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Paclitaxel-coated balloons and stents for the treatment of peripheral artery disease: proceedings from the Cardiovascular Research Technologies (CRT) 2019 Town Hall

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Drug-coated balloons (DCB) and stents with paclitaxel were introduced to treat superficial femoropopliteal artery (SFA) lesions in patients with claudication and/or critical limb ischaemia. Randomised controlled trials (RCTs) demonstrated reduction of restenosis and need for revascularisation for DCB in comparison with plain balloons and bare metal stents and were approved for marketing use in the USA by the Food and Drug Administration (FDA) in 2012. Specifically, multiple RCTs and registries evaluating the treatment of the SFA lesions in patients with claudication have shown the effectiveness of paclitaxel drug-coated balloons (P-DCB) and paclitaxel drug-eluting stents (P-DES). However, there have been conflicting results about their safety profile. A study-level meta-analysis (28 RCTs with 4,663 patients) concluded that paclitaxel-related devices led to a significantly increased risk of mortality at two years and five years[1].

This prompted the FDA to issue a letter to physicians on 17 January 2019[2], saying in part: "A recent meta-analysis of randomised trials suggests a possible increased mortality rate after two years in patients with peripheral artery disease (PAD) treated by paclitaxel-coated balloons and paclitaxel-eluting stents compared to patients treated with control devices (non-coated balloons or bare metal stents). The specific cause for this observation is yet to be determined". The FDA recommended, "Continue surveillance of patients who have been treated with paclitaxel-coated balloons and paclitaxel-eluting stents per the current standard of care. In clinical decision making, discuss the risks and benefits of all available treatment options for PAD with your patients. Report any adverse events or suspected adverse events experienced with the use of paclitaxel-coated balloons and paclitaxel-eluting stents".

For these reasons, a town hall with an advisory panel of experts in the field was convened during the Cardiovascular Research Technologies (CRT) 2019 meeting in Washington, DC, with the participation of stakeholders (physicians, investigators, sponsors, manufacturers, and FDA) to address in depth the mortality reports in DCB and stents coated with paclitaxel and their implication for future clinical usage of these devices in patients with SFA disease. This report summarises the proceedings of the town hall and the vote of the advisory panel.

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The safety signal issue: reports showed increase in mortality with P-DCB and P-DES

P-DCB and P-DES were introduced to minimise the restenosis and the need for repeat revascularisation after intervention of SFA lesions. There are more than 20 different devices available, but few have clinical data with long-term follow-up. These were discussed in detail at the DCB Safety Town Hall meeting at CRT 2019. The first report was that, at three years post procedure, P-DCB percutaneous transluminal angioplasty (PTA) with the IN.PACT Admiral, 3.5 µg/mm^2 (Medtronic, Santa Clara, CA, USA) in the femoropopliteal artery (FPA) had a higher mortality rate in the P-DCB group than in those receiving standard PTA (10.7% vs 1.9%, p=0.006)[3].

Katsanos and colleagues' systematic review and meta-analysis investigated P-DCB and P-DES in the FPA (89% claudication). Of note, these studies had different available follow-up time periods. At one year, the risk of death did not differ significantly between the use of P-DCB or P-DES and the control arms (2.3% vs 2.3%; risk ratio [RR] 1.08, 95% CI: 0.72-1.61). At two years and five years, however, the use of paclitaxel-related devices vs standard PTA was associated with a significantly increased risk of death, 7.2% versus 3.8% (RR 1.68, 95% CI: 1.15-2.47), and 14.7% versus 8.1% (RR 1.93, 95% CI: 1.27-2.93), respectively. The number needed to harm was 29 patients (95% CI: 19-59) and 14 patients (95% CI: 9-32), at two and five years, respectively.

A meta-regression analysis was also performed, exploring the association of the exposure to paclitaxel with all-cause mortality. In this sub-analysis, all 28 RCTs were included; the authors stated that a normalisation equation for paclitaxel dose-time by exposed area was performed. They showed an excess risk of death by 0.4±0.1% per year for each 1 mg of paclitaxel (p<0.001). Dr Gray M. Ansel (Ohio Health Heart and Vascular Physicians, Columbus, OH, USA) said the derivation of this term assumes a uniform and predictable balloon delivery of paclitaxel, which is unlikely because of operator handling, transit time, inflation time and pressure, excipient efficiency, crystallinity (amorphous, micro-, macro-, or admixture), vessel avidity for paclitaxel distal embolisation rates and solubilisation rates. Further, Dr Aloke V. Finn (CVPath, Gaithersburg, MD, USA) said the total amount of drug dose in paclitaxel-related devices is much lower than that used as chemotherapy for the treatment of cancer (paclitaxel is part of the standard treatment for a variety of cancers, including lung, breast, head and neck, and ovary; doses for chemotherapy 80-200 mg/m^2). Therefore, it is not clear whether the actual dose on the paclitaxel devices plays a role in the increased mortality rate. Even so, Katsanos et al postulated that late paclitaxel toxicity may be the reason for the observed increased death rate. They wrote, "Contrary to solvent-based (e.g., cremophor) intravenous paclitaxel used in cancer chemotherapy that has a half-life of around 6 hours, paclitaxel crystals loaded on DCB or DES [drug-eluting stents] for the peripheral arteries have a half-life of weeks to months, depending on the exact chemical properties of the applied paclitaxel formulation"[1].

In this meta-analysis, there are several limitations, as highlighted by Dr William A. Gray (Main Line Health, Wynnewood, PA, USA): first, a study-level meta-analysis is a common methodological practice, but it provides less robust results than a patient-level analysis. Second, most of the included studies had small sample sizes. The idea that pooling them all together will give more power to show differences in the assessment of low-frequency events has been challenged because, at two and five years, the total number of patients studied was 2,316 and 863, respectively. Third, there are limited data after >1-year follow-up because only 12 of the 28 studies and 3 of 28 studies had two-year and five-year clinical event data, respectively; further, the report included 24 P-DCB trials and only four P-DES trials. Because the amount of paclitaxel on P-DES is approximately 10% to 20% of the total amount on a P-DCB, it may not be appropriate to pool these studies. Fourth, from the statistical analysis, the authors did not adjust for a non-parametric (skewed) distribution. This could potentially lead to different conclusions. Lastly, overall, 10% to 15% of patients in the PTA arm were exposed to paclitaxel at one year. This percentage could be even higher because, in the Zilver PTX study, which is included in the meta-analysis, 40% of patients in the PTA group were treated with a Zilver PTX stent after the randomisation.

Regulatory implications of the safety signal observed with paclitaxel-coated products in peripheral intervention: final vote

A total of 14 experts including physicians and statisticians from the USA and Europe voted (responses were anonymous) on four questions after all presentations:

1) Given the data from the meta-analysis and other data that was presented today, is there a safety signal for DCB and DES in the SFA? Answer: 10 voted yes, 4 voted "I don't know", zero voted no.

One of the panellists who voted "I don't know" explained that he did so because the underlying "structure" of the data used for Katsanos' meta-analysis may not be right and that the ascertainment was not complete (which he regarded as the "biggest problem"). Another panellist who voted "yes" mentioned that the number of deaths "are in the wrong direction" and that is "what it is". A third panellist discussed the definition of "safety signal": if the definition is, "Do you see something?" the answer is yes, he said, but if the definition is, "Do you see something meaningful?" then you could vote no.

One other panellist concluded that it seemed there was no one who "thinks that this is nothing".

2) Should the current labelling for paclitaxel DES/DCB be restricted/changed/unchanged? Answer: 3 voted that it should be restricted, 3 voted that it should be changed, 8 voted that it should stay unchanged.

Panellists reacted on this question: "changed" was indefinite, as it could include expanding or restricting the use.

A panellist who voted for the option "unchanged" said that, until we know what the possible safety signal means, the practice

should remain as is. Another (who voted for "unchanged") commented that these technologies are used in critical limb ischaemia patients and that there may be confusion as to whether these devices can continue to be offered to those patients.

Panellists and other speakers at the town hall acknowledged that their practice has been affected since the publication of Katsanos' meta-analysis. They have somehow restricted the use of these devices.

3) Should patients be informed about the controversy prior to implantation with a paclitaxel device? Answer: 13 voted yes, zero voted no, 1 voted "I don't know".

A co-moderator of the town hall polled the audience. Nearly all audience members raised their hands to indicate that patients should be informed of the paclitaxel controversy. Ideally, one panellist said, the same message should be conveyed to patients around the world.

4) Is the patient-level data of all paclitaxel systems poolable for definitive analysis?

Answer: 9 voted yes, 1 voted no, 4 voted "I don't know".

One of those who voted "I don't know" explained that he did not know the quality of the data with regard to their utility for poolability and whether there was information about the adjudications of the cause of death and repeat exposure. Another panellist who voted "yes" said that the data are clearly poolable, but that this may not lead to a definitive analysis.

Thus, most of the panellists thought that there could be a paclitaxel-related device safety signal and that the patient-level clinical data can be pooled. All panellists agreed that patients should be informed about the controversy before implantation with a paclitaxel-coated product.

Closing remarks from the moderators of the town hall panel best describe the current state of the issue. Dr Jeffrey Popma (Beth Israel Deaconess Medical Center, Boston, MA, USA) said, "I came in with uncertainty, and now I'm going away with uncertainty, but we made tremendous progress". Dr David Kandzari (Piedmont Heart Institute, Atlanta, GA, USA) added: "I know I don't know".

Less than a week after the town hall meeting, the FDA released a regulatory review. The FDA updated the result of three RCTs using PCB with five years of follow-up. In total, among the 975 subjects, there was an approximately 50% increased risk of mortality in subjects treated with P-DCB versus PTA (20.1% versus 13.4%, respectively) (unpublished data). The FDA added: "These data should be interpreted with caution for several reasons. First, there is large variability in the risk estimate of mortality due to the limited amount of long-term data. Second, these studies were not originally designed to be pooled, introducing greater uncertainty in the results. Third, the specific cause and mechanism of the increased mortality is unknown". The FDA also provided some recommendations, which are shown in **Figure 1**.

The FDA's Circulatory System Devices Panel of the Medical Devices Advisory Committee will meet on 19 and 20 June 2019, during which these issues will be discussed and recommendations will be made.

- Continue diligent monitoring of patients who have been treated with paclitaxel-coated balloons and paclitaxel-eluting stents.
- When making treatment recommendations and as part of the informed consent process, consider that there may be an increased rate of long-term mortality in patients treated with paclitaxel-coated balloons and paclitaxel-eluting stents.
- Discuss the risks and benefits of all available PAD treatment options with your patients. For most patients, alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents should generally be used until additional analysis of the safety signal has been performed.
- For some individual patients at particularly high risk for restenosis, clinicians may determine that the benefits of using a paclitaxel-coated product may outweigh the risks.
- Ensure patients receive optimal medical therapy for PAD and other cardiovascular risk factors as well as guidance on healthy lifestyles including weight control, smoking cessation, and exercise.

Figure 1. *Food and Drug Administration recommendation on the use of paclitaxel-coated products.*

Conflict of interest statement

R. Waksman is on the advisory board of Abbott Vascular, Amgen, Boston Scientific, CardioSet, Cardiovascular Systems Inc., Medtronic, Philips Volcano, and Pi-Cardia Ltd., is a consultant for Abbott Vascular, Amgen, Biosensors, Biotronik, Boston Scientific, CardioSet, Cardiovascular Systems Inc., Medtronic, Philips Volcano, and Pi-Cardia Ltd., has received grant support from Abbott Vascular, AstraZeneca, Biosensors, Biotronik, Boston Scientific, and Chiesi, is on the Speakers Bureau of AstraZeneca and Chiesi, and is an investor in MedAlliance.

The other authors have no conflicts of interest to declare.

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