The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2022; 29: 1448-1457. http://doi.org/10.5551/jat.63225

Ten-Year Clinical Follow-Up Following Bare-Nitinol Stent Implantation for Femoropopliteal Artery Disease

Yoshimitsu Soga[1], Mitsuyoshi Takahara[2], Osamu Iida[3], Kenji Suzuki[4], Shinsuke Mori[5], Daizo Kawasaki[6], Kazuki Haraguchi[7], Terutoshi Yamaoka[8] and Kenji Ando[1]

[1]Department of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan
[2]Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[3]Cardiovascular Center, Kansai Rosai Hospital, Amagasaki, Japan
[4]Department of Cardiology, Tokyo Saiseikai Central Hospital, Tokyo, Japan
[5]Department of Cardiology, Yokohama-city Tobu Hospital, Yokohama, Japan
[6]Department of Cardiology, Morinomiya Hospital, Osaka, Japan
[7]Department of Cardiology, Shin-Koga Hospital, Kurume, Japan
[8]Department of Vascular Surgery, Matsuyama Red Cross Hospital, Matsuyama, Japan

Aim: More than 5-year clinical outcomes after femoropopliteal (FP) stenting with bare-nitinol stent (BNS) have not yet been unclear. We investigate the long-term patency and mortality following FP stenting with BNS.

Methods: This study was a multicenter retrospective study of a prospectively maintained database. From April 2004 to December 2011, 1824 consecutive patients (2211 limbs) who underwent FP stenting with BNS for de novo lesions were selected and analyzed. Primary endpoint was primary patency which was defined as treated vessel without restenosis and reintervention and its associated factors.

Results: The prevalence of diabetes mellitus and dialysis was 60.5% and 23.8%, respectively. Chronic limb-threatening ischemia (CLTI) accounted for 30.8%. Chronic total occlusion (CTO) was found in 52.7%, and lesion length was more than 20 cm in 22.6%. During the median follow-up of 3.8 years (interquartile range, 1.4 to 7.4 years), 1049 cases lost patency, whereas 355 cases were dead without experiencing loss of patency. The primary patency (95% CI) was estimated to be 74.8%, 47.3% and 29.1% at 1-, 5- and 10-year. On multivariate analysis, female sex, age ≥ 80 years, diabetes, dialysis, CLTI, CTO, arterial calcification, long lesion (>20 cm), and small vessel (≤ 4 mm) were the independent predictors of primary patency after FP stenting. In addition, the prognostic impact of age ≥ 80 years, CLTI, and arterial calcification was significantly attenuated afterwards ($P<0.05$).

Conclusions: Ten-year patency after BNS implantation for FP disease has been continuously reducing up to 10 years and the prognostic impact of risk factors was changed over time.

See editorial vol. 29: 1423-1424

Key words: Endovascular therapy, Femoropopliteal, Stent, Long-term

Introduction

Primary stenting with self-expandable bare-nitinol stent (BNS) has been reported to be more effective than standard balloon angioplasty in the treatment of femoropopliteal (FP) disease[1-4] and it has been widely performed in clinical setting. In terms of mid-term patency after the procedure for especially complex lesions, primary stenting was acceptable, but not enough[5, 6]. After that, restenosis has been dramatically reduced with advent of paclitaxel-coated balloon[7-9] and paclitaxel-eluting stent[10, 11]. On the

Address for correspondence: Yoshimitsu Soga, Department of Cardiology, Kokura Memorial Hospital, 3-2-1 Asano, Kokurakita-ku, Kitakyushu, Japan, 802-0001
E-mail: sogacchy@yahoo.co.jp

Received: August 17, 2021 Accepted for publication: October 25, 2021

other hand, mortality risk or signal after paclitaxel-eluting devices for FP lesion was reported[12, 13]. Although this safety concern is still in debate continuously[14-16], a conclusion hasn't been reached yet. the usage of BNS has been positively reconsidered due to this issue. In addition, the long-term outcome is very important to understand safety and effectiveness in BNS era and to compare with drug-eluting device era. However, the long-term patency and mortality following bare-nitinol stent implantation for FP lesion still remain unclear.

This study aimed to reveal the 10-year patency and mortality, and their associated factors in patients undergoing FP BNS implantation for symptomatic de novo FP artery disease.

Methods

Study Population

The study was performed as a multicenter retrospective analysis of a prospectively maintained database. This study analyzed the data of consecutive patients who underwent BNS implantation for symptomatic de novo FP artery disease between 2004 and 2011 at 13 cardiovascular centers in Japan. Of 2401 limbs of 1968 eligible patients, 190 limbs were excluded due to missing data on baseline characteristics. The remaining 2211 limbs of 1824 patients were finally included in the current study. Isolated common femoral and isolated popliteal artery disease were excluded from this study. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the institutional review boards of the participating institutions. The requirement to obtain any informed consent was waived. This study is registered with the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR), as accepted by the International Committee of Medical Journal Editors (No. UMIN000002726).

Procedures and Follow-Up

All patients were recommended to receive dual antiplatelet therapy (aspirin 100 mg/day, clopidogrel 75 mg/day, ticlopidine 100 mg twice a day or cilostazol 100 mg twice a day) by the day before EVT or earlier. Either ipsilateral or contralateral femoral puncture was used. After insertion of a 6-Fr sheath, an intra-arterial bolus of 5000 IU of heparin was injected and supplemented as required to maintain an active clotting time >200 s.

After passing the wire, pre-dilatation was performed with an appropriately sized angioplasty balloon before stenting. Six types of bare-nitinol stents were then implanted: S.M.A.R.T. (Cordis J&J, Miami, FL), Luminexx (Bard, Murray Hill, NJ), LIFE stent (Bard, Murray Hill, NJ), Zilver518 (Cook Medical, Bloomington, IN), MISAGO (Terumo, Tokyo, Japan), and INNOVA (Boston Scientific, Marlborough, MA, USA). The stent type was determined by the operator, and the stent size was chosen to be 1-2 mm larger than the reference vessel diameter. After stent placement, post-dilatation was added with approximately reference vessel diameter size if needed.

After the procedure, all patients were prescribed lifelong aspirin (100 mg/day) and prolonged (at least 1 month) clopidogrel 75 mg/day, ticlopidine 100 mg twice a day or cilostazol 100 mg twice a day was recommended. The presence of restenosis was monitored by duplex ultrasound respectively at least every 1 year in addition to perioperative period (within 2 month).

Outcome Measures

The primary outcome measure of this study was primary patency and its associated factors. The secondary outcome measures were freedom from reintervention, occlusion and bypass conversion, and mortality. Primary patency was defined as a treated vessel without restenosis and reintervention. Restenosis was defined as >2.4 times the peak systolic velocity ratio on duplex ultrasound. An undetectable signal in stented segments in duplex ultrasound was graded as complete occlusion. Below-the-knee (BTK) run-off and arterial calcification was assessed by angiography before or after the procedure.

Statistical Analyses

Data are presented as medians and interquartile ranges for continuous variables or as percentages for discrete variables, if not otherwise mentioned. A P value <0.05 was considered statistically significant and 95% confidence intervals (CI) were reported where appropriate. The primary patency, as well as freedom from reintervention, occlusion, and bypass conversion, was estimated using the cumulative incidence function, treating death as a competing risk. The association between baseline characteristics and loss of patency was analyzed using Fine and Gray's regression model for the subdistribution of competing risks, where we treated death as a competing risk. To address an issue of bilaterality, a frailty term of inter-subject variability was included as random effects in the model. The proportional hazards assumption regarding each variable of interest was checked by developing the model in which the variable and its interaction term with time were simultaneously

included. When the null hypothesis that the regression coefficient of the interaction term with time was zero was statistically denied, indicating that the proportional hazards assumption was violated, the interaction term with time was included in the subsequent multivariate model. Furthermore, as a supplementary analysis, we developed the multivariate model in which laboratory parameters were additionally entered. In the model, cases with missing data were excluded (i.e., listwise deletion). We additionally estimated the overall survival rate using the Kaplan-Meier method, and investigated the association between baseline characteristics and mortality risk using the Cox hazards regression model. All statistical analyses were performed using R version 3.6.0 (R Development Core Team, Vienna, Austria).

Results

Baseline characteristics of the study population are presented in **Table 1**. Mean age was 73 ± 9 years, and male gender, the prevalence of diabetes mellitus (DM) and dialysis-dependent renal failure was 70.1%, 60.5% and 23.8%, respectively. Chronic limb-threatening ischemia (CLTI) accounted for 30.8%. Chronic total occlusion (CTO) was found in 52.7%, and lesion length was more than 20 cm in 22.6%.

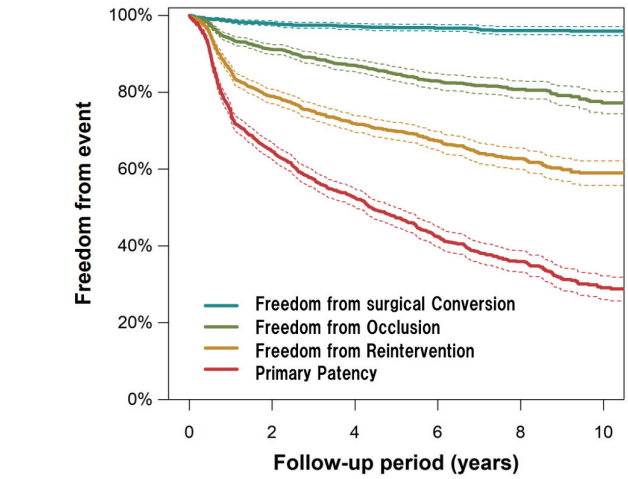
During the median follow-up of 3.8 years (interquartile range, 1.4 to 7.4 years; mean and standard deviation, 4.6 ± 3.6 years), 1049 cases lost patency, whereas 355 cases were dead without experiencing loss of patency. The follow-up rate (equal to 100% minus the proportion of cases censored without loss of patency or the competing risk [i.e., death] within a time point of interest) was 89.8% at 1 year, 81.3% at 3 years, 75.2% at 5 years, and 66.7% at 10 years. The primary patency (95% CI) was estimated to be 74.8% (72.9% to 76.7%) at 1 year, 57.5% (55.2% to 59.8%) at 3 years, 47.3% (44.8% to 49.9%) at 5 years, and 29.1% (26.0% to 32.2%) at 10 years **(Fig. 1)**. Cumulative incidence rate of reintervention, occlusion, and bypass conversion were estimated to be 14.4% (12.8% to 15.9%), 6.0% (5.0% to 7.1%) and 1.4% (0.9% to 2.0%) at 1 year, 24.9% (22.9% to 27.0%), 11.1% (9.6% to 12.6%) and 2.6% (1.8% to 3.3%) at 3 years, 30.2% (27.9% to 32.5%), 15.4% (13.5% to 17.2%) and 3.2% (2.3% to 4.0%) at 5 years, and 41.0% (37.9% to 44.2%), 22.8% (19.9% to 25.6%) and 4.1% (3.0% to 5.2%) at 10 years.

As shown in **Table 2**, age ≥ 80 years, dual antiplatelet therapy, statin use, heart failure, CLTI, severe calcification, and no BTK runoff, as well as C-reactive protein ≥ 0.3 mg/dl, demonstrated a significant interaction effect with time in respective crude models (all $P<0.05$), indicating that the assumption of proportional hazards was violated regarding these variables. We therefore subsequently developed the multivariate model in which these variables accompanied their interaction term with time, whereas the other variables did not. Consequently,

Table 1. Baseline characteristics of the study population

Patient characteristics	(*n* = 1824)
Male sex	1279 (70.1%)
Age (years)	73 ± 9
≥ 80 years	445 (24.4%)
Smoking history	1090 (59.8%)
Diabetes mellitus	1110 (60.9%)
Dialysis dependence	435 (23.8%)
Dual antiplatelet therapy*	1421 (77.9%)
Statin use	688 (37.7%)
Coronary artery disease	904 (49.6%)
Heart failure	201 (11.0%)
LDL cholesterol (mg/dl)	103 ± 33
≥ 100 mg/dl	817 (51.7%)
(missing data)	243 (13.3%)
HDL cholesterol (mg/dl)	48 ± 16
< 40 mg/dl	377 (30.6%)
(missing data)	592 (32.5%)
Triglycerides (mg/dl)	116 (83 - 161)
≥ 150 mg/dl	429 (29.4%)
(missing data)	367 (20.1%)
C-reactive protein (mg/dl)	0.20 (0.10 - 1.00)
≥ 0.3 mg/dl	669 (45.6%)
(missing data)	357 (19.6%)
Limb characteristics	(*n* = 2211)
Claudication	1529 (69.2%)
CLTI	682 (30.8%)
CTO	1165 (52.7%)
Arterial calcification	1238 (56.0%)
Lesion length (cm)	14 ± 9
> 20 cm	499 (22.6%)
RVD (mm)	5.4 ± 0.9
≤ 4 mm	212 (9.6%)
No below-the-knee runoff	207 (9.4%)
TASC II classification	
Class A	541 (24.5%)
Class B	567 (25.6%)
Class C	356 (16.1%)
Class D	747 (33.8%)

Data are means ± standard deviations, medians (interquartile ranges), or frequency (percentages). CLTI, chronic limb-threatening ischemia; CTO, chronic total occlusion; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RVD, reference vessel diameter.
*Dual antiplatelet therapy; aspirin (100 mg/day) plus clopidogrel 75 mg/day, ticlopidine 100 mg twice a day or cilostazol 100 mg twice a day.



Number at risk						
Surgical conversion	2211	1495	1062	692	545	302
Occlusion	2211	1383	970	630	434	190
Reintervention	2211	1191	796	518	350	184
Restenosis	2211	1025	639	367	228	104
Estimate ± SE						
Surgical conversion	100.0±0.0%	97.9±0.3%	97.1±0.4%	96.7±0.5%	96.1±0.5%	95.9±0.6%
Occlusion	100.0±0.0%	91.2±0.7%	87.0±0.8%	82.9±1.0%	80.7±1.2%	77.2±1.5%
Reintervention	100.0±0.0%	78.9±1.0%	71.8±1.1%	67.4±1.2%	62.7±1.4%	59.0±1.6%
Restenosis	100.0±0.0%	64.7±1.1%	52.5±1.2%	42.6±1.3%	36.0±1.4%	29.1±1.6%

Fig. 1. Limb outcomes after femoropopliteal stent implantation

The incidence rate was estimated by the cumulative incidence function in which death was treated as the competing risk. Dotted lines indicate 95% confidence intervals. SE, standard error.

Table 2. Change in the impact of baseline characteristics on the risk of patency loss during the follow-up period

	Fold change of hazard ratio per doubling of the follow-up time
Male sex	1.00 [0.93 to 1.09] (P=0.92)
Age ≥ 80 years	0.86 [0.79 to 0.94] (P=0.001)
Smoking history	1.05 [0.97 to 1.13] (P=0.27)
Diabetes mellitus	1.02 [0.94 to 1.11] (P=0.60)
Dialysis dependence	0.92 [0.85 to 1.00] (P=0.053)
Dual antiplatelet therapy	1.11 [1.02 to 1.21] (P=0.021)
Statin use	1.10 [1.02 to 1.19] (P=0.018)
Coronary artery disease	1.01 [0.94 to 1.09] (P=0.71)
Heart failure	0.88 [0.79 to 0.98] (P=0.025)
CLTI	0.82 [0.75 to 0.89] (P<0.001)
CTO	0.93 [0.86 to 1.01] (P=0.080)
Arterial calcification	0.90 [0.83 to 0.97] (P=0.009)
Lesion length >20 cm	0.92 [0.84 to 1.00] (P=0.055)
RVD ≤ 4 mm	1.02 [0.90 to 1.14] (P=0.78)
No below-the-knee runoff	0.88 [0.78 to 0.99] (P=0.030)
LDL cholesterol ≥ 100 mg/dl	0.98 [0.91 to 1.07] (P=0.69)
HDL cholesterol <40 mg/dl	0.94 [0.85 to 1.04] (P=0.25)
Triglycerides ≥ 150 mg/dl	1.06 [0.96 to 1.16] (P=0.26)
C-reactive protein ≥ 0.3 mg/dl	0.87 [0.80 to 0.95] (P=0.001)

Data are presented as the fold change in the hazard ratio of each variable per doubling of the follow-up time [95% confidence intervals] (P values), derived from the Fine and Gray's regression model for the subdistribution of competing risks in which each variable of interest and its interaction term with time were entered as the explanatory variables, and a frailty term of inter-subject variability was included as random effects. The fold changes in the hazard ratio by time were calculated as the exponential conversion of the regression coefficient for the interaction term with time. CLTI, chronic limb-threatening ischemia; CTO, chronic total occlusion; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RVD, reference vessel diameter.

Table 3. Impact of baseline characteristics on risk of patency loss

	Multivariate model 1	Multivariate model 2 (n=1137)
Male sex	0.74 [0.60 to 0.91] (P=0.004)	0.69 [0.52 to 0.93] (P=0.015)
Age ≥ 80 years	2.61 [1.18 to 5.75] (P=0.018)	2.66 [0.89 to 7.91] (P=0.079)
Interaction with time	0.89 [0.81 to 0.97] (P=0.011)	0.89 [0.78 to 1.01] (P=0.081)
Smoking history	0.98 [0.81 to 1.19] (P=0.84)	1.01 [0.75 to 1.36] (P=0.95)
Diabetes mellitus	1.41 [1.17 to 1.70] (P<0.001)	1.44 [1.11 to 1.86] (P=0.006)
Dialysis dependence	1.28 [1.02 to 1.61] (P=0.034)	1.30 [0.94 to 1.78] (P=0.11)
Dual antiplatelet therapy	0.48 [0.22 to 1.05] (P=0.066)	0.87 [0.31 to 2.47] (P=0.79)
Interaction with time	1.09 [0.99 to 1.19] (P=0.072)	1.00 [0.89 to 1.13] (P=0.98)
Statin use	0.60 [0.29 to 1.26] (P=0.18)	0.54 [0.20 to 1.46] (P=0.22)
Interaction with time	1.06 [0.97 to 1.15] (P=0.18)	1.08 [0.96 to 1.21] (P=0.21)
Coronary artery disease	0.94 [0.78 to 1.13] (P=0.50)	0.91 [0.70 to 1.17] (P=0.47)
Heart failure	2.35 [0.87 to 6.33] (P=0.092)	1.28 [0.36 to 4.60] (P=0.71)
Interaction with time	0.91 [0.81 to 1.03] (P=0.13)	0.97 [0.84 to 1.13] (P=0.72)
CLTI	3.90 [1.81 to 8.38] (P<0.001)	3.51 [1.16 to 10.57] (P=0.026)
Interaction with time	0.86 [0.79 to 0.94] (P=0.001)	0.87 [0.76 to 0.99] (P=0.029)
CTO	1.39 [1.15 to 1.67] (P=0.001)	1.71 [1.32 to 2.22] (P<0.001)
Arterial calcification	1.99 [0.98 to 4.03] (P=0.057)	1.18 [0.46 to 3.04] (P=0.73)
Interaction with time	0.93 [0.85 to 1.00] (P=0.057)	0.97 [0.87 to 1.08] (P=0.56)
Lesion length >20 cm	1.31 [1.05 to 1.62] (P=0.014)	1.30 [0.97 to 1.74] (P=0.085)
RVD ≤ 4 mm	2.41 [1.83 to 3.17] (P<0.001)	1.74 [1.17 to 2.61] (P=0.007)
No below-the-knee runoff	1.58 [0.55 to 4.51] (P=0.39)	1.90 [0.49 to 7.43] (P=0.36)
Interaction with time	0.93 [0.83 to 1.05] (P=0.26)	0.92 [0.79 to 1.09] (P=0.34)
LDL cholesterol ≥ 100 mg/dl	N/I	0.97 [0.76 to 1.25] (P=0.84)
HDL cholesterol <40 mg/dl	N/I	0.98 [0.74 to 1.30] (P=0.91)
Triglycerides ≥ 150 mg/dl	N/I	1.01 [0.76 to 1.35] (P=0.93)
C-reactive protein ≥ 0.3 mg/dl	N/I	1.54 [0.57 to 4.16] (P=0.40)
Interaction with time	N/I	0.94 [0.84 to 1.06] (P=0.29)

Data are presented as adjusted hazard ratios (HRs) for loss of patency and their 95% confidence intervals, derived from the Fine and Gray's regression model for the subdistribution of competing risks in which a frailty term of inter-subject variability was included as random effects. In the multivariate model 1, all the variables in the table except laboratory parameters were entered as explanatory variables, whereas in the multivariate model 2, laboratory parameters were additionally entered. Data on the interaction with time are presented as the fold change in the hazard ratio of each variable per doubling of the follow-up time. Note that cases with missing data were excluded in a listwise manner while the multivariate models were developed; the multivariate model 2 was developed with use of data in 1137 limbs. CLTI, chronic limb-threatening ischemia; CTO, chronic total occlusion; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RVD, reference vessel diameter. N/I, not included.

as summarized in the Multivariate model 1 in **Table 3**, female sex, age ≥ 80 years, DM, dialysis-dependent renal failure, CLTI, CTO, lesion length >20 cm, and reference vessel diameter (RVD) ≤ 4 mm was significantly associated with an increased risk of patency loss immediately after stent implantation (all P<0.05), while the prognostic impact of age ≥ 80 years and CLTI was significantly attenuated afterwards (P<0.05). When laboratory parameters were included in the model, none of them were significantly associated with the risk of patency loss (Multivariate model 2 in **Table 3**). In the Multivariate model 2, age ≥ 80 years, dialysis-dependent renal failure, and lesion length >20 cm lost statistical significance, probably due to a smaller sample size (n=1137).

Fig. 2 shows the Kaplan-Meier estimates of the overall survival rate and the details of death. The mortality (95% CI) was estimated to be 7.8% (6.5% to 9.1%) at 1 year, 17.8% (15.9% to 19.7%) at 3 years, 28.0% (25.5% to 30.4%) at 5 years, and 51.4% (47.7% to 54.8%) at 10 years. During the follow-up period, 583 patients died. Cardiac death occurred in 144 patients (25%) and cardiovascular death accounted for 37% of the deaths. Statin use, CLTI, lesion length >20 cm, and no BTK runoff, as well as C-reactive protein ≥ 0.3 mg/dl, demonstrated a significant interaction effect with time in respective crude models (all P<0.05) **(Table 4)**. The subsequent multivariate Cox regression model demonstrated that male sex, age ≥ 80 years, dialysis-dependent renal

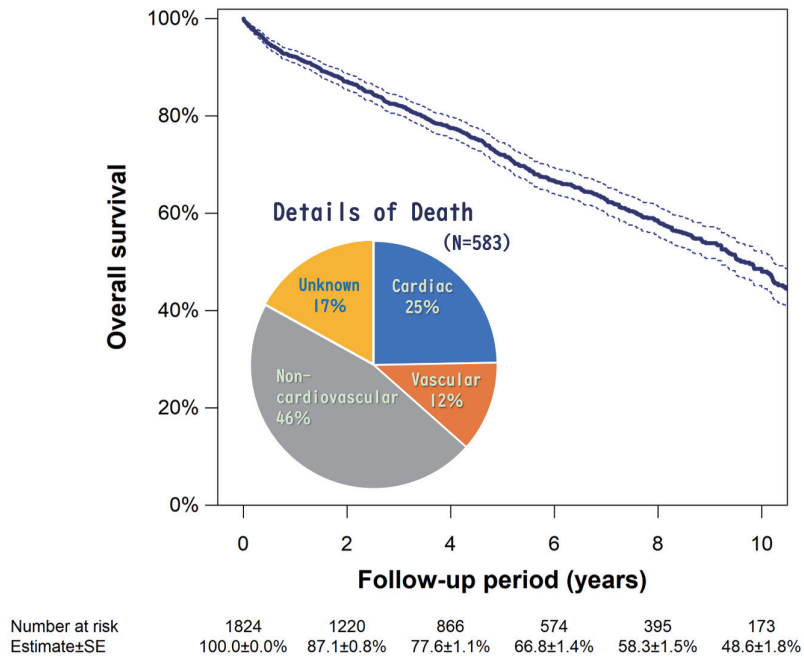


Fig. 2. Overall survival rate after FP stent implantation

The rate was estimated by the Kaplan-Meier method. Dotted lines indicate 95% confidence intervals. SE, standard error.

Table 4. Change in the impact of baseline characteristics on the risk of mortality during the follow-up period

	Fold change of hazard ratio per doubling of the follow-up time
Male sex	1.08 [0.99 to 1.18] (P=0.078)
Age ≥ 80 years	0.99 [0.91 to 1.08] (P=0.83)
Smoking history	1.04 [0.96 to 1.13] (P=0.39)
Diabetes mellitus	1.01 [0.93 to 1.09] (P=0.90)
Dialysis dependence	0.94 [0.86 to 1.02] (P=0.13)
Dual antiplatelet therapy	0.97 [0.89 to 1.07] (P=0.57)
Statin use	1.10 [1.00 to 1.21] (P=0.046)
Coronary artery disease	1.01 [0.94 to 1.10] (P=0.75)
Heart failure	0.96 [0.87 to 1.06] (P=0.46)
CLTI	0.71 [0.63 to 0.79] (P<0.001)
CTO	0.97 [0.90 to 1.05] (P=0.45)
Arterial calcification	0.96 [0.88 to 1.04] (P=0.31)
Lesion length >20 cm	0.91 [0.83 to 0.99] (P=0.037)
RVD ≤ 4 mm	1.00 [0.87 to 1.14] (P=0.96)
No below-the-knee runoff	0.87 [0.78 to 0.96] (P=0.006)
LDL cholesterol ≥ 100 mg/dl	1.04 [0.96 to 1.14] (P=0.32)
HDL cholesterol <40 mg/dl	0.24 [0.07 to 0.77] (P=0.017)
Triglycerides ≥ 150 mg/dl	1.11 [0.99 to 1.25] (P=0.081)
C-reactive protein ≥ 0.3 mg/dl	0.81 [0.73 to 0.89] (P<0.001)

Data are presented as the fold change in the hazard ratio of each variable per doubling of the follow-up time [95% confidence intervals] (P values), derived from the Cox regression model in which each variable of interest and its interaction term with time were entered as the explanatory variables. The fold changes in the hazard ratio by time were calculated as the exponential conversion of the regression coefficient for the interaction term with time. CLTI, chronic limb-threatening ischemia; CTO, chronic total occlusion; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RVD, reference vessel diameter.

Table 5. Impact of baseline characteristics on risk of mortality

	Multivariate model 1	Multivariate model 2 ($n=939$)
Male sex	1.42 [1.16 to 1.73] ($P=0.001$)	1.46 [1.10 to 1.93] ($P=0.009$)
Age ≥ 80 years	2.22 [1.83 to 2.70] ($P<0.001$)	2.10 [1.61 to 2.73] ($P<0.001$)
Smoking history	0.98 [0.81 to 1.18] ($P=0.81$)	0.88 [0.68 to 1.16] ($P=0.37$)
Diabetes mellitus	0.96 [0.81 to 1.14] ($P=0.66$)	0.99 [0.79 to 1.26] ($P=0.97$)
Dialysis dependence	2.18 [1.79 to 2.64] ($P<0.001$)	2.15 [1.64 to 2.80] ($P<0.001$)
Dual antiplatelet therapy	0.88 [0.73 to 1.06] ($P=0.17$)	0.89 [0.69 to 1.14] ($P=0.37$)
Statin use	0.68 [0.26 to 1.76] ($P=0.43$)	0.39 [0.10 to 1.50] ($P=0.17$)
Interaction with time	1.02 [0.92 to 1.12] ($P=0.73$)	1.08 [0.94 to 1.23] ($P=0.27$)
Coronary artery disease	1.15 [0.97 to 1.37] ($P=0.11$)	1.02 [0.81 to 1.29] ($P=0.85$)
Heart failure	1.74 [1.39 to 2.18] ($P<0.001$)	1.46 [1.09 to 1.96] ($P=0.011$)
CLTI	53.2 [17.2 to 165] ($P<0.001$)	27.0 [5.44 to 134] ($P<0.001$)
Interaction with time	0.73 [0.65 to 0.82] ($P<0.001$)	0.78 [0.66 to 0.91] ($P=0.002$)
CTO	1.05 [0.87 to 1.26] ($P=0.63$)	0.95 [0.74 to 1.22] ($P=0.70$)
Arterial calcification	1.22 [1.02 to 1.45] ($P=0.029$)	1.38 [1.08 to 1.76] ($P=0.009$)
Lesion length >20 cm	2.61 [1.11 to 6.13] ($P=0.028$)	2.28 [0.70 to 7.44] ($P=0.17$)
Interaction with time	0.92 [0.85 to 1.01] ($P=0.078$)	0.94 [0.83 to 1.06] ($P=0.30$)
RVD ≤ 4 mm	1.06 [0.79 to 1.42] ($P=0.69$)	1.06 [0.71 to 1.58] ($P=0.79$)
No below-the-knee runoff	2.32 [0.88 to 6.08] ($P=0.087$)	3.05 [0.81 to 11.50] ($P=0.10$)
Interaction with time	0.96 [0.86 to 1.07] ($P=0.44$)	0.92 [0.79 to 1.07] ($P=0.29$)
LDL cholesterol ≥ 100 mg/dl	N/I	0.82 [0.65 to 1.04] ($P=0.097$)
HDL cholesterol <40 mg/dl	N/I	1.06 [0.83 to 1.35] ($P=0.66$)
Triglycerides ≥ 150 mg/dl	N/I	0.77 [0.59 to 1.02] ($P=0.067$)
C-reactive protein ≥ 0.3 mg/dl	N/I	5.70 [1.37 to 23.8] ($P=0.017$)
Interaction with time	N/I	0.85 [0.74 to 0.98] ($P=0.028$)

Data are presented as adjusted hazard ratios (HRs) for mortality and their 95% confidence intervals, derived from the Cox regression model. In the multivariate model 1, all the variables in the table except laboratory parameters were entered as explanatory variables, whereas in the multivariate model 2, laboratory parameters were additionally entered. Data on the interaction with time are presented as the fold change in the hazard ratio of each variable per doubling of the follow-up time. Note that cases with missing data were excluded in a listwise manner while the multivariate models were developed; the multivariate model 2 was developed with use of data in 939 patients. CLTI, chronic limb-threatening ischemia; CTO, chronic total occlusion; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RVD, reference vessel diameter. N/I, not included.

failure, heart failure, CLTI, arterial calcification, and lesion length >20 cm was significantly associated with an increased risk of mortality immediately after stent implantation (all $P<0.05$), while the prognostic impact of CLTI was significantly attenuated afterwards ($P<0.001$) (Multivariate model 1 in **Table 5**). When laboratory parameters were included in the model, C-reactive protein ≥ 0.3 mg/dl was significantly associated with an increased risk of mortality, and its association was significantly attenuated afterwards (Multivariate model 2 in **Table 5**). In the Multivariate model 2, lesion length >20 cm lost statistical significance, probably due to a smaller sample size ($n=939$).

Discussion

In this study, we evaluated that the long-term outcomes (patency and mortality) and their prognostic factors in patients undergoing BNS implantation for symptomatic de novo FP artery disease. This study added as a new insight over 5-year vessel patency after that was not sufficient. Vessel patency has been continuously reducing after a year up to 10 years and the prognostic impact of risk factors was changed over time. One strength of our study was that the time-dependent impact of respective risk factors was assessed.

Vessel Patency

It is reported that restenosis occurrence in BNSs placed for FP lesions peaks after roughly 1 year[17], and that long-term efficacy is limited and decreases over time[18]. Even in this study, primary patency rapidly decreased during the first year or so **(Fig. 1)**. However, it did not subsequently plateau, instead continuing to decrease for two years and thereafter. From this we can see that after BNS implantation, the risk of restenosis continues to be present long after it has peaked.

There have been almost no studies that

investigate the differences between restenosis occurring in the short term and in the medium-to-long term after BNS implantation. An important point to consider when formulating treatment strategies to maintain patency long-term is whether in-stent neointimal growth continues into the chronic phase, or whether neoatherosclerosis[19] occurs. In the future, a study must be conducted that investigates this, addressing the associated pathologies.

The risk factors for restenosis in lower limb BNSs are female sex, an age of ≥ 80 years, DM, dialysis, CLTI, CTO, long lesion (>20 cm), and small vessel (RVD ≤ 4 mm). The impact of age (>80 years) and CLTI diminishes with time—we could say, in other words, that these have a major impact on restenosis in the short term after implantation. As female sex, diabetes, and small vessel pose the same risk after a certain amount of time has passed as they do in the short term (i.e. the risk of restenosis continues to be present in the chronic phase), BNS may be contraindicated in cases with several such risks.

It is reported that the primary patency of autogenous saphenous vein bypass grafts was 84% at 1 year, 72% at 5 years, and 55% at 10 years, and that the secondary patency of such surgeries is 91% at 1 year, 81% at 5 years, and 70% at 10 years[20]. Furthermore, better outcome from Japanese data has been reported even when prosthetic grafts were used[21]. Our study did not show satisfactory results with BNS in the long term (>5 years). It will be necessary in the future to investigate whether improved results are being obtained with drug-eluting devices not only in the short and medium terms but also in the long term (>5 years).

Freedom from reintervention was 59% at 10 years, and freedom from occlusion (secondary patency) was 77% at 10 years. As these results are almost on par with those obtained with autogenous saphenous vein bypass grafts, it was thought that BNS is acceptable long-term if patients are selected appropriately.

Mortality

The mortality risk factors in patients who underwent BNS implantation were male sex, an age of ≥ 80 years, dialysis, heart failure, CLTI, arterial calcification, and long lesion (>20 cm). The impact of CLTI decreased with time. This does not necessarily indicate that the mortality rate improved with time, but that the mortality rate was high in the short term after treatment, supporting the notion that life expectancy must be considered when treating CLTI patients[22-24]. Increased CRP levels would be another potential risk factor for the mortality risk. Future studies with a larger sample size will be needed to validate current findings.

An age of ≥ 80 years, dialysis, CLTI, and long lesion (>20 cm) were independent risk factors for both patency loss and mortality. It will be important to assess methods of revascularization and pharmacotherapy that take into account the balance between these risks from the perspectives of patency and prognosis for patients with one or more of these risk factors.

As in recent years it has been reported that anticoagulant therapy reduces the risk of ischemic events in PAD patients who undergo revascularization[25], it will be necessary, in the future, to identify an optimal medical therapy and assess its effectiveness even in high mortality risk groups such as those identified in this study.

Limitation

There are several limitations that may have affected our clinical outcomes. First, this study was a retrospective, non-randomized analysis, despite of a large-scale, multicenter study. Second, our study included only Japanese patients, so the results should be confirmed for other ethnic groups. Third, our study did not compare the durability of the implanted BNS to other devices. Whether the long-term results following BNS placement are similar to other devices in real-world practice remains unanswered. Fourth, the indication of endovascular treatment was unclear because of retrospective analysis. We cannot rule out the possibility of selection bias. Finally, multiple factors may influence the long-term outcome, but this study focused on database items only. Therefore, in addition to aging, other possible factors such as intravascular ultrasound-evaluated parameters, history of valvular disease, socioeconomic status, insurance status, and frailty[26, 27] that were not evaluated in this study may be prognostic factors.

Conclusion

Our data demonstrated that de novo or primary use of BNS may not be justified for FP artery disease in real-world setting up to 10-year due to the high restenosis rate. Indipendent predictors of primary patency were female sex, age ≥ 80 years, DM, dialysis, CLTI, CTO, long lesion (>20 cm), and small vessel (RVD ≤ 4 mm). Indipendent predictors of mortality were male sex, age ≥ 80 years, dialysis, heart failure, CLTI, severe calcification, and long lesion (>20 cm). In addition, the prognostic impact of age ≥ 80 years

and CLTI was significantly attenuated over time.

Financial Support

None.

Conflict of Interest

None declared.

References

1) Minar E, Pokrajac B, Maca T, Ahmadi R, Fellner C, Mittlböck M, Seitz W, Wolfram R, Pötter R. Endovascular brachytherapy for prophylaxis of restenosis after femoropopliteal angioplasty: results of a prospective randomized study. Circulation, 2000; 102: 2694-2699
2) van der Zaag ES, Legemate DA, Prins MH, Reekers JA, Jacobs MJ. Angioplasty or bypass for superficial femoral artery disease? A randomised controlled trial. Eur J Vasc Endovasc Surg, 2004; 28: 132-137
3) Schillinger M, Sabeti S, Loewe C, Dick P, Amighi J, Mlekusch W, Schlager O, Cejna M, Lammer J, Minar E. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. N Engl J Med, 2006; 354: 1879-1888
4) Mewissen MW. Primary nitinol stenting for femoropopliteal disease. J Endovasc Ther, 2009; 16: II63-81
5) Soga Y, Iida O, Hirano K, Yokoi H, Nanto S, Nobuyoshi M. Mid-term clinical outcome and predictors of vessel patency after femoropopliteal stenting with self-expandable nitinol stent. J Vasc Surg, 2010; 52: 608-615
6) Iida O, Soga Y, Hirano K, Suzuki K, Yokoi H, Nobuyoshi M, Muramatsu T, Inoue N, Nanto S, Uematsu M. Long-term outcomes and risk stratification of patency following nitinol stenting in the femoropopliteal segment: retrospective multicenter analysis. J Endovasc Ther, 2011; 18: 753-761
7) Rosenfield K, Jaff MR, White CJ, Rocha-Singh K, Mena-Hurtado C, Metzger DC, Brodmann M, Pilger E, Zeller T, Krishnan P, Gammon R, Müller-Hülsbeck S, Nehler MR, Benenati JF, Scheinert D; LEVANT 2 Investigators.. Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease. N Engl J Med, 2015; 373: 145-153
8) Steiner S, Schmidt A, Zeller T, Tepe G, Thieme M, Maiwald L, Schröder H, Euringer W, Ulrich M, Brechtel K, Brucks S, Blessing E, Schuster J, Langhoff R, Schellong S, Weiss N, Scheinert D. COMPARE: prospective, randomized, non-inferiority trial of high- vs. low-dose paclitaxel drug-coated balloons for femoropopliteal interventions. Eur Heart J, 2020; 41: 2541-2552
9) Torsello G, Stavroulakis K, Brodmann M, Micari A, Tepe G, Veroux P, Benko A, Choi D, Vermassen FEG, Jaff MR, Guo J, Dobranszki R, Zeller T; IN.PACT Global Investigators. Three-Year Sustained Clinical Efficacy of Drug-Coated Balloon Angioplasty in a Real-World Femoropopliteal Cohort. J Endovasc Ther, 2020; 27: 693-705
10) Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, Machan LS, Snyder SA, O'Leary EE, Ragheb AO, Zeller T; Zilver PTX Investigators. Durable Clinical Effectiveness With Paclitaxel-Eluting Stents in the Femoropopliteal Artery: 5-Year Results of the Zilver PTX Randomized Trial. Circulation, 2016; 133: 1472-1483
11) Gray WA, Keirse K, Soga Y, Benko A, Babaev A, Yokoi Y, Schroeder H, Prem JT, Holden A, Popma J, Jaff MR, Diaz-Cartelle J, Müller-Hülsbeck S; IMPERIAL investigators. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. Lancet, 2018; 392: 1541-1551
12) Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. 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, 2018; 7: e011245
13) Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Paraskevopoulos I, Karnabatidis D. Risk of Death and Amputation with Use of Paclitaxel-Coated Balloons in the Infrapopliteal Arteries for Treatment of Critical Limb Ischemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Vasc Interv Radiol, 2020; 31: 202-212
14) Beckman JA, White CJ. Paclitaxel-Coated Balloons and Eluting Stents: Is There a Mortality Risk in Patients With Peripheral Artery Disease? Circulation, 2019; 140: 1342-1351
15) Schneider PA, Laird JR, Doros G, Gao Q, Ansel G, Brodmann M, Micari A, Shishehbor MH, Tepe G, Zeller T. Mortality Not Correlated With Paclitaxel Exposure: An Independent Patient-Level Meta-Analysis of a Drug-Coated Balloon. J Am Coll Cardiol, 2019; 73: 2550-2563
16) Secemsky EA, Barrette E, Bockstedt L, Bonaca MP, Hess CN, Hanson T, Monteiro J, Manda B, Yeh RW. Long-Term Safety of Drug-Coated Devices for Peripheral Revascularisation. EuroIntervention, 2020 D22: EIJ-D-20-01018
17) Iida O, Uematsu M, Soga Y, Hirano K, Suzuki K, Yokoi H, Muramatsu T, Inoue N, Nanto S, Nagata S. Timing of the restenosis following nitinol stenting in the superficial femoral artery and the factors associated with early and late restenoses. Catheter Cardiovasc Interv, 2011; 78: 611-6117
18) Abdoli S, Katz S, Ochoa C. Long-Term Patency and Clinical Outcomes of Nitinol Stenting for Femoropopliteal Atherosclerotic Disease. Ann Vasc Surg, 2020; 66: 566-572
19) Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, Kolodgie FD, Finn AV, Virmani R. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. J Am Coll Cardiol, 2011; 57: 1314-1322
20) Miyazaki K, Nishibe T, Sata F, Miyazaki YI, Kudo FA, Flores J, Yasuda K. Prosthetic grafts for above-knee femoropopliteal bypass, A multicenter retrospective study of 564 grafts. Int Angiol, 2002; 21: 145-151

21) Shah DM, Darling RC 3rd, Chang BB, Fitzgerald KM, Paty PS, Leather RP. Long-term results of in situ saphenous vein bypass. Analysis of 2058 cases. Ann Surg, 1995; 222: 438-446
22) Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Röther J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I; ESC Scientific Document Group. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J, 2018; 39: 763-816
23) Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, Mills JL, Ricco JB, Suresh KR, Murad MH; GVG Writing Group. Global vascular guidelines on the management of chronic limb-threatening ischemia. J Vasc Surg, 2019; 69: 3S-125S.e40
24) Soga Y, Iida O, Takahara M, Hirano K, Suzuki K, Kawasaki D, Miyashita Y, Tsuchiya T. Two-year life expectancy in patients with critical limb ischemia. JACC Cardiovasc Interv, 2014; 7: 1444-1449
25) Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, Fanelli F, Capell WH, Diao L, Jaeger N, Hess CN, Pap AF, Kittelson JM, Gudz I, Mátyás L, Krievins DK, Diaz R, Brodmann M, Muehlhofer E, Haskell LP, Berkowitz SD, Hiatt WR. Rivaroxaban in Peripheral Artery Disease after Revascularization. N Engl J Med, 2020; 382: 1994-2004
26) Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci, 2004; 59: 255-263
27) Takeji Y, Yamaji K, Tomoi Y, Okazaki J, Tanaka K, Nagae A, Jinnouchi H, Hiramori S, Soga Y, Ando K. Impact of Frailty on Clinical Outcomes in Patients With Critical Limb Ischemia. Circ Cardiovasc Interv, 2018; 11: e006778