 with Zilver[®] PTX[®] (figure 1).

In the modified intention-to-treat analysis, Kaplan–Meier one-year estimates of freedom from in-stent restenosis were 88.6% (12 events) for Misago[®] and 91% (11 events) for Zilver[®] PTX[®] (HR=1.2 [95% CI 0.6-2.4]; $p=0.64$) (figure 2A). Comparing Misago[®] with Zilver[®] PTX[®], two-year estimates were 80.9% and 85.8% for freedom from in-stent restenosis (figure 2A). Per-protocol analysis within this initial cohort yielded similar results (data not shown).

Regarding thrombosis, there was no difference between both groups at one year (Misago[®] vs. Zilver[®] PTX[®]: 3.8% versus 6.1%; HR=0.9 [95% CI 0.3-2.3]; $p=0.75$) (figure 2B). At one year, primary patency was 84.8% and 85.1% (HR=1.2 [95% CI 0.6-2.1]; $p=0.62$) for the

Misago[®] and Zilver[®] PTX[®] groups, respectively (figure 2C). Misago[®]-treated patients demonstrated similar rates of TLR versus Zilver[®] PTX[®]-treated patients at one year (8.7% vs. 8.4%; HR=1.2 [95% CI 0.5-2.8]; p=0.69) (figure 2D). Target extremity revascularization was also similar (3.7% versus 4.8%; HR=0.4 [95% CI 0.1-1.3]; p=0.12). At one year, 62% and 38% of the patients in the Misago[®] group were asymptomatic or presented with claudication, respectively. For the Zilver[®] PTX[®] group, 53%, 43%, and 4% of the patients were asymptomatic, presented with claudication, or critical limb ischemia, respectively. Overall, symptoms, based on Rutherford status, was improved for both groups but with a difference observed between them at one year (p=0.04) (figure 3). The primary sustained clinical improvement at one year was 84.8% and 83.3% in the Misago[®] and the Zilver[®] PTX[®] groups, respectively (HR=0.9 [95% CI 0.5-1.6]; p=0.65). At one year, the resting ABI was significantly improved compared with baseline in both groups (Misago[®]: 0.96±0.19 from 0.71±0.21; Zilver[®] PTX[®]: 0.92±0.19 from 0.68±0.18) without any difference between the groups (p=0.33) (figure 4).

Sixty-eight and 76 patients completed two years of follow-up in the Misago[®] and Zilver[®] PTX[®] groups, respectively. Regarding all secondary endpoints, two-year results did not differ from the 1-year results (Table 3). At 2 years, no difference was observed in term of in-stent restenosis, mortality, in-stent thrombosis, patency and TLR in a post-hoc analysis comparing claudicant and critical limb ischemia patients in both arms. No difference was observed in dual antiplatelet therapy between both groups at one month (Misago[®]: 64%; Zilver[®] PTX[®]: 71%; p=0.30), one year (28% and 35%; p=0.35), and two years (28% and 33%; p=0.54). At two years of follow-up, no statistically significant difference was observed between study groups in term of MACE (Misago[®]: 6.4%, Zilver[®] PTX[®]: 1.2%; HR=7.3 [95% CI 0.9–59.3]; p=0.0632). Seven deaths were noted in the Misago[®] group and one in the Zilver[®] PTX[®] group (HR=7.3 [95% CI 0.9-59.3]; p=0.06) (figure 5). Deaths were not

related to the procedure, nor to the devices. In the Misago[®] group, deaths were related to pulmonary cancer (n=3), sepsis (n=2), trauma (n=1), and multi-system organ failure (n=1). One death was noted in the Zilver[®] PTX[®] group due to haemorrhagic shock. No major amputations were noted at two years. Other reported adverse events were noted in the Misago[®] group such as stroke (n=2), myocardial infarction (n=2), and acute ischemia of the target limb (n=1). In the Zilver[®] PTX[®] group, we observed one case of myocardial infarction and two cases of acute ischaemia of the target limb. Among the Misago[®] and Zilver[®] PTX[®] groups, two (one type III and one type IV) and one (type IV) stent fractures were observed at 12 months. The EQ-5D-3L questionnaire was completed at one, 12, and 24 months by 123 (72.0%), 107 (62.6%), and 103 (60.6%) patients, respectively (table 4). In both groups, the majority of patients had sustained improvement in the mobility and pain–discomfort dimensions of the EQ-5D-3L during all the study follow-up visits. At one month, one and two years, no difference in quality of life was observed between both groups, as assessed using the EQ-5D-3L questionnaire.

DISCUSSION

Recent guidelines proposed endovascular therapy as a first-choice strategy for femoro-popliteal lesions <25 cm, but further evidence is required to determine the algorithm to treat these lesions.¹ Although numerous previous studies have suggested that paclitaxel eluting devices appear to be the most promising treatment for femoropopliteal lesions, these studies compared drug-eluting devices to plain balloon angioplasty as the main comparator.¹¹⁻¹³ The BATTLE trial is the first randomized clinical trial to compare BMS with polymer-free PES with the objective of demonstrating the superiority of polymer-free PES in achieving freedom from in-stent restenosis at 12 months. In this trial, polymer-free PES failed to show superior efficacy compared with BMS for the treatment of patients with symptomatic superficial femoral and proximal popliteal PAD. Secondary endpoints such as sustained clinical

improvement, patency, and TLR also showed no significant differences between both groups. In BATTLE, the Zilver[®] PTX[®] seemed to achieve comparable outcomes to previous studies. Indeed, in the Zilver[®] PTX[®] randomised clinical trial, the mean lesion treated in the PES group was 6.64±3.89 cm long (versus 6.9±3.5 cm in BATTLE), and the primary patency and the TLR rates at one year were 83.1% and 9.5%, versus 85.1% and 8.4% in BATTLE,⁹ respectively. Therefore, the absence of a difference between groups in the BATTLE trial is not related to worse outcomes for Zilver[®] PTX[®]. Regarding Misago[®], previous randomized clinical trials are not available, but observational data from the main Misago[®] registries reported one year patency of 82.9–87.6% and TLR rates of 10.1–13.0%, which are consistent with BATTLE outcomes.^{14, 15}

Few head-to-head comparisons have been published comparing drug-eluting stent and BMS. A self-expanding sirolimus-eluting stent showed a trend toward reducing late lumen loss compared with BMS at six months, but without significant difference at 18 or 24 months.^{6, 7} Regarding PES, in the second arm of randomization of the Zilver[®] PTX[®] trial, patients who had acute failure in the angioplasty group underwent secondary random assignment to receive either provisional BMS or Zilver[®] PTX[®].⁹ The five-year patency and freedom from clinically driven TLR rate was significantly better for the provisional PES group than for the provisional BMS group, which demonstrates the efficacy of paclitaxel with a similar stent platform between both groups.¹⁶ However, the Zilver[®] PTX[®] trial was powered to assess the Zilver[®] PTX[®] stent versus angioplasty and conclusions could not be drawn from the second arm of randomization. In BATTLE, despite the absence of a difference between groups at one and two years, an effect of paclitaxel can be observed. Indeed, the shape of the Kaplan–Meier curves depicting freedom from in-stent restenosis were different between both groups. Interestingly, BMS curve declines mostly from four to eight months and then plateaus. With PES, the drop is delayed from seven to 12 months. This difference

in pattern between both curves may reflect the paclitaxel effect, which delays intimal hyperplasia, but without any advantage at 12 months in terms of in-stent restenosis and patency. The absence of a difference between both arms could be explained by the stent platform. The Misago[®] self-expandable stent utilizes a different stent platform which may reduce in-stent restenosis rate^{17, 18} Furthermore, drug release control could also contribute to the BATTLE results. Zilver[®] PTX does not utilize a polymer to release paclitaxel, delivering approximately 95% of the total drug within 24 hours of deployment, with sustained paclitaxel levels in the artery wall over 56 days.¹⁹ On the other hand, in-stent restenosis predominantly occurs within a year following nitinol stenting in the femoropopliteal segment.²⁰ As such, the kinetics of paclitaxel release by Zilver[®] PTX[®] do not match the kinetics of restenosis at the femoropopliteal level. Recently, Gray et al. published the findings of the IMPERIAL randomized controlled study, which compared Eluvia[®] (Boston Scientific, Marlborough, MA, USA), a polymer-coated paclitaxel-eluting stent with Zilver[®] PTX[®].²¹ At one year, primary patency and freedom from TLR were significantly superior for Eluvia[®], which may suggest the potential of polymer coating to obtain a sustained paclitaxel release and restenosis inhibition. At one year, in-stent thrombosis rates with Misago[®] and Zilver[®] PTX[®] were 6.7% and 7.6%, respectively. Thus, concerns regarding increase in-stent thrombosis using drug-eluting therapy may be unfounded. IMPERIAL also reported low rates of in-stent thrombosis with 1.7% in the Eluvia group and 4.0% in the Zilver[®] PTX[®] group, which was not significantly different between the groups.

Recently, Katsanos et al. published a meta-analysis of randomized clinical trials investigating the risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery.²² For PES, all-cause death was similar to control arms at one year but there was an increased risk of death with paclitaxel-coated stents at five years. Katsanos et al included one year BATTLE's data before the availability of the 2 year data.

Herein we observed a trend to have a higher mortality in the BMS group. In BATTLE, the causes of deaths are available and they were not related to the procedure, nor to the devices. It is tempting to compare these findings with paclitaxel-coated balloon trials. However, it is important to note that in most of the paclitaxel-coated balloon trials, calcified lesions and failure of vessel preparation were exclusion criteria, which was not the case in the BATTLE or IMPERIAL studies.¹¹⁻¹³ Further trials with direct comparisons between drug-eluting devices and bare metal stents are expected to provide information that would enable the development of a femoropopliteal treatment algorithm.

This study has several potential limitations. The generalization of BATTLE outcomes is limited to patients selected using rigid inclusion and exclusion criteria, and therefore cannot be extrapolated to longer femoropopliteal lesions. Indeed, lesions in the BATTLE study are <10 cm, similar to those included in the Zilver[®] PTX[®], IMPERIAL, and drug-coated balloon randomized studies. Moreover, BATTLE did not include a treadmill exercise test as a secondary endpoint and post-procedure exercise programs were not recorded. To date, Zilver[®] PTX[®] and IMPERIAL trials have shown improvement regarding functional status, but without any significant difference in clinical status between devices. Additionally, BATTLE included CLI patients, typically with more advanced disease and different treatment objectives, which could adversely affect study outcomes.²³ In BATTLE, independent core laboratory measures were blinded to treatment assignment but biases were possible for some variables since the treating physicians were not blinded to treatment assignment.

An ascertainment bias may have been introduced since the clinical follow up was at times provided by the operator rather than blinded site personnel. Finally, the absence of superiority of the Zilver[®] PTX[®] over Misago[®] does not mean a non-inferiority between both devices since the BATTLE study was underpowered to answer the non-inferiority question.

CONCLUSION

In conclusion, the BATTLE randomized clinical study demonstrated that Zilver[®] PTX[®], a polymer-free PES, is not superior to Misago[®], a bare metal stent, in treatment of symptomatic femoropopliteal disease. Determination of the advantages of drug-eluting therapy over bare metal stents is still required to define the optimal strategy for the treatment of intermediate-length femoropopliteal lesions.

ACKNOWLEDGEMENT

We would like to thank Damien Fairier, Samia Rim Maouche, Cyrielle Giroux, and Lucie Benech for their excellent technical support. An English Language edit of this manuscript was provided by Simon Rhead and Mark Davies, inScience Communications, funded by Terumo Medical Corporation.

PERSPECTIVES

WHAT IS KNOWN?

Bare metal stent and drug eluting devices have shown to be a more effective option than plain balloon angioplasty for the femoropopliteal treatment. Head to head randomized clinical trial are now required to develop an algorithm for treatment of the femoropopliteal lesions.

WHAT IS NEW?

BATTLE is the first randomized controlled trial to compare a paclitaxel-eluting stent with a bare metal stent as a primary treatment of femoropopliteal lesions. We found the paclitaxel-coated, polymer-free Zilver[®] PTX[®] stent was not superior to the bare metal stent, Misago[®] for freedom from in-stent restenosis.

WHAT IS NEXT?

More head to head comparisons between bare metal and drug eluting devices will be needed to define the optimal strategy for endovascular treatment of this

difficult lesion subset.

REFERENCES

1. Aboyans V, Ricco JB, Bartelink ML, et al. [2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)]. *Kardiol Pol.* 2017;75(11):1065-1160.
2. Bittl JA. Advances in coronary angioplasty. *The New England journal of medicine.* Oct 24 1996;335(17):1290-1302.
3. Bosiers M, Torsello G, Gissler HM, et al. Nitinol stent implantation in long superficial femoral artery lesions: 12-month results of the DURABILITY I study. *Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists.* Jun 2009;16(3):261-269.
4. Dick P, Wallner H, Sabeti S, et al. Balloon angioplasty versus stenting with nitinol stents in intermediate length superficial femoral artery lesions. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.* Dec 1 2009;74(7):1090-1095.
5. Schillinger M, Sabeti S, Loewe C, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. *The New England journal of medicine.* May 4 2006;354(18):1879-1888.
6. Duda SH, Bosiers M, Lammer J, et al. Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. *Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists.* Dec 2006;13(6):701-710.
7. Duda SH, Pusich B, Richter G, et al. Sirolimus-eluting stents for the treatment of obstructive superficial femoral artery disease: six-month results. *Circulation.* Sep 17 2002;106(12):1505-1509.
8. Lammer J, Bosiers M, Zeller T, et al. First clinical trial of nitinol self-expanding

everolimus-eluting stent implantation for peripheral arterial occlusive disease. *Journal of vascular surgery*. Aug 2011;54(2):394-401.

9. Dake MD, Ansel GM, Jaff MR, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. *Circulation. Cardiovascular interventions*. Oct 1 2011;4(5):495-504.

10. Goueffic Y, Kaladji A, Guyomarch B, et al. Bare metal stent versus paclitaxel eluting stent for intermediate length femoropopliteal arterial lesions (BATTLE trial): study protocol for a randomized controlled trial. *Trials*. 2014;15:423.

11. Rosenfield K, Jaff MR, White CJ, et al. Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease. *N Engl J Med*. Jul 9 2015;373(2):145-153.

12. Schroeder H, Werner M, Meyer DR, et al. Low-Dose Paclitaxel-Coated Versus Uncoated Percutaneous Transluminal Balloon Angioplasty for Femoropopliteal Peripheral Artery Disease: One-Year Results of the ILLUMENATE European Randomized Clinical Trial (Randomized Trial of a Novel Paclitaxel-Coated Percutaneous Angioplasty Balloon). *Circulation*. Jun 06 2017;135(23):2227-2236.

13. Tepe G, Laird J, Schneider P, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. *Circulation*. Feb 3 2015;131(5):495-502.

14. Ohki T, Angle JF, Yokoi H, et al. One-year outcomes of the U.S. and Japanese regulatory trial of the Misago stent for treatment of superficial femoral artery disease (OSPNEY study). *J Vasc Surg*. Feb 2016;63(2):370-376 e371.

15. Schulte KL, Kralj I, Gissler HM, et al. MISAGO 2: one-year outcomes after implantation of the Misago self-expanding nitinol stent in the superficial femoral and

popliteal arteries of 744 patients. *Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists*. Dec 2012;19(6):774-784.

16. Dake MD, Ansel GM, Jaff MR, et al. Durable Clinical Effectiveness With Paclitaxel-Eluting Stents in the Femoropopliteal Artery: 5-Year Results of the Zilver PTX Randomized Trial. *Circulation*. Apr 12 2016;133(15):1472-1483; discussion 1483.

17. Muller-Hulsbeck S, Keirse K, Zeller T, et al. Twelve-Month Results From the MAJESTIC Trial of the Eluvia Paclitaxel-Eluting Stent for Treatment of Obstructive Femoropopliteal Disease. *J Endovasc Ther*. Oct;23(5):701-707.

18. Zhao HQ, Nikanorov A, Virmani R, et al. Late stent expansion and neointimal proliferation of oversized Nitinol stents in peripheral arteries. *Cardiovasc Intervent Radiol*. Jul 2009;32(4):720-726.

19. Dake MD, Scheinert D, Tepe G, et al. Nitinol stents with polymer-free paclitaxel coating for lesions in the superficial femoral and popliteal arteries above the knee: twelve-month safety and effectiveness results from the Zilver PTX single-arm clinical study. *Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists*. Oct 2011;18(5):613-623.

20. Iida O, Uematsu M, Soga Y, et al. Timing of the restenosis following nitinol stenting in the superficial femoral artery and the factors associated with early and late restenoses. *Catheter Cardiovasc Interv*. Oct 1 2011;78(4):611-617.

21. Gray WA, Keirse K, Soga Y, 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*. Oct 27 2018;392(10157):1541-1551.

22. Katsanos K, Spiliopoulos S, Kitrou P, et al. Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the

Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc.* Dec 18 2018;7(24):e011245.

23. Morisaki K, Yamaoka T, Iwasa K, et al. Influence of frailty on treatment outcomes after revascularization in patients with critical limb ischemia. *J Vasc Surg.* Dec 2017;66(6):1758-1764.

Figure

FIGURE LEGENDS

Figure 1: Randomization and follow-up scheme.

Figure 2: Kaplan–Meier estimates of the rates of (A) freedom from in-stent restenosis, (B) freedom from in-stent thrombosis, (C) primary patency, and (D) target lesion revascularization. CI=confidence interval. HR=hazard ratio. ISR=in-stent restenosis. TLR=target lesion revascularization.

Figure 3: Distribution of Rutherford categories.

Figure 4: Resting ankle-brachial index. ABI=ankle-brachial index.

SD=standard deviation. D=day. M=month

Figure 5: Kaplan–Meier estimates of the survival rates. CI=confidence interval.

HR=hazard ratio.

Central illustration: Freedom from in-stent restenosis (left) and resting ABI (right) up to 2 years. CI=confidence interval. HR=hazard ratio. ISR=in-stent restenosis. ABI=ankle-brachial index. SD=standard deviation. D=day.

M=month

Table 1: Baseline demographic and clinical characteristics of the modified intention-to-treat

Population

	Misago [□] (n=85)	Zilver [□] PTX [□] (n=86)
Age (years)	68±12	71±12
Male	62 (73)	62 (72)
Hypertension	52 (61)	59 (69)
Hyperlipidemia	61 (73)	55 (65)
Diabetes	22 (26)	41 (48)
Smoking at baseline	28 (33)	20 (23)
Coronary artery disease	34 (40)	27 (31)
Renal insufficiency	6 (7)	8 (9)
Obesity (BMI>25)	54 (64)	58 (67)
History of ischemic stroke or transient ischemic attack	9 (11)	11 (13)
Vascular surgical history	26 (31)	26 (30)
History of lower limb amputation	1 (1)	0 (0)
Statin at baseline	66 (78)	67 (78)
ACE inhibitors at baseline	32 (38)	22 (26)
Antiplatelet drug at baseline	78 (92)	80 (93)
Dual antiplatelet drug at baseline	45 (53)	41 (48)
Rutherford at baseline		
2	14 (16)	16 (19)
3	56 (66)	52 (60)
4	12 (14)	12 (14)
5	3 (4)	6 (7)

Data are n (%), unless otherwise stated. Plus-minus values are means ± SD.
Rutherford stage

2 corresponds to moderate intermittent claudication, stage 3 severe intermittent claudication, stage 4 ischemic pain at rest, and stage 5 ischemic ulcers.
ACE=angiotensin-converting enzyme. BMI=body mass index.

Table 2: Baseline angiographic and procedural characteristics

	Misago [□] (n=85)	Zilver [□] PTX [□] (n=86)
Treated limb		
Right leg	45 (53)	44 (51)
Left leg	40 (47)	42 (49)
Lesion length (cm)	7.6±4.1	6.9±3.5
Reference vessel diameter (cm)	5.75±0.55	5.79±0.64
Occlusion	30 (35)	33 (38)
No of patent runoff vessels at baseline		
1	13 (15)	11 (13)
2	12 (14)	27 (31)
3	60 (71)	48 (56)
Anaesthesia		
Local+sedation	55 (65)	57 (67)
Local +regional	27 (32)	20 (23)
General	3 (4)	9 (10)
Duration of procedure (min)	53±34	52±29
Arterial access to the culprit SFA		
Femoral antegrade	27 (32)	35 (41)
Femoral retrograde	58 (69)	51 (59)
Brachial	0 (0)	0 (0)
Pre-dilatation	70 (83)	69 (80)
Number of stents during the procedure	102	117

1	68 (80)	57 (66)
2	17 (20)	27 (31)
3	0 (0)	2 (2)
Total stent length (cm)	11±6	10±5
Diameter per stent (mm)	6±0.5	6±0.5
Length per stent (cm)	9±4	7±3
Stented arterial segment*		
Proximal SFA	14/102 (14)	10/117 (9)
Mid SFA	55/102 (54)	56/117 (48)
Distal SFA	44/102 (43)	46/117 (39)
Proximal popliteal artery	15/102 (15)	11/117 (9)
Post-dilatation	73 (86)	79 (92)
Technical success	85 (100)	86 (100)
Concomitant ipsilateral procedure	16 (19)	19 (22)
Heparin		
intravenous bolus	83 (98)	82 (95)
Aspirin		
intravenous bolus	11 (13)	18 (21)
Arterial Hemostasis		
manual compression	31 (36)	39 (45)
closure device	56 (66)	54 (63)

Data are n (%), unless otherwise stated. Plus-minus values are means ± SD. *More than one

arterial segment per stent was allowed. SFA=superficial femoral artery.

Table 3: Secondary endpoints at two years after stent implantation in a modified intention-to-Treat Analysis

	Misago [□] (n=85)	Zilver [□] PTX (n=86)	HR [95% CI]	p-value
All cause of mortality	6.4	1.2	7.3 (0.9–59.3)	0.06
Major amputation	0	0	NA	NA
Primary sustained clinical improvement	77.6	77.8	0.9 (0.5–1.6)	0.65
Secondary sustained clinical improvement	89.1	87.6	0.7 (0.3–1.5)	0.33
In-stent restenosis	19.1	14.2	1.2 (0.6–2.4)	0.64
In-stent thrombosis	6.7	8.6	0.9 (0.3–2.3)	0.75
Primary patency	74.6	78.8	1.2 (0.6–2.1)	0.62
TLR	14.4	12.4	1.2 (0.5–2.8)	0.69
TER	3.7	10.1	0.4 (0.1–1.3)	0.12
Ankle-brachial index	0.9±0.2	0.9±0.2	NA	0.44
Stent fracture (n)	2	1	NA	0.61

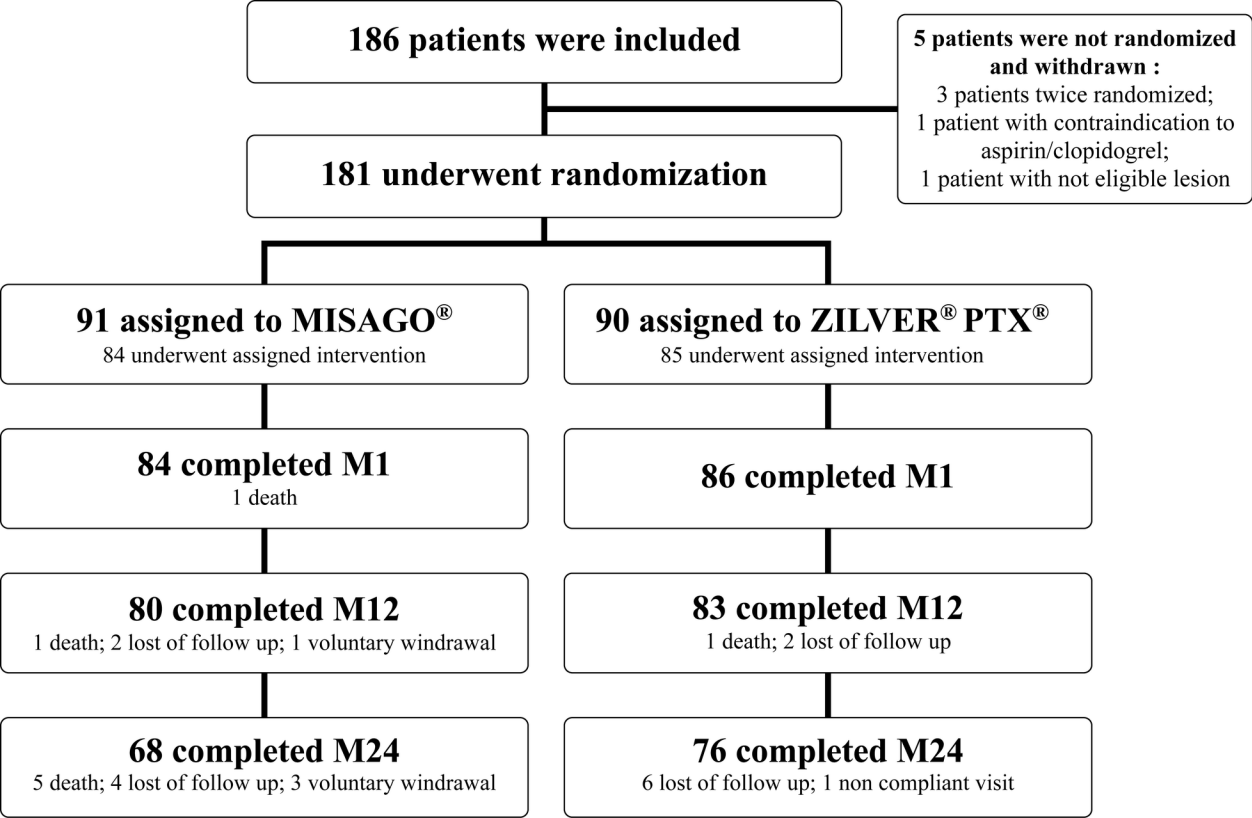
Data are Kaplan Meier estimates unless otherwise stated. NA=not available.
TLR=target

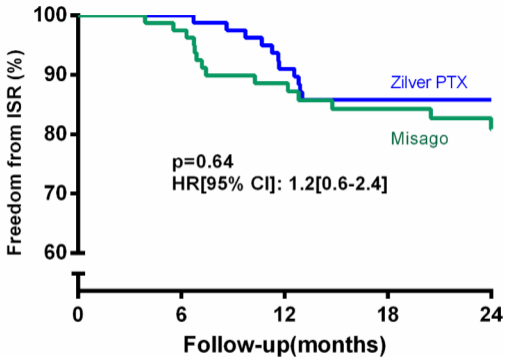
lesion revascularisation. TER=target extremity revascularisation.

Table 4: Health-related quality of life (EQ-5D-3L)

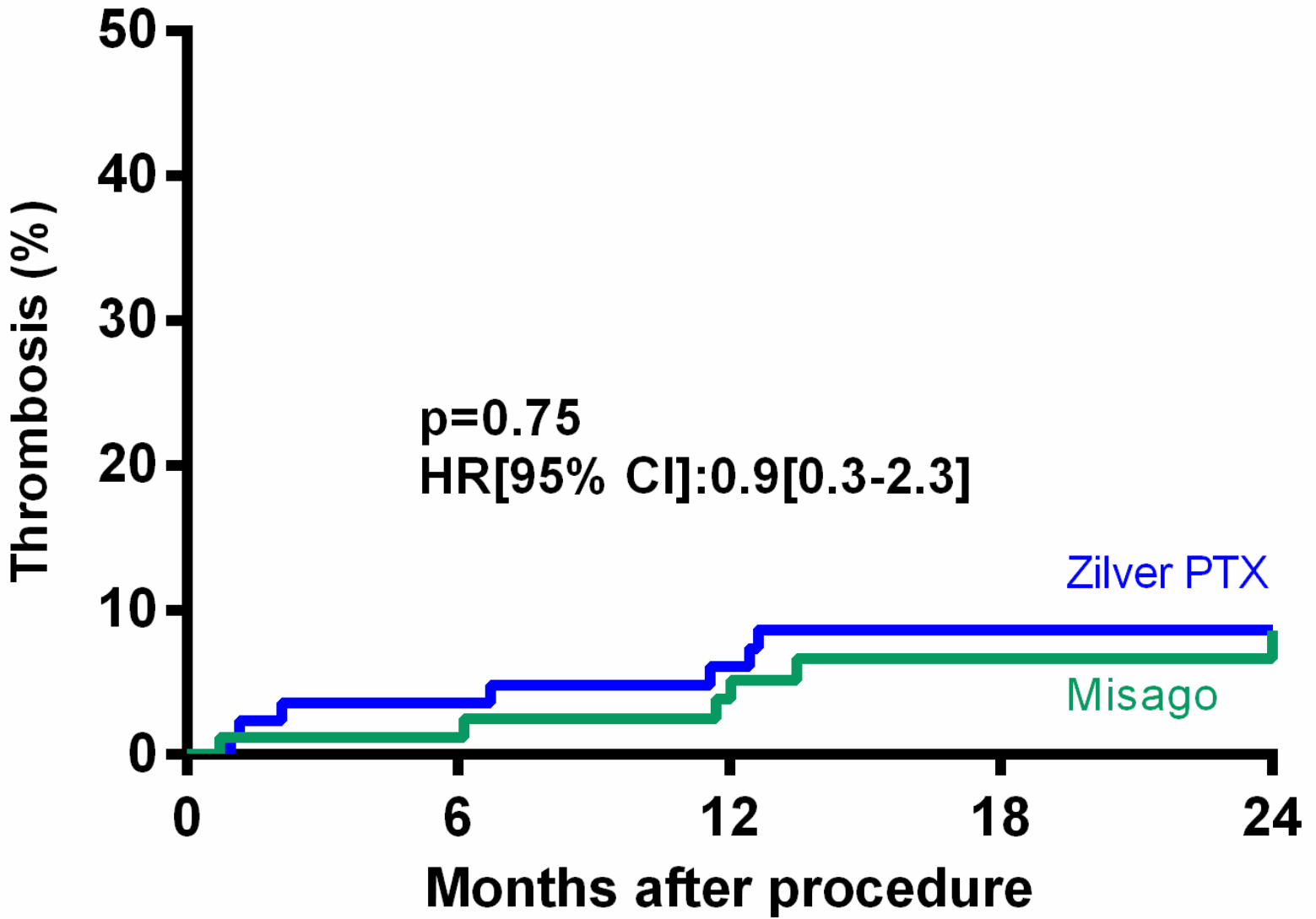
	Misago [□]	Zilver [□] PTX [□]	Difference [95% CI]	p-value
Baseline to 1 Month	n= 59	n=64		
Mobility	38 (64.4)	34 (53.1)	0.1 [-0.1 to 0.3]	0.20
Self-care	2 (3.4)	4 (6.3)	-0.0 [-0.1 to 0.1]	0.68
Usual activity	15 (25.4)	15 (23.4)	0.0 [-0.1 to 0.2]	0.79
Pain/ discomfort	37 (62.7)	34 (53.1)	0.1 [-0.0 to 1.0]	0.28
Anxiety	12 (20.3)	13 (20.3)	0.0 [-0.1 to 0.2]	0.99
Baseline to 12 Months	n= 55	n=52		
Mobility	28 (51)	25 (48.1)	0.0 [-0.2 to 0.2]	0.76
Self-care	0 (0.0)	3 (5.8)	-0.0 [-0.1 to 0.0]	0.11
Usual activity	17 (31)	13 (25)	0.0 [-0.1 to 0.2]	0.49
Pain/ discomfort	26 (47.3)	32 (61.5)	-0.1 [-0.3 to 0.0]	0.13
Anxiety	9 (16.4)	10 (19.2)	-0.0 [-0.2 to 0.1]	0.69
Baseline to 24 Months	n= 52	n=51		
Mobility	29 (55.8)	27 (53)	0.0 [-0.2 to 0.2]	0.77
Self-care	2 (3.9)	3 (5.9)	-0.0 [-0.1 to 0.1]	0.68
Usual activity	18 (34.7)	11 (21.6)	0.1 [-0.1 to 0.0]	0.14
Pain/ discomfort	29 (55.8)	26 (51)	0.1 [-0.1 to 0.2]	0.63
Anxiety	12 (23.0)	12 (23.6)	0.0 [-0.2 to 0.2]	0.96

Data are n (%)

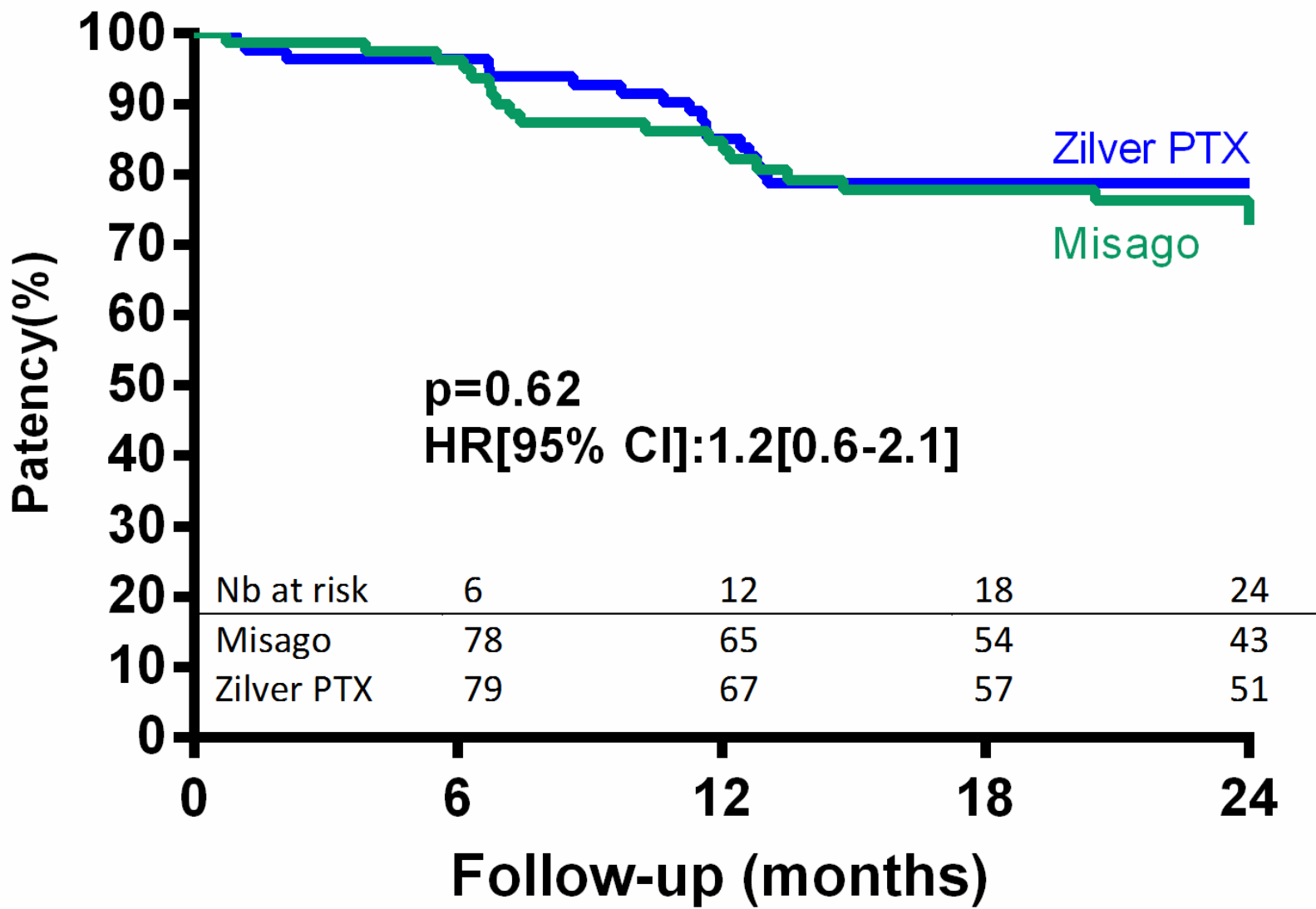


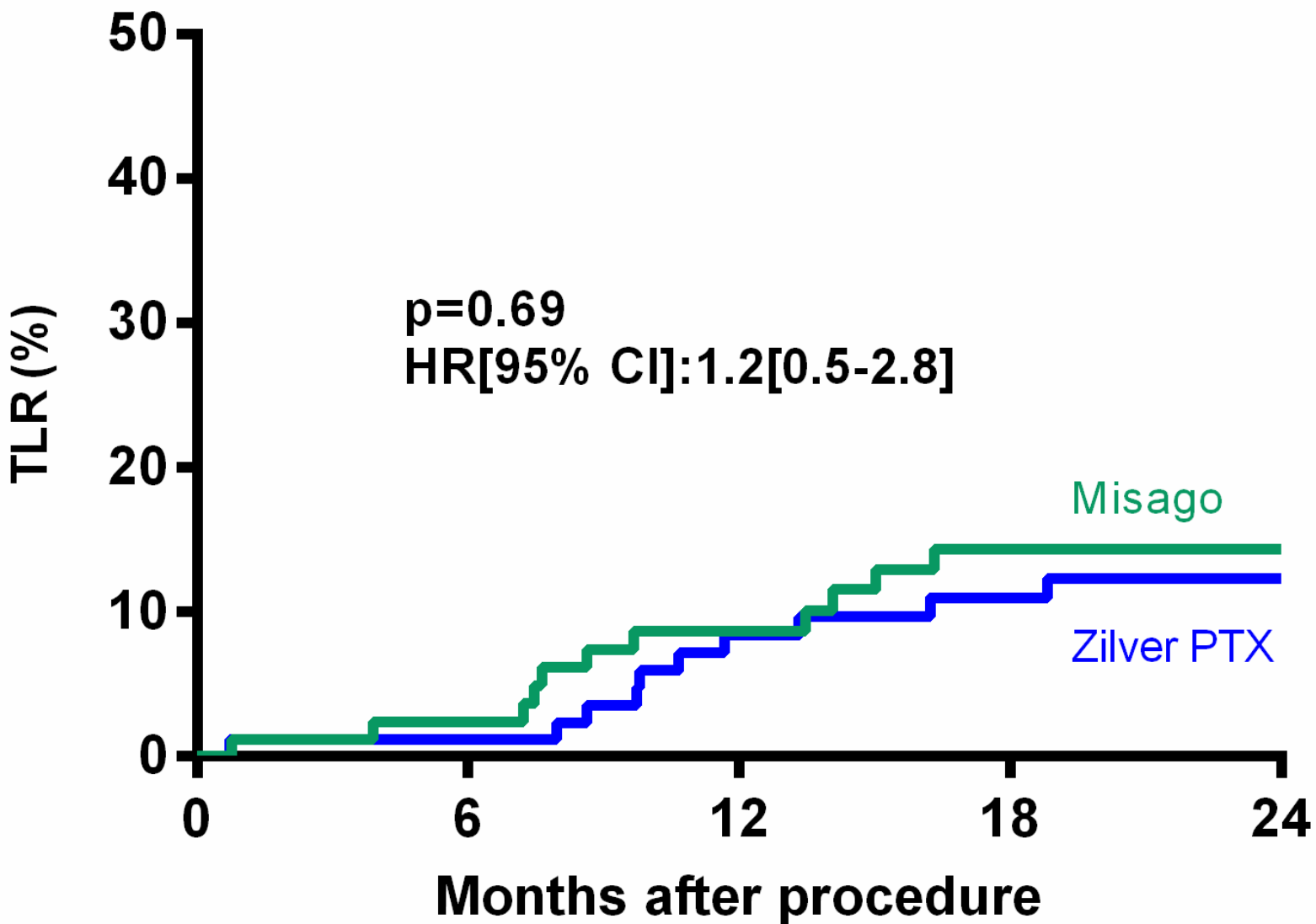


Nb at risk	6	12	18	24
Misago	77	67	56	44
Zilver PTX	81	69	61	54



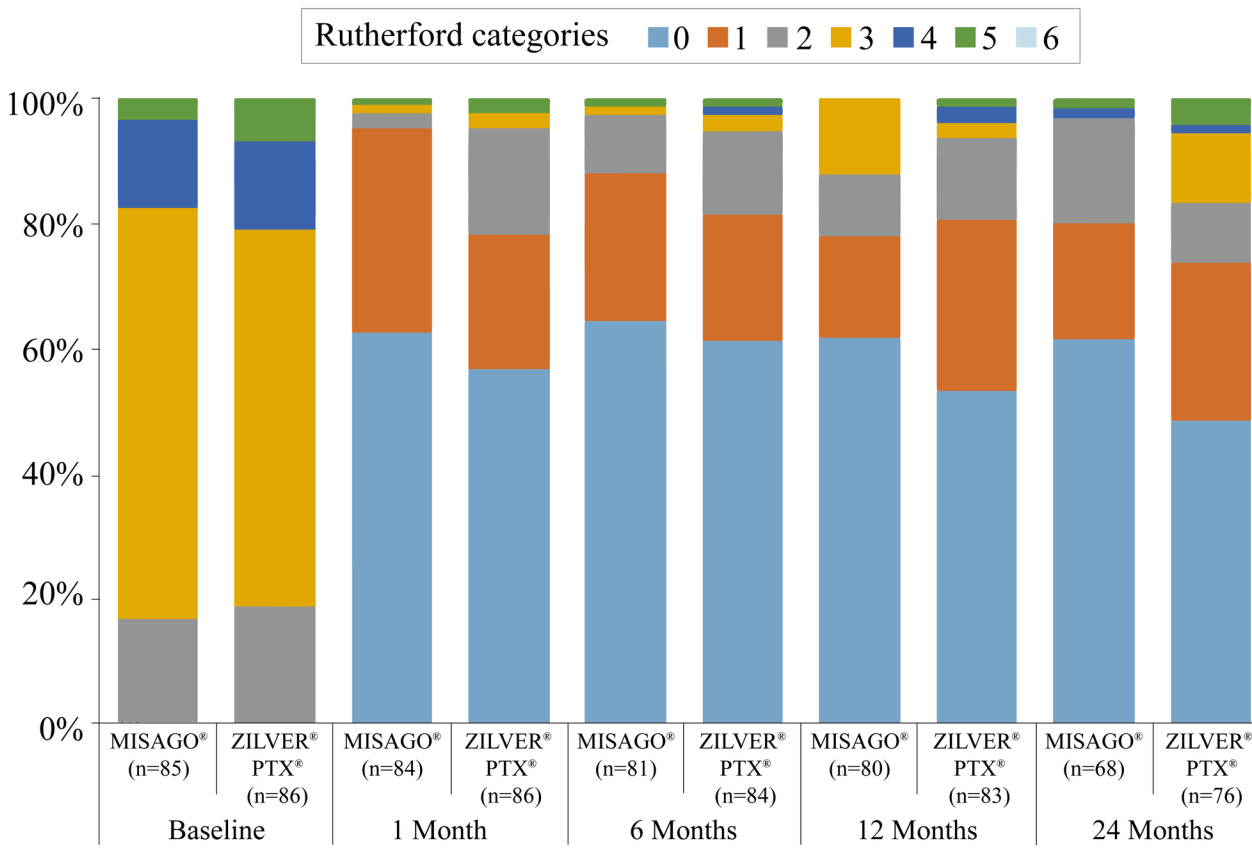
Nb at risk	6	12	18	24
Misago	78	71	63	51
Zilver PTX	79	74	67	58

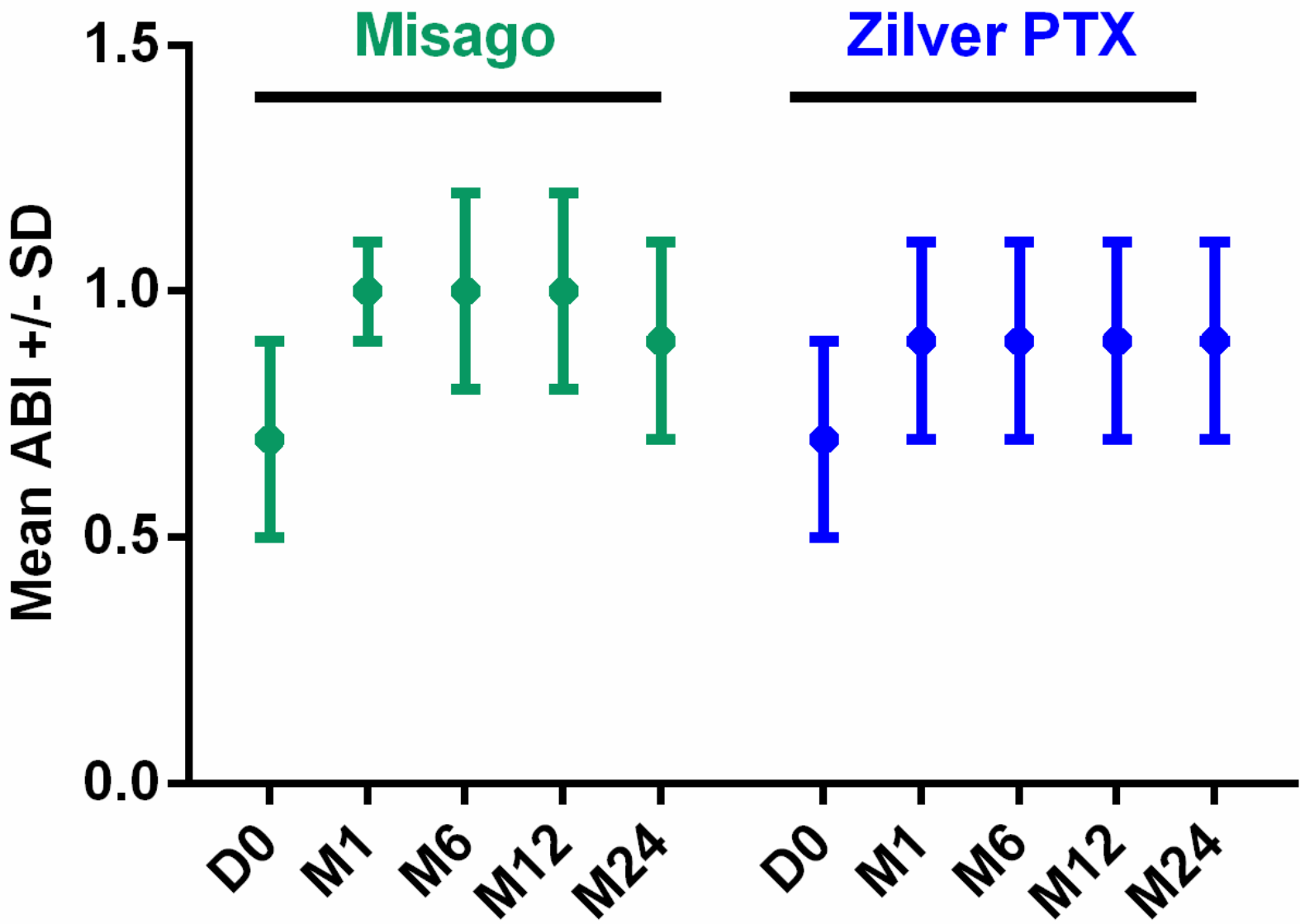


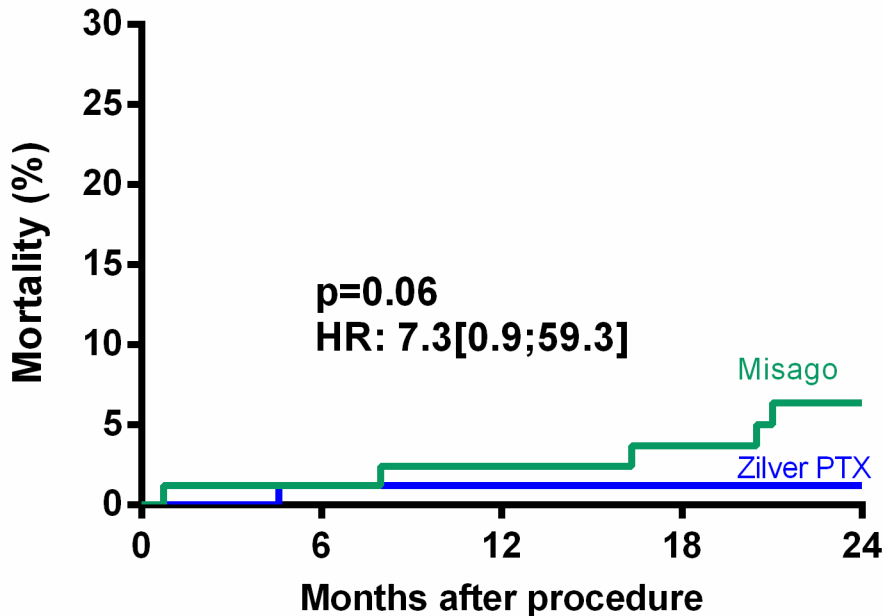


Nb at risk	6	12	18	24
Misago	78	71	60	48
Zilver PTX	83	74	66	58

Figure 3 : Distribution of Rutherford categories







Nb at risk	6	12	18	24
Misago	81	79	74	59
Zilver PTX	83	81	75	67