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EDITORIAL

The paclitaxel story in cardiovascular medicine

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This editorial refers to 'Mortality after use of paclitaxel-based devices in peripheral arteries: a real-world safety analysis', by E. Freisinger *et al.*, doi:10.1093/eurheartj/ehz698.

In the early 1990s, paclitaxel (Taxol®) was the first product of the taxane class approved for intravenous treatment of ovarian and breast cancer resistant to chemotherapy. To date, paclitaxel is globally the best-selling anti-cancer drug ever manufactured and belongs to the WHO Model List of Essential Medicines.[1] Average body weight adjusted doses applied in oncology lie between 200 mg and 300 mg per single dose, and cumulative repetitive treatment doses reach up to 1200 mg with low absolute neutrophil count as most relevant dose limiting acute and subacute toxic effect of paclitaxel in cancer therapy. Clinical use of paclitaxel, for its antiproliferative properties to reduce neointimal proliferation, was first described in patients undergoing percutaneous coronary stenting at the beginning of the twentieth century. Today, drug- eluting stents (DES) and drug-coated balloons (DCB) are widely used as antiproliferative drug vehicles, for the purpose of reducing post-interventional recurrent arterial stenosis. With regard to paclitaxel, the absolute coating dose usually is less than 10% of a single dose administered in anti-cancer therapy.

Several randomized clinical trials (RCT) in the coronaries confirmed superior efficacy of DES in reducing in-stent restenosis and target lesion revascularization against bare metal stents. However, some body of evidence from follow-up studies showed that patients receiving first generation DES were at higher risk of stent thrombosis after 1 year when compared to bare metal stents[3,4] and the US Food and Drug Administration (FDA) Circulatory System Devices Panel acknowledged the small, but significant increased risk to develop clinical events possibly related to late stent thrombosis with dual antiplatelet therapy given for too short a time. Noteworthy, the FDA already called for longer-term follow up in RCT and real-world randomized and registry studies. To date, there have been no late cardiovascular or non-cardiovascular deaths directly attributable to paclitaxel-eluting coronary stents.

In November 2018, a meta-analysis of 28 RCTs raised concerns regarding the long-term safety of paclitaxel-coated devices for treatment of femoropopliteal lower extremity artery disease (LEAD) by showing a two-fold increase in late all-cause mortality between 2 and 5 years after the intervention ($n = 4432$, hazard ratio 1.93, 95% confidence interval 1.27–2.93). [5] Although the meta-analysis did not provide an explanation for or proof of a causal relationship, the authors hypothesized a link between paclitaxel, paclitaxel dose, and mortality. Critical review of these data shows various relevant methodological limitations that reduce reliability of results. Analysis was not based on patient-level data with unknown cause of death and a significant number of patients was lost to follow-up not accounted for in the meta-analysis (informative censoring).[6] Participants withdrawn or lost to follow-up ranged from 14.4–46.3% at the 5-year meta-analysis time point. The proportion of excluded patients was of a magnitude similar to the all-cause mortality, which emphasizes a potential impact on this endpoint assessment. Importance of patients lost for follow- up was demonstrated in a recent analysis of 39 342 patients from the North America Vascular Quality Initiative. LEAD patients that remained in follow-up after lower extremity revascularization had significantly better survival than those lost (83.5% vs 43.2%, $P < 0.001$). After multivariable adjustment, loss to follow-up at 1 year was associated with a nearly 6.6-fold greater risk of death. [7] Despite potential shortcomings, the FDA released alerts and considered a possible association between paclitaxel-coated devices and late mortality not to be excluded due to lack of sufficient longitudinal information. Cautious interpretation was recommended as there was a large amount of missing follow- up and unclear underlying pathomechanistic causation to explain findings. 'Causality for the late mortality could not be determined. Additional data may be needed to further assess the magnitude of the late mortality signal, determine any potential causes, identify patient subgroups that may be at greater risk and to update risk considerations of this device class.'[8]

In response to the meta-analysis by Katsanos , multiple attempts were made to determine whether increased mortality risk due to paclitaxel- eluting devices has to be considered a safety issue. Patient-level, adjudicated data comparing the IN.PACT Admiral® DCB with standard balloon angioplasty found no difference in all-cause mortality through 5 years ($n = 1,980$, 15,1% vs. 11.2%) including survival stratified by paclitaxel dose exposure.[9] Consistently, all-cause mortality rates were not statistically different comparing the In.PACT Amphirion DCB® vs. standard balloon angioplasty in 358 patients

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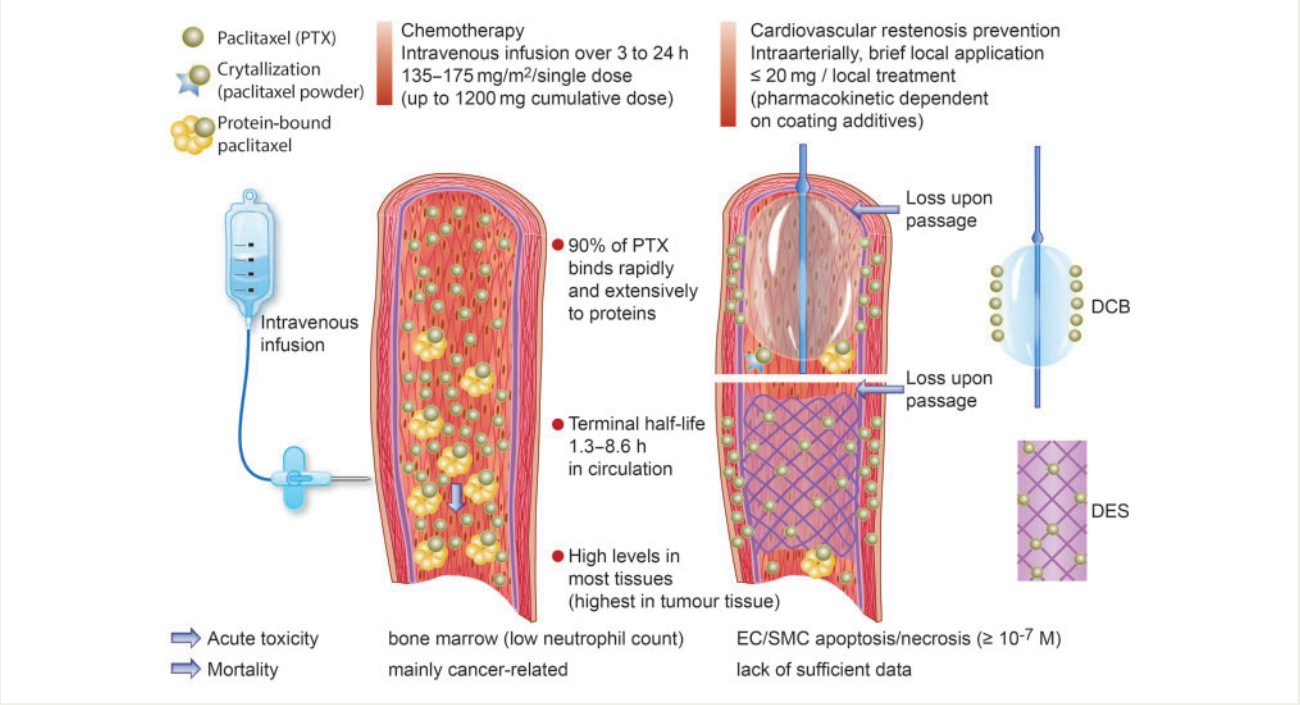

Take home figure Paclitaxel pharmacokinetics with intravenous anti-cancer directed chemotherapy and locoregional endovascular treatment to prevent neointimal proliferation: schematic view. Paclitaxel is lipophilic, which facilitates tissue uptake within the arterial wall even after brief exposure. In the circulation more than 90% of the drug binds rapidly and extensively to plasma proteins. The cytotoxic effect of paclitaxel is triggered via binding of microtubules and prevention of tubulin disassembly, necessary for cell division and migration (*Take home figure*).[2] DCB, drug- coated balloons; DES, drug- eluting stents; EC/SMC, endothelial cell/smooth muscle cell.

with critical limb ischaemia through 5 years (39,4% vs. 44.9%, log rank $P = 0.72$).[10] Zilver PTX® RCT and Zilver PTX®, and bare metal stent Japan post-market surveillance studies neither showed a difference in mortality (RCT [*n*=479]: 19.1% DES vs. 17.1% standard balloon angioplasty/bare metal stents through 5 years; Japan Japan post-marked surveillance study [*n*=1,094]: 15.8% DES vs. 15.3% bare metal stent through 3 years).[11] Two large analyses using Medicare beneficiary claim data demonstrated no association between drug-coated devices and long-term survival. The first, a retrospective analysis of 16 560 Medicare patients followed after femoropopliteal artery revascularization, with post-procedural follow-up of 389 days in median.[12] The authors found a lower cumulative incidence of all-cause mortality with drug-coated devices compared with non-drug-coated devices within 600 days after the intervention (32.5% vs 34.3%, $P = 0.007$). The second survival analysis focused on LEAD patients after implantation of DES vs. bare metal stents including 51 456 Medicare patients, with a median follow- up time of 2 years and a maximum follow-up of 4.1 years.[12,13] The authors found no difference in mortality (51.7% DES vs 50.1% for bare metal stents) that remained non-significant after multivariable adjustments.

The article from Freidinger *et al.* in this issue of the *European Heart Journal* represents the largest ever, real-world health claim data cohort to analyse the association of paclitaxel and all-cause mortality in patients with LEAD.[14] The uniqueness of the analysis is based on the fact that data derived from one public health insurance with 9.2 Mio insurances, representative of 10% of the German population, and with nearly complete availability of data overlooking 64 771 patients with 107 112 endovascular procedures over a median follow- up of 92 months. They found no difference in all-cause mortality whether paclitaxel- coated devices were used or not. The problem of various combinations of crossover procedures was elegantly covered by a time-dependent multivariable Cox regression (never drug- eluting procedure, *n*=56 263, drug- eluting index procedure, or drug- eluting device procedure during follow- up, *n*=8 508). In general, RCTs provide high-quality data on restricted patient populations, whereas high-volume, routinely collected data, as those used by Freidinger and Secemsky, have the potential to provide insights into the health situation and treatment effectiveness in a more representative diversity of patients. Insurance claims databases can be a valuable resource for research if they are used correctly and if their limitations are well understood.

Prioritization of safety endpoints, such as all-cause and cardiovascular mortality, in current and future clinical trials evaluating drug-coated devices and long-term surveillance need to be stressed. The current example of drug-coated devices testing highlights the obvious shortcoming in device- testing scenarios, namely the lack of consistent longitudinal clinical outcome data. Standards that have been used in pharmaco-medical trials need to be compulsory in device trials as well: EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease), the largest ever LEAD trial, enrolled 13 885 patients. Over a mean of 30 months' loss to follow- up or informed consent withdrawal was limited to less than 2% of patients.[15] More robust

follow- up, event adjudication, and stringent endpoint definition will reduce the risk of future controversies. Failure to understand statistical aspects of survival analyses could lead to grossly erroneous results from perfectly well-conducted studies and meta-analyses.

Conflict of interest: none declared.

References

1. World Health Organization. WHO model list of essential medicines. https://www.who.int/selection_medicines/committees/expert/20/EML_2015_FINAL_amended_AUG2015.pdf (27 November 2019).
2. Kampan NC, Madondo MT, McNally OM, Quinn M, Plebanski M. Paclitaxel and its evolving role in the management of ovarian cancer. *Biomed Res Int*. **2015**;2015:413076.
3. Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med*. 2007;**356**:998–1008.
4. Jeremias A, Kirtane A. Balancing efficacy and safety of drug-eluting stents in patients undergoing percutaneous coronary intervention. *Ann Intern Med*. 2008;**148**:234–238.
5. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. 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;**7**:e011245.
6. Kereiakes DJ. The emperor's new clothes: another cypher versus taxus post-hoc meta-analysis. *J Am Coll Cardiol*. 2007;**50**:1381–1385.
7. Wang GJ, Judelson DR, Goodney PP, Bertges DJ. Loss to follow-up 1 year after lower extremity peripheral vascular intervention is associated with worse survival. *Vasc Med*. 2019;**24**:332–338.
8. U.S. Food and Drug Administration. FDA executive summary. Circulatory System Devices Panel Meeting. https://www.fda.gov/media/127698/download (27 November 2019).
9. Schneider PA, Laird JR, Doros G, Gao Q, Ansel G, Brodmann M, Micari A, Shishehbor MH, Tepe G, Zeller T. Mortality not correlated with paclitaxel exposure: an independent patient-level meta-analysis of a drug-coated balloon. *J Am Coll Cardiol*. 2019;**73**:2550–2563.
10. Zeller TM, Micari A, Scheinert D, Baumgartner I, Bosiers M, Vermassen FEG, Banyai M, Shishehbor MH, Wang H, Brodmann M, for the IN.PACT DEEP Inverstigators. The IN.PACT DEEP clinical drug-coated balloon trial 5-year outcomes. *JACC Cardiovasc Interventions*. 2019; accepted for publication.
11. Dake MD, Ansel GM, Bosiers M, Holden A, Iida O, Jaff MR, Lottes AE, O'Leary EE, Saunders AT, Schermerhorn M, Yokoi H, Zeller T. Paclitaxel-coated zilver ptx drug-eluting stent treatment does not result in increased long-term all-cause mortality compared to uncoated devices. *Cardiovasc Intervent Radiol*. 2019, Sep 9 https://doi.org/10.1007/s00270-019-02324-4.
12. Secemsky EA, Kundi H, Weinberg I, Jaff MR, Krawisz A, Parikh SA, Beckman JA, Mustapha J, Rosenfield K, Yeh RW. Association of survival with femoropopliteal artery revascularization with drug-coated devices. *JAMA Cardiol*. 2019;**4**:332–340.
13. Secemsky EA, Ferro EG, Rao SV, Kirtane A, Tamez H, Zakroysky P, Wojdyla D, Bradley SM, Cohen DJ, Yeh RW. Association of physician variation in use of manual aspiration thrombectomy with outcomes following primary percutaneous coronary intervention for ST-elevation myocardial infarction: the National Cardiovascular Data Registry CathPCI Registry. *JAMA Cardiol*. 2019;**4**:110–118.
14. Freisinger E, Koeppe J, Gerss J, Goerlich D, Malyar NM, Marschall U, Faldum A, Reinecke H. Mortality of paclitaxel-based devices - a real-world safety analysis. *EHJ*. 2019;doi:10.1093/eurheartj/ehz698.
15. Hess CN, Hiatt WR. Lost in translation: why 'lost to follow-up' matters. *Vasc Med*. 2019;**24**:339–340.