Recommendations from the independent Expert Advisory Group on the use of Paclitaxel Drug Coated Balloons (DCBs) and Drug Eluting Stents (DESs) to the MHRA

June 2019

MHRA

Contents

The independent Expert Advisory Group (EAG) on the use of Paclitaxel Drug Coated Balloons (DCBs) and Drug Eluting Stents (DESs) was established by the MHRA regulatory centre to consider issues related to these devices. The MHRA provided support to the EAG to facilitate its work.

Executive summary

The meta-analysis of randomised controlled trials (RCTs) by Katsanos et al on the use of paclitaxel coated/eluting devices (balloons and stents) in the femoral and/or popliteal arteries showed statistically significant increased all-cause mortality from 2 to 5 years post treatment compared with patients treated with plain balloons or bare-metal stents. These findings raised significant concerns on their use in clinical practice and clinical trials.

The independent Paclitaxel Expert Advisory Group (EAG) has been established with two main objectives: 1. to review the relationship between the clinical use of paclitaxel coated/eluting devices and increased mortality; 2. to inform the MHRA on the benefit/risk profile of the clinical use of paclitaxel-coated/eluting devices and to provide recommendations to MHRA on the benefit/risks of the use of these devices in such procedures.

The EAG review concluded that the statistical analysis in the Katsanos' paper is robust. There is a possible dose dependent effect of the use of paclitaxel coated/eluting devices on mortality although no scientific or clinical explanation is currently available. There are some established causal links between multiple factors and mortality, but the association of increased mortality and the use of paclitaxel coated/eluting devices is established by RCTs which control for confounding in known factors. There is no evidence to suggest that confounding persisted within these studies. Current knowledge gaps include dose-time relationship, outcomes of paclitaxel coated balloons versus paclitaxel eluting stents, patient factors, effect on patients with claudication compared with those with critical limb ischaemia, peer-reviewed publication of commercial evidence, mechanistic explanation, and biological evidence.

Following risk-benefit assessments based on current Level 1 evidence, the EAG recommended withholding the use of paclitaxel coated/eluting devices from routine clinical use in patients with intermittent claudication. The devices may still be considered in patients with critical limb ischaemia (CLI) taking NICE Guidance into consideration in conjunction with appropriate informed consent and an enhanced patient follow-up. Formal post marketing long-term surveillance is essential through high quality registries including an endpoint of all-cause mortality.

In terms of future evidence and evaluation, the EAG concluded that paclitaxel coated/eluting devices may still be considered a treatment option within ethically approved trials following appropriate informed consent. In particular, currently suspended RCTs involving patients with CLI should consider resumption in recruitment.

Ongoing and completed trials that have reported results from one or two-year follow-up should continue or reopen patient follow-up to establish the longer-term mortality status of all patients, up to at least 5 years post-treatment. Future research is recommended to evaluate the causal relationship between paclitaxel coated/eluting

devices and mortality including a mechanistic scientifically plausible explanation(s) and the clinical relevance. All approved trials should be submitted for peer review publication regardless of outcome.

The EAG strongly encouraged a collaborative approach among regulatory bodies, trial Data Monitoring Committees and other relevant multidisciplinary groups. An ongoing review of upcoming Level 1 evidence is essential for safe and clinically appropriate use of paclitaxel and other newer drug coated/eluting devices. The current European regulatory classification of drug coated/eluting technologies should be reviewed with a view to enhancing the extent of risk/benefit assessment of the drug in its device-related application, towards that required for medicinal products.

Expert advisory group (EAG) membership

Member	Title and affiliation
Daniel Carradice MB ChB FRCS MD(H) PGD Health Econ PGC Med US (D)	• Senior Lecturer and Honorary Consultant Vascular and Endovascular Surgeon, Hull York Medical School and Hull University Teaching Hospitals NHS Trust
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Teik Choon See (Chair) MB BCh BAO FRCS FRCR FBIR	• Consultant Interventional Radiologist, Cambridge University Hospitals NHS Foundation Trust • Chair of Safety & Quality Committee, BSIR • National Patient Safety Advisor, Royal College of Radiologists

The EAG also received expert advisory support from MHRA's Expert Statistical Assessor and Toxicology Assessor.

EAG terms of reference

The Paclitaxel Expert Advisory Group have been established to consider the issues related to Stents and Balloons in combination with Paclitaxel.

- Reviewing the relationship between paclitaxel and increased mortality
    - Including consideration of the robustness of the statistics of the papers reviewed
    - Offer comment on the credibility of findings from related studies
- Assist in determining if there is evidence that any one DCBs or DES is greater cause for concern than others.
- Investigate evidence of a causal relationship between the observed increased mortality and the paclitaxel coating (including dose dependency) or with any other unexpected patient or procedural variable.
- Provide MHRA with recommendations regarding whether the risk/benefit profile justifies continued use of paclitaxel DCBs and DESs, stratified if appropriate by device class, model and/or patient indications/circumstances.
    - Including advice on further clinical studies or analysis that should be generated or are already underway that could impact conclusions over the continued use of these devices.

EAG review methodology

The review process involved critical appraisal of the following documents or sources, where applicable:

- Katsanos K et al paper. https://www.ahajournals.org/doi/10.1161/JAHA.118.011245

- Sources obtained by the MHRA from the industry. These included information not directly available in the public domain and additional information that the companies were asked to clarify.

Sources from the following industry:

Company	Products	
	DCBs	DESs
Bard	Lutonix	
B Braun	SeQuent Please	
Biotronik	Passeo-18 Lux	
Boston Scientific	Ranger	Eluvia
Cardionovum	LegFlow	
Cook		Zilver PTX
IVascular	Luminor	
Medtronic	In.PACT	
Spectranetics	Stellarex	

- Comments from the Vascular InterVentional Advances (VIVA) Vascular Leaders Forum 1-2 March 2019.

- Additional more up to date publications, comments, and clarifications.

The review process included the following:

- Review proforma (**Appendix A**) – EAG Chair allocated source documents from the industry to each EAG member who reviewed them at their own time, completed and returned the proforma, and discussed them with the group.

- Web conferences – EAG members and MHRA colleagues discussed and debated the outcome of the review and any other evidence.

- Email discussion and sharing – EAG members and MHRA colleagues shared new findings, opinions, and clarification.

Review outcomes

1. Is the correlation in the Katsanos paper statistically robust:

    a. At 1 years, 2 years and 5 years.
    Yes.
    b. For any of the individual devices or device classes (i.e. DCB vs DES).
    Yes, for both device classes combined, but not possible to separate the two as this would significantly reduce the statistical power.

2. Is there any evidence of a causal relationship between paclitaxel and increased mortality, including?

    a. Is there evidence of a dose dependence to the effect?
    Possible. There is some supportive evidence of this. This requires further evaluation.
    b. Is there a plausible explanation for the effect, taking account of the release profile/timescale and paclitaxel half-life?
    Currently no scientific or clinical explanation available.
    c. Is this conclusion different for DCBs vs DES or for any individual device?
    The conclusion is for DCBs and DESs combined. The event rate is too low to separate the two without losing statistical power.

3. Is there evidence of a causal link between mortality and any other unexpected procedural / patient / lifestyle / other factors, not negated by randomisation?
    There are some known causal links between multiple factors and mortality, confirmed by the existing evidence base. It is, however, crucial to note that the association of increased mortality and paclitaxel use is established in RCTs which control for confounding in known factors. There is no evidence to suggest that confounding persisted within these studies.

    Is paclitaxel a surrogate for something else?
    Unlikely in view of the fact that analysis was of RCTs.

4. Are there any critical studies currently underway that could significantly impact conclusions?
    All current trials/ studies performed by the industry and others should be continued, or re-opened where necessary, to obtain at least 2 and preferably 5 years patient follow up. Also need to await outcome of patient level analysis currently underway.

5. What gaps in current knowledge would need newly designed studies in order to provide the answers?

    - outcomes of DCBs vs DESs
    - patient factors
    - effect on patients with claudication vs critical limb ischaemia

- outcomes from other studies using the same devices e.g. arterio-venous fistula
- peer-reviewed publication of commercial evidence
- independent expert group analysis rather than sponsor generated results
- mechanistic explanation
- Paclitaxel dose-time analysis
- animal study
- biological evidence including muscle biopsies and other tissue sampling

6. Overall conclusions based upon currently available evidence:

   a. Does the EAG consider the benefits currently outweigh the risks for all/some of these devices?
   Based on current available Level 1 evidence, the risks outweigh the benefits for the routine clinical use of paclitaxel coated devices in patients with intermittent claudication. The devices may still be a treatment option within ethically approved trials following appropriate informed consent, or for patients with critical limb ischaemia.

   b. Is there evidence that one of the DCBs or DES is greater cause for concern than others?
   No.

Recommendations

Relating to routine clinical use

1. The use of paclitaxel coated balloons and paclitaxel eluting stents should be withheld from routine use in patients with intermittent claudication until further Level 1 evidence on their safety profile is available.

2. The use of paclitaxel coated balloons and paclitaxel eluting stents can be considered in patients with critical limb ischaemia, if it is felt that the benefits outweigh the risks and taking NICE Guidance into account. If paclitaxel coated/eluting devices are to be used there should be enhanced patient follow-up which may include telephone consultation or review in the community, where appropriate. This should include at a minimum follow up until death and reporting of serious adverse events and cause of death.

3. The process of informed consent on the use of paclitaxel coated balloons and paclitaxel eluting stents should include a risk-benefit discussion with patients regarding the uncertainty in long-term outcomes with these devices, and the current evidence which indicates an increased mortality rate.

4. Ensure local procedures, taking duty of candour into account, are in place for the continued management of patients who have already been treated with paclitaxel coated balloons and paclitaxel eluting stents. Consider the need for follow-up, which may include telephone consultation or review in the community, where appropriate. This should include reporting of serious adverse events and cause of death.

5. The situation should be reviewed again following completion of the meta-analysis using patient level data from currently available RCTs.

Relating to clinical trials

6. BASIL 3 and other suspended randomised controlled trials involving patients with critical limb ischaemia, should consider resumption in recruitment.

7. Ongoing and completed trials that have reported results from one or two-year follow-up should continue or reopen patient follow-up to establish the longer-term mortality status of all patients, up to at least 5 years.

Relating to the need for further evaluation

8. Results from clinical trials on the use of paclitaxel coated devices in other conditions including arterio-venous fistula should be reviewed and shared, where relevant.

9. The causal relationship between paclitaxel coated devices and mortality will require further evaluation. Research on mechanistic relevance is essential including a critical reappraisal of the existing premarket studies.

General

10. All approved trials (pre and post market) should be submitted for peer review publication regardless of outcome. If not accepted, results should be made available in the public domain.

11. Post marketing surveillance is essential through the best quality of registries. This should include safety reporting mechanisms for serious adverse events and deaths. A mandatory national registry, subject to independent scrutiny, is strongly recommended.

12. A collaborative approach among regulatory bodies, trial Data Monitoring Committees and other relevant multidisciplinary groups is strongly encouraged.

13. There should be an increased awareness of potential systemic effects from other newer drug coated/eluting technologies which do not use paclitaxel.

14. A standard of safety evidence from RCTs is required without which a device cannot be used outside of research. Devices that have limited studies without appropriate safety outcomes to encompass potential systemic effects should not be considered safe and may pose significant risk.

15. The current classification of drug coated/eluting technologies should be reviewed. A technology used for delivering a drug should have enhanced medicines scrutiny.

Appendix A

Expert Advisory Group: Paclitaxel DCSs & DCBs review proforma

1	Article (title, journal, date); level of evidence
2	Relevant to review? Accept/ reject (why)
3	Types of devices
4	Patient selection
5	Methodology
6	Outcome measures
7	Morbidity & mortality
8	Statistical concern
9	Causal relationship of DESs/DEBs with mortality – dose dependent? Other explanation?
10	Causal relationship with other factors – patient characteristics? Concurrent interventions? Other medications?
11	Further evidence/document required as a result of this review?
12	Further review by EAG/ statistician / toxicologist?
13	Additional comments