EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

05 August 2024
European Medicines Agency

Advice from the medical devices Expert Panels

Mandate[1] and Advice provided to the Medical Device Coordination Group (MDCG)

[1] According to the section 6.3 of the Rules of procedure of the European Commission expert panels on medical devices and in vitro diagnostic medical devices.

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2. Mandate from the Medical Device Coordination Group (MDCG)

2.1. Legal basis for the request

Article 106 (10) (a) and (b) of Regulation (EU) 2017/745 on medical devices.

2.2. Party requesting the advice

The Medical Device Coordination Group (MDCG)

2.3. Timelines for providing the advice

Start of the advice procedure: 05 June 2024

Advice delivered to the MDCG: 05 August 2024

2.4. Relevant medical field and areas of competence required

Vascular medicine, clinical, epidemiology, biostatistics.

2.5. Specific thematic panel or panel sub-group best suited to address the request for advice (if applicable)

Circulatory system

2.6. Complexity of the request according to the criteria established in Table 2 of the Commission Implementing Decision (EU) 2019/1396 Annex

☒ Category I — simple matter
☐ Category II — complex matter
☐ Category III — very complex matter

2.7. Consultation or collaboration with other scientific bodies for the preparation of the advice (if applicable)

n/a

2.8. Scientific context and background information

Paclitaxel-coated balloons and paclitaxel-eluting stents are intended to treat both new and recurring atherosclerotic lesions in the femoropopliteal artery (located in the upper leg). The balloon and stent work to mechanically open the blocked blood vessel. Paclitaxel is then delivered from the balloon or stent to prevent scar tissue formation in the blood vessel that can re-narrow the artery.

A meta-analysis of randomized controlled trials published in December 2018 by Katsanos et. al. (see Annex II) identified an increased risk of late mortality at 2 years and beyond for paclitaxel-coated balloons and paclitaxel-eluting stents used to treat femoropopliteal arterial disease. In response to these data, FDA performed a patient level meta-analysis of long-term follow-up data from the pivotal

premarket randomized trials of paclitaxel coated devices used to treat femoropopliteal disease using available clinical data through May 2019. The meta-analysis also showed a late mortality signal in study subjects treated with paclitaxel-coated devices compared to patients treated with uncoated devices. Specifically, in the 3 randomized trials with a total of 1090 patients and available 5-year data, the crude mortality rate was 19.8% (range 15.9% - 23.4%) in patients treated with paclitaxel-coated devices compared to 12.7% (range 11.2% - 14.0%) in subjects treated with uncoated devices. The relative risk for increased mortality at 5 years was 1.57 (95% confidence interval 1.16 - 2.13), which corresponds to a 57% relative increase in mortality in patients treated with paclitaxel-coated devices. As presented at the June 2019 FDA Advisory Committee Meeting, an independent meta-analysis of similar patient-level data provided by VIVA Physicians, a vascular medicine organization, reported similar findings with a hazard ratio of 1.38 (95% confidence interval 1.06 - 1.80). Additional analyses have been conducted and are underway that are specifically designed to assess the relationship of mortality to paclitaxel-coated devices.

The presence and magnitude of the late mortality risk should be interpreted with caution because of multiple limitations in the available data, including wide confidence intervals due to a small sample size, pooling of studies of different paclitaxel-coated devices that were not intended to be combined, substantial amounts of missing study data, no clear evidence of a paclitaxel dose effect on mortality, and no identified pathophysiologic mechanism for the late deaths.

Paclitaxel-coated balloons and stents improve blood flow to the legs and decrease the likelihood of repeat procedures to reopen blocked blood vessels compared to uncoated devices. The benefits of paclitaxel coated devices (e.g., reduced reinterventions) should be considered in individual patients along with potential risks (e.g., late mortality).

In 2019, in the context of the vigilance coordination it was decided amongst the EU regulators to include in the IFUs of the products a warning on the matter. This warning (see Annex II) continues in the IFUs of the products today. In addition to this requirement for manufacturers, several European Competent Authorities have published recommendations for patients and physicians.

French example: https://ansm.sante.fr/actualites/traitement-de-larteriopathie-obliterantedes-membres-inferieurs-aomi-lutilisation-de-ballons-ou-de-stents-au-paclitaxel-doittoujours-etre-reservee-aux-patients-les-plus-severes)

In October 2023 a new study was published in The Lancet "Mortality in randomised controlled trials using paclitaxel-coated devices for femoropopliteal interventional procedures: an updated patient-level meta-analysis", The Lancet, 24/10/2023. This study, linked below, may warrant a change in the regulatory approach with regard to the paclitaxel-coated balloons and paclitaxel-eluting stents.

2.9. Scope of the advice

The MDCG has requested the Expert Panels to address the following questions:

1. Does the new data available provide sufficient reassurance concerning the risk of increased mortality associated with the use of paclitaxel-coated devices?
2. Provide an opinion on the necessity to maintain the IFU warning (See Annex II)
3. If an update of the recommendations for patients and physicians is needed, provide advice on what are the elements that need to be included.

3. Advice provided by the Circulatory system Expert Panel

3.1. Questions and answers

3.1.1. Does the new data available provide sufficient reassurance concerning the risk of increased mortality associated with the use of paclitaxel-coated devices?

Paclitaxel-coated balloons (PCBs) and paclitaxel-eluting stents (PESs) are medical devices used to treat peripheral artery disease (PAD). PAD is a narrowing of the arteries in the legs, which can reduce blood flow and cause pain, cramping, and even limb loss. PCBs and PESs use paclitaxel as an ancillary substance to help prevent the arteries from re-narrowing after treatment. However, there have been concerns about the safety of these devices, particularly regarding the risk of increased mortality.

In 2018, Katsanos et al[2] published a meta-analysis that seemed to identify an increased risk of death at 2 years and 5 years following femoropopliteal application of paclitaxel-coated balloons and stents in the lower limbs and advised for further research. As this study had several methodological shortcomings, namely the lack of completeness of long-term follow-up of the patients included (e.g., the long-term follow-up of deaths was suboptimal), further studies have been published since to further investigate the existence of such risk.

From the many studies reviewed on this topic, two were considered to be particularly relevant to answer this question, due to their methodological nature (meta-analysis studies) and recent publication date.

The study conducted by Parikh et al[3] is a patient-level pooled analysis of trials, designed with the support of the US Food and Drug Administration, and having as primary objective a comparison of the risk of death with paclitaxel-coated versus control devices. It included 10 trials with a total of 2666 patients and a median follow-up of 4.9 years. The authors found an overall hazard ratio (HR) for the intention-to-treat (ITT) population of 1·14 (95% CI 0·93–1·40). In conclusion, there seems to be a slight increase in the risk of mortally in the paclitaxel devices group, although not statistically significant, meaning that the hypothesis of association between the use of paclitaxel devices and increased risk of death cannot be accepted nor rejected. Also worth noticing that there is a significant heterogeneity of results across the trials included in the study. This can be attributed to multiple causes, including differences within the target patient population and variations in the clinical standards used for treatment and follow-up across the different centres/countries.

Additionally, the analysis of the risk of mortality by dose after adjusting for lesion length (in order not to confound the randomisation, as higher doses would probably be associated with longer lesions) yielded estimated HRs of similar magnitude to the overall HR of 1.14: HR=1.15 (0.86–1.54) for the first dose tercile, HR=1.13 (0.87–1.48) for the second dose tercile and HR=1.10 (0.81–1.49) for the third dose tercile.

[2] Katsanos K, Spiliopoulos S, Kitrou P, 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. J Am Heart Assoc. 2018 Dec 18;7(24):e011245. doi: 10.1161/JAHA.118.011245. PMID: 30561254; PMCID: PMC6405619.
[3] Parikh SA, Schneider PA, Mullin CM, Rogers T, Gray WA. Mortality in randomised controlled trials using paclitaxel-coated devices for femoropopliteal interventional procedures: an updated patient-level meta-analysis. Lancet. 2023;402(10415):1848-56.

Finally, the authors report imbalances in other baseline characteristics that make challenging the interpretation of these results: "Regardless of propensity score adjustment, imbalances remained in lesion length, hyperlipidaemia, smoking status, history of percutaneous coronary intervention, and beta-blocker use, all of which have potential influences on death.".

The second study this expert panel considered to be relevant for this advice was the meta-analysis done by D'Oria[4] et al. In this study, there seemed to be evidence that paclitaxel-based endovascular therapy increased all-cause mortality at mid-term, with a calculated pooled risk ratio (RR) of 2.05 (1.21, 3.24) for follow-ups of 2-3 years and a reduced RR=0.66 (0.31, 3.42) for a longer follow-up of 4-5 years. This change from risk to protective effect requires additional interpretation. A possible explanation is that it may suggest a selection bias leading to include more severe patients (more likely to die earlier) in the paclitaxel device group, so that the patients that survive have the greater benefit from the drug-coated device. In any case, the authors considered this to be weak evidence due to the low fragility index of the studies used, e.g., the relationship between the use of paclitaxel-coated devices and all-cause mortality at mid-term showed very low robustness (FI=4 and FQ=0.2%).

Another important conclusion mentioned in the study is that "… if the signal is weak and the RCT was affected by methodological flaws, minor changes could influence primary outcomes accordingly. The fact that a few events could change the statistical significance of the all-cause mortality signal from the pooled femoral popliteal paclitaxel-based RCT data underscores the reality that investigators cannot rely on the limited available trial data to evaluate an association with mortality". Hence, it is the authors recommendation that further data is gathered from "… future RCTs designed with adequate power and follow-up time to assess the impact that paclitaxel-based endovascular interventions in the femoral-popliteal artery may have on amputation and mortality".

In conclusion, with the data made available to this expert panel, at this moment, it is not possible to either confirm or exclude an association between the use of paclitaxel-covered devices and an increased risk of mortality.

3.1.2. Provide an opinion on the necessity to maintain the IFU warning.

It is not possible for this expert panel to ascertain on the need to maintain the use of the IFU warning as a preventive risk-management measure because no definitive conclusion can be made on the association of the use of paclitaxel-coated devices with increased mortality, as mentioned in the answer provided to question 3.1.1. Additionally, for a complete opinion to be provided on that matter, the panel would need information on the estimated effectiveness of the measure and on the specificities of use of PCB/PES across the Member States, as well as the availability of alternatives.

[4] D'Oria M, Mastrorilli D, Secemsky E et al. Robustness of Longitudinal Safety and Efficacy After Paclitaxel-Based Endovascular Therapy for Treatment of Femoro-Popliteal Artery Occlusive Disease: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials. Annals of Vascular Surgery, Volume 101, 2024, Pages 164-178, ISSN 0890-5096, https://doi.org/10.1016/j.avsg.2023.11.024.

3.1.3. If an update of the recommendations for patients and physicians is needed, provide advice on what are the elements that need to be included.

At this moment, this expert panels did not identify the need for an update of such recommendations.