Risk Factors for Below-the-Knee Amputation in Japanese Patients with Critical Limb Ischemia Who Underwent Plain Old Balloon Angioplasty Therapy: A Claims Database Analysis

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Background

- Critical limb ischemia (CLI) is the most severe clinical manifestation of peripheral artery disease (PAD) that can increase the risk of amputation.
- Plain old balloon angioplasty (POBA) is a common endovascular therapy for below-the-knee lesions in patients with CLI. However, restenosis often develops, resulting in amputation.
- This study examined the risk factors for below-the-knee amputation (BKA) in CLI patients that underwent POBA.

Methods

Study design

- Claims based study
- The risk factors for BKA were estimated by a proportional hazard analysis.

Data source

- Japanese claims database provided by Medical Data Vision Co., Ltd. (Tokyo, Japan)
  - ✓Consists of data from acute hospitals that apply the Japanese Diagnosis and Procedure Combination/Per-Diem Payment System (called DPC hospitals)
  - ✓Data period: April 2008−September 2020
- The dataset for this study included 818,486 patients with any of the diagnoses associated with PAD.
- Observation period for each patient is the period between the earliest and latest dates of any medical practice recorded in the database.

Patients

- Target patients were identified from the dataset as following (Figure 1).
  1. Having first CLI diagnosis (defined by disease name) during the observation period
  2. Having POBA
     - POBA: defined by the records of procedure (K616: vasodilation/thrombus ablation in the limbs) and percutaneous transluminal angioplasty (PTA) balloon catheter (defined by claim code) on the same day.
     - Index: the date of the first POBA within the data period.
  3. Having neither stent nor drug-coated balloons (defined by claim code) on the index
  4. Having first CLI diagnosis before the index
  5. Not having amputation before the index
- Subgroups: the target patients were divided into two groups, calcification group and non-calcification group, which were classified based on the number of PTA balloon catheter at the index: ≥3 and <3, respectively.

Analysis

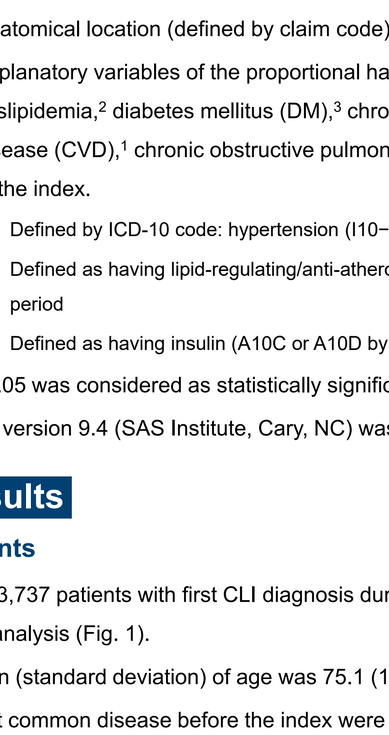
- Attributes of the target patients at the index, including age, percentage of women, and percentage of patients diagnosed with each disease included in the explanatory variables were tabulated.
- Hazard ratio of BKA was estimated from the index to the earliest BKA in each anatomical location or any of the locations by a proportional hazard analysis.
  - ✓Anatomical location (defined by claim code): toe, foot, and lower leg
  - ✓Explanatory variables of the proportional hazard analysis: age at index, sex (1: men, 2: women), and history of hypertension,[1] dyslipidemia,[2] diabetes mellitus (DM),[3] chronic kidney disease (CKD),[1] cerebrovascular disease (CVA),[1] cardiovascular disease (CVD),[1] chronic obstructive pulmonary disease (COPD)[1] before the index, and smoking status (>0 of smoking index) at the index.
    1. Defined by ICD-10 code: hypertension (I10−I13), CKD (Y84.1, N18), CVA (I60−I64, I66, I69), CVD (I25), COPD (J44)
    2. Defined as having lipid-regulating/anti-atheroma preparations (C10 by ATC code) prescriptions before index and during the observation period
    3. Defined as having insulin (A10C or A10D by ATC code) prescriptions before index and during the observation period
- p <0.05 was considered as statistically significant.
- SAS version 9.4 (SAS Institute, Cary, NC) was used for the analyses.

Results

Patients

- Of 13,737 patients with first CLI diagnosis during the observation, 7,289 underwent POBA and 2,408 patients were identified for the analysis (Fig. 1).
- Mean (standard deviation) of age was 75.1 (10.9) years, and 36.3% were women in all target patients (Table 1).
- Most common disease before the index were hypertension (67.9%) followed by CKD (53.5%), DM (42.1%), and dyslipidemia (30.6%) among the diseases included in the explanatory variables in all target patients (Table 1).
- When comparing the subgroups, mean age was 2 years younger and more men were included in the calcification group. Percentage of patients with CKD was >10% higher, but that with other diseases were lower in the calcification group.

Figure 1. Flow diagram for patients identification



CLI, critical limb ischemia; POBA, plain old balloon angioplasty; w/, with; w/o, without

Table 1. Patient characteristics at the index

		All	Calcification	
			Yes	No
Number of patients		2,408	620	1,788
Age (mean)		75.1	73.7	75.7
Age (SD)		10.9	10.5	11.0
% of patients	**Women**	36.3	33.4	37.2
	Hypertension	67.9	65.0	69.0
	Dyslipidemia	30.6	26.6	32.0
	DM	42.1	39.2	43.0
	CKD	53.5	62.1	51.0
	CVA	0	0	0
	CVD	4.6	4.2	5.0
	COPD	1.9	1.9	2.0
	Smoking	30.2	28.9	31.0

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular disease; CVD, cardiovascular disease; DM, diabetes mellitus; SD, standard deviation.

Incidence of BKA

- The incidences of BKA by anatomical location are shown in Table 2.
- Among the anatomical locations, the incidence was the highest in toe followed by lower leg and foot. The percentages of BKA by the anatomical locations were similar or lower in calcification group compared with non-calcification group (Table 2)..

Table 2. Incidence of BKA by anatomical location

		All	Calcification	
			Yes	No
Number of patients		2,408	620	1,788
Incidence of BKA by anatomical location (%)	**Toe**	13.1	12.3	13.4
	Foot	6.3	6.5	6.2
	Lower leg	9.5	9.2	9.6
	Any	24.4	23.5	24.7

Risk factors for BKA

- Among the 10 explanatory variables, DM was significantly associated with increasing the risk of BKA across all and any anatomical locations (any locations, hazard ratio: 1.968, p<0.001; Tables 3A−3D).
- Other than DM, CKD was significantly associated with increasing the risk of BKA across all locations (except foot), and dyslipidemia was significantly associated with decreasing the risk in toe BKA (Table 3A), and lower age was significantly associated with increasing the BKA risk in lower leg and any of the anatomical locations (Tables 3C and 3D). On the other hand, other variables were not significantly associated with the BKA risk in foot (Table 3B).
- DM was also significantly associated with increasing the risk regardless of the anatomical locations in both subgroups. Higher age was significantly associated with increasing the risk in toe BKA in calcification group.

Table 3. Hazard ratio by the proportional hazard analysis with the stepwise method by anatomical location: (A) toe, (B) foot, and (C) lower leg and (D) any of them across all patients.

(A)

Variables	HR	P-value
Sex	1.051	0.699
Age	0.998	0.739
Hypertension	0.983	0.896
Dyslipidemia	**0.694**	0.006
DM	**1.670**	<0.001
CKD	**1.434**	0.003
CVA	-	-
CVD	0.739	0.289
COPD	0.172	0.079
Smoking	1.057	0.663

(B)

Variables	HR	P-value
Sex	1.111	0.580
Age	0.996	0.650
Hypertension	0.745	0.109
Dyslipidemia	0.863	0.418
DM	**2.777**	<0.001
CKD	1.298	0.138
CVA	-	-
CVD	1.351	0.342
COPD	0.396	0.356
Smoking	1.203	0.309

(C)

Variables	HR	P-value
Sex	1.276	0.109
Age	**0.984**	0.012
Hypertension	0.776	0.087
Dyslipidemia	**0.701**	0.021
DM	**1.846**	<0.001
CKD	**1.477**	0.007
CVA	-	-
CVD	1.025	0.931
COPD	1.423	0.440
Smoking	1.235	0.154

(D)

Variables	HR	P-value
Sex	1.195	0.059
Age	**0.992**	0.040
Hypertension	0.884	0.189
Dyslipidemia	**0.723**	<0.001
DM	**1.968**	<0.001
CKD	**1.282**	0.005
CVA	-	-
CVD	1.036	0.849
COPD	0.562	0.162
Smoking	1.089	0.363

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular disease; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio.

HRs with statistically significant were indicated in boldface.

Discussions

- Regardless of the anatomical locations, DM was significantly associated with increasing the risk of BKA. DM complications can include nerve damage and poor blood circulation, leading to skin ulcers and possibly resulting in lower limb amputation [1]. This risk may appear after undergoing POBA for patients with CLI.
- Association of CKD to BKA in some anatomical locations was also indicated.
- Dyslipidemia was suggested to be lower risk of BKA in toe, lower foot, and any of them. One of the reason may be associated with that the patients were defined based on the treatment. Consequently, the patients may well manage their conditions, possibly resulting in reducing the risk of BKA.

Limitations

- Accuracy of the claims data used in the study affects the results.
- The database did not include record of diagnoses and treatments outside. Therefore, although we included patients with first CLI diagnosis during the observation period who underwent POBA after the first CLI diagnosis, and excluded those with amputation before the first POBA, as the first CLI diagnosis and first POBA may not be the first ones for the patients, and amputation underwent outside were not captured. Moreover, BKA after the index was also not captured if it was undergone outside. Nevertheless, as DPC hospitals are mostly special hospitals, most patients who underwent POBA are likely to visit the same hospital to follow up and undergo BKA there if needed.
- As we used the database from DPC hospitals, the patients may have more severer symptoms and/or have more complications than other Japanese patients with CLI.

Conclusions

- DM is suggested as a risk factor for BKA regardless of below-the-knee anatomical location in CLI patients who underwent POBA.
- This information may be useful in the management of patients undergoing POBA to prevent BKA.

References
1. Walicka M, et al. Amputations of Lower Limb in Subjects with Diabetes Mellitus: Reasons and 30-Day Mortality. J Diabetes Res. 2021;2021:8866126.

ISPOR Europe 2022, 3-6 Nov, Vienna, Austria