February 18, 2021
Division for Safety of Medical Devices
Office of Manufacturing Quality and Vigilance for Medical Devices
Pharmaceuticals and Medical Devices Agency (PMDA)

Paclitaxel-coated Balloons and Stents in the Femoropopliteal Artery (Update)

In April 2019, PMDA released a Risk Information of Ongoing Evaluation regarding Paclitaxel-coated balloons and stents (hereinafter referred to as “PTX devices”) in the femoropopliteal artery[1)]. Recently, in cooperation with related academic associations, data analysis of post-marketing surveillance data, etc., held by individual marketing authorization holders (MAHs) was performed under the Health and Labour Sciences Research Grant (“Long-term Safety of Devices Utilizing Paclitaxel in the Femoropopliteal Artery (Principal Investigator: Masato Nakamura (Toho University))). In addition, based on the research results, 3 related academic societies (Japanese Association of Cardiovascular Intervention and Therapeutics, Japanese Society of Interventional Radiology, Japanese Society for Vascular Surgery) have released a joint statement (hereinafter referred to as “Joint Statement”) on January 2021.

PMDA believes that it is necessary to objectively communicate the scientific facts to the medical field, and has summarized the related information below.

(1) About the study that triggered the risk assessment

In December 2018, Katsanos et al. published the results of a meta-analysis for PTX devices in the femoropopliteal artery (hereinafter referred to as the “Katsanos meta-analysis”)[2)]. According to this article, although all-cause mortality in patients treated with PTX devices did not differ from the control arms using uncoated devices at 1 year, it was higher at 2 years and 5 years, suggesting a possible increased mortality rate associated with PTX devices. Please refer to the original article for details of analysis results.

(2) Actions taken by international regulators

In 2019, the US Food and Drug Administration (FDA), the UK Medicines and Healthcare Products Regulatory Agency (MHRA), and the French National Agency for Medicines and Health care Products Safety (Agence Nationale de Sécurité du Médicament et des Produits de Santé：ANSM) have provided health care professionals using PTX devices with information on the content of this article and the fact that risk evaluations are being conducted in various countries[3),4),5)]. In addition, FDA communicated its second information on March 15, 2019 that the agency encourages treatment options other than PTX devices until completion of its risk evaluation based on the analysis of follow-up results of the pre-marketing clinical trials for the devices (hereinafter referred to as "FDA Data Analysis") [6)]. The actions taken by each country is as follows.

a. United States

The FDA has held a public hearing in June 2019, and issued the following information in August 2019[7)].

- Continue diligent monitoring of patients who have been treated with PTX devices.
- In the process of obtaining informed consent, explain that there may be an increased rate of long-term mortality in patients treated with PTX devices.
- Discuss the risks and benefits of all available treatment options with your patients. Explain that, for many patients, alternative treatment options to PTX devices provide a more favorable benefit-risk profile based on currently available information. On the other hand, for individual patients judged to be at particularly high risk of repeated femoropopliteal interventions for restenosis, treatment with PTX devices may be appropriate.
- FDA is working with the manufactures to investigate additional clinical data and update the labeling for PTX devices

b. Europe

In response to the recommendations from expert committees, ANSM in May 2019 and MHRA in June 2019 have advised that PTX devices only be used for patients with high necessity of such devices, and to adequately

discuss the risks and benefits[8),9)]. In June 2020, a joint Field Safety Notice from relevant manufacturers was posted on the website of the regulatory authorities of each country including MHRA, ANSM[10)]. The contents of revision of the Instruction For Use are as follows.

- Warning: wording directing physicians to discuss the results of the Katsanos meta-analysis and the benefits and risk of available treatment options was added.
- Summary of the meta-analysis: wording describing the Katsanos meta-analysis, FDA Data Analysis, and information regarding clinical date for the specific product were added.

c. Others

Similar information to a) was provided by Health Canada in May 2019, and the Therapeutic Goods Administration in August 2019[11),12)].

(3) Mortality risk in Japanese population

Discussions in related academic associations in Japan regarding the Katsanos meta-analysis mentioned in section (1) have raised concerns that limited number of studies in which long-term prognosis was analyzed, a lot of missing data, and no adjustment made for important confounding factors. Furthermore, in the FDA Data Analysis, problems such as ethnic factors and short investigation period, small sample size, and follow-up issues were discussed. Based on the above backgrounds, the necessity of data analysis based on Japanese populations was noted, and a study was conducted under a Health and Labour Sciences Research Grant (hereinafter the “MHLW Study”)[13)]. Please refer to the clinical study report of the MHLW Study. In addition, based on this MHLW Study and recent international findings, the following related academic associations issued a multi-society Joint Statement on 29 January 2021[14),15),16)].

- Japanese Society for Vascular Surgery
- Japanese Society of Interventional Radiology
- Japanese Association of Cardiovascular Intervention and Therapeutics

a. Excerpt of the overview of the MHLW Study from the Joint Statement (modified)

A third party independently performed a meta-analysis of 2581 anonymized individual level Japanese cases (12 GCP-compliant clinical trials and GPSP-compliant post-marketing surveillance performed by 6 manufacturers). The 5-year cumulative crude mortality rate in PTX device group was 24.4%,significantly better than 27.4% in non-PTX group(p=0.02), but there was no significant difference in 5-year life prognosis between these groups after adjusting for patient backgrounds (hazard ratio 1.01, 95% CI: 0.39-2.58, p=0.99). Additionally, there was no difference in incidence of amputation between the two groups. Based on these results, there was no increased mortality risk of PTX devices compared to non-PTX devices in Japan.

b. Excerpt from the summary research report of the MHLW Study (modified)

	Predicted 5-year mortality		Hazard Ratio	95% CI	p-value
	PTX devices	Non-PTX devices			
Controlled clinical trial[1]	11.7%	13.9%	0.88	0.35-2.22	0.79
Controlled clinical trial[2]	11.7%	15.4%	0.81	0.44-1.51	0.51
Single-arm study cases[3]	26.4%	31.0%	0.77	0.63-0.93	0.007
All cases	24.4%	27.4%	0.81	0.67-0.97	0.02

[1] : Clinical trials for marketing authorization of PTX devices utilizing balloon dilation as control, performed by Cook Medical Japan G.K., Medtronic Japan Co. Ltd., and Medicon Inc.

[2] : Boston Scientific Japan K.K., Terumo Co., and Cardinal Health Japan LLC. added to Controlled clinical trial[1]

[3] : Patients that were excluded in controlled clinical trials such as patients with critical limb ischaemia and dialysis are included.

c. The opinion of the related academic associations (excerpt from the Joint Statement)

The related academic associations (Japanese Society for Vascular Surgery, Japanese Society of Interventional Radiology, Japanese Association of Cardiovascular Intervention and Therapeutics) shared these results and came to the common conclusion that "PTX devices do not pose a risk to long-term mortality in Japan, and this current analysis is valuable foundational information for considering the risks and benefits, as well as informed consent process."

Therefore, we make the following recommendations to healthcare providers.
1. Use PTX devices based on the risks and benefits considering patient conditions
2. In addition to overseas data, use the outcomes of this study as representative of Japanese outcomes in obtaining informed consent

(4) The effectiveness of PTX devices in the femoropopliteal artery

Excerpt from the clinical study report of the MHLW Study (modified) :

According to a pooled meta-analysis of 26 controlled clinical trials, the 24-month repeated revascularization rate for PTA balloons was 38.5%, 26.9% for bare metal stents, 19.4% for drug-eluting stents, and 17.6% for drug-coated balloons, demonstrating that PTX related devices achieve better 24-moth repeated revascularization than non-related devices (Fig. 1).

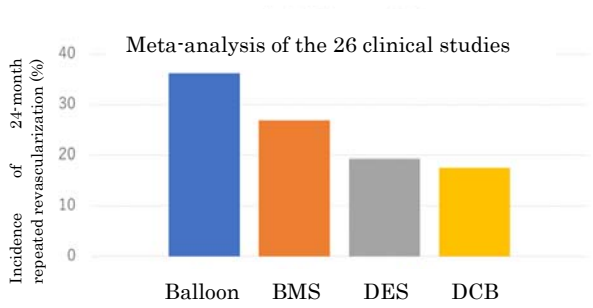

Fig. 1 Pooled meta-analysis of controlled clinical trials related to PTX devices.
(BMS: Bare metal stent, DES: Drug-eluting stent, DCB: Drug-coated balloon)

(5) Other recent international studies (as of February 2021)

In December 2020, a comparative study using Swedish registry database

(100% follow-up rate) found no difference in mortality at 2.5 years follow-up, and was published in the New England Journal of Medicine[17].

(6) PMDA's evaluation results

Based on the above information, and also considering the deliberations at an Expert Discussion, PMDA believes that based on the research results explained in section (3), there is currently insufficient scientific evidence to justify restricting the use of PTX devices in Japan.

At the same time, we acknowledge that the mortality associated with PTX devices is still under investigation in various countries and will continue to be published.

Therefore, we ask that MAHs of PTX devices, in addition to the actions of (7), maintain up-to-date package inserts to provide the most recent information based on the newest findings.

Also, we request that health care professionals who use PTX devices keep in mind the following.

- Please explain the risk and benefits of using PTX devices showing the latest scientific findings outlined in this document during the informed consent process, and select an appropriate device taking into account the risks and benefits based on patient conditions.
- Additional information may be provided from international regulators and MAHs, so please continue to actively gather the latest information.
- Please forward any occurrences of malfunctions and serious health damages associated with PTX devices you may identify to the relevant MAHs of the products. In addition, please report the information to PMDA according to the Drugs and Medical Devices Safety Information Reporting System. (https://www.pmda.go.jp/safety/reports/hcp/pmd-act/0003.html, only in Japanese).

As of February 2021, PTX devices in the femoropopliteal artery marketed in Japan are as follows.

Brand Name	Marketing Authorization Holder
Zilver PTX Drug-Eluting Peripheral	Cook Medical Japan G.K.

Brand Name	Marketing Authorization Holder
Stent	
Eluvia Drug-Eluting Stent	Boston Scientific Japan K.K.
Ranger Drug-Coated Balloon Catheter	
Lutonix Drug-Coated Balloon Catheter (for femoropopliteal arteries)	Medicon Inc.
IN.PACT Admiral Drug-Coated Balloon Catheter	Medtronic Japan CO., Ltd.

(7) Actions taken by the Ministry of Health, Labour and Welfare

In response to the progress to date, the MHLW has issued a notification (February 18, 2021, Pharmaceutical Safety and Environmental Health Bureau/Director of Medical Device Evaluation Division Notification No. 0218-1-,Pharmaceutical Safety and Environmental Health Bureau/Director of Pharmaceutical Safety Division Director Notification No.0218-1, Self-inspection of Package Inserts for Paclitaxel-coated Balloons and Stents in the Femoropopliteal Artery) to MAHs to confirm that the following contents are included.

1) Confirm that the following is included in [Important Precautions] section, under [Precautions].

・Use this product taking into consideration the risks and benefits based on patient conditions.

・In addition to foreign information, the representative results in Japan (refer to the [Main References and Reference Provider] section) should be used to obtain informed consent.

2) In [References Request and Contact Information] section, at present, verify that at least the following references should be included.

・Katsanos K, 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", Journal of the American Heart Association, 2018; 7: e011245

・Health and Labour Science Special Research Grants “Long-term Safety of Devices Utilizing Paclitaxel in the Femoropopliteal Artery” (Principal investigator: Masato Nakamura)

・“Statement on Paclitaxel-coated balloons and stents in the femoropopliteal artery”(Japanese Society for Vascular Surgery, Japanese Society of Interventional Radiology, Japanese Association of Cardiovascular Intervention and Therapeutics)

・Nordanstig J, et al., "Mortality with Paclitaxel-Coated Devices in Peripheral Artery Disease", N Engl J Med, 2020; 383:2538-2546

References

1) Paclitaxel-coated Balloons and Stents in the Femoropopliteal Artery（April 19, 2019）
https://www.pmda.go.jp/files/000229174.pdf (only in Japanese)
https://www.pmda.go.jp/files/000235788.pdf
2) Katsanos K, 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”, Journal of the American Heart Association, 2018; 7: e011245
3) Information provided by FDA (January 17, 2019)
https://www.fda.gov/MedicalDevices/Safety/LetterstoHealthCareProviders/ucm629589.htm
4) Information provided by MHRA (March 8, 2019)
https://www.gov.uk/government/news/expert-advisory-group-set-up-to-review-paclitaxel-drug-coated-balloon-catheters-and-drug-eluting-stents
5) Information provided by ANSM (February 27, 2019)
https://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Traitement-de-l-arteriopathie-obliterante-des-membres-inferieurs-AOMI-a-l-aide-de-dispositifs-medicaux-au-paclitaxel-Point-d-Information
6) Information provided by FDA (March 15, 2019)
https://www.fda.gov/MedicalDevices/Safety/LetterstoHealthCareProviders/ucm633614.htm?utm_campaign=FDA+MedWatch+Paclitaxel-Coated+Balloons+and+Paclitaxel-Eluting+Stents&utm_medium=email&utm_source=Eloqua
7) Information provided by FDA (August 7, 2019)
https://www.fda.gov/medical-devices/letters-health-care-providers/august-7-2019-update-treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel
8) Information provided by ANSM (May 13, 2019)
https://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Recommandations-de-traitement-de-l-arteriopathie-obliterante-des-membres-inferieurs-AOMI-a-l-aide-de-dispositifs-medicaux-au-paclitaxel-Point-d-information
9) Information provided by MHRA (June 4, 2019)

https://www.gov.uk/drug-device-alerts/recommendations-for-ongoing-use-of-paclitaxel-drug-coated-balloons-dcbs-and-implantable-drug-eluting-stents-dess-in-the-treatment-of-patients-with-peripheral-artery-disease-pad-mda-2019-023

10) Field Safety Notice for Europe (Posted by MHRA)
https://www.gov.uk/drug-device-alerts/field-safety-notices-29-june-to-03-july-2020

11) Information from Health Canada (May 6, 2019)
https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2019/69848a-eng.php

12) Information from TGA (August 12, 2019)
https://www.tga.gov.au/publication-issue/paclitaxel-coated-products-used-peripheral-arteries

13) FY2019 Health and Labour Science Program Grant for Government Policy Research Area. Health and Labour Science Special Research Report “Long-term Safety of Devices Utilizing Paclitaxel in the Femoropopliteal Artery”
https://mhlw-grants.niph.go.jp/niph/search/NIDD00.do?resrchNum=201906018A (only in Japanese)

14) Statement from the Japanese Society for Vascular Surgery
http://www.jsvs.org/ja/info/pdf/2021012902.pdf (only in Japanese)

15) Statement from the Japanese Society of Interventional Radiology
https://www.jsir.or.jp/wp-content/uploads/2015/03/PXT_210118.pdf (only in Japanese)

16) Statement from the Japanese Association of Cardiovascular Intervention and Therapeutics
http://www.cvit.jp/files/news/2021/0129.pdf (only in Japanese)

17) Nordanstig J, et al., “Mortality with Paclitaxel-Coated Devices in Peripheral Artery Disease”, N Engl J Med, 2020; 383:2538-2546