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Paclitaxel and mortality: Where are we now?

Christopher P. Twine[1]

Hasan H. Dosluoglu[2]

1. Department of Vascular Surgery, North Bristol NHS Trust. Bristol, UK.
2. Division of Vascular Surgery, Department of Surgery, SUNY at Buffalo, Buffalo, NY; VA Western NY Healthcare System, Buffalo, NY.

Email: chris_twine@hotmail.com

The high-quality adjusted case series by Saratzis et al[1] puts another strong counterargument to the Paclitaxel-increases-mortality debate started by the meta-analysis from Katsanos et al in 2018.[2] The reaction to that meta-analysis was unprecedented in recent times, halting international practice despite widespread adoption of the technology and derailing randomised trials.

Saratzis et al examined a series of 2,071 patients with claudication or Chronic Limb Threatening Ischaemia (CLTI) and found that there was no excess mortality in the group receiving Paclitaxel after careful confounder adjustment.[1] The usual quality arguments against this approach apply in that it is retrospective data with inherent biases. However the authors have done their best to statistically adjust for these, and importantly, have a relatively high event rate for their primary outcome (death) because of a 50% proportion of patients with CLTI. Different but equally valid quality arguments can be applied against the low-quality trials included in the Katsanos analysis which included a predominance (90%) of patients with claudication, a lower

subsequent event rate for death, and were underpowered to report accurately on mortality. Long-term follow up from a local dataset is always challenging as accurately determining whether a patient is alive or dead is often unclear after the last local follow up. Without truncated follow up at a clear event such as a scan or clinic appointment, or data linkage to a validated dataset, morality reporting may be unreliable. While the quality of truncated follow up in the Saratzis study is unclear, the trials in the Katsanos analysis suffer from the same follow up problem. Additionally, none of the studies in the Katsanos analysis were designed for 5-year mortality comparisons and ascertainment bias in mortality assessment was likely. This is evidenced by the decrease in the mortality signal with longer term patient follow-up from the included studies, as well as the lack of a signal in the Japanese IMPACT trial, with more complete follow up data.[3]

Saratzis et al's study adds to previously published large cohort analyses examining the effect of Paclitaxel devices on mortality.[4-6] Mortality rates were found to be similar, or even less, with Paclitaxel-eluting endovascular technologies in these studies based on large, validated administrative databases with reliable information on all-cause mortality and on co-morbidities.[4-5] With over 60,000 patient, robustly adjusted cohort data showing no problem with Paclitaxel devices and strong arguments against the quality of included studies in the Katsanos analysis of 5000 patients (with only 1429 included in the 5-year mortality analysis), where are we now in the Paclitaxel-increases-mortality debate? The answer is that there was highly likely to be confounding and bias in the studies included in the Katsanos analysis.

The remaining problem is the signal towards mortality from each of the included studies in Katsanos analysis. It has been argued that these can only

‘definitively’ be proved as a cluster by a large randomised trial. It’s just as well these have managed to start recruiting again.

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