The Japanese Regulatory Landscape for Venous Interventional Devices

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Agenda

01 Treatment of symptomatic deep vein incompetence

02 Device for DVT: Aspiration thrombectomy catheter

- Discussion point① The clinical positioning and the target patients in Japan
- Discussion point② The necessity of safety measures in the post market phase

03 Device for DVT, PTS: Venous stent

- Discussion point① The clinical positioning and the target patients in Japan
- Discussion point② The necessity of safety measures in the post market phase

Treatment of symptomatic deep vein incompetence

		Acute Deep Vein Thrombosis (DVT)	Post-Thrombotic Syndrome (PTS)	Non-Thrombotic Iliac Vein Lesion (NIVL)
Etiology		Obstructive disease due to venous thrombosis, most often in the leg	Symptomatic chronic venous insufficiency after DVT	Extrinsic compression by other anatomical structures
Conventional treatment	Conservative treatment	• Anticoagulant & DOAC • Compression stockings		
	Interventional treatment	• Catheter-directed thrombolysis (CDT) • Transcatheter thrombectomy • Surgical thrombectomy		
		• Endovascular treatment (Balloon angioplasty, Stent placement)		
Treatment purpose		• Prevent thrombus extension and embolism • Avoidance of limb amputation		
		• Symptomatic relief		
Required device performance		• Improvement of venous blood flow by removing thrombus	• Improvement of venous blood flow by maintaining vascular patency	

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2022 Request for early introduction of thrombectomy devices due to **shortage of urokinase supply** by the academic society

2023 **Indigo Aspiration System** was approved

Device for DVT: Aspiration thrombectomy catheter -Discussion points of review①-

Consider the clinical role and the target patients in Japan

- ✓ CDT is considered one of the standard treatments for severe acute DVT
- ✓ Aspiration thrombectomy was expected to be a substitute for CDT

Setting the Intended use based on the clinical needs and the positioning

Intended use (including arterial disease)

Used to restore blood flow in patients with acute limb ischemia, acute superior mesenteric artery occlusion, or severe acute deep vein thrombosis who require immediate treatment and for whom surgical thrombectomy is difficult or who are not expected to respond effectively to treatment.

《Guidelines for Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis（JCS 2017）》

	COR	LOE
Catheter treatment is performed for severe acute iliofemoral vein thrombosis with arterial ischemia.	I	C
Catheter-directed thrombolysis is performed for acute iliofemoral vein thrombosis in the early stages of onset with severe symptoms and low bleeding risk.	IIa	B
Aspiration thrombectomy is performed for acute iliofemoral vein thrombosis in the early stages of onset with and severe symptoms.	IIb	C

COR: Class of Recommendation, LOE: Level of Evidence

Device for DVT: Aspiration thrombectomy catheter
-Discussion points of review②-

Consider the necessity of safety measures in the post market phase

- ✓ No experience of use in Japan
- ✓ Differences in available concomitant therapies (e.g. CDT) between Japan and other countries

It is necessary to provide information and take additional risk reduction measures as necessary based on the domestic results collected through post-marketing surveillance

《Post-Marketing Surveillance》

Purpose	To confirm the efficacy and safety of the product in the domestic medical environment where concomitant thrombolytic therapy is difficult to use
Target disease	Acute limb ischemia, acute superior mesenteric artery occlusion and severe acute deep vein thrombosis
Surveillance period	6-month follow-up
Surveillance item	Vascular recanalization, successful procedure, death, salvage limb, additional treatment, compartment syndrome, fasciotomy, pulmonary embolism, vascular injury, hemorrhagic event, etc.

Treatment of symptomatic deep vein incompetence

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		● Endovascular treatment (Balloon angioplasty, **Stent placement**)		
Treatment purpose		● Prevent thrombus ex… and embolism ● Avoidance of limb a…		
		● Symptomatic relief		
Required device performance		● Improvement of ven… flow by removing th…		

2021 Selected as a high medical need device

2022 **Zilver Vena Venous Stent** was approved

2023 **VENOVO Venous Stent System** was approved

Device for DVT, PTS: Venous stent

《Summary of the clinical study of the Zilver Vena Venous Stent (VIVO study)》

Item	Outline
Type of study	Single-arm, prospective, multi-center clinical study
Study population	Symptomatic venous outflow obstruction in one iliofemoral venous segment (i.e., one limb) per patient, demonstrated by: • **CEAP "C" ≥ 3, or** • **VCSS pain score ≥ 2**
Number of patients enrolled	247
Primary endpoints	Safety endpoint: 30-day freedom from major adverse events (MAE) Efficacy endpoint: 12-month primary quantitative patency **<Results>** **Safety endpoint: 96.7% (95% CI 93.5-98.6%) > Performance Goal 87%** **Efficacy endpoint: 89.9% (95% CI 85.1-93.4%) > Performance Goal 76%**
Secondary endpoints	Change from baseline in the Venous Clinical Severity Score (VCSS) at 1 and at 12 months **<Results>** **1 month: -3.0 (95% CI:-3.5 to -2.6), 12 month: -4.2 (95% CI: -4.7 to -3.7)**

Device for DVT, PTS: Venous stent
-Discussion points of review①-

Consider the clinical role and the target patients in Japan

- ✓ **Acute DVT**: Conservative treatment → CDT, Thrombectomy → **Stents if there is a compressive lesion causing clinically significant symptoms**
- ✓ **PTS**: Conservative treatment → Treatment of superficial and perforator veins → **Stents if clinically significant symptoms do not improve**
- ✓ **NIVL**: Patients with no thrombus and only anatomic compression are rare in Japan

» **Target patients are those who are difficult to treat with existing therapies**

Intended use

Used to maintain the lumen of the iliofemoral venous for symptomatic venous outflow obstruction that is difficult to treat with existing therapies.

《Target patients in Japanese guideline for proper use》

Acute DVT	• Severe cases with arterial ischemia (Phlegmasia cerulea dolens, etc.) • Daily pain or discomfort (i.e. limits most regular daily activities): VCSS pain score 3
PTS	• CEAP "C" 5 or 6 • CEAP "C" 3 or 4 and VCSS pain score 3

Device for DVT, PTS: Venous stent
-Discussion points of review②-

Consider the necessity of safety measures in the post market phase

- ✓ Limited evidence on the effectiveness of stenting in improving clinical symptoms and the risks associated with long-term implantation
- ✓ Proper size selection is important to prevent migration
- ✓ Since the evidence for drug therapies such as anticoagulation during venous stenting has not been established, appropriate postoperative management should be performed considering the risk-benefit balance

Establishment of the guidelines for proper use

《Requirements for operators and institutions in Japanese guideline for proper use》

Requirements for operators	• IVR specialist, cardiovascular surgeon, certified cardiovascular interventionist, certified endovascular surgeon by the Japanese Society for Vascular Surgery • Completed the training program
Requirements for medical institutions	• Certified facilities for vein compression treatment or affiliated facilities • Facilities where doctors who meet the requirements for operators are permanently stationed and provide medical treatment for acute DVT and PTS

Device for DVT, PTS: Venous stent
-Discussion points of review②-

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《Post-Marketing Surveillance》

Purpose	To confirm the efficacy and safety of the product in the domestic medical environment
Target disease	causes of symptomatic iliofemoral artery outflow obstruction
Surveillance period	3-year follow-up
Key surveillance items	Safety endpoint: 30-day freedom from major adverse events (MAE) Efficacy endpoint: 12-month primary quantitative patency, change from baseline in the VCSS at 1 and at 12 months
Other surveillance items	Patient characteristics, successful procedure, adverse events, clinical symptoms of venous insufficiency (VDS, CEAP, VCSS, Vilalta scale QOL), device migration, etc.

Summary

- In recent years, venous interventional devices have been approved without domestic data in response to clinical needs in Japan.
- It is important to continue evaluation by PMS based on differences in disease incidence, available devices, etc. between Japan and the countries where the clinical trials were conducted.
- Cooperation from academic societies is required to ensure that the product is used safely and effectively in appropriate cases in clinical practice.
- By confirming long-term data, efficacy and safety in a more diverse patient population in PMS, we will continue to discuss appropriate patient selection, appropriate use, and the need for additional risk minimization measures.

Harmonization by doing

- Devices have been approved without domestic data in response to clinical needs in Japan.
  - **Shouldn't the development of other devices in Japan have been considered before the urokinase problem arose?**

    Was it possible to conduct global clinical trials including Japan and global development?
- Continuous evaluation by PMS is essential.
  - **It is important to maintain an appropriate balance in pre- and post-marketing evaluations, taking into consideration the burden on clinical sites.**

It is necessary to discuss the harmonization of venous interventional device development with industry, government, and academia in Japan and the U.S.