Cardiovasc Intervent Radiol (2019) 42:1508–1509
https://doi.org/10.1007/s00270-019-02297-4

COMMENTARY

Commentary on Drug-Eluting Technologies

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Received: 19 July 2019 / Revised: 19 July 2019 / Accepted: 24 July 2019 / Published online: 5 August 2019

In November 2018, Katsanos et al.[1] published a systematic review and meta-analysis that demonstrated an increased risk of death following application of paclitaxel-coated balloons and stents. They analysed 28 randomised trials, the majority including patients with claudication. At 1 year, the all-cause death rate was similar for the paclitaxel-treated group and the controls. However, at 2 and 5 years there was a significant increase in all-cause mortality for the paclitaxel-treated group. At 2 years, this translated into a number needed to harm of 29 patients, and at 5 years, 14. Meta-regression showed a significant relationship between exposure to paclitaxel and the absolute risk of death. Of note, there were 12 trials at 2 years and only 3 at 5 years.

This resulted in considerable concern for doctors, patients, regulatory authorities, and manufacturers. Prior to this article, the majority of the debate surrounding these technologies centred on their effectiveness/cost-effectiveness in reducing target lesion restenosis and need for revascularisation. Many guideline-producing bodies were tending towards recommending their regular use.

This meta-analysis has been debated at numerous international meetings and congresses, including a convened meeting of VIVA in March 2019.

Regulatory authorities, including the FDA (US Food and Drug Administration)[2] and MHRA (UK Medicines and Healthcare products Regulatory Authority)[3] have issued alerts and guidance for clinicians and healthcare providers.

The situation is complex. The scientific integrity of the Katsanos publication was subject to widespread review and in general considered as sound as such analyses can be. Independent statistical review suggested potential flaws, but overall did not find the analysis to be incorrect. As levels of evidence are concerned, there are limited options for more reliable data—a patient-level meta-analysis is ongoing. One significant concern is the small number of studies that have reported results beyond 2 years. The situation has not been advanced by the finding of at least two errors in the reporting of the original trials.

There have been multiple attempts to find a casual link between the addition of paclitaxel to the devices and increased mortality as yet none has been identified.

The current situation leaves patients, Interventional Radiologists, and Vascular Surgeons with problems. A significant number of such devices have been utilised with the good intention of improving patient outcomes, there is no known causal link, and there is no treatment that will reduce or remove that risk. Whilst the statistical analysis of the trial outcome data appears robust, there remain experts who consider that an analysis of patient-level data may offer a different result, and others disagree.

We have a duty to be open with our patients, and many drug-eluting devices have been used for patients with claudication, and long life expectancy. There is a substantial risk of causing anxiety for those who have received drug-eluting technologies, which we are able to explain, but unable to mitigate. Going forward, this information must be included as a part of the process of informed consent, if paclitaxel device usage is being contemplated. Further, some institutions have moved to treating a high

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proportion of patients with such devices, and it may be advisable to reconsider and limit their use (perhaps to those with early recurrence or where the risk of early restenosis outweighs the increased risk)[4].

One lesson that can be learned is that devices gain CE mark on the basis of safety data. A proportion of those safety studies are not published, and the length of follow-up, prior to approval, can be short. These requirements warrant review.

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