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Clinical impact and risk stratification of balloon angioplasty for femoropopliteal disease in nitinol stenting era: Retrospective multicenter study using propensity score matching analysis

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Abstract

Objective: Nitinol stenting could bring the better outcome in endovascular therapy for femoropopliteal disease. However, it might be expected that recent marked advances in both device technology and operator technique had led to improved efficacy of balloon angioplasty even in this segment. The aims of this study were to evaluate the clinical impact of balloon angioplasty for femoropopliteal disease and make risk stratification clear by propensity score matching analysis.

Methods: Based on the multicenter retrospective data, 2758 patients (balloon angioplasty: 729 patients and nitinol stenting: 2029 patients), those who underwent endovascular therapy for femoropopliteal disease, were analyzed.

Results: The propensity score matching procedure extracted a total of 572 cases per group, and the primary patency rate of balloon angioplasty and nitinol stenting groups after matching was significantly the same (77.2% vs 82.7% at 1 year; 62.2% vs 64.3% at 3 years; 47.8% vs 54.3% at 5 years). In multivariate Cox hazard regression analysis, significant predictors for primary patency were diabetes mellitus, regular dialysis, cilostazol use, chronic total occlusion, and intra-vascular ultrasonography use. The strategy of balloon angioplasty was not evaluated as a significant predictor for the primary patency. After risk stratification using five items (*d*iabetes mellitus, regular *d*ialysis, no use of *i*ntra-vascular ultra-sonography, *c*hronic total occlusion, and no use of *c*ilostazol: the DDICC score), the estimated primary patency rates of each group (low, DDICC score 0–2; moderate, DDICC score 3; high risk, DDICC score 4–5) were 88.6%, 78.3%, and 63.5% at 1 year; 75.2%, 60.7%, and 39.8% at 3 years; and 66.0%, 47.1%, and 26.3% at 5 years ($p < 0.0001$). The primary patency rate of balloon angioplasty and nitinol stenting groups was significantly the same in each risk stratification.

Conclusion: This study suggests that balloon angioplasty does not have inferiority to nitinol stenting but does have favorable efficacy in femoropopliteal segment by careful risk stratification with the recent advance of technique.

Keywords

Balloon angioplasty, femoropopliteal segment, endovascular therapy, propensity score matching analysis, multivariate analysis, risk stratification

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Introduction

Nitinol stent could bring the better outcome in endovascular therapy (EVT) for femoropopliteal segment.[1–6] But there remains high-risk cases and lesions for vessel patency after EVT, such as female gender, diabetes mellitus, end stage of renal disease, critical limb ischemia (CLI), long lesion, chronic total occluded lesion (CTO), and poor below-the-knee run-off lesions.[7–9] For a solution of this issue, a development of new stent platforms has been ongoing, and the new strategy by use of the drug-coated balloon (so-called nothing left behind strategy) is also going to challenge it. However, improved efficacy of plain balloon angioplasty (BA) might be expected by recent marked advances in both device technology and operator technique. However, only a few studies estimated the current efficacy of BA for this segment in daily clinical settings.[5,6,10]

With this background, those might be important to reevaluate the impact of BA compared with nitinol stenting (NT) and make appropriate candidates for BA clear. It should be the best to build up the data by high-volume controlled prospected multicenter study, but it might be hard to make a protocol. Propensity score matching technique was first reported in the 1980s[11] and has been widely used to minimize the baseline differences due to treatment selection bias in clinical observational studies. So, the aims of this study were to evaluate the clinical impact of plain BA for femoropopliteal lesions in NT era and make risk stratification clear by propensity score matching analysis, based on high-volume retrospective multicenter registry data.

Method

Patient

From January 2004 to December 2011, consecutive 5002 patients who underwent EVT for femoropopliteal lesions in 13 centers in Japan were enrolled in the Retrospective Multicenter Analysis for Femoropopliteal stenting (REAL-FP) registry. Of them, 2254 cases were excluded because of past history of revascularization (1651 cases), lost during follow-up (323 cases), procedure failure (152 cases), and acute limb ischemia (128 cases). Therefore, 2758 patients who underwent successful EVT (BA: 729 cases and NT: 2029 cases) for de novo femoropopliteal lesions were identified retrospectively and included in this study. Propensity score matching was performed for minimizing intergroup baseline differences due to an operator's bias. The study protocol was designed in accordance with the Declaration of Helsinki, approved by the ethics committee of each participating hospital, and registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR; no. UMIN000010986). All patients gave written informed consent for both intervention and inclusion in this study prior to procedure.

Procedure and follow-up

The procedure and follow-up protocol were described in the former report based on this registry database.[4] At each procedure, a kind of guide-wire, use of intra-vascular ultra-sonography (IVUS), size of balloon, necessity of adjunctive stenting, and choice of nitinol self-expandable stents (Luminexx (Bard, Murray Hill, NJ) or S.M.A.R.T. (Cordis J&J, Miami, FL)) were left to each operator's discretion. After the procedure, all patients were prescribed lifelong aspirin (100 mg/day), and prolonged dual anti-platelet therapy (aspirin 100 mg/day + clopidogrel 75 mg/day or ticlopidine 200 mg/day or cilostazol 200 mg/day) was recommended. The classification of the Rutherford categories, physical findings, the resting ankle-brachial index, and duplex ultrasound scan for treated segment were monitored within 30 days and every 6 months thereafter. Repeated revascularization was performed based on clinical symptoms and findings on duplex sonography or angiography.

Definitions

Nonambulatory status was defined as wheelchair bound or bedridden. Lesion length (LL) referred to was the whole portion that was dilated by a balloon or treated with stenting. Reference diameter was visually estimated on angiography compared with an easy ruler put beside a foot in cases without IVUS use. In cases with IVUS use, the reference diameter was estimated by its findings. Calcification was defined as obvious densities noted within the apparent vascular wall on angiography. Poor run-off was defined as one vessel or none below-the-knee run-off assessed by the angiography before or after the procedure. Restenosis was defined as >2.4 of peak systolic velocity ratio by duplex scan or >50% stenosis by angiography. Primary patency was defined as a treated vessel without restenosis and any repeat revascularization. Limb salvage was defined as free from any amputation above the ankle.

Statistical analysis

Continuous variables with or without normal distributions were compared between groups using either the unpaired t-test or the Mann–Whitney U test, respectively. Variables with a normal distribution were expressed as mean values ± standard deviation (SD), while median and interquartile range was used for asymmetrically distributed data. Chi-square test was used to compare proportions between groups. Each outcome was estimated using the Kaplan–Meier method and compared using the log rank test. Statistical significance level was set at $p < 0.05$.

To adjust for baseline differences between groups, propensity score matching analysis[11] was performed using the following variables: age, gender, ambulatory status, hypertension, dyslipidemia, diabetes mellitus, regular dialysis, current

Table 1. Baseline characteristics and procedure detail before and after propensity score matching.

	Before matching			After matching		
	BA group	NT group	p-value	BA group	NT group	p-value
Patient characteristics, n	729	2029		572	572	
Age (years; mean ± SD)	72 ± 9	73 ± 9	0.9341	72 ± 9	73 ± 10	0.7712
Female, n (%)	240 (33)	596 (29)	0.0738	163 (28)	179 (31)	0.3015
Ambulatory, n (%)	596 (82)	1746 (86)	0.0068	475 (83)	487 (85)	0.3320
Hypertension, n (%)	582 (80)	1724 (85)	0.0017	472 (83)	473 (83)	0.9378
Dyslipidemia, n (%)	340 (47)	1006 (50)	0.1827	287 (50)	288 (50)	0.9528
Diabetes mellitus, n (%)	436 (60)	1215 (60)	0.9968	349 (61)	343 (60)	0.7167
Regular dialysis, n (%)	237 (33)	469 (23)	<0.0001	169 (30)	159 (28)	0.5133
Current smoking, n (%)	157 (22)	523 (26)	0.0238	144 (25)	151 (26)	0.6361
Cilostazol, n (%)	255 (35)	1028 (51)	<0.0001	218 (38)	225 (39)	0.6709
Statin, n (%)	256 (35)	768 (38)	0.1981	216 (38)	208 (36)	0.6243
ACEI/ARB, n (%)	343 (47)	1071 (53)	0.0087	293 (51)	286 (50)	0.6789
CLI, n (%)	249 (34)	630 (31)	0.0971	174 (30)	176 (31)	0.8979
Lesion characteristics, n	950	2520		572	572	
TASC II C/D, n (%)	113 (12)	1255 (50)	<0.0001	93 (16)	104 (18)	0.3890
LL (mm; mean ± SD)	64 ± 60	141 ± 88	<0.0001	78 ± 68	80 ± 59	0.5873
Reference diameter (mm; mean ± SD)	4.9 ± 1.1	5.3 ± 0.9	<0.0001	5.2 ± 1.1	5.1 ± 0.8	0.2749
Calcification, n (%)	609 (64)	1439 (57)	0.0002	326 (57)	346 (60)	0.2297
CTO, n (%)	251 (26)	1322 (52)	<0.0001	192 (34)	201 (35)	0.5753
Poor run-off, n (%)	382 (40)	1058 (42)	0.0179	242 (42)	237 (41)	0.7644
Procedure detail, n	950	2520		572	572	
IVUS use, n (%)	115 (12)	621 (25)	<0.0001	96 (17)	96 (17)	1.0000

SD: standard deviation; BA: balloon angioplasty; NT: nitinol stenting; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CLI: critical limb ischemia; TASC: Trans-Atlantic Inter-Society Consensus; LL: lesion length; CTO: chronic total occlusion; IVUS: intra-vascular ultrasonography.

smoking, cilostazol use, statin use, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) use, CLI, Trans-Atlantic Inter-Society Consensus (TASC) II C/D lesions, LL, reference diameter, arterial calcification, chronic total occlusion (CTO), poor below-the-knee run-off, and IVUS use. According to Austin's[12] recommendation, BA group and NT group were matched 1:1 on the logit of the propensity score within the caliper of 0.2 standard deviation of the logit of the propensity score.

Independent outcome determinants were identified by the Cox proportional hazard ratio in multivariable analysis including all variables from univariable analysis with a p-value of <0.05.

Propensity score matching was performed with R (version 3.1.2; R Foundation for Statistical Computing, Vienna, Austria), whereas other statistical analyses were performed using the Statistical Package for Social Sciences (SPSS; SPSS, Inc., Chicago, IL) software.

Results

For baseline characteristics before propensity score matching, there were significant differences between the BA group and the NT group, in ambulatory status, hypertension, regular dialysis, current smoking, administration of cilostazol, ACEI or ARB, TASC II C/D prevalence, LL, reference diameter, appearance of vessel calcification, CTO, poor below-the-knee run-off, and IVUS use (Table 1). Table 2 shows all perioperative complications which had no significant difference between the groups.

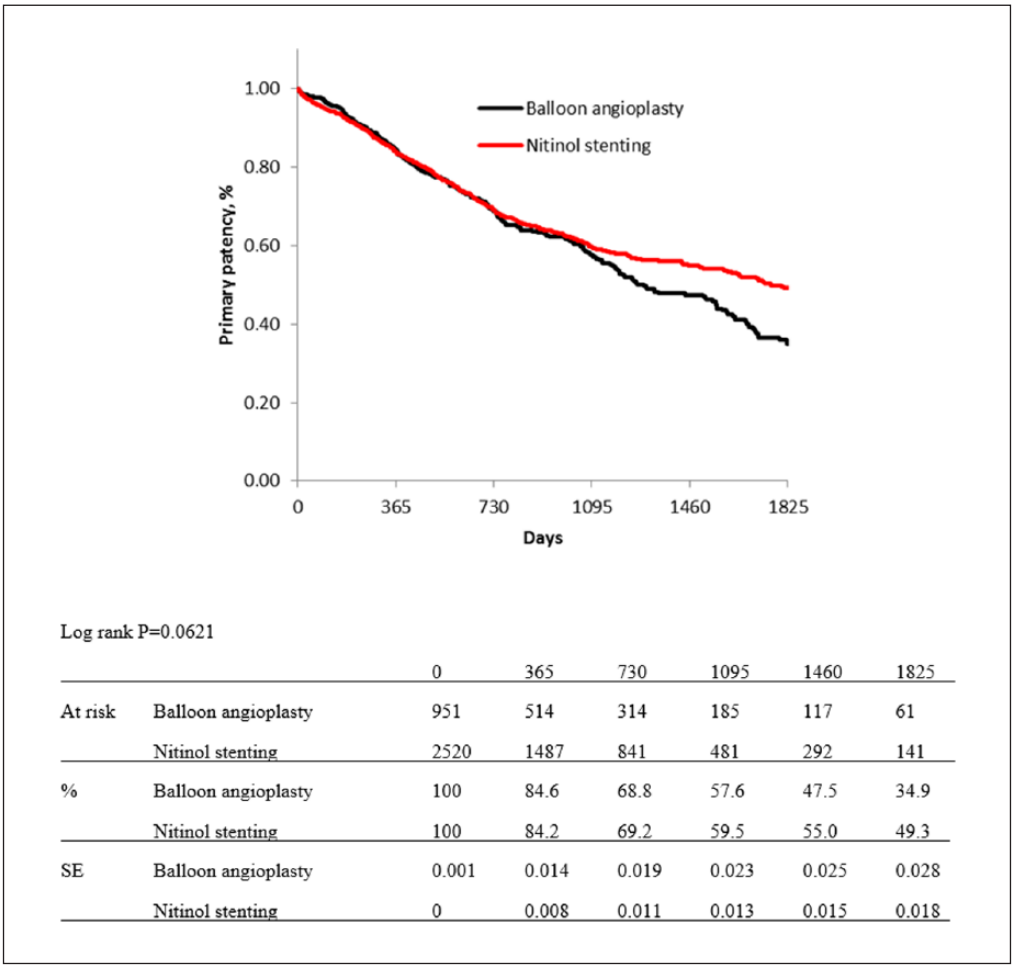
Figures 1 and 2 show Kaplan–Meier curves for primary patency and limb salvage rates of both groups before propensity score matching. The estimated primary patency rates were 84.6% in the BA group versus 84.2% in the NT group at 1 year, 68.8% versus 69.2% at 2 years, 57.6% versus 59.5% at 3 years, 47.5% versus 55.0% at 4 years, and 34.9% versus 49.3% at 5 years (p = 0.0621; Figure 1). The estimated limb salvage rates of both groups were kept over 96% for 5 years, and there were no significant differences between the groups (p = 0.5188; Figure 2).

In the propensity score matching procedure, 255 cases with missing data on variables of interest were excluded, and a total 572 cases per group were extracted. Table 1 shows baseline characteristics of both groups, which were adjusted not to have significant differences. Figures 3 and 4 show Kaplan–Meier curves for primary patency and limb salvage rates of both groups after propensity score matching. The estimated primary patency rate after adjusting was 77.2% in BA group versus 82.7% in NT group at 1 year, 69.6% versus 72.2% at 2 years, 62.2% versus 64.3% at

Table 2. Perioperative complications before propensity score matching.

	BA group (n = 729)	NT group (n = 2029)	p-value
All perioperative complications, n (%)	43 (5.9)	158 (7.8)	0.1687
Distal embolism, n (%)	5 (0.7)	21 (1.0)	0.4044
Bypass conversion, n (%)	4 (0.5)	20 (1.0)	0.2770
Blood transfusion, n (%)	19 (2.6)	63 (3.1)	0.4999
Temporary hemodialysis, n (%)	1 (0.1)	5 (0.2)	0.5880
Pseudo-aneurysm, n (%)	2 (0.3)	14 (0.7)	0.2062
Hematoma, n (%)	12 (1.6)	35 (1.7)	0.8866

BA: balloon angioplasty; NT: nitinol stenting.



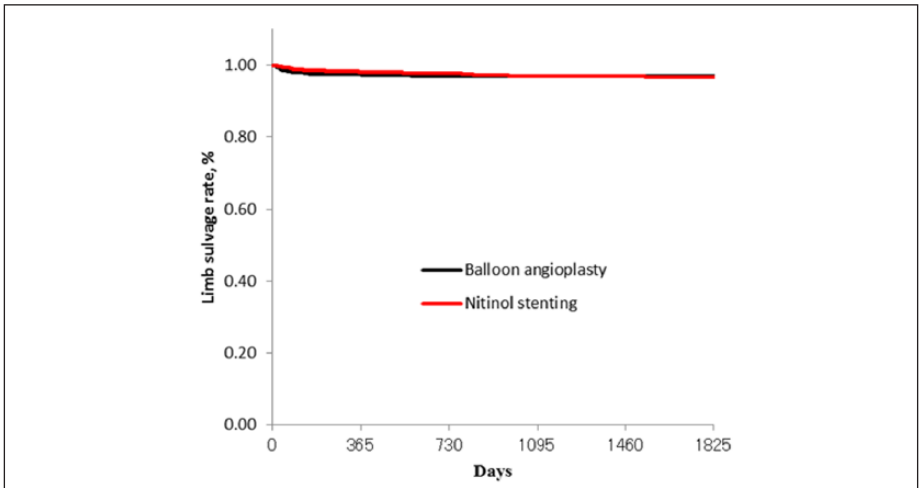
		0	365	730	1095	1460	1825
At risk	Balloon angioplasty	951	514	314	185	117	61
	Nitinol stenting	2520	1487	841	481	292	141
%	Balloon angioplasty	100	84.6	68.8	57.6	47.5	34.9
	Nitinol stenting	100	84.2	69.2	59.5	55.0	49.3
SE	Balloon angioplasty	0.001	0.014	0.019	0.023	0.025	0.028
	Nitinol stenting	0	0.008	0.011	0.013	0.015	0.018

Figure 1. Kaplan–Meier curves show primary patency rate of balloon angioplasty and nitinol stenting groups before propensity score matching.

3 years, 54.2% versus 60.5% at 4 years, and 47.8% versus 54.3% at 5 years (p = 0.1081; Figure 3). The estimated limb salvage rates of both groups were kept over 96% for 5 years, and there were no significant difference between the groups (p = 0.9857; Figure 4).

Table 3 shows multivariate Cox hazard regression analysis for association of primary patency with baseline characteristics. In multivariate analysis, which included diabetes mellitus, regular dialysis, administration of cilostazol, administration of ACEI or ARB, CLI, LL ⩽ 100 mm, reference diameter ⩾ 6 mm, lesion calcification, CTO, and IVUS use, significant predictors for primary patency were diabetes mellitus, regular dialysis, administration of cilostazol, CTO, and IVUS use.

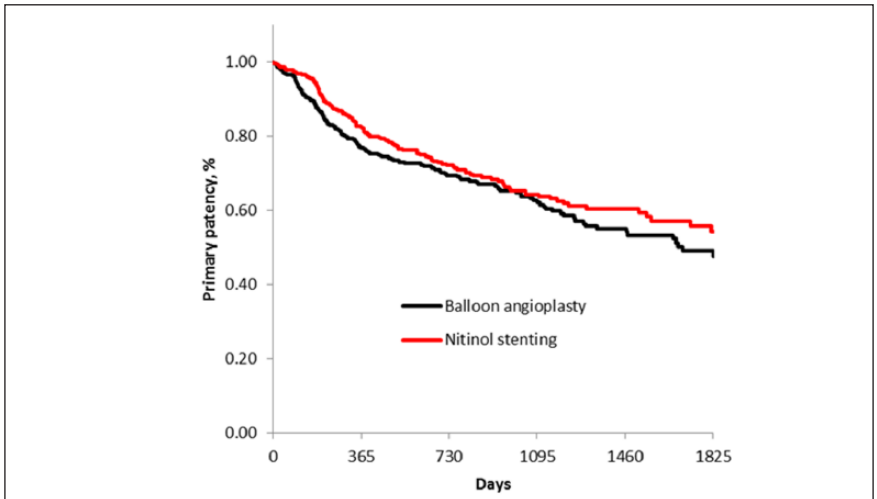
For risk stratification, all cases were classified into three groups, as low-, moderate-, and high-risk groups. Five items from independent predictors for primary patency were selected for this classification: *d*iabetes mellitus, regular



Log rank P=0.5188

		0	365	730	1095	1460	1825
At risk	Balloon angioplasty	951	660	438	271	172	95
	Nitinol stenting	2520	1830	1151	690	451	269
%	Balloon angioplasty	100	97.4	97.1	96.8	96.8	96.8
	Nitinol stenting	100	98.1	97.6	97.0	96.9	96.6
SE	Balloon angioplasty	0	0.005	0.006	0.006	0.006	0.006
	Nitinol stenting	0	0.003	0.003	0.004	0.004	0.005

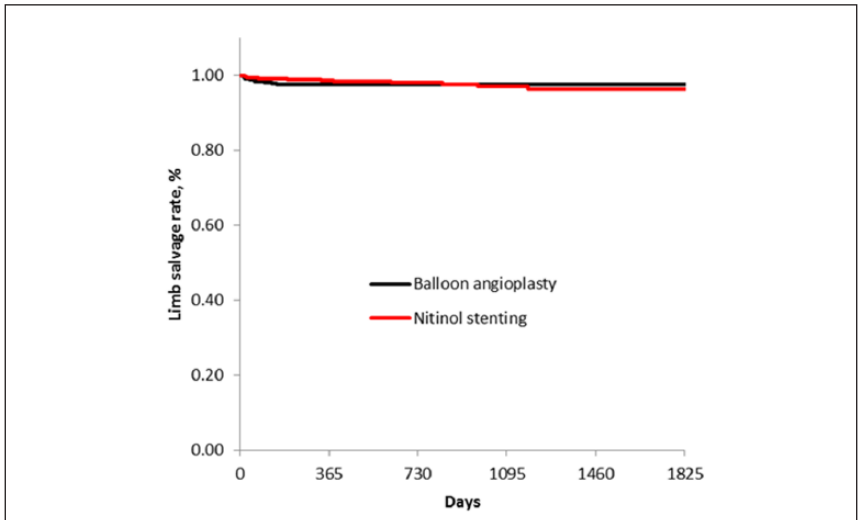
Figure 2. Kaplan–Meier curves show limb salvage rate of balloon angioplasty and nitinol stenting groups before propensity score matching.



Log rank P=0.1081

		0	365	730	1095	1460	1825
At risk	Balloon angioplasty	572	317	200	114	69	36
	Nitinol stenting	572	342	188	113	66	38
%	Balloon angioplasty	100	77.2	69.6	62.2	54.2	47.8
	Nitinol stenting	100	82.7	72.2	64.3	60.5	54.3
SE	Balloon angioplasty	0	0.019	0.022	0.027	0.032	0.038
	Nitinol stenting	0	0.017	0.022	0.027	0.030	0.038

Figure 3. Kaplan–Meier curves show primary patency rate of balloon angioplasty and nitinol stenting groups after propensity score matching.



Log rank P=0.9857

		0	365	730	1095	1460	1825
At risk	Balloon angioplasty	572	403	271	164	104	60
	Nitinol stenting	572	408	252	162	100	63
%	Balloon angioplasty	100	97.8	97.5	97.5	97.5	97.5
	Nitinol stenting	100	98.6	98.1	97.1	96.4	96.4
SE	Balloon angioplasty	0	0.006	0.007	0.007	0.007	0.007
	Nitinol stenting	0	0.005	0.007	0.009	0.011	0.011

Figure 4. Kaplan–Meier curves show limb salvage rate of balloon angioplasty and nitinol stenting groups after propensity score matching.

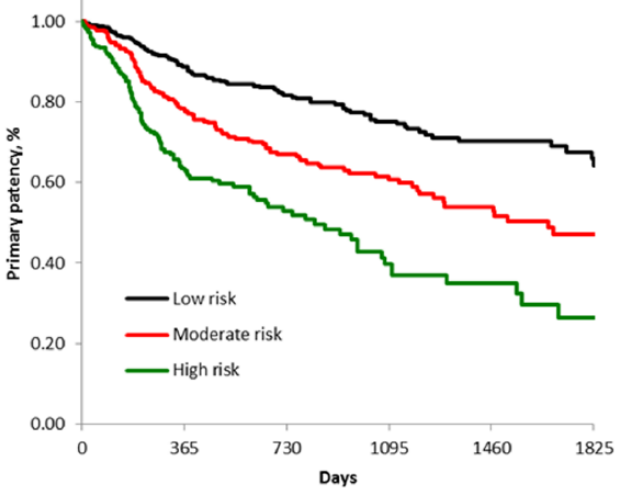
Table 3. Association of primary patency with baseline characteristics after propensity score matching.

	Univariate analysis	Multivariate analysis
Patient characteristics		
Age	1.0 (1.0–1.0)	–
Female gender	1.2 (0.9–1.5)	–
Ambulatory	0.8 (0.6–1.2)	–
Hypertension	1.1 (0.8–1.4)	–
Dyslipidemia	1.1 (0.9–1.3)	–
Diabetes mellitus	1.4 (1.1–1.8)***	1.4 (1.1–1.7)**
Regular dialysis	1.7 (1.4–2.2)******	1.4 (1.1–1.8)*
Current smoking	1.0 (0.8–1.3)	–
Cilostazol	0.6 (0.5–0.8)******	0.6 (0.5–0.8)******
Statin	1.0 (0.8–1.2)	–
ACEI or ARB	0.8 (0.6–1.0)*	0.9 (0.7–1.1)
CLI	1.5 (1.2–1.9)****	1.2 (0.9–1.6)
Lesion characteristics		
TASC II C/D	1.6 (1.2–2.1)****	–
Lesion length	1.0 (1.0–1.0)******	–
⩽150 mm	0.7 (0.5–1.0)*	–
⩽100 mm	0.7 (0.5–0.9)***	0.8 (0.6–1.1)
⩽50 mm	0.7 (0.6–0.9)***	–
Reference diameter	0.8 (0.7–0.9)******	–
⩾7 mm	0.8 (0.5–1.3)	–
⩾6 mm	0.7 (0.6–0.9)*	0.8 (0.6–1.0)

Table 3. (Continued)

	Univariate analysis	Multivariate analysis
⩾5 mm	0.8 (0.6–1.0)	–
Calcification	1.5 (1.2–1.9)****	1.1 (0.9–1.5)
CTO	1.4 (1.1–1.7)***	1.3 (1.1–1.7)*
Poor run-off	1.2 (1.0–1.5)	–
Procedure details		
Balloon angioplasty	1.2 (1.0–1.5)	–
IVUS use	0.6 (0.4–0.8)****	0.5 (0.4–0.7)*****

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CLI: critical limb ischemia; TASC: Trans-Atlantic Inter-Society Consensus; CTO: chronic total occlusion; IVUS: intra-vascular ultra-sonography.
Data are hazard ratios and 95% confidence intervals.
*p < 0.05, **p < 0.01, ***p < 0.005, ****p < 0.001, *****p < 0.0005, ******p < 0.0001.

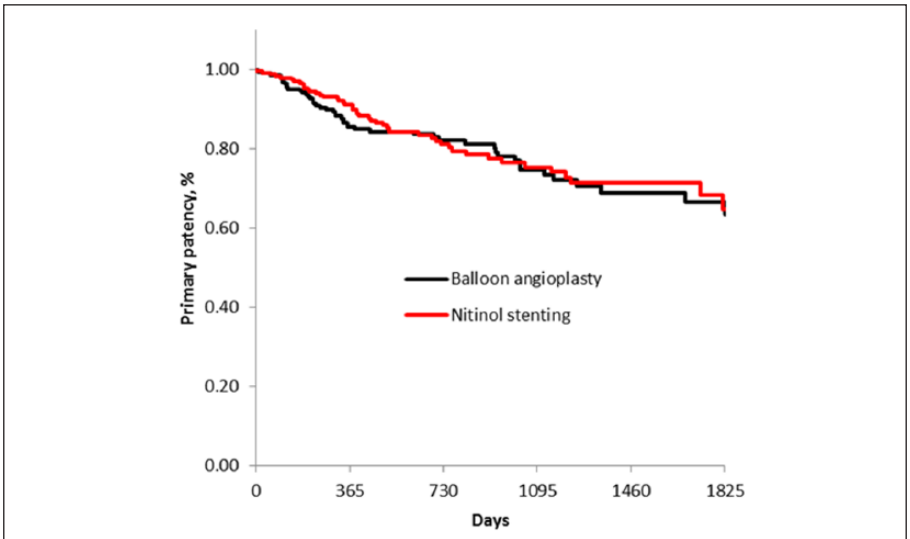


Log rank P<0.0001

		0	365	730	1095	1460	1825
At risk	Low risk group	507	341	202	123	73	40
	Moderate risk group	379	213	131	77	46	26
	High risk group	258	104	54	27	17	7
%	Low risk group	100	88.6	81.7	75.2	70.3	66.0
	Moderate risk group	100	78.3	67.1	60.7	54.0	47.1
	High risk group	100	63.5	52.9	39.8	35.0	26.3
SE	Low risk group	0	0.015	0.020	0.026	0.030	0.040
	Moderate risk group	0	0.023	0.028	0.032	0.037	0.044
	High risk group	0	0.035	0.039	0.047	0.049	0.060

Figure 5. Kaplan–Meier curves show primary patency rate of each risk group after risk stratification using five items: diabetes mellitus, regular dialysis, no IVUS use, no cilostazol use, and CTO.

*d*ialysis, no use of *I*VUS, *C*TO, and no administration of *c*ilostazol: the DDICC score. These five items were each scored as 1 point. Therefore, the total score ranged from 0 to 5 points, and scores of 0–2, 3, and 4–5 points were used to indicate low-, moderate-, and high-risk patients, respectively. Kaplan–Meier curves for primary patency of each group based on the DDICC score are shown in Figure 5. The estimated primary patency rates of each group



Log rank P=0.6798

		0	365	730	1095	1460	1825
At risk	Balloon angioplasty	245	155	102	61	36	21
	Nitinol stenting	262	187	100	62	37	20
%	Balloon angioplasty	100	85.6	82.2	74.9	69.0	66.7
	Nitinol stenting	100	91.4	81.2	75.5	71.6	64.9
SE	Balloon angioplasty	0	0.025	0.028	0.037	0.044	0.056
	Nitinol stenting	0	0.019	0.029	0.035	0.040	0.058

Figure 6. Kaplan–Meier curves show primary patency rate of balloon angioplasty and nitinol stenting in low-risk group.

(low-, moderate-, and high-risk group) were 88.6%, 78.3%, and 63.5% at 1 year; 81.7%, 67.1%, and 52.9% at 2 years; 75.2%, 60.7%, and 39.8% at 3 years; 70.3%, 54.0%, and 35.0% at 4 years; and 66.0%, 47.1%, and 26.3% at 5 years ($p < 0.0001$). Figures 6–8 show no significant differences in primary patency rates between BA and NT groups in each risk stratification (low-risk group, $p = 0.6798$; moderate-risk group, $p = 0.1720$; high-risk group, $p = 0.3048$; log rank test).

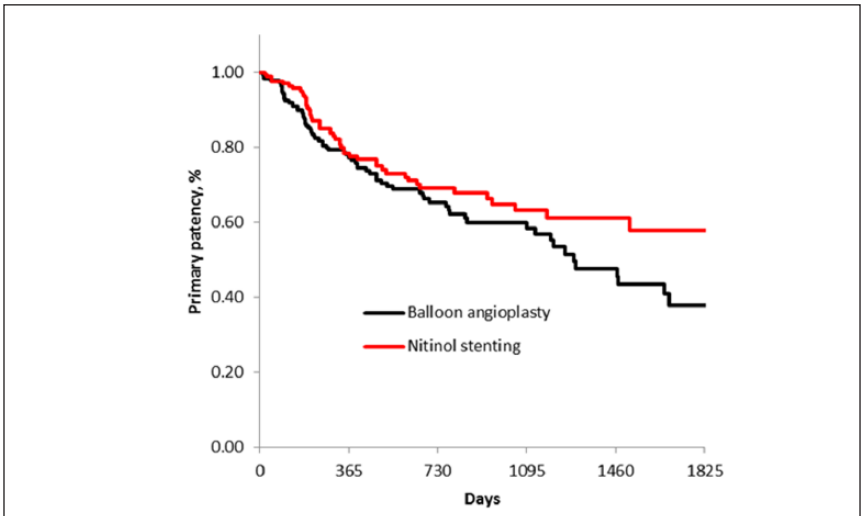
In association of primary patency with BA in each subgroup, unfavorable impact was observed in patients over 80 years old, female gender, hypertension, no use of ACEI or ARB, or over 150 cm LL compared with nitinol stenting (Table 4).

Discussion

Recent advances in both technology and operator technique could have been related to improved procedure success rate in EVT and expansion of the number of patients with peripheral artery diseases who are candidates for nonsurgical revascularization.[13–15] Even in femoropopliteal segment, mid-term vessel patency had also improved through use of a nitinol stent[1–5] in combination with pharmacotherapy,[16–18] compared to conventional endovascular treatment before the use of nitinol stents. And to gain the efficacy of EVT in this segment, several studies with new technologies, such as drug-eluting stents,[19,20] atherectomy,[21] laser,[22] and drug-coated balloon,[23,24] have challenged. In most of these studies, inclusion criteria chose up to 10 cm in length, and their efficacy was evaluated in comparison with plain conventional BA. On this background, it might be important to reevaluate the impact of BA from a high-volume registry database. In our limited acknowledgement, this study was the highest volume study.

The mid-term efficacy of BA for de novo femoropopliteal segment showed statistically the same results with that of NT in this study despite both groups having quite different baseline characteristics. The estimated primary patency rates of BA at 1, 2, and 3 years (84.6%, 68.8%, and 57.6%) were quite acceptable compared with recent reports.[3,5,6,10] Also, the limb salvage rate could have been kept quite high despite the fact that CLI cases were included in this study (30%). The appropriate selection bias left to each operator's discretion might contribute to this result.

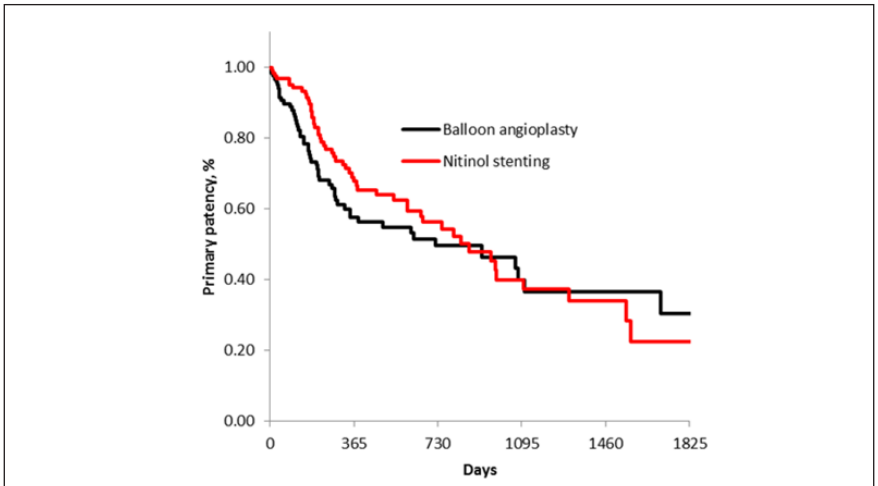
By the propensity score matching procedure, several differences in baseline characteristics between the groups were adjusted. Most of these extracted patients had TASC II A/B lesions and reference diameters which were equalized to over 5 mm in diameter. After propensity score matching, the primary patency of both groups was



Log rank P=0.1720

		0	365	730	1095	1460	1825
At risk	Balloon angioplasty	202	116	73	41	24	11
	Nitinol stenting	177	97	59	36	22	15
%	Balloon angioplasty	100	78.1	65.4	60.0	47.6	38.0
	Nitinol stenting	100	78.5	69.1	63.2	61.2	58.0
SE	Balloon angioplasty	0	0.031	0.039	0.044	0.056	0.062
	Nitinol stenting	0	0.035	0.041	0.047	0.050	0.065

Figure 7. Kaplan–Meier curves show primary patency rate of balloon angioplasty and nitinol stenting in moderate-risk group.



Log rank P=0.3048

		0	365	730	1095	1460	1825
At risk	Balloon angioplasty	125	47	25	12	9	4
	Nitinol stenting	133	58	30	15	8	4
%	Balloon angioplasty	100	57.6	49.6	39.8	36.5	30.4
	Nitinol stenting	100	69.0	56.3	40.0	33.9	22.6
SE	Balloon angioplasty	0	0.050	0.055	0.069	0.069	0.089
	Nitinol stenting	0	0.046	0.054	0.066	0.068	0.080

Figure 8. Kaplan–Meier curves show primary patency rate of balloon angioplasty and nitinol stenting in high-risk group.

Table 4. Hazard ratios of balloon angioplasty for primary patency compared with nitinol stenting in each subgroup after propensity score matching.

	n (%)	Hazard ratio (95% CI)
Patient characteristics		
Age > 80 years	220 (19)	1.8 (1.1–3.0)*
Female gender	342 (30)	1.6 (1.1–2.4)*
Nonambulatory	182 (16)	0.9 (0.5–1.6)
Hypertension	945 (83)	1.4 (1.1–1.7)*
Dyslipidemia	575 (50)	1.1 (0.8–1.5)
Diabetes mellitus	692 (60)	1.0 (0.8–1.4)
Regular dialysis	328 (29)	1.3 (0.9–1.9)
Current smoking	295 (26)	1.1 (0.7–1.6)
No use of cilostazol	701 (61)	1.1 (0.9–1.5)
No use of statin	720 (63)	1.2 (0.9–1.5)
No use of ACEI or ARB	565 (49)	1.5 (1.1–2.0)*
CLI	350 (29)	1.3 (0.9–1.9)
Lesion characteristics		
TASC II C/D	197 (17)	1.4 (0.9–2.2)
Lesion length		
>150 mm	138 (12)	2.1 (1.1–3.9)*
>100 mm	246 (22)	1.1 (0.7–1.7)
Reference diameter		
<6 mm	805 (70)	1.2 (0.9–1.5)
<5 mm	337 (29)	1.2 (0.8–1.8)
Calcification	672 (59)	1.3 (1.0–1.7)
CTO	393 (34)	1.3 (0.9–1.8)
Poor run-off	479 (42)	1.3 (1.0–1.9)

CI: confidence interval; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CLI: critical limb ischemia; TASC: Trans-Atlantic Inter-Society Consensus; CTO: chronic total occlusion.
*$p < 0.05$.

statistically the same, and the strategy of BA was not a significant predictor for the primary patency. The short- to mid-term estimated primary patency rates of BA after the propensity score matching were acceptable (77.2% at 1 year, 69.6% at 2 years, and 62.2% at 3 years), in comparison with outcomes of conventional BA arms in recent clinical trials[23,24] those that evaluated the efficacy of drug-coated balloon in femoropopliteal segment. Mid- to long-term efficacy of drug-coated balloon might be expected to overcome the present results.

Even after the propensity score matching procedure, the limb salvage rate could have been kept high with no significant deference observed between the groups. This might be due to a relatively small prevalence of CLI cases. It needs a further study to examine whether BA for femoropopliteal lesions in CLI cases could be appropriate or not.

In multivariate analysis for association of primary patency with baseline characteristics, LL ⩽ 100 mm and reference diameter ⩾ 6 mm could not remain as significant predictors. This might be due to adjusting LL to around 80 mm and reference diameter to over 5 mm by the propensity score matching procedure. Diabetes mellitus, regular dialysis, and CTO lesions are well known as risk factors which affect the outcome of patients who underwent interventions. Clinical impact of cilostazol was already reported,[16,17] and it was recognized that cilostazol administration could bring better outcome for the patients who underwent not only NT but also BA from this study. In previous reports[25,26] that demonstrated the efficacy of IVUS use in coronary intervention, clinical impact of IVUS use in this segment might be thought due to recognition of guide-wire passage in true lumen, appropriate selection of device size, and/or recognition of concealed flow-limiting dissection which could not be detected on flash angiography.

Risk stratification of the patients who might be considered as the candidates for recanalization is important.[27–29] This study tried risk stratification using five items, such as *d*iabetes mellitus, regular *d*ialysis, no use of *I*VUS, no use of *c*ilostazol, and *C*TO: the DDICC score. In the condition of <10 cm LL and over 5 mm reference diameter, clinical efficacy of BA could be favorable in the patients with low risk (DDICC score, 0–2 points). It could also be acceptable in the patient with moderate risk (DDICC score, 3 points), but it seemed to keep falling even after 3 years compared with the NT group. It would be necessary for the patients with moderate risk to be paid careful follow-up over 3 years. Clinical efficacy of intervention, not only BA but also NT, was poor for the patients with high risk (DDICC

score, 4–5 points). Therefore, other types of devise are promising and might be expected to bring the better outcomes even in such high-risk cases.

The overall estimation of clinical impact of BA showed no inferiority compared with NT; however, unfavorable impacts were still observed in extreme conditions, such as octogenarian and/or over 150-cm-long lesions.

It is clear that nitinol stent could bring the better outcome of EVT for femoropopliteal segment in this decade; however, this strategy is facing another issue, how to manage in-stent restenosis. In this point of view, easy metal implantation might be implemented and new drug-coated balloons would also be expected to bring better outcomes compared with plain BA. However, multiple nitinol stent implantation would still be required for immediate anatomical improvement in EVT against tough lesions, such as very long CTO lesions. Besides further development of stent platforms and drug technology, challenging effort to construct an appropriate strategy is necessary to improve the efficacy of EVT for high-risk cases.

Study limitations

This study was a retrospective and nonrandomized study despite the use of a prospectively maintained database with a large number of consecutive patients with femoropopliteal lesions. Patients considered unsuitable for revascularization, those who were failed in index intervention, or treated with bypass surgery were not managed in the study. In addition, a selection of strategy through all procedures was left to the physicians' discretion, so that the failure rate of BA and prevalence of provisional stenting could not be evaluated. The available nitinol stents for femoropopliteal segments in this study period in Japan were only Luminexx (Bard) and S.M.A.R.T. (Cordis J&J) stents. The long-term efficacy of the next generations of nitinol stent is expected superior to those stents. Propensity score matching analysis was used for minimizing intergroup differences in characteristics. Cases with missing data on variables of interest were excluded during this procedure, and this exclusion could affect the results. Because of a lack of details about the indication of IVUS and/or its findings, it was uncertain how IVUS could affect the better outcome in this segment. A further prospective controlled study would be expected to estimate the relation between IVUS use and outcome.

Conclusion

In conclusion, this study based on high-volume multicenter registry data using propensity score matching analysis suggests that BA does not have inferiority to NT in femoropopliteal segment by close examination, not only anatomical condition but also patients' backgrounds, effective pharmacotherapy, and the optional informative modality, such as IVUS.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from the institutional review boards at all 13 participating cardiovascular and vascular institutions in Japan (UMIN000010986).

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Informed consent

Written informed consent was obtained from all subjects before the study.

Trial registration

Retrospective Multicenter Analysis for Femoropopliteal stenting (REAL-FP) registry: the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR; UMIN000010986).

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