# FDA Executive Summary

Circulatory System Devices Panel Meeting

June 19 and 20, 2019

General Issues Panel

Paclitaxel-Coated Drug Coated Balloon and Drug-Eluting Stent
Late Mortality Panel

# Table of Contents

## List of Tables

## List of Figures

## List of Appendices



## Sponsor Provided Summaries:



## List of Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| API | Active Pharmaceutical Ingredient |
| AT | As-Treated |
| AVF | Arteriovenous Dialysis Fistula |
| BMS | Bare Metal Stent |
| BSC | Boston Scientific Corp. |
| BTK | Below-the-knee |

| | |
|---|---|
| CDRH | Center for Devices and Radiological Health |
| CDTLR | Clinically-Driven Target Lesion Revascularization |
| CEC | Clinical Events Committee |
| CLI | Critical Limb Ischemia |
| COPD | Chronic Obstructive Pulmonary Disease |
| DCB | Drug-Coated Balloon |
| DES | Drug-Eluting Stent |
| FDA | Food and Drug Administration |
| ITT | Intent-to-Treat |
| LTFU | Lost to Follow-Up |
| LTX | Lutonix |
| mAT | Modified As-Treated |
| MDT | Medtronic |
| OUS | Outside the United States |
| PAD | Peripheral Arterial Disease |
| PAS | Post-approval Study |
| PH | Proportional Hazard |
| PK | Pharmacokinetic |
| PMA | Premarket Application |
| POBA | Plain Old Balloon Angioplasty |
| PPA | Proximal Popliteal Artery |
| PTA | Percutaneous Transluminal Angioplasty |
| PTX | Paclitaxel |
| RCT | Randomized Control Trial |
| RD | Risk Difference |
| RR | Relative Risk / Risk Ratio |
| RVD | Reference Vessel Diameter |
| RWE | Real-world Evidence |
| SAE | Serious Adverse Events |
| SFA | Superficial Femoral Artery |

# 1. Introduction

This is an Executive Summary for the General Issues Panel Meeting on the late mortality safety signal associated with paclitaxel-coated products (i.e., paclitaxel-coated balloons and paclitaxel-eluting stents) used to treat peripheral arterial disease in the femoropopliteal arteries. This meeting is being held to review the available information and provide feedback on: (1) the presence and magnitude of a late mortality safety signal; (2) whether all paclitaxel-coated vascular products (regardless of device platform or dose) are associated with the signal; (3) the impact of missing data and covariates on the signal; (4) potential mechanism of death (causality) considering drug dose exposure and pre-clinical data; (5) reconsideration of the benefit-risk profile related to the use of these products; (6) the need for the collection of additional data and/or device labeling changes; and (7) the impact of the signal on ongoing femoropopliteal disease clinical trials as well as on paclitaxel-coated products marketed or under clinical evaluation for other indications (e.g., treatment of stenoses in arteriovenous dialysis fistulae, critical limb ischemia).

The Executive Summary provides information regarding the disease condition and currently-marketed devices used for treatment, an overview of the meta-analysis demonstrating a late mortality safety signal and published literature, analyses conducted by the Food and Drug Administration (FDA or "the Agency"), and FDA's current thinking on these issues. The Panel's review and discussion of the information will inform the Agency's recommendations on appropriate regulatory actions regarding approved devices and ongoing clinical trials.

# 2. Background

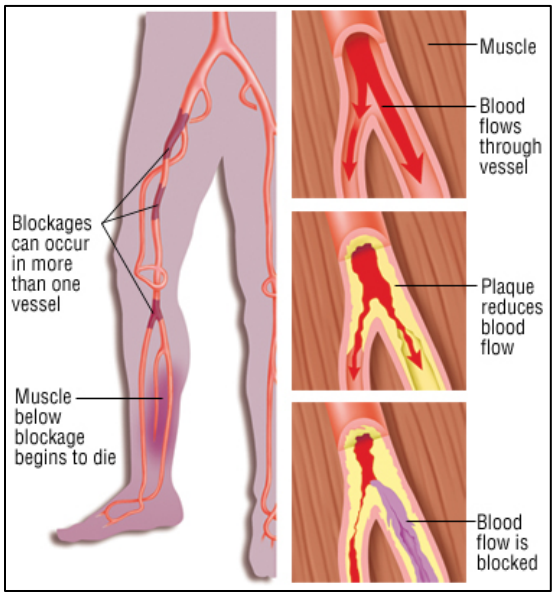
## 2.1 *Peripheral Arterial Disease Therapies*

Peripheral arterial disease (PAD) results from inadequate blood flow in peripheral arteries, typically due to atherosclerosis and most commonly occurring in the lower extremities. Lower extremity PAD in the femoropopliteal segment may lead to a progression of clinical symptoms ranging from leg pain when walking (claudication) to tissue loss, which may ultimately lead to amputation (critical limb ischemia). The current mortality signal was detected in patients who had a femoropopliteal arterial intervention with a paclitaxel-coated product to treat claudication. Risk factors associated with PAD include smoking, hypertension, diabetes, hyperlipidemia, and age. Men and woman are equally affected by PAD, and black race/ethnicity is associated with increased risk. Approximately 8.5 million people in the United States (US) have PAD, including 12-20% of individuals older than 60 years (Center for Disease Control and Prevention 2016, July 12).

Current endovascular therapies for PAD include percutaneous transluminal angioplasty (PTA), often referred to as "POBA" (i.e., plain old balloon angioplasty), stenting, atherectomy, and bypass surgery. These mechanical therapies are often associated with a high incidence of restenosis (i.e., re-narrowing of the treated vessel segment) due to a neointimal proliferation in response to vessel injury. Over the past decade, drug-coated devices, including drug-coated balloons (DCB) and drug-eluting stents (DES), have been approved for use in the US to treat *de*

*novo* and restenotic lesions in the superficial femoral arteries (SFA) and proximal popliteal arteries (PPA) in PAD patients.

**Figure 1. Peripheral Arterial Disease**




https://www.drugs.com/health-guide/peripheral-arterial-disease.html

## 2.2 *Drug-coated Balloons and Drug-eluting Stents*

DCB and DES include a balloon catheter or stent, respectively, coated with an anti-proliferative active pharmaceutical ingredient (API) with or without other materials, called excipients, that help transfer the drug to the vessel wall. DCB and DES are considered combination products with the primary regulatory review assigned to the Center for Devices and Radiological Health (CDRH). The primary mode of action for DCB and DES is vessel wall expansion, and the secondary/ancillary mode of action is inhibition of restenosis. (Note that the DES platform may allow for less non-target particulate embolization but requires a permanent implant.) A reduced rate of restenosis is achieved by the local action of the API that inhibits vascular smooth muscle cell proliferation and the synthesis of extracellular matrix. Clinical trials of DCB and DES demonstrate a more effective PAD treatment than POBA or the implantation of uncoated stents.

Currently, there are five paclitaxel-coated devices that are FDA-approved to treat *de novo* and restenotic lesions in the femoropopliteal arteries in PAD patients, including two DES and three DCB (described below and summarized in **Table 1**).

*Cook Medical – Zilver PTX DES*

The Zilver PTX Drug-Eluting Peripheral Stent (Zilver PTX DES) is indicated for improving luminal diameter for the treatment of *de novo* or restenotic symptomatic lesions in native vascular disease of the above-the-knee femoropopliteal arteries having reference vessel diameter from 4 mm to 7 mm and total lesion lengths up to 300 mm per patient. The system includes a delivery system and implant, which is a self-expanding nitinol stent coated on its

outer surface with the drug paclitaxel (without any polymer, binder, or excipient) at a dose density of 3 μg/mm$^2$ (based on the abluminal stent surface area). This device was approved on November 14, 2012 (FDA 2012).

*BD/BARD – LUTONIX 035 DCB*

The LUTONIX 035 Drug Coated Balloon (LUTONIX DCB) is indicated for PTA, after appropriate vessel preparation, of *de novo*, restenotic or in-stent restenotic lesions up to 300 mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-7 mm. The LUTONIX DCB is coated with a specialized immediate release non-polymer based coating formulation that includes the anti-proliferative drug, paclitaxel, at a dose density of 2 μg/mm$^2$, and excipients polysorbate and sorbitol. This device was approved on October 9, 2014 (FDA 2014b).

*Medtronic (MDT) – IN.PACT Admiral DCB*

The IN.PACT Admiral DCB (IN.PACT DCB) is indicated for PTA, after appropriate vessel preparation, of *de novo*, restenotic, or in-stent restenotic lesions with lengths up to 360 mm in superficial femoral or popliteal arteries with reference vessel diameters of 4-7 mm. The IN.PACT DCB balloon is coated with FreePac™, a proprietary paclitaxel-eluting coating with a nominal drug dose density of 3.5 μg/mm$^2$ of the expanded balloon surface. The coating utilizes urea as an excipient to facilitate the release and transfer of paclitaxel into the arterial vessel wall. This device was approved on December 30, 2014 (FDA 2014a).

*Philips – Stellarex 035 DCB*

The Stellarex 035 DCB (Stellarex DCB) is indicated for PTA, after appropriate vessel preparation, of *de novo* or restenotic lesions up to 180 mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-6 mm. The balloon coating contains paclitaxel at a nominal dose density of paclitaxel of 2 μg/mm$^2$. The coating excipients are PEG 8000 and USP Iodine. This device was approved on July 26, 2017 (FDA 2017b).

*Boston Scientific Corp. (BSC) – ELUVIA Drug-Eluting Vascular Stent*

The ELUVIA Drug-Eluting Vascular Stent System (ELUVIA DES) is indicated for improving luminal diameter in the treatment of symptomatic *de novo* or restenotic lesions in the native superficial femoral artery (SFA) and/or proximal popliteal artery with reference vessel diameters (RVD) ranging from 4.0 - 6.0 mm and total lesion lengths up to 190 mm. The ELUVIA stent is a laser cut self-expanding stent composed of nitinol. The ELUVIA stent coating is composed of a PBMA (poly (n-butyl methacrylate)) polymer primer layer, an active layer consisting of PVDF-HFP (copolymer of vinylidene fluoride and hexafluoropropylene) polymer, and the anti-proliferative drug paclitaxel at a dose density of 0.167 μg/mm$^2$ (based on the total stent surface area). This device was approved on September 18, 2018 (FDA 2018).

**Table 1. Summary of Device Attributes**

| Device Name | Platform | Nominal Dose | Potential Dose Range[1] | Dose Range in RCT[2] | Excipient | Lengths | Diameters |
|---|---|---|---|---|---|---|---|
| Zilver PTX DES | Stent | 3 μg/mm$^2$ | 0.2-1.3 mg | 0.3-3.5 mg | None | 40-140 mm | 5-8 mm |
| LUTONIX DCB | Balloon | 2 μg/mm$^2$ | 1.0-9.7 mg | 1.0-11.3 mg | Polysorbate and Sorbitol | 40-220 mm | 4-7 mm |
| IN.PACT DCB | Balloon | 3.5 μg/mm$^2$ | 1.1-17.0 mg | 1.9-21.7 mg | Urea | 20-250 mm | 4-7 mm |
| Stellarex DCB | Balloon | 2 μg/mm$^2$ | 1.1-4.7 mg | 1.3-9.4 mg | PEG 8000 and Iodine | 40-120 mm | 4-6 mm |
| Eluvia DES | Stent | 0.167 μg/mm$^2$ | 0.1-0.4 mg | 0.1-1.1 mg | PVDF-HFP | 40-120 mm | 6-7 mm |

1. Potential Dose Range represents the range of doses available on the platform from the smallest, shortest device to the largest, longest device. Note that multiple devices of the same type could be used in the clinical trials to treat the longest approved lesion length, which may result in a larger administered dose.
2. Dose Range in RCT reflects the range of doses used in the pivotal clinical trial. In some cases, extension of the allowable treated lesion length (and maximum dose) was subsequently approved as supported by adjunctive clinical data.

Because these devices were approved for use in the US to treat PAD between 2012-2018, long-term follow-up data through 5 years are available on the pivotal trial cohort for only the first three devices (i.e., Zilver PTX DES, LUTONIX DCB, and IN.PACT DCB) with limited long-term follow-up data for the Stellarex DCB and Eluvia DES. (The LUTONIX DCB was FDA-approved to treat stenoses in arteriovenous dialysis fistula (AVF) on August 25, 2017, so limited long-term follow-up is available in this patient population.)

According to ClinicalTrials.gov, there are currently several ongoing clinical trials for paclitaxel-coated devices for the treatment of SFA and PPA, PAD, AVF stenosis, and below-the-knee (BTK) lesions in patients with critical limb ischemia (CLI). There are currently no DCB or DES approved in the US specifically for the treatment of BTK disease.

### 2.3 *Paclitaxel use in DCB and DES*

Drug-eluting coronary stents have been available in the US since 2003 and have used a variety of APIs, including paclitaxel and limus-based drugs (e.g., sirolimus, everolimus, zotarolimus). Currently-marketed coronary DES contain a limus-based drug whereas all currently-approved DCB and DES marketed in the US to treat PAD use paclitaxel as the API. To date, no signal related to late mortality has been noted for this device class.

#### 2.3.1 *Physiological Mechanism*

Paclitaxel is an antineoplastic agent that was initially approved as a chemotherapeutic medication to treat various types of cancer due to its cytotoxic effects at high doses (e.g., 50-100 ng/mg). Paclitaxel has high protein binding (95%). Its elimination half-life is 13-20 hours following IV infusion for 3 hours with an apparent volume of distribution ranging from 227 to 688 L/m$^2$, indicating extensive extravascular distribution and/or tissue binding. At lower doses (~1 ng/mg),

paclitaxel inhibits arterial smooth muscle and endothelial cell proliferation after a brief exposure. For PAD treatment, the principal mechanism by which paclitaxel inhibits neointimal growth is through the stabilization of microtubules by preventing their depolymerization during the final G2/M phase of cell division. Due to its lipophilicity, paclitaxel diffuses into the arterial wall with higher concentration in the deeper smooth muscle cells and fibroblast layer. By stabilizing microtubules paclitaxel inhibits: smooth muscle cell and fibroblast proliferation; smooth muscle cell, fibroblast and white blood cell migration; and extracellular matrix synthesis (Ng et al. 2015). In human arterial smooth muscle cells, the half maximal inhibitory concentration ($IC_{50}$) of paclitaxel is approximately 2 nM (1.7 ng/g). The design of DCB and DES allow for an initial drug dose followed by a sustained cytostatic drug level to inhibit smooth muscle cell proliferation and neointimal growth, leading to reduced restenosis rates (Gray and Granada 2010).

A dose-limiting toxicity of paclitaxel is bone marrow suppression, primarily resulting in neutropenia. At cytotoxic concentrations, paclitaxel has been shown to induce chromosome aberrations in human lymphocytes *in vitro* and mutagenicity in the micronucleus test in mice *in vivo*. Paclitaxel is highly lipophilic and freely enters the cell without a transporter, becomes ionized, and accumulates intracellularly. Its physicochemical properties are characterized by rapid cellular uptake, preferential partitioning towards the lipid bilayer, and prolonged tissue retention, making it candidate agent for its use in drug-coated interventional devices.

### 2.3.2 *Drug Morphology and Coating Composition*

Paclitaxel uptake and retention depend on the formulation (amorphous versus crystalline) of the drug and physicochemical properties of the excipients, if included. The kinetics of drug release rely on numerous factors, including the type of the carrier excipient, degree of coating crystallinity, drug dose density, and total drug load. An increased amorphous content generally facilitates a durable coating of the drug on the balloon during tracking of the device to the target lesion, while increased drug crystallinity generally helps achieve higher tissue uptake and prolonged retention (Granada et al. 2014; Ng et al. 2015). Currently-marketed devices initially source similar crystalline paclitaxel, but the processing of individual devices likely results in differing ratios of amorphous and crystalline content.

DCB and DES that are coated with paclitaxel may be combined with an excipient. The excipient enables uniform distribution of the drug on the device and facilitates drug transfer upon balloon inflation or stent implantation during contact with the endoluminal surface. The choice of an excipient impacts various device properties, including systemic drug loss during transit to the lesion site, drug release during inflation/implantation, tissue retention, and local drug transfer. Microparticle formation from these coatings is often observed, which may embolize to the downstream systemic circulation. The amount of particulate formation varies depending on device design and processing.

The paclitaxel used for intravenous administration in cancer patients is a non-aqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Often,

Cremophor (polyoxyethylated castor oil) is used as the formulation vehicle for paclitaxel and acts as an emulsified and solubilizer. The paclitaxel used in DCB and DES is dissolved in various solvents. Excipients are added to improve drug delivery. This liquid solution is then coated onto the stent or balloon (using various methods), and the solvents are evaporated resulting in a solid, mostly crystalline coating on the balloon or stent surface.

Given the differences in formulation, excipient, and delivery method, *in vivo* drug retention, bioavailability, behavior, and elimination are expected to differ between the paclitaxel used to treat femoropopliteal stenoses and as a chemotherapeutic agent. Further details regarding retention and elimination are provided below.

### 2.3.3 *Drug Dosage and Pharmacokinetics*

The approved DCB and DES have varying characteristics, such as differences in drug dose density that range from 0.167 µg/mm$^2$ to 3.5 µg/mm$^2$ on the coated portion of the device, the maximum total drug load (which ranges from 0.1 mg to 17 mg based on the device size matrix and the total approved lesion length), and the types of solvents and excipients used. As shown in **Table 1**, the dose ranges for each device vary, and thus, the treatment dosages vary as well. The lower end of the treatment dosage in the pivotal clinical trials was approximately 1 mg or less. However, multiple devices are often used to treat long lesions, resulting in drug dosage levels exceeding 20 mg for some individual patients enrolled in the pivotal clinical trials. In registry studies, where a more real-world population was studied, including longer lesion lengths, drug dosages exceeded 70 mg in some instances (though doses this high were uncommon). In pivotal clinical trials, the drug dose range (**Table 1**) was markedly lower for DES (0.1 – 3.5 mg) compared to DCB (1.0 – 21.7 mg).

To provide an administered dose comparison for cancer treatment compared to PAD treatment with DCB/DES, paclitaxel chemotherapy doses typically range between 135-170 mg/m$^2$ administered over a period of 3 to 24 hours. For the average adult human with a body surface area of 1.7 m$^2$, this results in a total dosage of approximately 230-300 mg for a single administration, with repeat administrations common. For cancer treatment, an intravenous infusion of paclitaxel (sold under the brand name Taxol) at a dosage of 135 mg/m$^2$ can achieve systemic concentration ($C_{max}$) of 195 ng/mL and $AUC_0$6300 ng·h/mL, according to drug labeling for paclitaxel. Tissue concentrations of >100 µg/g have been reported in the literature when mice were injected with 40 mg/kg (human equivalent of 120 mg/m$^2$) of free paclitaxel through IV injection ($C_{max}$ of 255.8, 331.8, 131.4, and 80.2 µg/g in the liver, lung, kidney, spleen, respectively) (Wang et al. 2010).

Paclitaxel was approved for use by the FDA in 1992, and it has been used to treat a range of malignancies including breast and ovarian cancer. Of note, paclitaxel is generally considered safe when given during pregnancy following fetal organogenesis (e.g., second and third trimesters) (Cardonick and Iacobucci 2004). However, paclitaxel transfer across the placenta is limited even following long exposures (Ali et al. 2018; Nekhayeva et al. 2006).

Although the paclitaxel dose during DCB and DES treatment may be orders of magnitude less than intravenous administration, it is important to consider that differences in drug formulation and the route of administration may affect drug activity and metabolism. A summary of the detectable drug levels in local tissue, plasma, and downstream organs and tissues when using DCB and DES to treat lower limb vasculature in pre-clinical animal models is provided in Section 5.4. Please note that due to the differences in methods, species, and delivery method, these numbers are not directly comparable to IV injection.

*Local Vessel Concentration.* DCB and DES act by local delivery of paclitaxel into the vessel wall at the lesion. The excipients and/or polymers help with drug transfer into the vessel wall. From pre-clinical animal studies conducted on the approved DCB and DES, the pharmacokinetic (PK) data demonstrate that drug levels are detectable in the local vasculature (i.e., target lesion/artery wall) beyond 60 days with some studies demonstrating local arterial tissue levels above the level of quantitation at 180 and 270 days. While the specific methods, including the number of devices and dosage administered, vary among studies, paclitaxel levels detected on day 1 ranged from approximately 1-200 ng/mg and were typically below 1 ng/mg by day 60 and beyond.

*Plasma Concentration.* Drug levels for the DCB and DES were evaluated in the plasma in the pre-clinical animal studies until the levels were below the level of quantitation. The levels detected with each device varied due to the unique device design, drug coating constituents, and study methods. In general, paclitaxel in plasma cleared rapidly from systemic circulation. Immediately post-procedure, detectable levels ranged from approximately 1.0-5.0 ng/mL and generally declined to levels below quantitation between 6 to 24 hours. Drug levels were also evaluated in the human pivotal clinical trials and declined rapidly within 24 hours and generally undetectable in the plasma within a few days.

*Downstream Tissues and Organs of Elimination Concentration.* In animal studies, drug levels were also evaluated in downstream tissues (e.g., gluteus maximus, gracilis, semitendinosus, and semimembranosus muscles, and coronary bands) and organs of elimination (i.e., kidneys, liver, lung, and spleen). The detectable drug levels in these tissues and organs were assessed at acute time points through study termination (usually 180 days or beyond) or until the levels were below quantitation level. The levels detected for each device varied due to the unique device design, drug coating constituents, dose administered, and the study methods. Further, since these studies were conducted over a wide duration, the evaluated tissues and the time points varied based on FDA recommendations at that time, with some studies lacking evaluations currently recommended by FDA. In general, the PK data demonstrate that drug levels were detectable in the downstream tissues and organs of elimination beyond 90 days in most cases (when data were available). Paclitaxel levels detected in the lungs on day 1 were generally below 1 ng/mg and declined thereafter, although levels were still detectable at 90 days and beyond in some cases. The highest drug levels in the lung were within the cytostatic potency range for paclitaxel. Levels were generally lower in the liver and kidneys and cleared more quickly. In downstream

and distal tissues, levels were also generally below 1 ng/mg, but persisted until day 90 or beyond in some cases.

While paclitaxel levels following DCB and DES use appear significantly lower than studies of intravenous administration, the data are not directly comparable. Data for all tissues cannot be obtained from human patients, and different species and animal models in the pre-clinical studies were utilized to capture the data discussed. The values reported above (i.e., $C_{max}$ of 255.8, 331.8, 131.4, and 80.2 µg/g in the liver, lung, kidney, spleen, respectively), were reported in the literature for mice that were injected with 40 mg/kg (human equivalent of 120 mg/m$^2$) of free paclitaxel through IV injection. Most of the animal studies conducted to assess DCB and DES were conducted in porcine models, and different methods and dosages were used. While a direct comparison among studies cannot be made, it is important to note that even though significantly lower dosages are administered when using DCB and DES (versus use in chemotherapy), detectable levels in local and downstream vessels and organs were noted well beyond the acute administration period (to 90 and even 180 days and beyond in some cases). Further details regarding preclinical studies are provided in Section 5.4.

### 2.3.4 *Potential Adverse Effects Related to Paclitaxel*

Adverse effects associated with parenteral paclitaxel to treat cancer include neutropenia, peripheral neuropathy, hypersensitivity (skin reactions, dyspnea, hypotension), cardiovascular effects (hypotension, bradycardia, hypertension), myalgia, myelotoxicity, anaphylaxis, and nausea. Many of these effects resolve within a few days. However, some adverse effects, such as peripheral neuropathy and hypersensitivity may worsen with repeat exposure.

The potential long-term effects of paclitaxel exposure and retention in local and downstream tissues after DCB and DES exposure in patients with PAD are largely unknown. Though some information can be found in animal studies, these studies were not designed to determine potential downstream or long-term effects from drug exposure. As discussed in depth below in Section 5.4, data from previously conducted pre-clinical safety studies were re-assessed and did not identify a potential cause for a late mortality signal in humans.

There is evidence in the literature to suggest that paclitaxel effects are concentration-dependent. At clinically-high concentrations, paclitaxel kills cells (i.e., cytotoxic/chemotherapeutic), and efficiently blocks the progression of malignancies. In contrast, at low concentrations (equivalent to tissue levels following paclitaxel-coated devices), the drug exhibits pro-inflammatory and pro-angiogenic activity, initiates epithelial-to-mesenchymal transition, activates NF-kB, and induces stress genes, which may support a microenvironment for tumor cell dissemination (Chang et al. 2017). These biphasic effects may explain how a cytotoxic drug could paradoxically promote tumor metastasis at low concentrations. In a study comparing high dose of paclitaxel (20 mg/kg) vs low dose (1 mg/kg) in tumor-bearing nude mice, the high dose suppressed metastatic colonization of tumor cells, whereas the low dose increased circulating tumor cells (Li et al. 2016). These observations suggest that consideration should be given to the potential adverse

effects associated with the low concentration of paclitaxel in crystalline formulation in tissue and that the effects may be different than those noted for higher dose intravenous administration.

# 3. Late Mortality Signal

## 3.1 *Background*

On December 6, 2018, Katsanos, et al (2018), published a meta-analysis of long-term mortality rates in 28 RCTs in patients who were treated with paclitaxel-coated devices, compared to uncoated control devices, in the femoral and/or popliteal arteries (see Appendix A). The meta-analysis included publicly available data from clinical trials evaluating DCB and DES, including devices available in the US or outside the United States (OUS). It included data from four US-marketed devices: Cook's Zilver PTX DES, Medtronic's IN.PACT DCB, LUTONIX DCB, and Stellarex DCB.

The outcome of interest for this analysis was all-cause mortality. The authors analyzed the 1, 2 and 5-year study-level mortality data stratified by treatment. Within each study, the difference in mortality rates between treatment arms [Risk Difference (RD)] and the ratio of mortality rates in treatment arm versus control arm [Risk Ratio (RR)] were calculated. Fixed effect and random effect models were then applied to pool data across studies. The meta-analysis showed that the all-cause death rate at 1 year (28 RCTs with 4,432 patients) was similar between the paclitaxel-coated device group and the control group (RR: 1.08, 95% CI: 0.72-1.61). However, the all-cause death rate at 2 years (12 RCTs with 2,316 patients) significantly increased for the paclitaxel-coated device group versus the control group (RR: 1.68, 95%CI: 1.15-2.47). At 5-years, the all-cause death rate (3 RCTs with 863 patients) increased further for the paclitaxel-coated device group versus the control group (RR: 1.93, 95%CI: 1.27-2.93).

It is important to note limitations associated with the study-specific summary level data utilized in the Katsanos meta-analysis. The authors did not have access to patient-level data, cause of death information, detailed paclitaxel dose information, and information regarding missing data (patients who withdrew or were lost to follow-up). Also, longer-term data to five years included an RCT for a non-FDA approved DCB with a fair amount of missing follow-up data. For these reasons, FDA believed it prudent to obtain the updated information on FDA-approved products in order to address these limitations.

## 3.2 *Preliminary Analysis Replicating the Katsanos Meta-analysis*

To confirm the potential long-term mortality signal associated with paclitaxel-coated devices presented by Katsanos, the FDA review team replicated the 1, 2 and 5-year meta-analysis using data provided in Figures 1, 2 and 3 of the paper. FDA reproduced the same results based on fixed and random effects models shown in the paper.

Overall, the Katsanos meta-analysis raised concerns for an increased late-term mortality signal following treatment with paclitaxel-coated products in the SFA/PPA, and FDA replicated the results using the Katsanos' data. FDA's next step was to evaluate the patient-level data from five

pivotal clinical RCTs from the US-approved DCB and DES, while accounting for the strengths and limitations of meta-analytic approaches.

# 4. Mortality Evaluation of Clinical Data for US-Approved Devices

FDA evaluated the mortality data available for the five FDA-approved paclitaxel-coated devices using similar and alternate methods as used for the Katsanos meta-analysis. A summary of the methods and results is summarized in the sections below.

## 4.1 *Methodology and Definitions*

### 4.1.1 *Clinical Studies*

FDA's analyses included all available clinical studies conducted with the FDA-approved devices that met the following criteria:

- Any randomized, controlled trial (e.g., First-in-human, OUS, pivotal, post-market); or
- Registries (single-arm) that included at least 200 patients and had at least 2-year follow-up

Based on these criteria, the studies listed in **Table 2** were included in the analyses:

**Table 2. Paclitaxel-Coated Device Clinical Trials**

| Trial Name | Study Description | Max Follow-Up (year) | As Treated*, N (n test; n control)) | Study Status |
|---|---|---|---|---|
| **Cook Zilver PTX DES:** | | | | |
| ZILVER PTX RCT | US/OUS PMA Pivotal 1:1 RCT DES v PTA w/ secondary randomization (BMS:DES) and protocol-defined crossover of PTA failures in the 1st year to DES | 5 | 474 (300; 174) (excludes 5 live cases) | 5-year follow-up complete |
| REAL PTX | OUS 1:1 RCT DES v DCB | 3 | 150 (75;75) | 3-year follow up complete |
| JAPAN POST-MARKET REGISTRY | OUS All-Comers Registry (DES v BMS) | 5 | 1112 (922; 190) | 5-year follow-up complete for treatment; 3-year follow-up completed for control |
| ZILVER SAS | US/OUS All-Comers Registry | 2 | 787 | 2-year follow-up complete |
| **Lutonix 035 DCB:** | | | | |
| LEVANT 2 | US/OUS PMA Pivotal 2:1 RCT DCB v PTA | 5 | 476 (316; 160) | 5-year follow-up complete |
| LEVANT 2 CONTINUED ACCESS | US/OUS Safety Registry | 5 | 713 (657 Continued Access + 56 Roll-In) | 5-year follow-up complete |
| LEVANT 1 | OUS 1:1 RCT DCB v PTA | 2 | 101 (49;52) | 2-year follow up complete |
| JAPAN RCT | OUS (Japan) 2:1 RCT DCB v PTA | 2 | 109 (71;38) | 2-year follow up complete |

| Trial Name | Study Description | Max Follow-Up (year) | As Treated*, N (n test; n control)) | Study Status |
|---|---|---|---|---|
| LUTONIX GLOBAL | All-Comers Registry | 2 | 691 | 2-year follow up complete |
| SAFE-DCB | All-Comers Registry | 3 | 1005 | Ongoing; 2-year follow-up complete |
| **Medtronic IN.PACT Admiral DCB:** | | | | |
| IN. PACT SFA I & SFA II | US/OUS PMA Pivotal 2:1 RCT DCB v PTA | 5 | 330 (220;110) | 5-year follow up complete |
| IN. PACT JAPAN | OUS (Japan) RCT 2:1 DCB v PTA | 3 | 100 (68;32) | 3-year follow up complete |
| IN.PACT GLOBAL | OUS All-Comers Registry | 5 | 1406 | Ongoing; 3-year follow-up complete |
| **Philips Stellarex DCB:** | | | | |
| ILLUMENATE | US/OUS PMA Pivotal 2:1 RCT | 5 | 300 (200; 100) | ongoing: 3-year follow up complete |
| ILLUMENATE EU | OUS 3:1 RCT DCB v PTA | 5 | 291 (219; 72) | ongoing: 3-year follow up complete |
| ILLUMENATE GLOBAL | OUS All-Comers Registry | 5 | 371 | ongoing: 3-year follow up complete |
| **Boston Scientific Eluvia DES:** | | | | |
| IMPERIAL | US/OUS PMA Pivotal 2:1 RCT Eluvia DES v Zilver DES | 5 | 465 (310;155) | ongoing: 1-year follow up complete |
| EMINENT RCT | OUS (Europe) 2:1 RCT Eluvia DES v BMS | 3 | 750 (500;250) | Enrolling, currently at 516 (332, 184) with 1-3 year follow up ongoing |
| * As-Treated population is defined in Section 4.1.2. | | | | |

FDA's primary analysis of patient-level data was limited to the four pivotal RCTs of paclitaxel-coated devices versus non-paclitaxel-coated devices that supported PMA approval. These trials are as follows:

1) Cook Zilver PTX DES – ZILVER PTX RCT
2) LTX 035 DCB - LEVANT 2
3) MDT IN.PACT Admiral DCB - IN.PACT SFA I & II
4) Philips Stellarex DCB – ILLUMENATE

The fifth pivotal trial BSC's IMPERIAL randomized the Eluvia DES to the Zilver PTX DES. Because this study did not use an uncoated device control group, this study was not included in FDA's primary meta-analysis. However, mortality results are provided for comparison purposes. FDA performed analyses using pivotal RCT devices with available data (e.g., through 5-year completed follow-up data). Supplementary analyses were conducted on the OUS RCTs and registry data. Pertinent figures and tables are included in this summary, and supplementary results can be found in the Appendices.

### 4.1.2 *Analysis Populations*

While the pivotal trial designs are generally similar, some details regarding patient treatment differ, including allowances for bailout stenting and crossover. In other words, some patients initially randomized to the control groups received a drug-coated device at the index procedure or later (if crossover was allowed). Because increased late mortality has been linked to the paclitaxel-coated devices, FDA considered it important to analyze the results for multiple patient populations, according the following definitions:

Intent-to-Treat (ITT) Population: Subjects were assigned into either the drug-coated device group or the control group according to their randomization assignment. Day 0 was the day of the index procedure.

As-Treated (AT) Population: The treatment group assignment was based on the actual treatment a subject received during the index procedure (after the primary randomization and the secondary randomization, if applicable). If a subject received drug-coated device treatment of the target lesion during the index procedure, this patient was counted in the drug-coated device group. Otherwise, this subject was counted into the control device group. Day 0 was the day of the index procedure.

Modified As-Treated (mAT) Population: The treatment group assignment was based on whether a subject received a drug-coated device treatment of the target lesion(s) at any point during the first 12 months (i.e., during crossover) based on the study design. If a control subject crossed over by receiving a drug-coated device (on the target lesions) during the follow-up period, Day 0 was the day of the drug-coated device treatment. Otherwise, Day 0 was the day of the index procedure.

Mortality assessments were based on ITT and AT populations for all studies. For the majority of the pivotal clinical trials, the ITT and AT populations are identical or only differ by a few patients. For the ZILVER PTX RCT, analysis populations differed due to the trial design that included a primary and secondary randomization followed by crossover during the first year). Additional details and analyses are included in Appendices D and E. The mAT population was also evaluated for the ZILVER PTX RCT, because this trial included a protocolized option for crossover if repeat revascularization was warranted.

FDA considered the AT population as the most relevant cohort for the primary analysis population to evaluate late mortality because the use of drug-coated devices in repeat procedures was not consistently captured for all trials, and therefore, the AT population provided the most meaningful comparison between patients across trials. FDA analyses and data described below are for the AT population; ITT and mAT analysis results are included in the Appendices.

#### 4.1.3 *Analyses*

To facilitate the Panel's discussion regarding the late mortality signal following femoropopliteal treatment with a paclitaxel-coated device, FDA completed the following analyses using data available out to 5 years from the pivotal clinical trials described above:

- Comparison of patient baseline characteristics across four pivotal RCTs
- Subject Accountability and Assessment for Missing Data
- Crude All-Cause Mortality Rates
- Kaplan-Meier Estimation and Curves for Time to Death
- Relative Risk of Mortality (paclitaxel-coated vs. uncoated devices)
- Cause of Death for Cardiovascular and Non-Cardiovascular Deaths and Death Subtypes
- Associations of the following Parameters and their Relationship to All-Cause Death
  - Total Paclitaxel Dose
  - Geography (US vs OUS)
  - Gender (male vs female)
- Clinically-Driven Target Lesion Revascularization (CDTLR) to Reassess Benefit-Risk

Full details regarding the analyses are summarized below. Evaluations conducted on the OUS RCTs were considered supplementary analyses. Due to confounding factors (e.g., the lack of a comparator, missing data), limited evaluations were conducted on data from the global registries. In recent conference presentations, pivotal randomized trial data have been combined with single arm data to examine the mortality signal. However, FDA believes that potential differences in unknown covariates, enrollment criteria, adjunctive treatment, the robustness of patient follow-up compromise the scientific value of analyses that combine single arm study patients with RCT patients.

Additional analyses are on-going and may be presented at the time of panel. The Panel will be asked to comment on additional analyses that may be valuable to evaluate the late mortality signal post-panel.

### 4.2 *Primary Analysis and Results*

#### 4.2.1 *Study Comparison*

As shown above in **Table 2**, the five pivotal RCTs for FDA-approved DCB and DES enrolled between 300-500 patients using a 1:1 or 2:1 randomization scheme. While the study designs and endpoints differed, the primary safety endpoint typically included freedom from all-cause or related death, amputation, or target vessel revascularization post-procedure. The primary effectiveness endpoint typically evaluated primary patency with a secondary endpoint examining target lesion revascularization (TLR).

The assessment of the AT population baseline covariates across the four pivotal RCTs that compared paclitaxel-coated devices with non-paclitaxel-coated devices is shown in **Table 3**. Instances where baseline characteristic differed across trials ($p < 0.0001$) are noted for lesion

length, region, smoking status, hyperlipidemia, CAD, previous peripheral revascularization, and restenotic lesions. The impact of these differences on the combined mortality signal is unclear.

**Table 3. Baseline Comparability Across the Four Pivotal RCTs of Paclitaxel-Coated Devices vs. Uncoated Devices (As-Treated Population)**

| Demographic and Baseline Characteristic[1] | Zilver PTX RCT (N=474) | LEVANT 2 RCT (N=476) | IN.PACT SFA I & II (N=330) | ILLUMENATE RCT (N=300) | P-value[2, 3] |
|---|---|---|---|---|---|
| Age (years) | 67.8 ± 10.1 | 68.2 ± 9.7 | 67.7 ± 9.4 | 68.8 ± 10.2 | 0.7107 |
| Target Lesion Length (mm) | 56.9 ± 43.4 | 62.8 ± 41.0 | 89.4 ± 49.3 | 82.7 ± 45.7 | <0.0001 |
| Gender | | | | | 0.2524 |
| Male | 64.8% (307/474) | 63.0% (300/476) | 65.8% (217/330) | 58.7% (176/300) | |
| Female | 35.2% (167/474) | 37.0% (176/476) | 34.2% (113/330) | 41.3% (124/300) | |
| Hispanic | 6.3% (26/416) | | | 14.2% (38/267) | |
| Black | 11.5% (48/416) | 5.5% (25/456) | | 18.9% (54/286) | |
| Region | | | | | <0.0001 |
| US | 81.4% (386/474) | 63.2% (301/476) | 54.5% (180/330) | 91.0% (273/300) | |
| OUS | 18.6% (88/474) | 36.8% (175/476) | 45.5% (150/330) | 9.0% (27/300) | |
| Smoking | | | | | <0.0001 |
| Active | 31.7% (150/473) | 34.7% (165/476) | 37.6% (124/330) | 35.7% (107/300) | |
| Previous | 53.7% (254/473) | 45.6% (217/476) | 29.4% (97/330) | 45.7% (137/300) | |
| Never | 14.6% (69/473) | 19.7% (94/476) | 33.0% (109/330) | 18.7% (56/300) | |
| Hypertension | 85.2% (404/474) | 88.7% (422/476) | 90.3% (298/330) | 93.7% (281/300) | 0.0028 |
| Hyperlipidemia | 73.0% (346/474) | 88.4% (421/476) | 83.9% (277/330) | 88.7% (266/300) | <0.0001 |
| Diabetes Mellitus | 45.8% (217/474) | 42.9% (204/476) | 43.3% (143/330) | 50.3% (151/300) | 0.1892 |
| Insulin Dependent Diabetes Mellitus[5] | | 17.4% (83/476) | 17.6% (58/330) | 6.9% (11/160) | |
| CAD | 19.2% (91/474) | 49.4% (235/476) | 34.0% (105/309) | 22.3% (67/300) | <0.0001 |

| Demographic and Baseline Characteristic[1] | Zilver PTX RCT (N=474) | LEVANT 2 RCT (N=476) | IN.PACT SFA I & II (N=330) | ILLUMENATE RCT (N=300) | P-value[2, 3] |
|---|---|---|---|---|---|
| CHD | | | 56.5% (182/322) | 52.7% (158/300) | |
| Obesity | | | | | 0.0600 |
| BMI ≥ 30 kg/m$^2$ | 31.4% (149/474) | 33.4% (159/476) | 26.7% (88/330) | 36.3% (109/300) | |
| BMI < 30 kg/m$^2$ | 68.6% (325/474) | 66.6% (317/476) | 73.3% (242/330) | 63.7% (191/300) | |
| Renal Insufficiency[4] | | | | | |
| Baseline Serum creatinine ≥ 1.5 ng/dl | 10.3% (49/474) | 6.2% (28/449) | 7.7% (25/325) | 12.4% (37/298) | |
| Baseline Serum creatinine < 1.5 ng/dl | 89.7% (425/474) | 93.8% (421/449) | 92.3% (300/325) | 87.6% (261/298) | |
| On Dialysis | | | 0.3% (1/327) | | |
| Previous Peripheral Revascularization | 5.7% (27/472) | 45.0% (214/476) | 45.8% (151/330) | 42.7% (128/300) | <0.0001 |
| Previous Target Limb Amputation | | 0.0% (0/476) | 0.6% (2/330) | | |
| Previous Non-Target Limb Amputation | | 0.2% (1/476) | 1.2% (4/330) | | |
| Rutherford Category | | | | | 0.0528 |
| ≤ 3 | 91.1% (430/472) | 92.0% (438/476) | 94.5% (312/330) | 95.7% (287/300) | |
| > 3 | 8.9% (42/472) | 8.0% (38/476) | 5.5% (18/330) | 4.3% (13/300) | |
| Target Lesion Type | | | | | <0.0001 |
| Restenotic | 5.7% (27/472) | 14.9% (71/476) | 5.2% (17/330) | 12.3% (37/300) | |
| De Novo | 94.3% (445/472) | 85.1% (405/476) | 94.8% (313/330) | 87.7% (263/300) | |
| History of MI | 19.2% (91/474) | 19.1% (91/476) | | 21.3% (64/300) | |
| History of PCI | | 16.8% (80/476) | | | |
| History of CABG | | 15.1% (72/476) | | | |
| History of COPD | | | | 17.7% (53/300) | |
| History of Heart Failure | 11.2% (53/474) | 4.8% (23/476) | | 10.7% (32/300) | |
| ICD in situ | | | | | |

| Demographic and Baseline Characteristic[1] | Zilver PTX RCT (N=474) | LEVANT 2 RCT (N=476) | IN.PACT SFA I & II (N=330) | ILLUMENATE RCT (N=300) | P-value[2, 3] |
|---|---|---|---|---|---|
| Anti-Thrombotic Medication | | 94.5% (450/476) | 93.0% (307/330) | 97.7% (293/300) | |
| Statins | | 77.7% (370/476) | 31.8% (105/330) | 75.3% (226/300) | |
| Beta Blocker | | 56.9% (271/476) | 25.2% (83/330) | | |
| ACEI/ARB | | 68.7% (327/476) | 31.2% (103/330) | | |

[1] Continuous data are presented as Mean ± SD. Categorical data are presented as %(n/N).
[2] P-value is from a Kruskal-Wallis test for a continuous variable, or a Chi-square test for a categorical variable.
[3] Statistical tests are only performed for variables available for all four studies.
[4] Details of renal insufficiency were not collected in the ZILVER PTX RCT; instead, renal disease status at discretion of investigator (Yes vs. No) was provided.
[5] Diabetes type was collected but insulin dependence was not collected for the ZILVER PTX RCT.

The baseline comparability between patients treated with paclitaxel-coated devices versus uncoated devices in the AT population is shown in Appendix B. In general, the comparison of baseline and demographic characteristics suggests that the treatment groups were similar. Instances where baseline characteristic differed ($p < 0.1$) were as follows: ZILVER PTX – more hyperlipidemia noted in the DES arm; Levant 2 – higher proportion of black ethnicity/race in the PTA arm; and ILLUMENATE – longer target lesion length and a higher proportion of restenotic target lesions in the PTA arm. None of these differences in baseline covariates would likely account for a late mortality signal.

### 4.2.2 *Patient Accountability*

Three of the five pivotal studies (ZILVER PTX RCT, LEVANT 2, and SFA I&II) have patient follow-up out to 5 years. The ILLUMENATE RCT has complete data out to 3 years with planned follow-up to 5 years, and the IMPERIAL study has completed follow-up through 2 years with planned follow-up to 5 years. Patient attrition in these studies was as expected for pivotal clinical trials conducted in the US in PAD patients. A summary of patient accountability for the five studies is provided in **Table 4**. Out of the 5 pivotal trials, only the Cook ZILVER PTX trial had notable differences in enrollment for the AT, ITT and mAT populations. Therefore, all three populations are reported in **Table 4** below.

The numbers of patients that were withdrawn, lost-to-follow-up (LTFU), or missing were reported as cumulative. Withdrawn patients were defined as patients who withdrew prior to their annual follow-up visit, for whom there were no data at the current timepoint or any subsequent timepoints. Lost-to-follow-up patients were defined as patients in whom the last contact was prior to the annual follow up visit, and there were no data at the current timepoint or beyond. Pending data (not shown) was defined as patients that had no available data, because their visit window was not open or completely closed for a specific timepoint. Missing data was defined as the sum of withdrawn, LTFU, and pending patients over the total enrolled. The accountability for the pivotal studies was only considered for timepoints in which follow-up had been completed.


# Table 4. Accountability, AT Population for Pivotal RCT

| Sponsor | Device | Study Name | Device Type | Total Enrolled | Withdrawn (%) | | | | | Lost to Follow-up (%) | | | | | Missing Data (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Y1 | Y2 | Y3 | Y4 | Y5 | Y1 | Y2 | Y3 | Y4 | Y5 | Y1 | Y2 | Y3 | Y4 | Y5 |
| **Cook** | Zilver PTX | ZILVER PTX RCT (AT, no live cases) | DES | 300 | 2.0 (6/300) | 4.0 (12/300) | 7.3 (22/300) | 10.3 (31/300) | 12.7 (38/300) | 2.3 (7/300) | 8.0 (24/300) | 12.3 (37/300) | 17.3 (52/300) | 25.7 (77/300) | 4.3 (13/300) | 12.0 (36/300) | 19.7 (59/300) | 27.7 (83/300) | 38.3 (115/300) |
| | | | PTA | 174 | 2.9 (5/174) | 6.3 (11/174) | 7.5 (13/174) | 7.5 (13/174) | 9.8 (17/174) | 4.0 (7/174) | 9.8 (17/174) | 16.1 (28/300) | 20.7 (36/174) | 26.4 (46/174) | 6.9 (12/174) | 16.1 (28/174) | 23.6 (41/174) | 28.2 (49/174) | 36.2 (63/174) |
| **Cook** | Zilver PTX | ZILVER PTX RCT (ITT, no live cases) | DES | 236 | 1.7 (4/236) | 3.8 (9/236) | 7.2 (17/236) | 10.6 (25/236) | 12.7 (30/236) | 2.5 (6/236) | 9.3 (22/236) | 13.6 (32/236) | 18.6 (44/236) | 27.1 (64/236) | 4.2 (10/236) | 13.1 (31/236) | 20.8 (49/236) | 29.2 (69/236) | 39.8 (94/236) |
| | | | PTA | 238 | 2.9 (7/238) | 5.9 (14/238) | 7.6 (18/238) | 8.0 (19/238) | 10.5 (25/238) | 3.4 (8/238) | 8.0 (19/238) | 13.9 (33/238) | 18.5 (44/238) | 24.8 (59/238) | 6.3 (15/238) | 13.9 (33/238) | 21.4 (51/238) | 26.5 (63/238) | 35.3 (84/238) |
| **Cook** | Zilver PTX | ZILVER PTX RCT (MAT, with 5 live cases) | DES | 336 | 1.8 (6/336) | 4.2 (14/336) | 7.1 (24/336) | 9.8 (33/336) | 11.9 (40/336) | 2.1 (7/336) | 7.7 (26/336) | 12.2 (41/336) | 17.6 (59/336) | 25.9 (87/336) | 3.9 (13/336) | 11.9 (40/336) | 19.3 (65/336) | 27.4 (92/336) | 37.8 (127/336) |
| | | | PTA | 143 | 3.5 (5/143) | 6.3 (9/143) | 7.7 (11/143) | 7.7 (11/143) | 10.5 (15/143) | 4.9 (7/143) | 10.5 (15/143) | 17.5 (25/143) | 21.0 (30/143) | 26.6 (38/143) | 8.4 (12/143) | 16.8 (24/143) | 25.2 (36/143) | 28.7 (41/143) | 37.1 (53/143) |
| **Lutonix** | Lutonix 035 | LEVANT 2 | DCB | 316 | 3.8 (12/316) | 6.0 (19/316) | 8.2 (26/316) | 9.2 (29/316) | 9.2 (29/316) | 2.5 (8/316) | 3.8 (12/316) | 4.1 (13/316) | 4.7 (15/316) | 5.7 (18/316) | 6.3 (20/316) | 9.8 (31/316) | 12.3 (39/316) | 13.9 (44/316) | 15.8 (50/316) |
| | | | PTA | 160 | 5.6 (9/160) | 6.9 (11/160) | 10.0 (16/160) | 10.0 (16/160) | 10.0 (16/160) | 1.3 (2/160) | 1.9 (3/160) | 2.5 (4/160) | 2.5 (4/160) | 3.8 (6/160) | 6.9 (11/160) | 8.8 (14/160) | 12.5 (20/160) | 12.5 (20/160) | 14.4 (23/160) |
| **Medtronic** | IN.PACT Admiral | SFA I & SFA II | DCB | 220 | 5.0 (11/220) | 6.8 (15/220) | 10.5 (23/220) | 13.6 (30/220) | 15.0 (33/220) | 0.0 (0/220) | 0.5 (1/220) | 0.9 (2/220) | 2.3 (5/220) | 4.1 (9/220) | 5.0 (11/220) | 7.3 (16/220) | 11.4 (25/220) | 15.9 (35/220) | 19.1 (42/220) |
| | | | PTA | 110 | 2.7 (3/110) | 4.5 (5/110) | 7.3 (8/110) | 10.9 (12/110) | 10.9 (12/110) | 0.0 (0/110) | 0.9 (1/110) | 0.9 (1/110) | 2.7 (3/110) | 3.6 (4/110) | 2.7 (3/110) | 5.5 (6/110) | 8.2 (9/110) | 13.6 (15/110) | 14.5 (16/110) |
| **Philips** | Stellarex | ILLUMENATE | DCB | 200 | 0.5 (1/200) | 5.0 (10/200) | 6.5 (13/200) | | | 1.5 (3/200) | 2.5 (5/200) | 15.5 (31/200) | | | 2.0 (4/200) | 7.5 (15/200) | 22.0 (44/200) | | |
| | | | PTA | 100 | 0.0 (0/100) | 2.0 (2/100) | 5.0 (5/100) | | | 1.0 (1/100) | 3.0 (3/100) | 18.0 (18/100) | | | 1.0 (1/100) | 5.0 (5/100) | 23.0 (23/100) | | |
| **Boston Scientific** | Eluvia | IMPERIAL | DES - E | 310 | 1.3 (4/310) | 3.5 (11/310) | | | | 0.3 (1/310) | 1.6 (5/310) | | | | 1.6 (5/310) | 5.2 (16/310) | | | |
| | | | DES - Z | 155 | 2.6 (4/155) | 4.5 (7/155) | | | | 0.0 (0/155) | 1.3 (2/155) | | | | 2.6 (4/155) | 5.8 (9/155) | | | |

The proportion of missing data varied across individual trials and follow-up times. The percent of missing data from patients treated with the paclitaxel-coated devices was slightly higher at the longest follow-up time points in all studies except ILLUMENATE, with SFA I & II having the largest relative difference. The percentages of withdrawn patients between treatment groups was generally consistent within studies, except for IN.PACT SFA I & II which had a numerically higher number of withdrawn subjects in the DCB group compared to POBA at 5 years (15.0% vs 10.9%). The percentage of subjects LTFU was generally comparable between the treatment and control groups within each trial. However, the ZILVER PTX RCT experienced a much higher LTFU rate than other trials (~26% in each ZILVER PTX RCT treatment group compared to 3.6-5.7% in LEVANT 2 and IN.PACT SFA I & II).

At the time of this Executive Summary, the industry is attempting to gather missing mortality information from LTFU study subjects for further analyses. However, given the importance of the mortality signal, the analyses below were conducted prior to receiving any updated information.

To assess potential differences in evaluable versus LTFU/withdrawn patients within each study, patient baseline characteristics were compared between patient cohorts who had a known mortality status to those without a known mortality status at the longest follow-up time (5 years for ZILVER PTX RCT, LEVANT 2 RCT, and IN.PACT SFA I & II; 3 years for ILLUMENATE RCT). The observed differences in baseline characteristics in each of the four pivotal studies comparing paclitaxel-coated devices with non-paclitaxel devices with a p-value <0.10 are shown in **Table 5**. The complete analyses can be found in Appendix C.

**Table 5. Baseline Comparisons Between Patients with a Known vs a Missing Mortality Status[1]**

| | **Patients with a Known Mortality Status** | **Patients without a Known Mortality Status** | **p-value[2]** |
|---|---|---|---|
| **ZILVER PTX RCT** | N=296 | N=178 | |
| Hispanic | 3.8% (10/260) | 10.3% (16/156) | 0.0117 |
| Black | 8.5% (22/260) | 16.7% (26/156) | 0.0167 |
| Region (% US) | 74.0% (219/296) | 93.8% (167/178) | <0.0001 |
| Hyperlipidemia | 70.3% (208/296) | 77.5% (138/178) | 0.0885 |
| | | | |
| **LEVANT 2** | N=403 | N=73 | |
| Smoking | | | 0.0299 |
| Active | 34.0% (137/403) | 38.4% (28/73) | |
| Previous | 47.9% (193/403) | 32.9% (24/73) | |
| Never | 18.1% (73/403) | 28.8% (21/73) | |
| History of Myocardial | 17.6% (71/403) | 27.4% (20/73) | 0.0737 |

| | Patients with a Known Mortality Status | Patients without a Known Mortality Status | p-value[2] |
|---|---|---|---|
| Infarction | | | |
| | | | |
| **IN.PACT SFA I & II** | N=272 | N=58 | |
| Obesity (BMI ≥ 30 kg/m$^2$) | 29.4% (80/272) | 13.8% (8/58) | 0.0141 |
| | | | |
| **ILLUMENATE RCT** | N=233 | N=67 | |
| Region (% US) | 93.6% (218/233) | 82.1% (55/67) | 0.0069 |
| Diabetes Mellitus | 55.4% (129/233) | 32.8% (22/67) | 0.0014 |

[1] For ILLUMENATE RCT, the comparisons were between patients with and without known 3-year mortality status, for the other three studies, the comparisons were between patient with and without known 5-year mortality status

[2] p-value is from a Wilcoxon rank sum test for a continuous variable, or an Exact test for a categorical variable.

Overall, there were no clinically-meaningful differences in baseline co-variates between patients with and without known mortality status across the four pivotal trials that would likely account for a late mortality signal.

### 4.2.3 *All-Cause Mortality Results*

Crude all-cause mortality rates were determined for all five studies using available data out to 5 years. Given differences in follow-up windows for these studies, strict annual time points were used for reporting. The rates were determined by using the cumulative death rates in evaluable subjects (i.e., those that were known to be dead or those that were known to be alive). If patients had a missing death status at a certain visit but were alive at a later visit, they were counted as alive and included in the denominator. The mortality rates for each trial are reported in Appendix D. For the pivotal trials, the AT population mortality rates (percent of evaluable patients) are summarized in **Table 6** and **Figure 2-Figure 5** for the five pivotal studies at years 1, 2, 3, and 5, respectively. Note that the IMPERIAL study compared two paclitaxel DES devices.

At one year, the crude mortality rates were generally low in the paclitaxel-coated and control device groups. However, at two years, the observed mortality rates for the paclitaxel-coated device group were higher for the ZILVER PTX, LEVANT 2 and IN.PACT SFA I & II trials, while the ILLUMENATE trial did not demonstrate this trend. The crude mortality rates increased over the two to five year observed follow-up period for both paclitaxel-coated devices and control devices, which is expected in this patient population. Only the ZILVER PTX RCT, LEVANT 2 and IN.PACT SFA I & II studies had follow up to five years. For these studies, an increased mortality rate was noted at years 3 through 5. For the ZILVER PTX RCT, an increase in the crude mortality rate (at years 3 through 5) was noted in the drug-coated device group compared to control group across the ITT, AT, and mAT patient populations (**Appendix D**). However, the ILLUMENATE trial which only has follow-up completed to 3 years did not show increase mortality at 3 years.

**Table 6. Crude mortality rate for pivotal RCTs: AT Population**

| Sponsor | Device | Study Name | Device Type | Total Enrolled | Crude Mortality Rate (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Y1 | Y2 | Y3 | Y4 | Y5 |
| **Cook** | Zilver PTX | ZILVER PTX* | DES | 300 | 2.8 (8/287) | 6.8 (18/264) | 12.9 (31/241) | 16.1 (35/217) | 25.9 (48/185) |
| | | | PTA | 174 | 2.5 (4/162) | 5.5 (8/146) | 9.0 (12/133) | 11.2 (14/125) | 14.4 (16/111) |
| **Lutonix** | Lutonix 035 | LEVANT 2 | DCB | 316 | 2.0 (6/296) | 6.7 (19/285) | 10.1 (28/277) | 16.2 (44/272) | 20.3 (54/266) |
| | | | PTA | 160 | 2.7 (4/149) | 5.5 (8/146) | 6.4 (9/140) | 9.3 (13/140) | 12.4 (17/137) |
| **Medtronic** | IN.PACT Admiral | SFA I & SFA II | DCB | 220 | 1.9 (4/209) | 7.8 (16/204) | 10.8 (21/195) | 13.0 (24/185) | 16.9 (30/178) |
| | | | PTA | 110 | 0.0 (0/107) | 1.0 (1/104) | 2.0 (2/101) | 7.4 (7/95) | 9.6 (9/94) |
| **Philips** | Stellarex | ILLUMENATE | DCB | 200 | 2.0 (4/196) | 7.0 (13/185) | 10.9 (17/156) | | |
| | | | PTA | 100 | 1.0 (1/99) | 7.4 (7/95) | 13.0 (10/77) | | |
| **Boston Scientific** | Eluvia | IMPERIAL | DES - E | 310 | 2.0 (6/304) | 7.1 (21/293) | | | |
| | | | DES - Z | 155 | 4.0 (6/151) | 8.2 (12/146) | | | |

*ZILVER PTX excludes 5 live cases, as these subjects were not subject to randomization

**Figure 2. Crude Mortality Rates (%), Pivotal RCTs, 1 year (AT Population)**

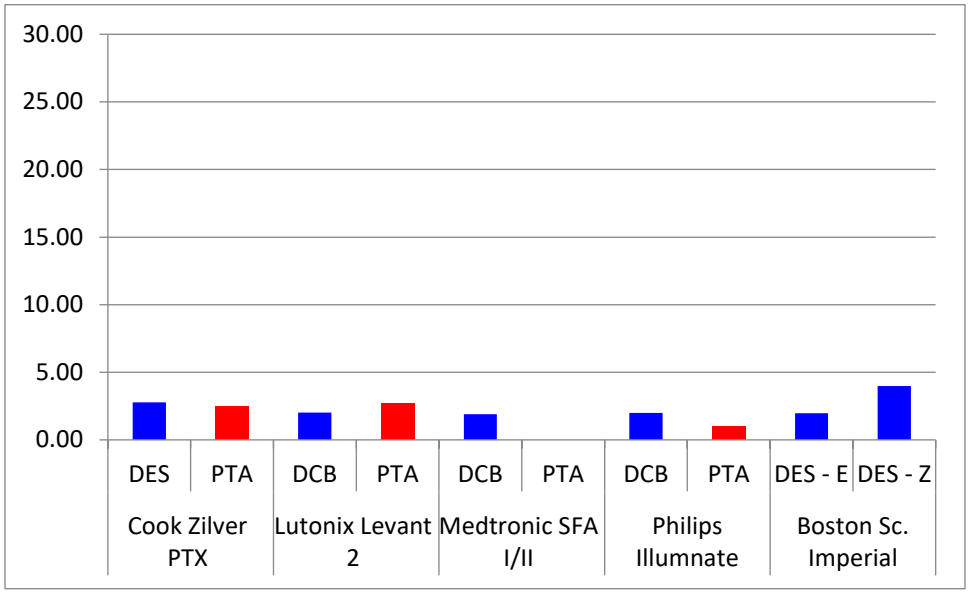


**Figure 3. Crude Mortality Rates (%), Pivotal RCTs, 2 years (AT Population)**

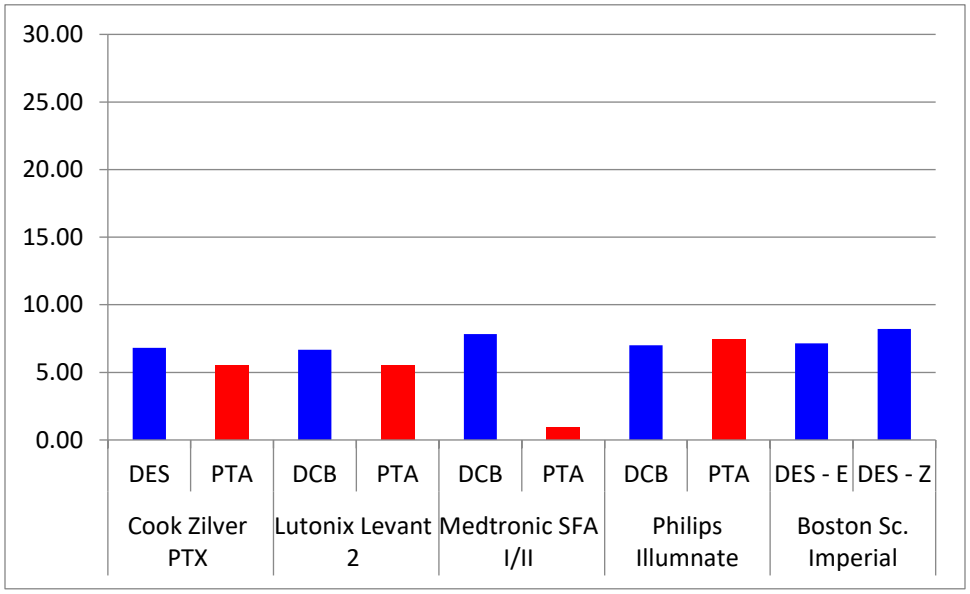



**Figure 4. Crude Mortality Rates (%), Pivotal RCTs, 3 years (AT Population)**

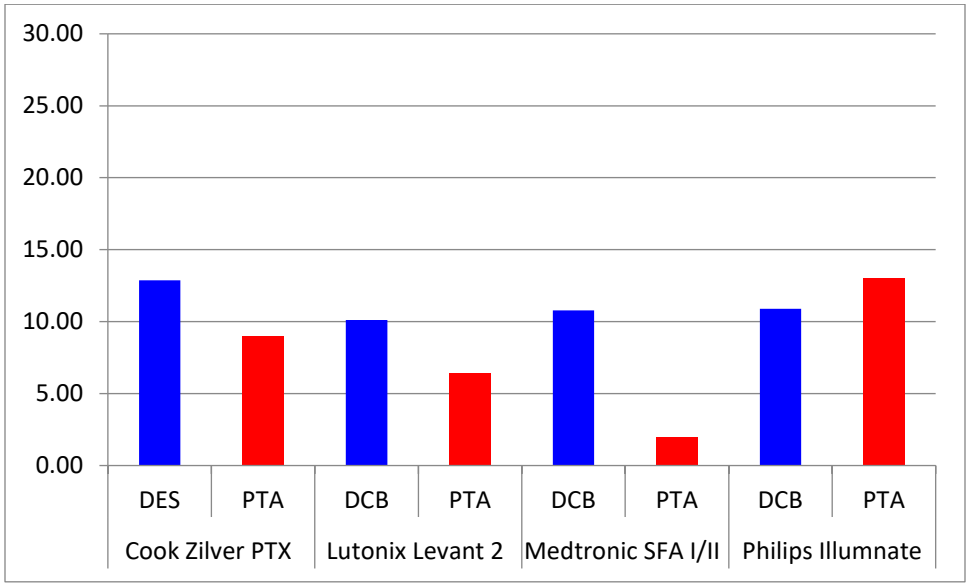
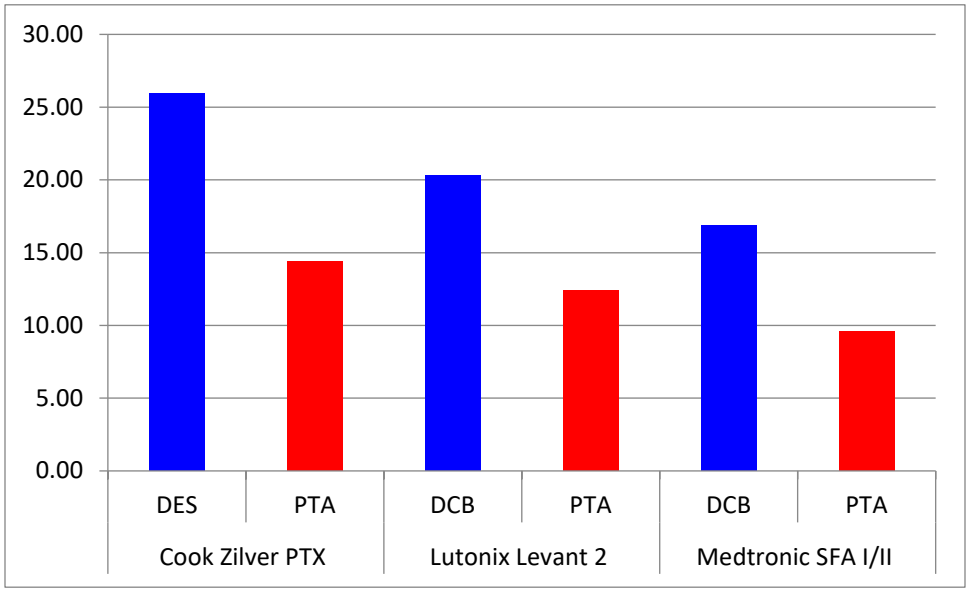


**Figure 5. Crude Mortality Rates (%), Pivotal RCTs, 5 years (AT Population)**




### 4.2.4 *Kaplan-Meier Estimation and Curves for Time to Death*

Kaplan-Meier (K-M) plots were generated for the pivotal clinical studies to display time to all-cause death based on the currently available follow-up data. The number of patients at risk is also presented in the K-M plots. As noted above, the AT population was considered the most informative for this analysis, so K-M plots based on only the AT populations are presented (**Figure 6 - Figure 10**).

**Figure 6. Kaplan-Meier Plot for Freedom from All-Cause Mortality: ZILVER PTX RCT (AT Population)**

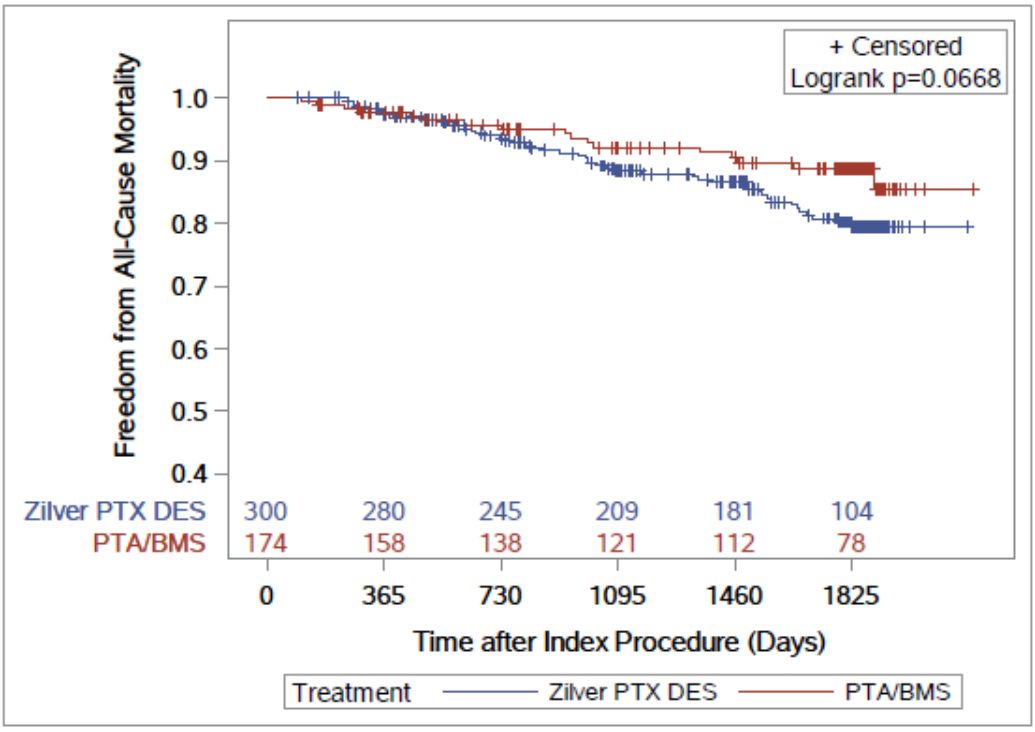



**Figure 7. Kaplan-Meier Plot for Freedom from All-Cause Mortality: LEVANT 2 RCT (AT Population)**

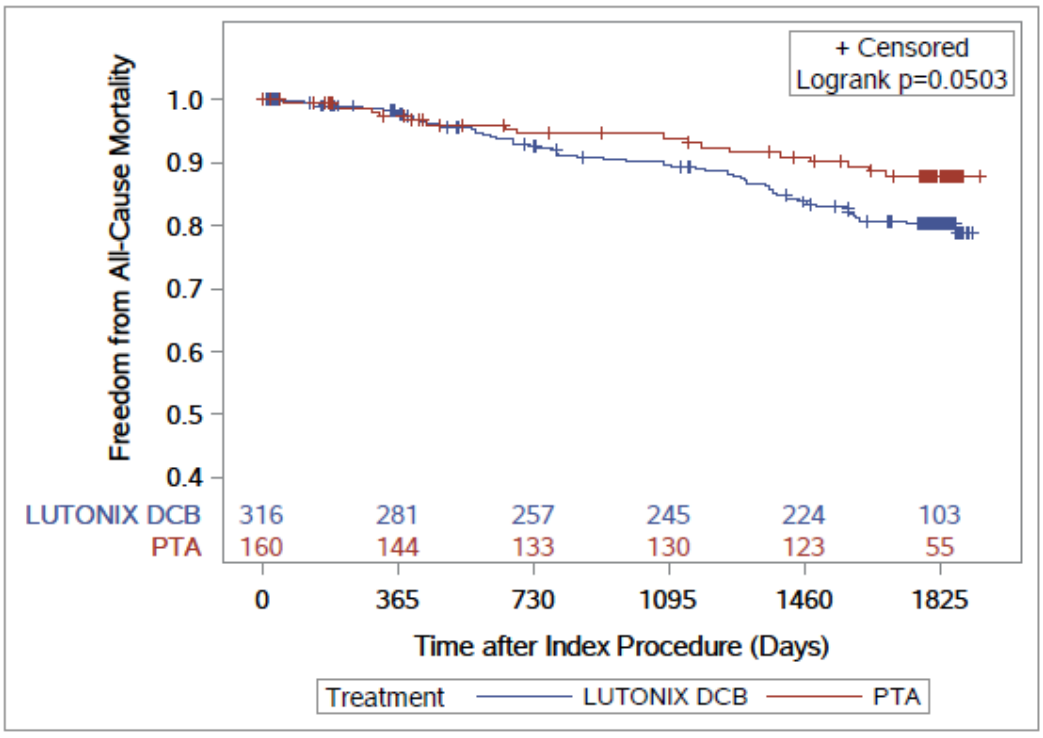


**Figure 8. Kaplan-Meier Plot for Freedom from All-Cause Mortality: IN.PACT SFA I & II (AT Population)**

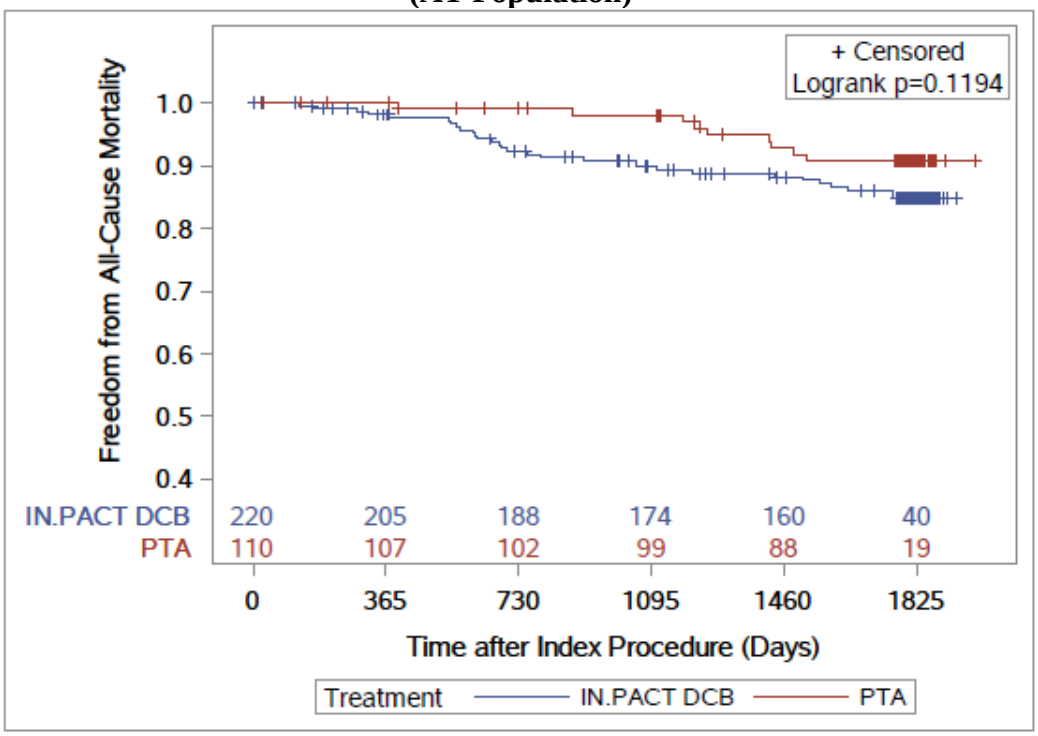
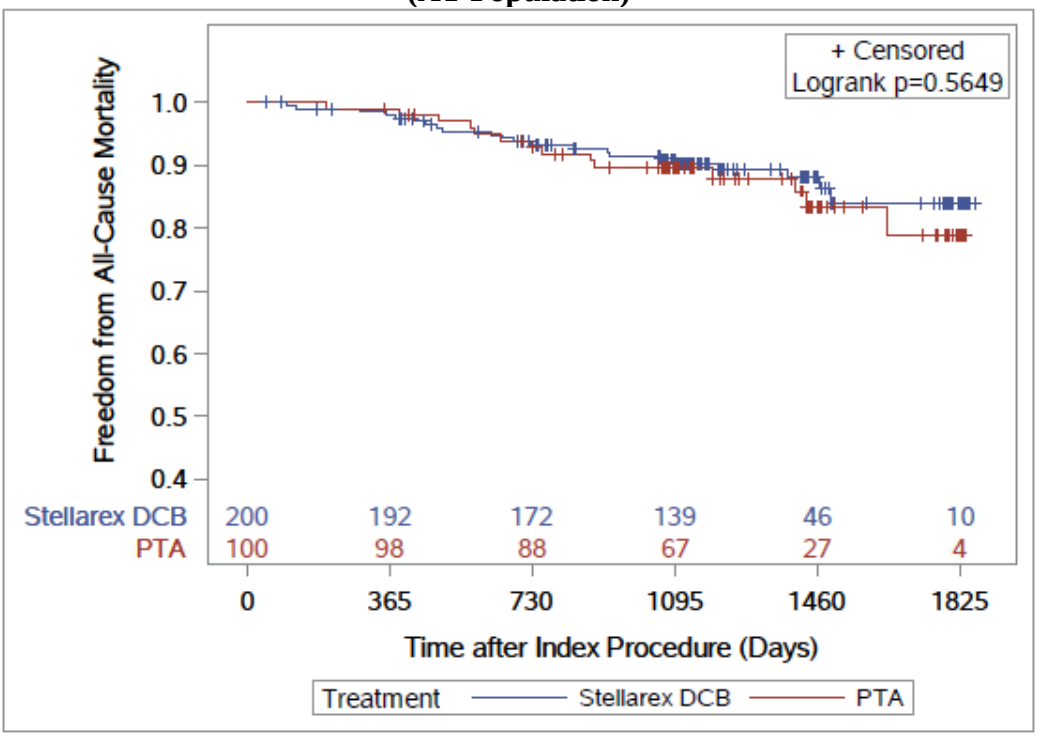
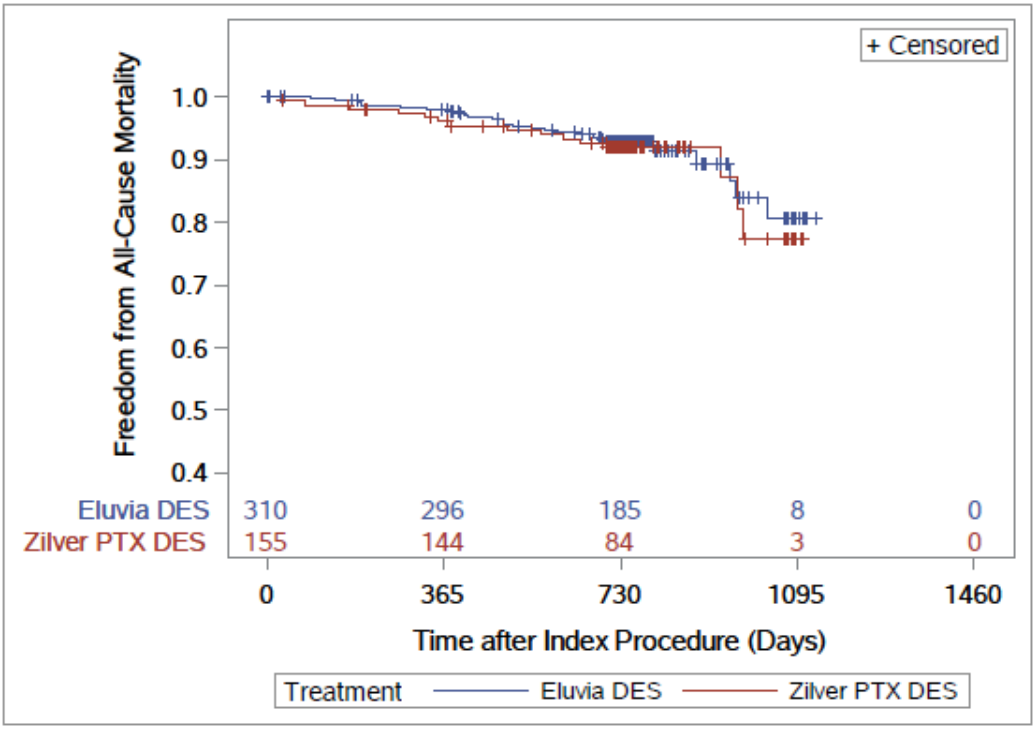



**Figure 9. Kaplan-Meier Plot for Freedom from All-Cause Mortality: ILLUMENATE RCT (AT Population)**




*The study is ongoing. By November 30, 2018 (data lock date), there were 117 patients with pending year-4 visits and 184 patients with pending year-5 visits.

**Figure 10. Kaplan-Meier Plot for Freedom from All-Cause Mortality: IMPERIAL RCT (AT Population)**




*The IMPERIAL study compares the Eluvia paclitaxel-coated DES to the Zilver PTX coated DES

The K-M plots provide an efficient means to estimate the survival function under the assumption of noninformative censoring, which means that knowledge of a censoring time of a subject provides no further information about this subject's likelihood of survival at a future time, had the subject continued to be observed in the study. With the exception of the ILLUMENATE RCT, the 5-year curves for the ZILVER PTX, IN.PACT SFA I&II and LEVANT 2 RCTs demonstrate a similar separation in all-cause mortality over time, with subjects treated with paclitaxel-coated devices having increased late mortality.

K-M plots for the ITT population can be found in Appendix E. The mortality trends for the ITT population were similar to the AT population. For ZILVER PTX RCT, the K-M plot of the mAT population showed a mortality pattern that appeared to differ from the ITT and AT analyses (Appendix E). The all-cause mortality over time demonstrated minimal separation between subjects treated with and without paclitaxel-coated devices.

### 4.2.5 *Relative Risk of Mortality*

The relative risk of mortality was estimated at annual time points up to 5 years using fixed effects and random effects models. A fixed effects model is defined as:

$$y_i = \mu + e_i$$

where $y_i$ denotes the estimated treatment effect (such as relative risk or risk difference), μ is the overall treatment effect in the population, $e_i \sim N(0, \sigma_i^2)$, i=1,…, *m*, and *m* is the number of trials. Here, $\sigma_i^2$ is the sample variance of $y_i$. Further details of implementation of this model are provided in Appendix F.

The fixed effects model assumes that there is a common effect that exists across trials, and the estimated treatment effects from the individual studies come from a homogeneous population. Some researchers suggest that this assumption may not be appropriate when the studies are different in several aspects, such as patient population (Riley, Higgins, and Deeks 2011). To address the heterogeneity across the population, a random effects model can be used. In this context, a random effects model is defined as:

$$y_i = \mu + v_i + e_i, \text{ where, } v_i \sim N(0, \tau^2),\ e_i \sim N(0, \sigma_i^2), \text{ i=1, .., } m,$$

where, *m* is the number of trials. The unknown parameter $\tau^2$ characterizes the heterogeneity among the studies. Since a random effects model accounts for heterogeneity among trials, it potentially better reflects the uncertainty associated with the risk estimate and thus leads to a wider confidence interval. Note that the estimation of between-trial variability may not be reliable when the number of trials is small. Also, the power of the heterogeneity test is typically low when there are small number of studies available (Higgins, Thompson, and Spiegelhalter 2009).

Separate meta-analyses were conducted for each year. Meta-analysis results for the relative risk and risk difference are provided in **Table 7**. Relative risk forest plots were created for the four pivotal RCTs of paclitaxel-coated versus uncoated devices for the AT and ITT populations at each timepoint. A complete description of these results can be found in Appendix F. The 1-, 2-, 3- and 5-year forest plots are presented for the AT populations in **Figure 11** - **Figure 14**, respectively. Results for the ITT populations are in Appendix F.

**Table 7. Meta-analysis results for the AT population: Relative risk and Risk Difference**

| | | | | | Relative-risk (RR) | | | Risk-difference (RD) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Year | Number of studies | Treatment group (#Event/ #Evaluable) | Control group (#Event/ #Evaluable) | Model | Point estimate | Lower (95% CI) | Upper (95% CI) | Point estimate | 95% CI (Lower) | 95% CI (Upper) |
| 1 | 4 | **22/988** | **9/517** | **Fixed** | 1.25 | 0.59 | 2.65 | 0.01 | -0.01 | 0.02 |
| | | | | **Random** | 1.15 | 0.53 | 2.49 | 0.01 | -0.01 | 0.02 |
| 2 | 4 | **66/938** | **24/491** | **Fixed** | 1.44 | 0.91 | 2.27 | 0.02 | 0.00 | 0.05 |
| | | | | **Random** | 1.31 | 0.75 | 2.29 | 0.03 | -0.01 | 0.06 |
| 3 | 4 | **97/869** | **33/451** | **Fixed** | 1.53 | 1.05 | 2.23 | 0.04 | 0.01 | 0.07 |
| | | | | **Random** | 1.48 | 0.85 | 2.57 | 0.04 | 0.00 | 0.09 |
| 4 | 3 | **103/674** | **34/360** | **Fixed** | 1.62 | 1.13 | 2.34 | 0.06 | 0.02 | 0.10 |
| | | | | **Random** | 1.62 | 1.12 | 2.33 | 0.06 | 0.02 | 0.10 |
| 5 | 3 | **132/629** | **42/342** | **Fixed** | 1.72 | 1.25 | 2.37 | 0.09 | 0.04 | 0.14 |
| | | | | **Random** | 1.72 | 1.22 | 2.38 | 0.09 | 0.04 | 0.13 |

**Figure 11. Forest plot of relative risk for the AT population based on 1-year data**

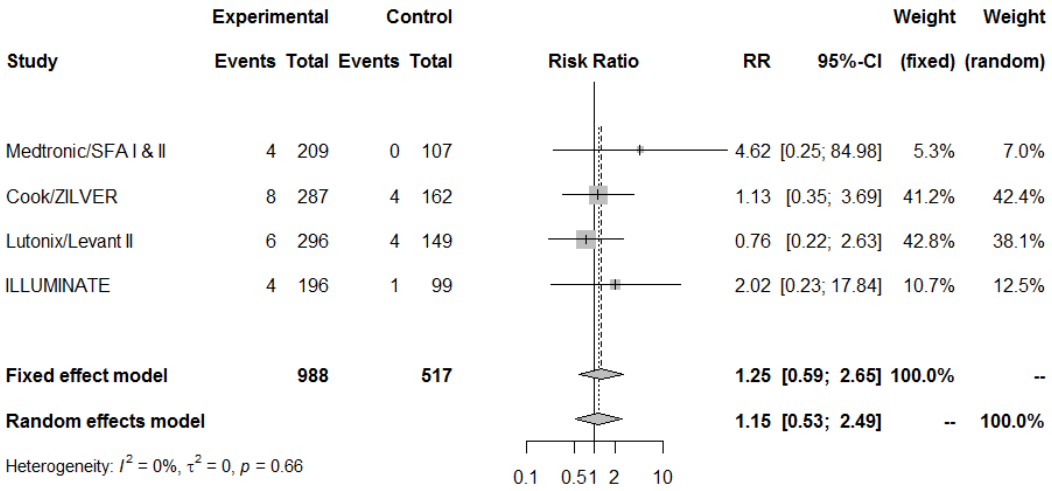



**Figure 12. Forest plot of relative risk for the AT population based on 2-year data**

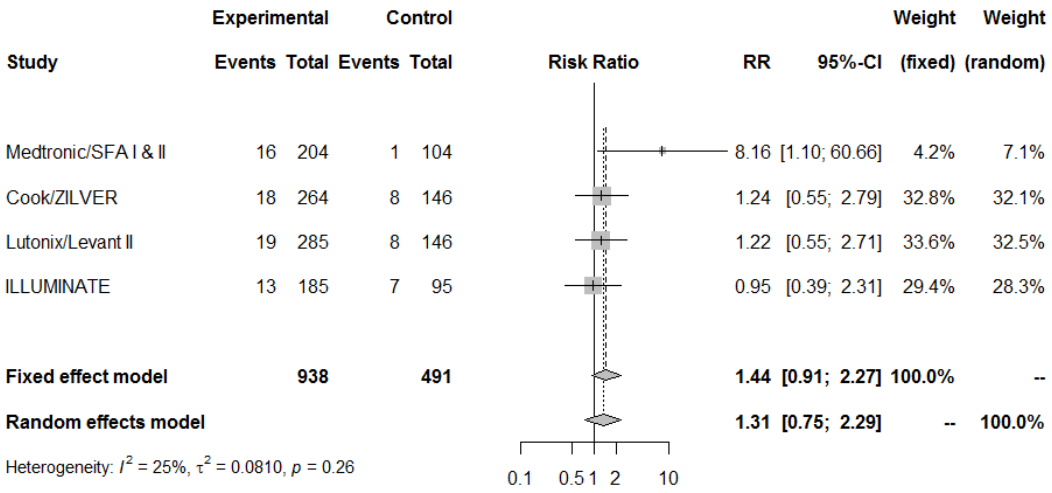


**Figure 13. Forest plot of relative risk for the AT population based on 3-year data**

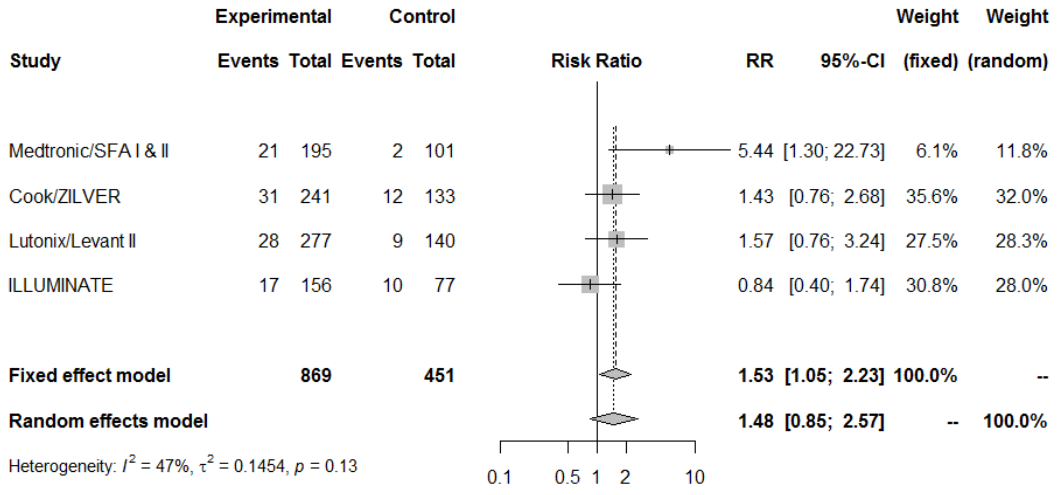
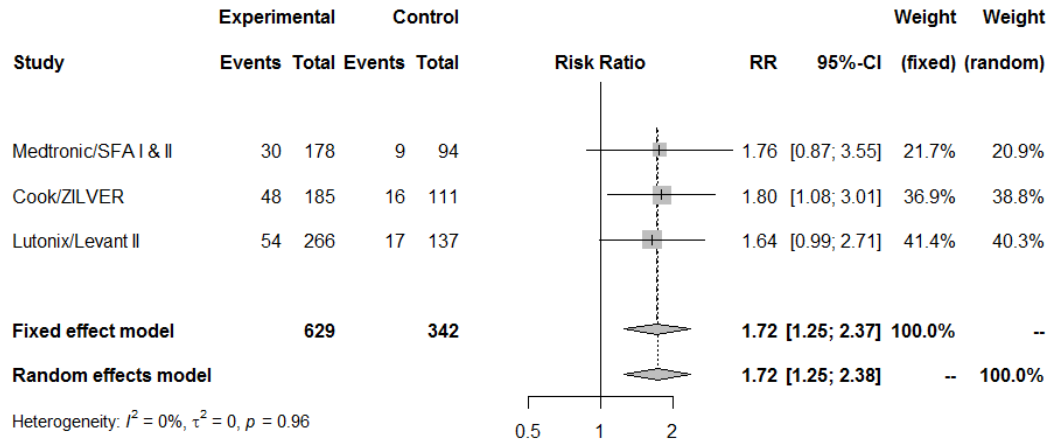



**Figure 14. Forest plot of relative risk for the AT population based on 5-year data**




Results of analyses of year 1, year 2, and year 3 data, which consist of four pivotal RCTs, show a trend of an increasing relative risk point estimate for mortality in patients treated with paclitaxel-coated devices compared to control devices. This trend continued in year 4 (see Appendix F, Figure F.9) and year 5, which included three pivotal RCTs. The RR estimate based on 5-year data is 1.72 with the lower limit of the 95% CI >1.

Based on the available information, the Panel will be asked to discuss and comment on the presence and clinical significance of the late mortality signal (Question 1), and whether the signal likely represents a class effect among paclitaxel-coated devices (Question 2).

### 4.3 *Supplementary Analysis and Results*

In addition to the pivotal RCTs, manufacturers have continued to evaluate paclitaxel-coated devices in both RCTs and registries. Given the limited long-term follow-up for these studies, FDA considers these analyses supplementary to the pivotal RCTs for evaluating the late mortality signal.

#### 4.3.1 *Additional Paclitaxel-coated Device Randomized Controlled Trials*

Additional OUS RCTs evaluating paclitaxel-coated devices are summarized below:

1) Cook ZILVER PTX DES - REAL PTX RCT (Zilver DES vs DCB)
2) LUTONIX DCB - LEVANT I (DCB vs PTA)
3) LUTONIX DCB - JAPAN RCT (DCB vs PTA)
4) MDT IN.PACT DCB – IN.PACT Japan (DCB vs PTA)
5) Philips Stellarex DCB - ILLUMENATE EU (DCB vs PTA)
6) BSC Eluvia DES - EMINENT RCT (DES vs BMS)

The first five studies listed above have completed between two and three years of follow-up with additional follow-up on-going. The EMINENT study has not completed 1-year follow-up and was therefore not included in the accountability assessment.

##### *4.3.1.1 Patient Accountability and Assessment for Missing Data*

Patient accountability is described in **Table 8**. With the exception of the EMINENT RCT, these studies have complete data out to at least 2 years. Overall, at year 3 (in studies with complete 3-year data), these trials observed a 0% to 37.3% LTFU rate, and 3% to 18.7% of patients withdrew consent from study participation. The rate of missing data at 3 years for the Zilver REAL PTX trial and the ILLUMENATE RCT was considerably higher than the rates seen in the pivotal RCTs. In addition, the PTA groups in the additional OUS RCTs had numerically higher missing data rates versus the pivotal RCTs.


**Table 8. Accountability for Additional RCTs with Paclitaxel-coated devices**

| Sponsor | Device | Study Name | Device Type | Total Enrolled | Withdrawn (%) | | | Lost to Follow-up (%) | | | Missing Data (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Y1 | Y2 | Y3 | Y1 | Y2 | Y3 | Y1 | Y2 | Y3 |
| **Cook** | Zilver PTX | REAL PTX | DES | 75 | 8.0 (6/75) | 13.3 (10/75) | 18.7 (14/75) | 1.3 (1/75) | 2.7 (2/75) | 32.0 (24/75) | 9.3 (7/75) | 16.0 (12/75) | 50.7 (38/75) |
| | | | DCB | 75 | 4.0 (3/75) | 9.3 (7/75) | 10.7 (8/75) | 1.3 (1/75) | 2.7 (2/75) | 37.3 (28/75) | 5.3 (4/75) | 12.0 (9/75) | 48.0 (36/75) |
| **Lutonix** | Lutonix 035 | LEVANT 1 | DCB | 49 | 4.1 (2/49) | 4.1 (2/49) | | 0.0 (0/49) | 0.0 (0/49) | | 4.1 (2/49) | 4.1 (2/49) | |
| | | | PTA | 52 | 9.6 (5/52) | 9.6 (5/52) | | 0.0 (0/52) | 0.0 (0/52) | | 9.6 (5/52) | 9.6 (5/52) | |
| | | JAPAN RCT | DCB | 71 | 0.0 (0/71) | 0.0 (0/71) | | 0.0 (0/71) | 0.0 (0/71) | | 0.0 (0/71) | 0.0 (0/71) | |
| | | | PTA | 38 | 2.6 (1/38) | 2.6 (1/38) | | 5.3 (2/38) | 5.3 (2/38) | | 7.9 (3/38) | 7.9 (3/38) | |
| **Medtronic** | IN.PACT Admiral | IN.PACT JAPAN | DCB | 68 | 0.0 (0/68) | 1.5 (1/68) | 2.9 (2/68) | 1.5 (1/68) | 1.5 (1/68) | 1.5 (1/68) | 1.5 (1/68) | 2.9 (2/68) | 4.4 (3/68) |
| | | | PTA | 32 | 0.0 (0/32) | 9.4 (3/32) | 9.4 (3/32) | 0.0 (0/32) | 0.0 (0/32) | 0.0 (0/32) | 0.0 (0/32) | 9.4 (3/32) | 9.4 (3/32) |
| **Philips** | Stellarex | ILLUMENATE EU | DCB | 219 | 2.3 (5/219) | 4.6 (10/219) | 7.8 (17/219) | 3.2 (7/219) | 4.6 (10/219) | 12.8 (28/219) | 5.5 (12/219) | 9.1 (20/219) | 20.5 (45/219) |
| | | | PTA | 72 | 12.5 (9/72) | 13.9 (10/72) | 18.0 (13/72) | 1.4 (1/72) | 1.4 (1/72) | 13.9 (10/72) | 13.9 (10/72) | 15.3 (11/72) | 31.9 (23/72) |

### *4.3.1.2 Crude All-Cause Mortality Rates*

Crude all-cause mortality rates in the AT population were determined for five OUS RCTs, up to the year when follow-up was complete. Mortality rates were determined similarly to the method described above for the pivotal RCTs and are shown in **Table 9**.

**Table 9. Crude Mortality Rate for Additional Studies with Paclitaxel-coated Devices (AT Population)**

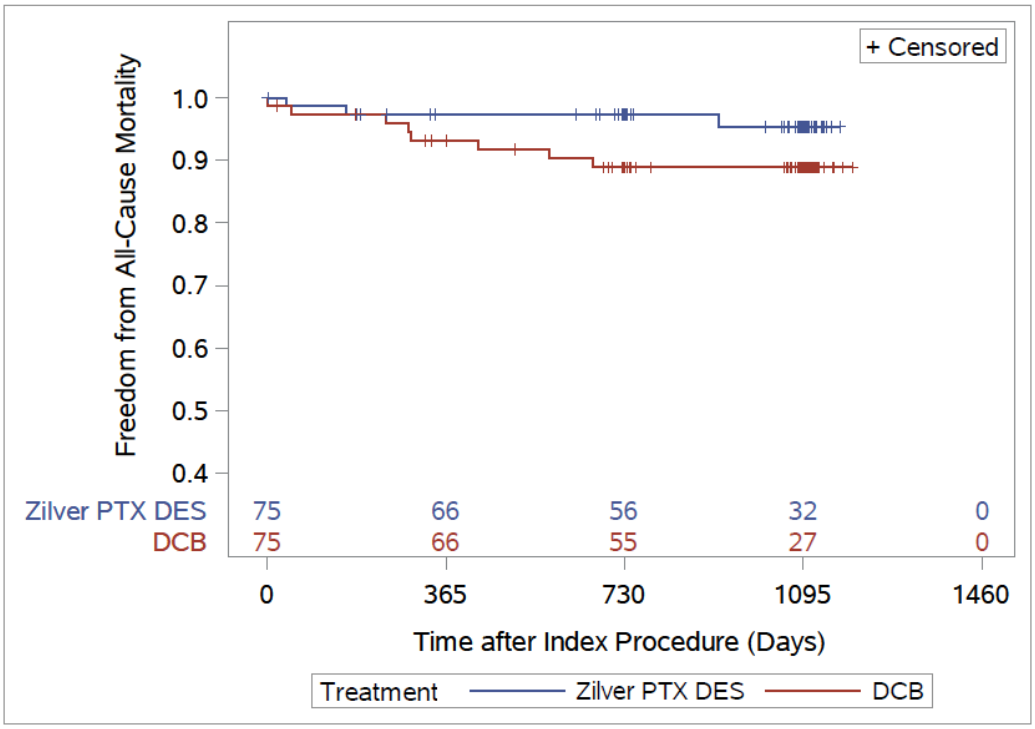
| Sponsor | Device | Study Name | Device Type | Total Enrolled | Crude Mortality Rate (%) | | |
|---|---|---|---|---|---|---|---|
| | | | | | Y1 | Y2 | Y3 |
| **Cook** | Zilver PTX | REAL PTX | DES | 75 | 2.9 (2/68) | 3.2 (2/63) | 8.1 (3/37) |
| | | | DCB | 75 | 7.0 (5/71) | 12.1 (8/66) | 20.5 (8/39) |
| **Lutonix** | Lutonix 035 | LEVANT 1 | DCB | 49 | 4.3 (2/47) | 8.5 (4/47) | |
| | | | PTA | 52 | 8.5 (4/47) | 8.5 (4/47) | |
| | | JAPAN RCT | DCB | 71 | 1.4 (1/71) | 2.8 (2/71) | |
| | | | PTA | 38 | 2.9 (1/35) | 8.6 (3/35) | |
| **Medtronic** | IN.PACT Admiral | IN.PACT JAPAN | DCB | 68 | 0.0 (0/67) | 6.1 (4/66) | 6.2 (4/65) |
| | | | PTA | 32 | 0.0 (0/32) | 3.4 (1/29) | 6.9 (2/29) |
| **Philips** | Stellarex | ILLUMENATE EU | DCB | 219 | 1.4 (3/207) | 6.5 (13/199) | 10.3 (18/174) |
| | | | PTA | 72 | 1.6 (1/62) | 3.3 (2/61) | 10.2 (5/49) |

In the OUS RCTs with data out to three years, the comparative mortality rates between paclitaxel coated devices and uncoated devices varied. IN.PACT Japan and ILLUMENATE EU demonstrated similar mortality rates for the DCB versus the PTA group (6.2% vs 6.9% and 10.3% vs 10.2%, respectively). The LEVANT 1 trial also demonstrated comparable mortality rates in both treatment groups at 2 years (8.5%). The LUTONIX Japan trial reported a higher crude mortality rate for the control versus the DCB (8.6% vs 2.8%, respectively). The REAL PTX trial compared a paclitaxel-coated DCB to a paclitaxel-coated DES, and patients treated with the DCB had numerically higher mortality rates at years 2 and 3. Additional crude mortality data can be found in Appendix D.

Kaplan-Meier plots for freedom from all-cause mortality (with number of patients at risk) were generated for the OUS RCTs based on longest-term follow-up (**Figure 15 - Figure 19)**. The K-M plots show no clear separations of the survival curves between paclitaxel-coated devices and uncoated devices over the follow-up period.

It is notable that the sample sizes are smaller and follow-up periods are shorter for the majority of the OUS RCTs compared to the pivotal trials. Therefore, the duration of follow-up may be inadequate to address the late mortality signal.

**Figure 15. Kaplan-Meier Plot for Freedom from All-Cause Mortality for REAL PTX RCT (AT Population)**




*The REAL RCT compares the Zilver PTX coated DES to DCB

**Figure 16. Kaplan-Meier Plot for Freedom from All-Cause Mortality: LEVANT 1 (AT Population)**

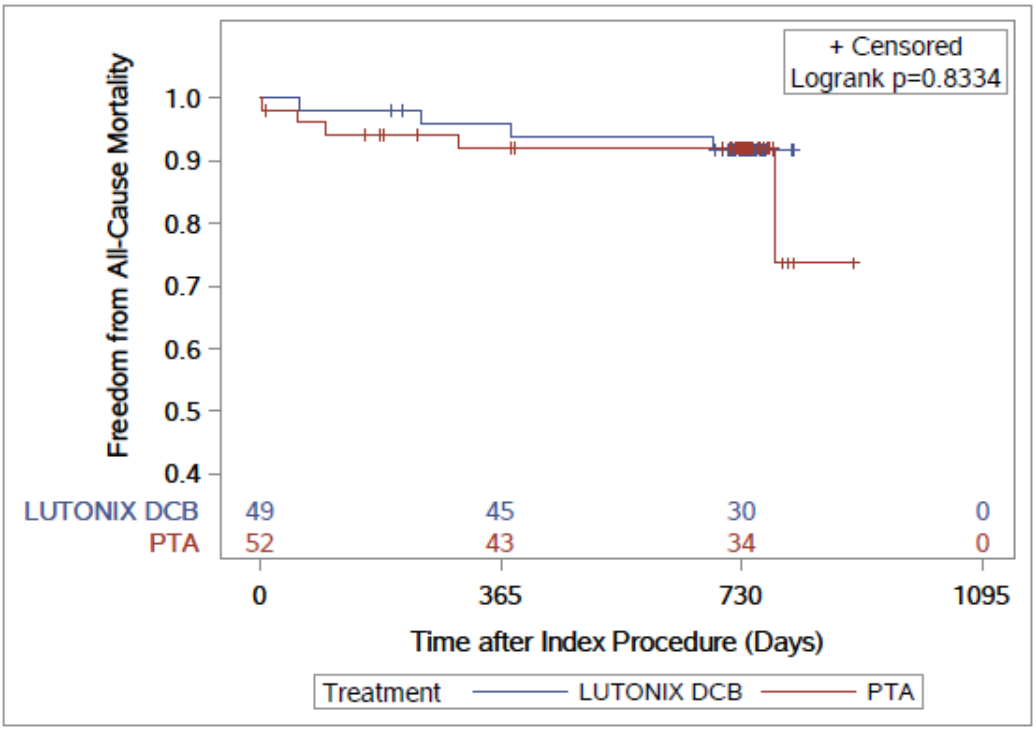



**Figure 17. Kaplan-Meier Plot for Freedom from All-Cause Mortality: LUTONIX JAPAN RCT (AT Population)**

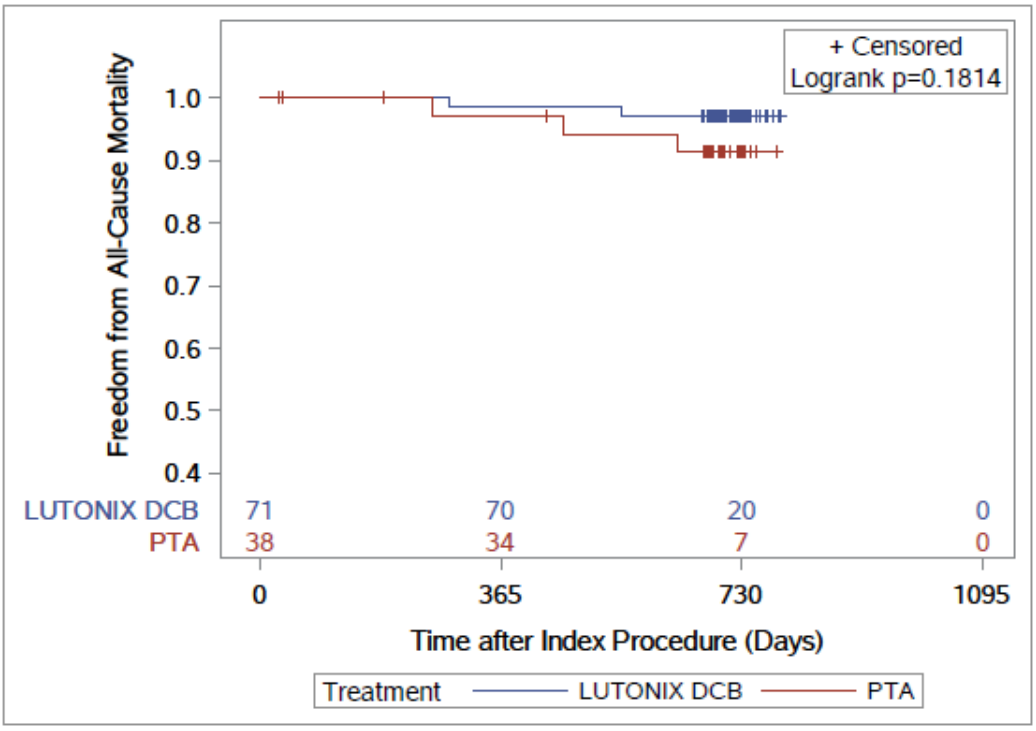


**Figure 18. Kaplan-Meier Plot for Freedom from All-Cause Mortality: IN.PACT Japan (AT Population)**

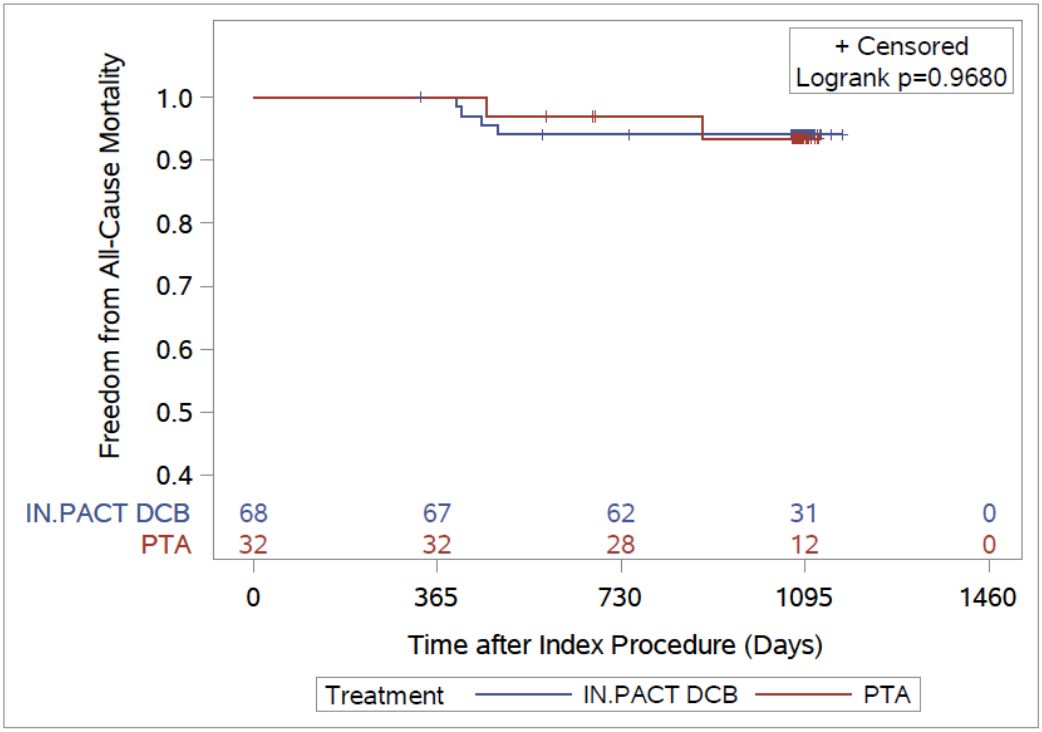
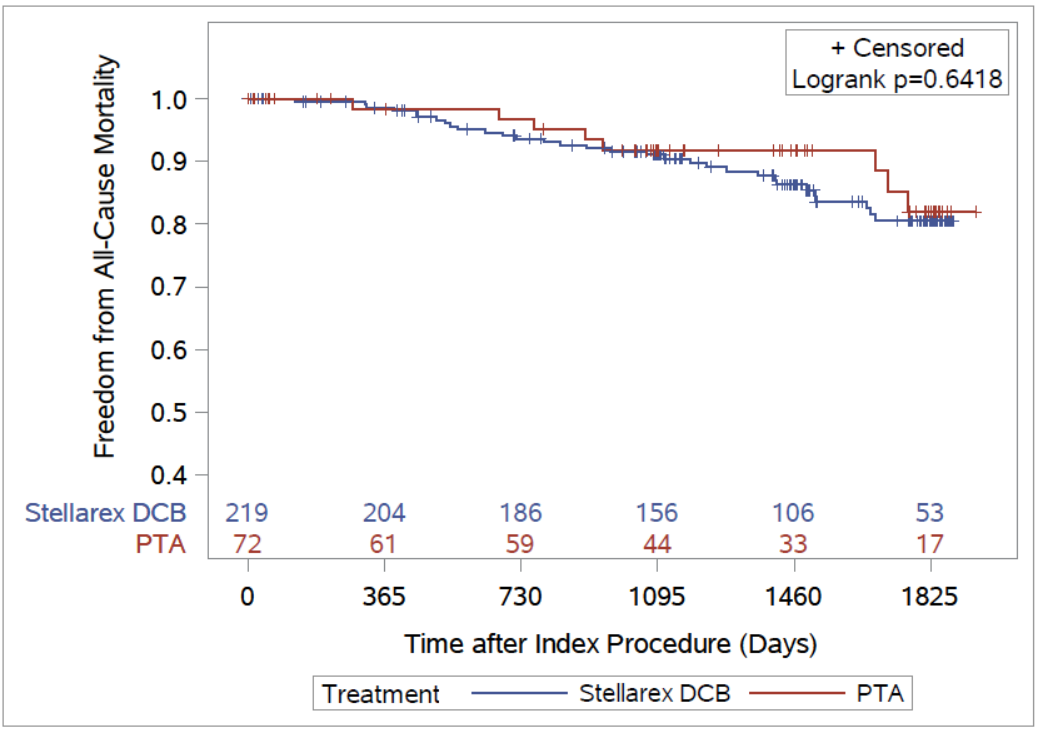



**Figure 19. Kaplan-Meier Plot for Freedom from All-Cause Mortality: ILLUMENATE EU (AT Population)**



### *4.3.1.3 Relative risk of Mortality*

FDA used the same meta-analysis method described in Section 4.2.5 to generate relative risk forest plots for the pivotal and OUS RCTs for the AT and ITT populations. The complete analyses can be found in Appendix F. Forrest plots for 1 and 2-year data are shown in **Figure 20** and **Figure 21,** respectively. Since ILLUMENATE EU had limited data beyond 3-years follow-up, it is removed from the 4 and 5-year analyses. Hence, the 4- and 5-year meta-analysis only included the 3 pivotal trials (see **Figure 14**).

**Figure 20. Forest plot of relative risk for the AT population, pivotal trials and OUS RCTs based on 1-year data**

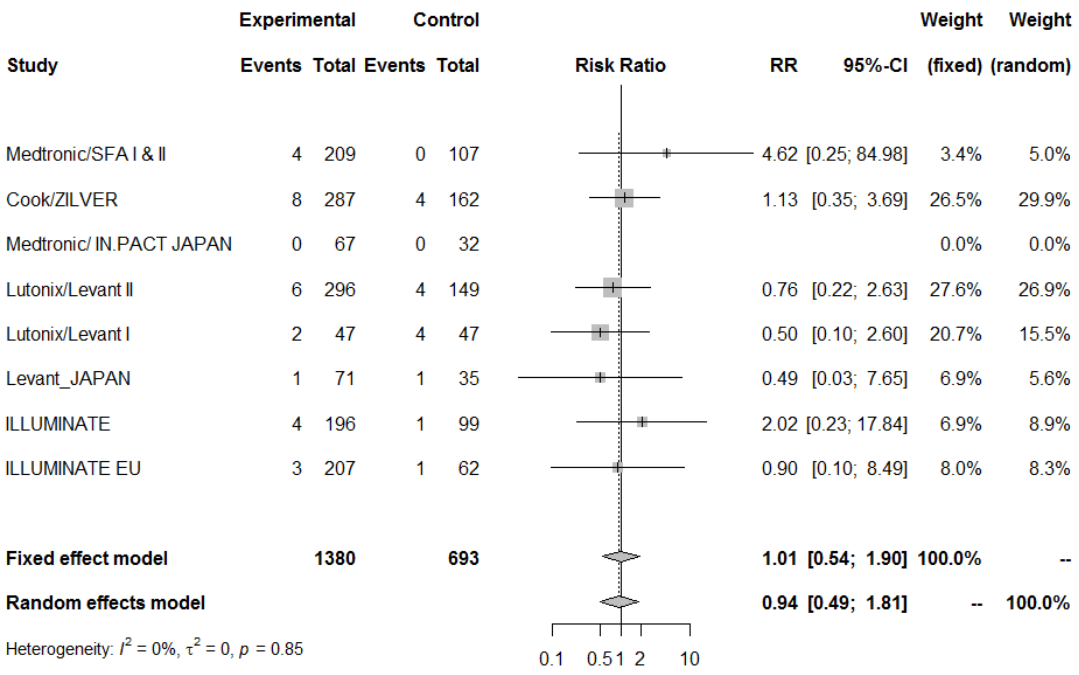
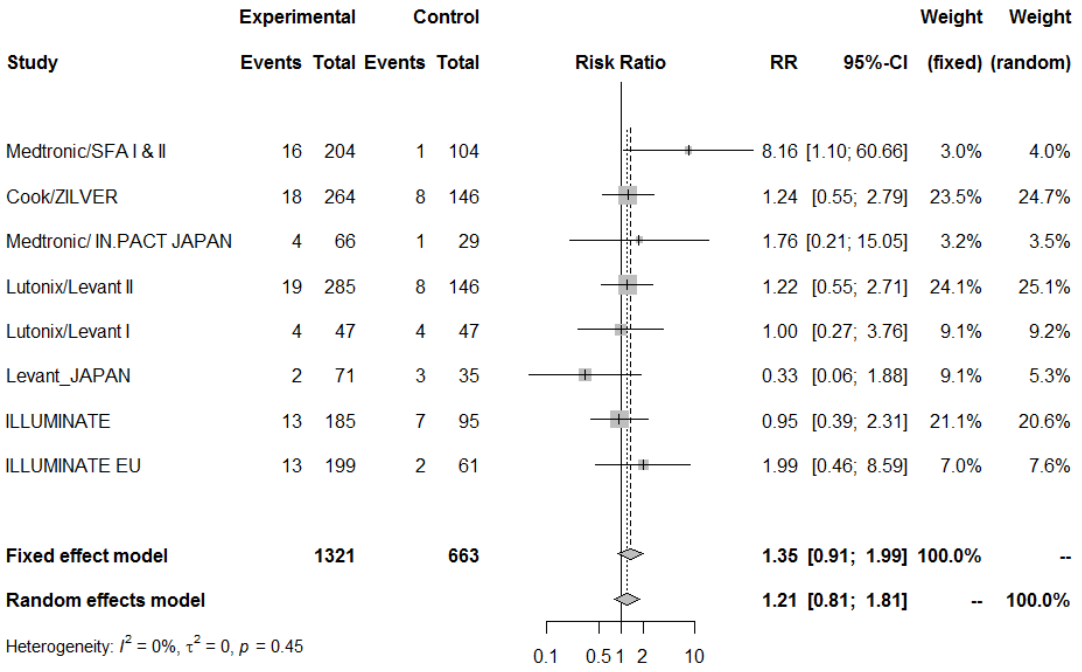


**Figure 21. Forest plot of relative risk for the AT population, pivotal trials and OUS RCTs based on 2-year data**




When combining the pivotal RCTs with the additional OUS RCTs, the risk ratios between the paclitaxel-coated devices and uncoated show a similar trend seen for the pivotal RCTs alone for years 1 and 2; the RR was >1 but the 95% CI crossed the line of unity. However, the OUS RCTs provide little data to assess the late mortality signal.

### 4.3.2 *Registry Studies*

Four paclitaxel-coated devices have been evaluated in the following six US and OUS registry studies with 2-5 year follow-up data:

1) MDT IN.PACT Admiral – IN.PACT Global
2) Philips Stellarex DCB - ILLUMENATE Global
3) LUTONIX Randomized Plus Continued Access Registry (CAR)
4) LUTONIX 035 DCB – LUTONIX Global
5) LUTONIX 035 DCB – SAFE-DCB
6) Cook Zilver PTX DES – ZILVER Japan Post-Market Registry

These six studies were considered supplementary information to evaluate the late mortality signal, and limited analyses were conducted. The first five studies are single-arm post-market surveillance registries evaluating paclitaxel-coated devices. The ZILVER Japan post-market registry includes concurrently enrollment of patients treated with the Zilver bare-metal stent or the Zilver PTX DES. A summary of these analyses, data, and conclusions are provided below.

#### *4.3.2.1 Patient Accountability and Assessment for Missing Data*

These registry studies have complete data through 2 years with 3-year data available for most studies. Only the paclitaxel-coated stent group of the ZILVER Japan Post-Market Registry has data to 5 years. A summary of patient accountability for the studies is shown **Table 10**.

There is a large proportion of missing data for these registry studies at three years, ranging from 13.6% (IN.PACT Global) to 74.0% (SAFE-DCB). Mortality data based on these studies should be interpreted with caution given the large amount of missing data, potential differences in patient/lesion selection, lack of an active comparator, variability in the robustness of data collection, and the lack of consistent independent adjudication of events and imaging findings.

# Table 10. Accountability, AT Population for Registry Studies

| Sponsor | Device | Study Name | Device Type | Enrolled Patients | Withdrawn (%) | | | | | Lost to Follow-up (%) | | | | | % Missing Data | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Y1 | Y2 | Y3 | Y4 | Y5 | Y1 | Y2 | Y3 | Y4 | Y5 | Y1 | Y2 | Y3 | Y4 | Y5 |
| **Cook** | Zilver PTX | JAPAN POST-MARKET REGISTRY | DES | 922 | 1.2 (11/922) | 3.8 (35/922) | 6.4 (59/922) | 8.0 (74/922) | 9.2 (85/922) | 4.6 (42/922) | 11.4 (105/922) | 17.4 (160/922) | 22.5 (207/922) | 25.1 (231/922) | 5.7 (53/922) | 15.2 (140/922) | 23.8 (219/922) | 30.5 (281/922) | 34.3 (316/922) |
| | | | BMS | 190 | 2.6 (5/190) | 3.7 (7/190) | 6.8 (13/190) | | | 12.6 (24/190) | 23.7 (45/190) | 26.3 (50/190) | | | 15.3 (29/190) | 27.4 (52/190) | 33.2 (63/190) | | |
| | | ZILVER SAS | DES | 787 | 1.4 (11/787) | 3.9 (31/787) | | | | 0.9 (7/787) | 2.5 (20/787) | | | | 2.3 (18/787) | 6.5 (51/787) | | | |
| **Lutonix** | Lutonix 035 | LEVANT 2 CONTINEUD ACCESS | DCB | 713 | 3.4 (24/713) | 6.5 (46/713) | 8.4 (60/713) | 8.7 (62/713) | 8.8 (63/713) | 0.7 (5/713) | 1.1 (8/713) | 1.5 (11/787) | 2.2 (16/713) | 2.2 (16/713) | 4.1 (29/713) | 7.6 (54/713) | 10.1 (72/713) | 11.1 (79/713) | 11.6 (83/713) |
| | | LUTONIX GLOBAL | DCB | 691 | 1.4 (10/691) | 2.5 (17/691) | | | | 1.0 (7/691) | 1.0 (7/691) | | | | 2.5 (17/691) | 3.5 (24/691) | | | |
| | | SAFE-DCB | DCB | 1005 | 3.2 (32/1005) | 6.3 (63/1005) | | | | 3.4 (34/1005) | 4.6 (46/1005) | | | | 8.1 (81/1005) | 16.0 (161/1005) | | | |
| **Medtronic** | IN.PACT Admiral | IN.PACT GLOBAL | DCB | 1406 | 4.0 (56/1406) | 7.0 (98/1406) | 10.3 (145/1406) | | | 1.0 (14/1406) | 2.2 (31/1406) | 3.3 (46/1406) | | | 5.0 (70/1406) | 9.2 (129/1406) | 13.6 (191/1406) | | |
| **Philips** | Stellarex | ILLUMENATE GLOBAL | DCB | 371 | 3.0 (11/371) | 7.3 (27/371) | 9.4 (35/371) | | | 0.8 (3/371) | 1.9 (7/371) | 23.2 (86/371) | | | 3.8 (14/371) | 9.2 (34/371) | 32.6 (121/371) | | |

#### *4.3.2.2 Crude All-Cause Mortality Rates*

Crude all-cause mortality rates were determined for all six studies (**Table 11**). Rates were determined up to the year when follow-up was complete, and the method was the same as the analysis of the pivotal RCTs. Kaplan-Meier plots of the time to death (with number of patients at risk) are shown in Appendix E.3.

**Table 11. Crude Mortality Rate for Registry Studies (AT Population)**

| Sponsor | Device | Study Name | Device Type | Total Enrolled | Crude Mortality Rate (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Y1 | Y2 | Y3 | Y4 | Y5 |
| **Cook** | Zilver PTX | JAPAN POST-MARKET REGISTRY* | DES | 922 | 5.5 (48/869) | 12.4 (97/782) | 18.2 (128/703) | 25.6 (162/634) | 31.3 (187/598) |
| | | | BMS | 190 | 5.0 (8/161) | 10.9 (15/138) | 17.3 (22/127) | | |
| | | SINGLE ARM | DES | 787 | 3.3 (25/758) | 6.1 (44/725) | | | |
| **Lutonix** | Lutonix 035 | LEVANT 2 CONTINEUD ACCESS | DCB | 713 | 1.5 (10/684) | 3.6 (24/659) | 7.5 (48/641) | 11.4 (72/634) | 14.3 (90/630) |
| | | LUTONIX GLOBAL | DCB | 691 | 2.5 (17/674) | 5.1 (34/667) | | | |
| | | SAFE-DCB | DCB | 1005 | 7.4 (68/924) | 14.0 (118/844) | | | |
| **Medtronic** | IN.PACT Admiral | IN.PACT GLOBAL | DCB | 1406 | 3.4 (46/1336) | 7.8 (100/1277) | 12.1 (147/1215) | | |
| **Philips** | Stellarex | ILLUMENATE GLOBAL | DCB | 371 | 0.6 (2/357) | 2.7 (9/337) | 6.4 (16/250) | | |

*Follow-up in the ZILVER Japan BMS group was completed at 3 years

The crude all-cause mortality rates varied among the studies. However, because many of these studies are single-arm and have limited follow-up, conclusions cannot be made regarding the late mortality signal.

## 4.4 *Subgroup Analyses*

FDA evaluated the mortality results for subgroups based on geography (US vs. OUS) and gender. The Panel will be asked to comment on these subgroup analyses in Question 4.

### 4.4.1 *Geography (US vs. OUS)*

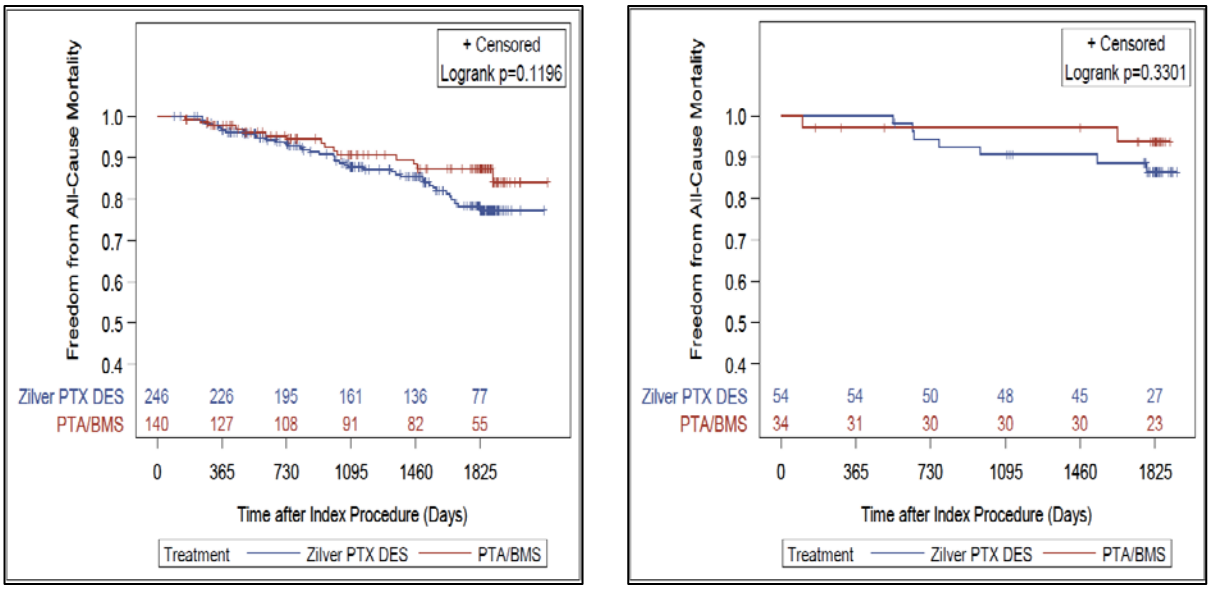
The evaluation of treatment effect homogeneity for survival times across geography (US vs. OUS) was conducted on the AT population. The Kaplan-Meier curves for freedom from all-cause mortality were estimated and stratified by treatment group and geography for each pivotal RCT. To further explore a treatment by geography interaction, a Cox proportional hazard (PH) model was fitted with time to all-cause mortality as the response variable, and the following

three terms as the explanatory variables: treatment, geography, and interaction between geography and treatment.

*Cook ZILVER PTX RCT.* Of 474 AT patients in ZILVER PTX RCT, 386 (81.4%) patients enrolled in the US, and 88 (18.6%) patients enrolled OUS. The Kaplan-Meier plots ( **Figure** 22) show freedom from all-cause mortality in Zilver PTX DES patients vs. POBA patients, by geography. The p-value of treatment by geography interaction term in the Cox PH model was 0.7204, suggesting no evidence of a differential treatment effect between geographies.

**Figure 22. Kaplan-Meier Plots for Freedom from All-Cause Mortality: Geography Analysis for ZILVER PTX RCT (AT Population)**

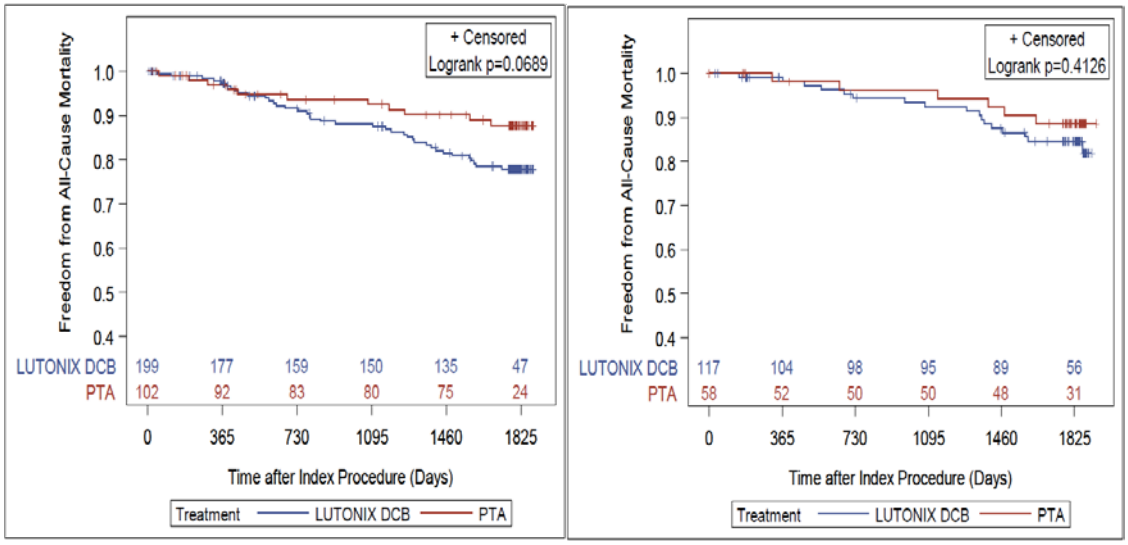
**US Patients** **OUS Patients**




*LUTONIX LEVANT 2 RCT.* Of 476 AT patients in the LEVANT 2 RCT, 301 (63.2%) enrolled in the US, and 175 (36.8%) enrolled OUS. The Kaplan-Meier plots (**Figure 23**) show freedom from all-cause mortality in LUTONIX 035 DCB patients vs. POBA patients, by geography. The p-value of treatment by geography interaction term in the Cox PH model was 0.6892, suggesting no evidence of a differential treatment effect between geographies.

**Figure 23. Kaplan-Meier Plots for Freedom from All-Cause Mortality: Geography Analysis for LEVANT 2 RCT (AT Population)**

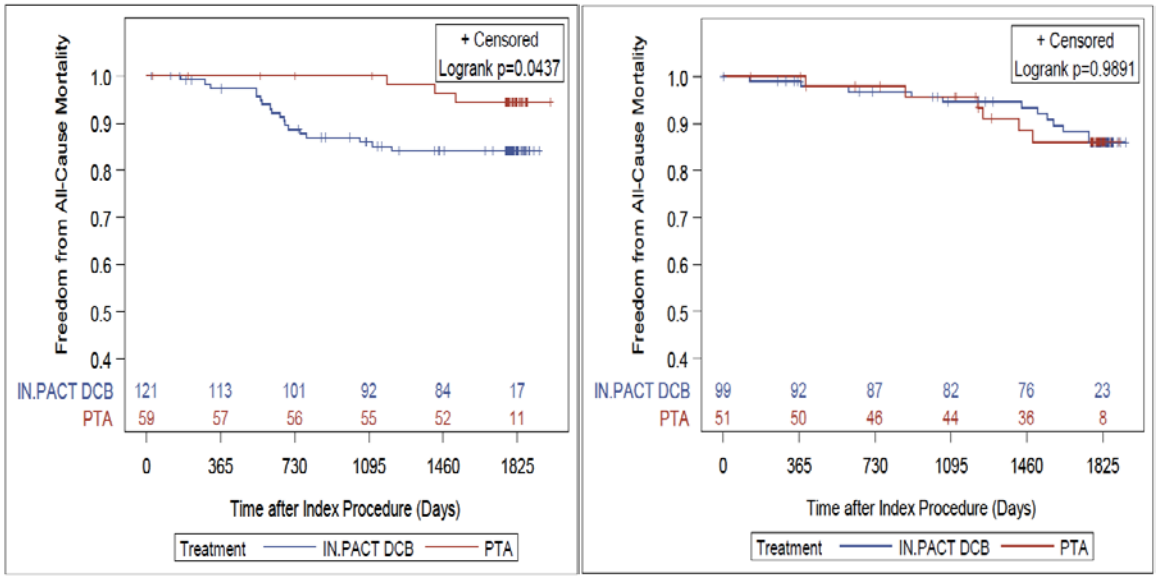
**US Patients** **OUS Patients**




*Medtronic IN.PACT SFA I & II.* Of 330 AT patients in IN.PACT SFA I & II RCT, 180 (54.5%) patients enrolled in the US, and 150 (45.5%) patients enrolled OUS. The Kaplan-Meier plots **Figure 24**, show freedom from all-cause mortality in IN.PACT Admiral DCB patients vs. POBA patients, by geography. The p-value of treatment by geography interaction term in the Cox PH model was 0.1325, suggesting possible heterogeneity in the treatment effect between geographies. This difference in treatment effect between geographies was not noted for the primary endpoints at 12-months.

**Figure 24. Kaplan-Meier Plots for Freedom from All-Cause Mortality: Geography Analysis for IN.PACT SFA I & II RCT (AT Population)**

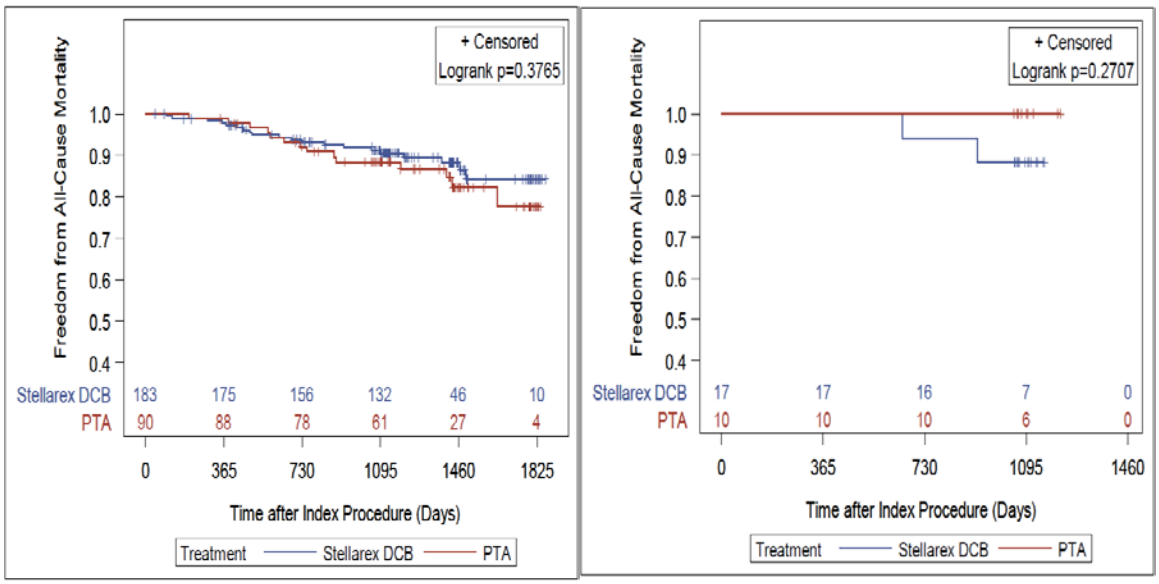
**US Patients** **OUS Patients**




*Philips ILLUMENATE RCT*. Of 300 AT patients in the ILLUMENATE RCT, 273 (91.0%) patients enrolled in the US, and 27 (9.0%) patients enrolled OUS. The Kaplan-Meier plots (**Figure 23**) show freedom from all-cause mortality in Stellarex DCB patients vs. POBA patients, by geography. The p-value of treatment by geography interaction term in the Cox PH model was 0.9894, suggesting no evidence of a differential treatment effect between geographies.

**Figure 25. Kaplan-Meier Plots for Freedom from All-Cause Mortality: Geography Analysis for ILLUMENATE RCT (AT Population)**

**US Patients** **OUS Patients**



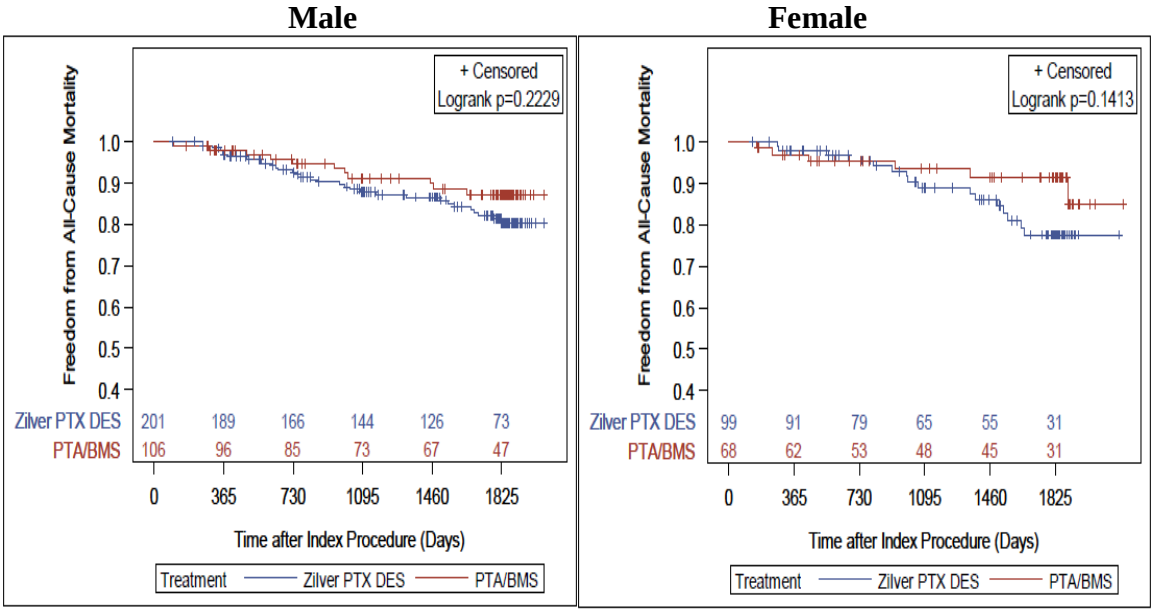

In summary, except for the IN.PACT SFA I &II study, no evidence of a differential treatment effect between geographies was observed.

### 4.4.2 *Gender (male vs. female)*

The evaluation of homogeneity of treatment effect for survival times between genders (male vs. female) was conducted on the AT population using the similar approaches presented in the US vs. OUS analysis.

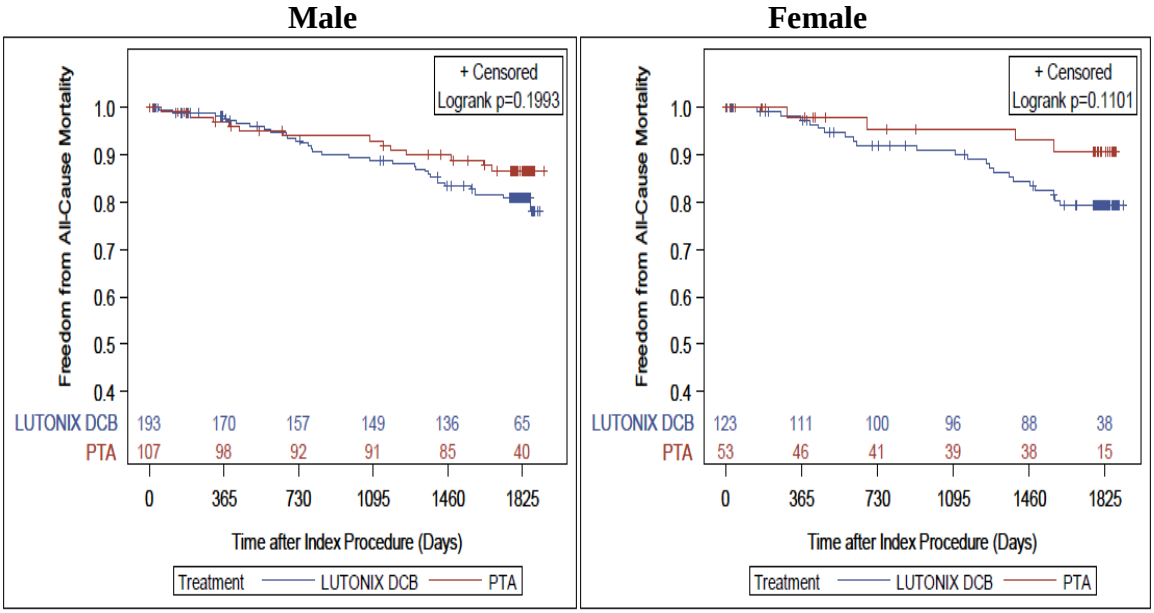
*Cook ZILVER PTX RCT.* Of 474 patients in the ZILVER PTX RCT, 307 (64.8%) were male and 167 (35.2%) female. The Kaplan-Meier plots (**Figure 26**) show freedom from all-cause mortality in Zilver PTX DES patients vs. POBA patients, by gender. The p-value of treatment by gender interaction term in the Cox PH model was 0.6800, suggesting no evidence of a differential treatment effect between gender groups.

**Figure 26. Kaplan-Meier Plots for Freedom from All-Cause Mortality: Gender Analysis for ZILVER PTX RCT (AT Population)**



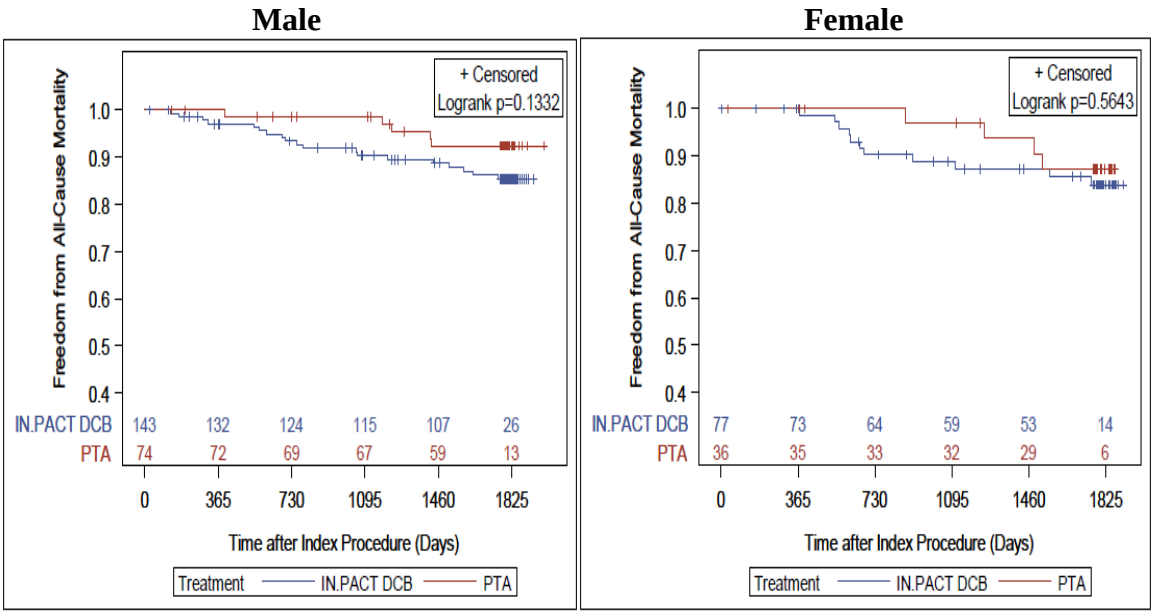

*LUTONIX LEVANT 2 RCT.* Of 476 patients in the LEVANT 2 RCT, 300 (63.0%) were male and 176 (37.0%) female. The Kaplan-Meier plots (**Figure 27**) show freedom from all-cause mortality in Lutonix 035 DCB patients vs. POBA patients, by gender. The p-value of treatment by gender interaction term in the Cox PH model was 0.5083, suggesting no evidence of a differential treatment effect between gender groups.

**Figure 27. Kaplan-Meier Plots for Freedom from All-Cause Mortality: Gender Analysis for LEVANT 2 RCT (AT Population)**



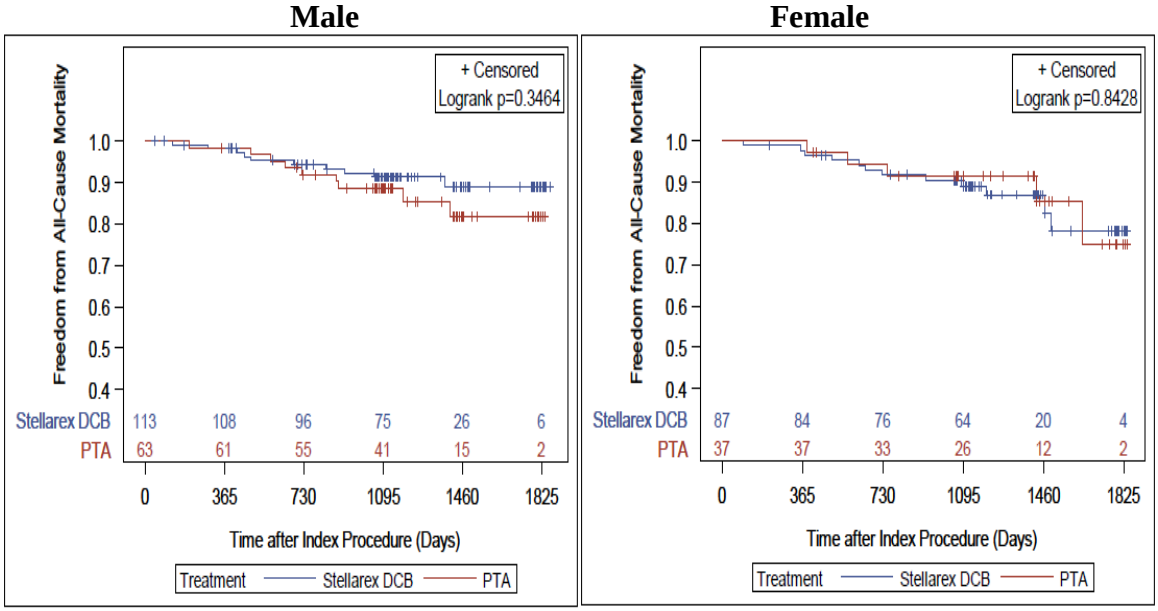

*Medtronic IN.PACT SFA I & II RCT.* Of 330 patients in the IN.PACT SFA I & II RCT, 217 (65.8%) were male and 113 (34.2%) female. The Kaplan-Meier plots (**Figure 28**) show freedom from all-cause mortality in IN.PACT Admiral DCB patients vs. POBA patients by gender. The p-value of treatment by gender interaction term in the Cox PH model was 0.5991, suggesting no evidence of a differential treatment effect between gender groups.

**Figure 28. Kaplan-Meier Plots for Freedom from All-Cause Mortality: Gender Analysis for IN.PACT SFA I & II (AT Population)**



*Philips Illumenate RCT*. Of 300 patients in the ILLUMENATE RCT, 176 (58.7%) were male and 124 (41.3%) female. The Kaplan-Meier plots (**Figure 29**) show freedom from all-cause mortality in Stellarex DCB patients vs. POBA patients by genders. The p-value of treatment by gender interaction term in the Cox PH model was 0.4520, suggesting no evidence of a differential treatment effect between genders.

**Figure 29. Kaplan-Meier Plots for Freedom from All-Cause Mortality: Gender Analysis for ILLUMENATE RCT (AT Population)**




Overall, for all four pivotal RCTs, no evidence of a differential treatment effect between genders was observed.

## 5. Evaluation of Potential Trends for Biological Mechanism or Causality for Increased Mortality

To determine potential causes for increased late mortality rates in patients treated with paclitaxel-coated devices, FDA analyzed clinical and pre-clinical data for the five FDA-approved devices. Using the patient-level data available from the five pivotal trials, FDA evaluated the cause of death from the Clinical Events Committee (CEC)-adjudicated death narratives to investigate potential causality. FDA also evaluated paclitaxel dosage at patient-level to examine a potential correlation between death and total treatment dosage. Finally, FDA evaluated available pre-clinical safety information to examine if local adverse effects and/or systemic toxicity may be a potential biological mechanism for the increased late mortality observed in clinical trial patients. The Panel will be asked to review these analyses and discuss the potential causes for the late mortality signal.

### 5.1 *Cause of Death Analyses*

All deaths in the five pivotal trials were CEC-adjudicated to determine relatedness to the device and/or procedure. It is important to note adjudication process limitations prior to discussing FDA's analyses, which include the specificity and comprehensiveness of the death evaluations. In cases in which deaths were adjudicated to be non-device related, it is unclear whether the CEC included members with sufficient pharmacology/toxicology expertise, and whether CEC members were provided with detailed clinical information to fully assess if deaths may have been device or drug-related. Secondly, there is no established method for categorizing deaths in these types of trials. Therefore, deaths were adjudicated using differing categorization schemes among trials [e.g., MedDRA, International Classification of Diseases (ICD), sponsor-specific methods]. FDA concluded that the death categories proposed by Hicks et. al. (2018) (see **Appendix G**) could provide consistent terminology among trials and requested that companies reclassify deaths into those categories. See **Table 12** for a summary of the categories.

**Table 12. Cause of Death Categorization**

| (FDA Code) Cardiovascular Sub-Types | (FDA Code) Non-Cardiovascular Sub-Types |
|---|---|
| (MI) Acute Myocardial Infarction<br>(SD) Sudden cardiac death<br>(HF) Heart Failure<br>(ST) Stroke<br>(CP) CV procedure<br>(CH) CV hemorrhage<br>(CO) Other: CV<br><br>(CU) CV- Unknown category added | (P) Pulmonary(R) Renal<br>(GI) Gastrointestinal<br>(HB) Hepatobiliary<br>(included under GI) Pancreatic<br>(I) Infection<br>(I) Inflammatory/ immune (including autoimmune)<br>(H) Hemorrhage<br>(NP) Non-CV procedure or surgery<br>(T) Trauma<br>(S) Suicide<br>(D) Drug reaction or overdose<br>(N) Neurological<br>(M) Malignancy<br>(O) Other: non-CV<br><br>NCU Non-CV – Unknown category added |

However, even with death re-classification per Hicks et. al., additional limitations remained. Many patients had multiple medical conditions, which could have contributed to death; however, the final adjudication only considered a single category. Further, late mortality often occurred in non-hospital settings, in which detailed information regarding symptoms, signs, and medical evaluations were lacking. In these cases, deaths were listed as "unknown" or "other" or categorized as a general cardiovascular death.

While recognizing these limitations, FDA nonetheless evaluated the death narratives and cause of death information to identify potential trends regarding potential biological mechanisms associated with the late mortality. A summary of the cause of death information, using the categorization scheme described above, is provided in **Table 13**. Data for these analyses include:

ZILVER PTX, LEVANT 2 and IN.PACT SFA I&II RCTs through 5 years; ILLUMENATE RCT through 3 years; and IMPERIAL RCT through 2 years. Note that the ILLUMENATE and IMPERIAL have limited long-term data and that the IMPERIAL trial included a paclitaxel-coated device in both study arms.

## Table 13. Causes of Death Categories for Maximum Completed Follow-Up (AT Population)

| | | Cook – Zilver PTX DES | | | | LUTONIX 035 DCB | | | | MDT - IN.PACT Admiral DCB | | | | Philips - Stellarex DCB | | | | BSC - Eluvia DES | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ZILVER PTX RCT | | | | LEVANT 2 | | | | IN.PACT SFA I & II | | | | ILLUMENATE | | | | IMPERIAL | | | |
| | Follow-Up Completed (Years) | 5 | | | | 5 | | | | 5 | | | | 3 | | | | 2 | | | |
| | Follow-Up Planned (Years) | 5 | | | | 5 | | | | 5 | | | | 5 | | | | 5 | | | |
| | Study Arm | DES | | PTA/BMS | | DCB | | PTA | | DCB | | PTA | | DCB | | PTA | | DES - E | | DES – Z | |
| | | | n=305[1] | | n= 174 | | N=316 | | N=160 | | n= 220 | | n= 110 | | n= 200 | | n= 100 | | n= 310 | | n= 155 |
| | Total Deaths to Maximum Completed Follow-Up | | 48 | | 16 | | 54 | | 17 | | 30 | | 9 | | 17 | | 10 | | 20 | | 12 |
| | Denominator (from AT Accountability Table) at latest completed year | | 225 | | 134 | | 266 | | 137 | | 178 | | 94 | | 156 | | 77 | | 294 | | 146 |
| | Crude Mortality Rate (Total Deaths to Max Years/Denominator) | | 21.3% | | 11.9% | | 20.3% | | 12.4% | | 16.9% | | 9.6% | | 10.9% | | 13.0% | | 6.8% | | 8.2% |
| | Cardiovascular | 17 | 7.6% | 7 | 5.2% | 19 | 7.1% | 5 | 3.6% | 11 | 6.2% | 3 | 3.2% | 6 | 3.8% | 6 | 7.8% | 11 | 3.7% | 9 | 6.2% |
| MI | Acute MI | 0 | 0.0% | 0 | 0.0% | 4 | 1.5% | 1 | 0.7% | 2 | 1.1% | 0 | 0.0% | 0 | 0.0% | 1 | 1.3% | 3 | 1.0% | 3 | 2.1% |
| SD | Sudden cardiac death | 0 | 0.0% | 0 | 0.0% | 5 | 1.9% | 2 | 1.5% | 3 | 1.7% | 1 | 1.1% | 1 | 0.6% | 0 | 0.0% | 2 | 0.7% | 2 | 1.4% |
| HF | Heart Failure | 5 | 2.2% | 3 | 2.2% | 3 | 1.1% | 1 | 0.7% | 2 | 1.1% | 0 | 0.0% | 2 | 1.3% | 0 | 0.0% | 2 | 0.7% | 1 | 0.7% |
| ST | Stroke | 1 | 0.4% | 1 | 0.7% | 3 | 1.1% | 1 | 0.7% | 2 | 1.1% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 0.7% |
| CP | Cardiovascular Procedure | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 0.6% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| CH | Cardiovascular Hemorrhage | 0 | 0.0% | 0 | 0.0% | 1 | 0.4% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| CO | Other - Cardiovascular Disease | 10 | 4.4% | 2 | 1.5% | 3 | 1.1% | 0 | 0.0% | 0 | 0.0% | 1 | 1.1% | 2 | 1.3% | 2 | 2.6% | 0 | 0.0% | 0 | 0.0% |

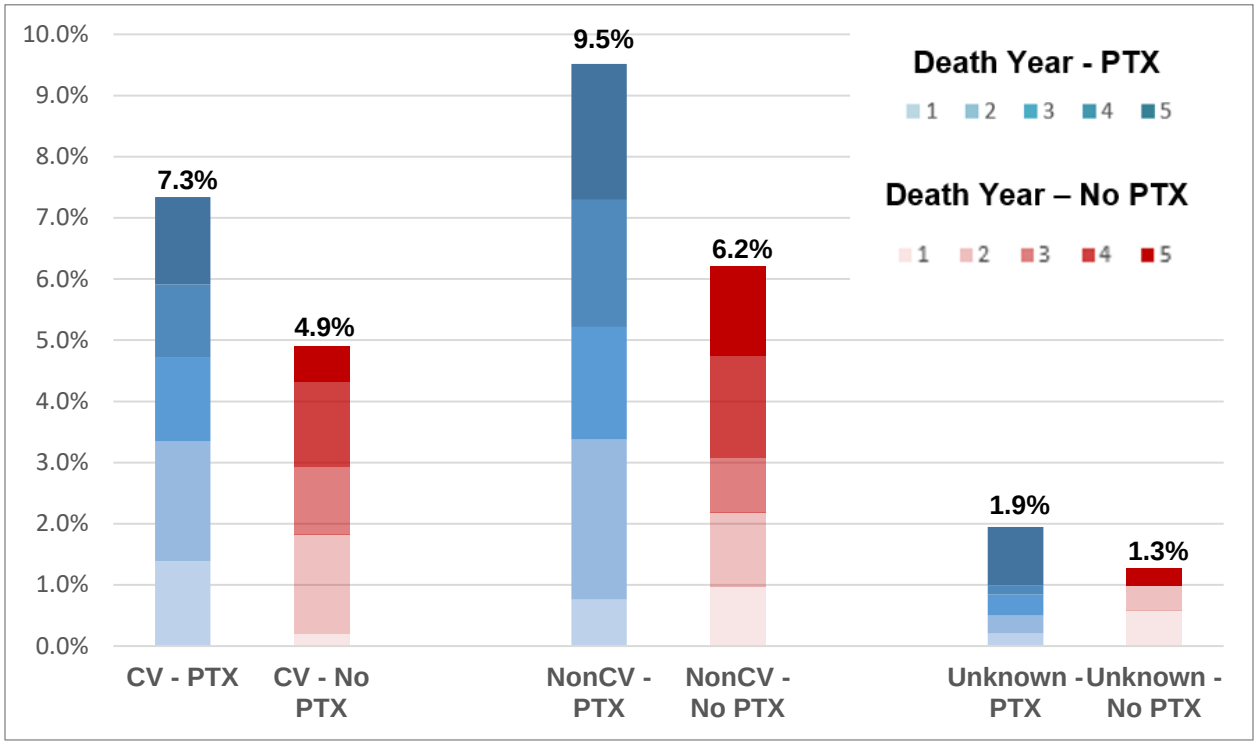
| | | Cook – Zilver PTX DES | | | | LUTONIX 035 DCB | | | | MDT - IN.PACT Admiral DCB | | | | Philips - Stellarex DCB | | | | BSC - Eluvia DES | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ZILVER PTX RCT | | | | LEVANT 2 | | | | IN.PACT SFA I & II | | | | ILLUMENATE | | | | IMPERIAL | | | |
| | **Follow-Up Completed (Years)** | 5 | | | | 5 | | | | 5 | | | | 3 | | | | 2 | | | |
| | **Follow-Up Planned (Years)** | 5 | | | | 5 | | | | 5 | | | | 5 | | | | 5 | | | |
| | **Study Arm** | DES | | PTA/BMS | | DCB | | PTA | | DCB | | PTA | | DCB | | PTA | | DES - E | | DES – Z | |
| | **Other Description** | | | | | | Cardiac arrest/failure (2), cerebrovascular (1) | | | | NA | | ruptured thoracic aortic aneurysm | | cardiopulmonary arrest (1), coronary artery disease (1), | | cardiopulmonary arrest (1), coronary artery disease (1) | | | | |
| CU | **Cardiovascular Unknown** | 1 | 0.4% | 1 | 0.7% | 0 | 0.0% | 0 | 0.0% | 1 | 0.6% | 1 | 1.1% | 1 | 0.6 | 3 | 3.9 | 4 | 1.4% | 2 | 1.4% |
| | **Non-Cardiovascular** | **24** | 10.7% | **6** | 4.5% | **25** | 9.4% | **10** | 7.3% | **19** | **10.7%** | **6** | **6.4%** | **11** | **7.1%** | **4** | **5.2%** | **9** | **3.1%** | **3** | **2.1%** |
| P | **Pulmonary** | 7 | 3.1% | 2 | 1.5% | 3 | 1.1% | 0 | 0.0% | 2 | 1.1% | 0 | 0.0% | 1 | 0.6% | 0 | 0.0% | 2 | 0.7% | 1 | 0.7% |
| R | **Renal** | 0 | 0.0% | 0 | 0.0% | 1 | 0.4% | 1 | 0.7% | 2 | 1.1% | 0 | 0.0% | 1 | 0.6% | 0 | 0.0% | 0 | 0.0% | 1 | 0.7% |
| GI | **Gastrointestinal (Including Pancreatic)** | 1 | 0.4% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 4 | 2.2% | 1 | 1.1% | 1 | 0.6% | 0 | 0.0% | 2 | 0.7% | 0 | 0.0% |
| HB | **Hepatobiliary** | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 0.6% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| I | **Infection/Sepsis (Including Inflammatory)** | 0 | 0.0% | 0 | 0.0% | 2 | 0.8% | 3 | 2.2% | 1 | 0.6% | 1 | 1.1% | 2 | 1.3% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| H | **Hemorrhage** | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 0.3% | 0 | 0.0% |
| NP | **Non-CV procedure** | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| T | **Trauma** | 0 | 0.0% | 1 | 0.7% | 0 | 0.0% | 1 | 0.7% | 0 | 0.0% | 0 | 0.0% | 1 | 0.6% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| S | **Suicide** | 0 | 0.0% | 1 | 0.7% | 1 | 0.4% | 0 | 0.0% | 1 | 0.6% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| N | **Neurological** | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 2 | 1.1% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 0.3% | 0 | 0.0% |
| D | **Drug reaction/overdose** | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| M | **Malignancy** | 15 | 6.7% | 2 | 1.5% | 17 | 6.4% | 5 | 3.6% | 5 | 2.8% | 4 | 4.3% | 5 | 3.2% | 3 | 3.9% | 3 | 1.0% | 1 | 0.7% |

| | | Cook – Zilver PTX DES | | | | LUTONIX 035 DCB | | | | MDT - IN.PACT Admiral DCB | | | | Philips - Stellarex DCB | | | | BSC - Eluvia DES | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ZILVER PTX RCT | | | | LEVANT 2 | | | | IN.PACT SFA I & II | | | | ILLUMENATE | | | | IMPERIAL | | | |
| | **Follow-Up Completed (Years)** | **5** | | | | **5** | | | | **5** | | | | **3** | | | | **2** | | | |
| | **Follow-Up Planned (Years)** | **5** | | | | **5** | | | | **5** | | | | **5** | | | | **5** | | | |
| | **Study Arm** | **DES** | | **PTA/BMS** | | **DCB** | | **PTA** | | **DCB** | | **PTA** | | **DCB** | | **PTA** | | **DES - E** | | **DES – Z** | |
| O | **Other** | 1 | 0.4% | 0 | 0.0% | 1 | 0.4% | 0 | 0.0% | 1 | 0.6% | 0 | 0.0% | 0 | 0.0% | 1 | 1.3% | 0 | 0.0% | 0 | 0.0% |
| NCU | **Non-Cardiovascular Unknown** | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | | | | |
| U | **Unknown (Uncertain whether CV or nonCV death)** | **7** | 3.1% | **3** | 2.2% | **10** | 3.8% | **2** | 1.5% | **0** | **0%** | **0** | **0%** | **0** | **0%** | **0** | **0%** | **0** | **0.0%** | **0** | **0.0%** |

[1]Includes 5 patients who participated as live cases and were randomized in the ZILVER PTX trial

The rates of CV and non-CV deaths from years one to five are shown in **Figure 30** and **Figure 33**. All study treatment groups were combined, and the overall death rates are reported. Because the five RCTs had different maximum follow-up times, rates are stacked by death year to allow for a qualitative comparison of death types over time. The overall combined (and in most cases the yearly) rates of cardiovascular (CV) and non-CV deaths were higher in the paclitaxel-coated device arm versus the non-paclitaxel-coated device arm.

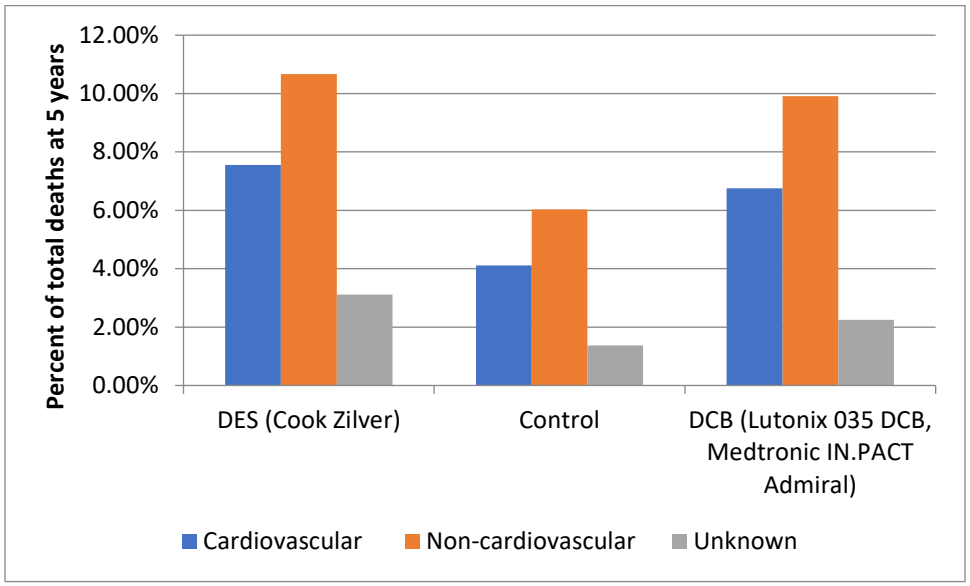
**Figure 30. Combined Mortality Rates for CV versus NonCV Deaths**




1. The paclitaxel (PTX) group includes DES/DCB devices, and the No PTX group includes BMS/PTA devices. Both DES arms of the IMPERIAL Trial are included in the PTX group.

Only RCTs with 5-year data (ZILVER PTX, LEVANT 2 and IN.PACT SFA I & II) were included in **Figure 31**. FDA evaluated whether there were differences in the death types for DES vs. DCB devices compared to controls. Qualitatively, at 5 years, both DES and DCB groups had higher mortality rates compared to PTA.

**Figure 31. Percent of Total CV and Non-CV Deaths through 5 Years for DES, DCB, and Paclitaxel-free Control**




The most common CV death sub-types stratified by treatment group in the pivotal trials is shown **Table 14** and **Figure 32**. The mortality rate for each CV subtype was higher for the combined paclitaxel-coated device group vs. controls for all categories except unknown.

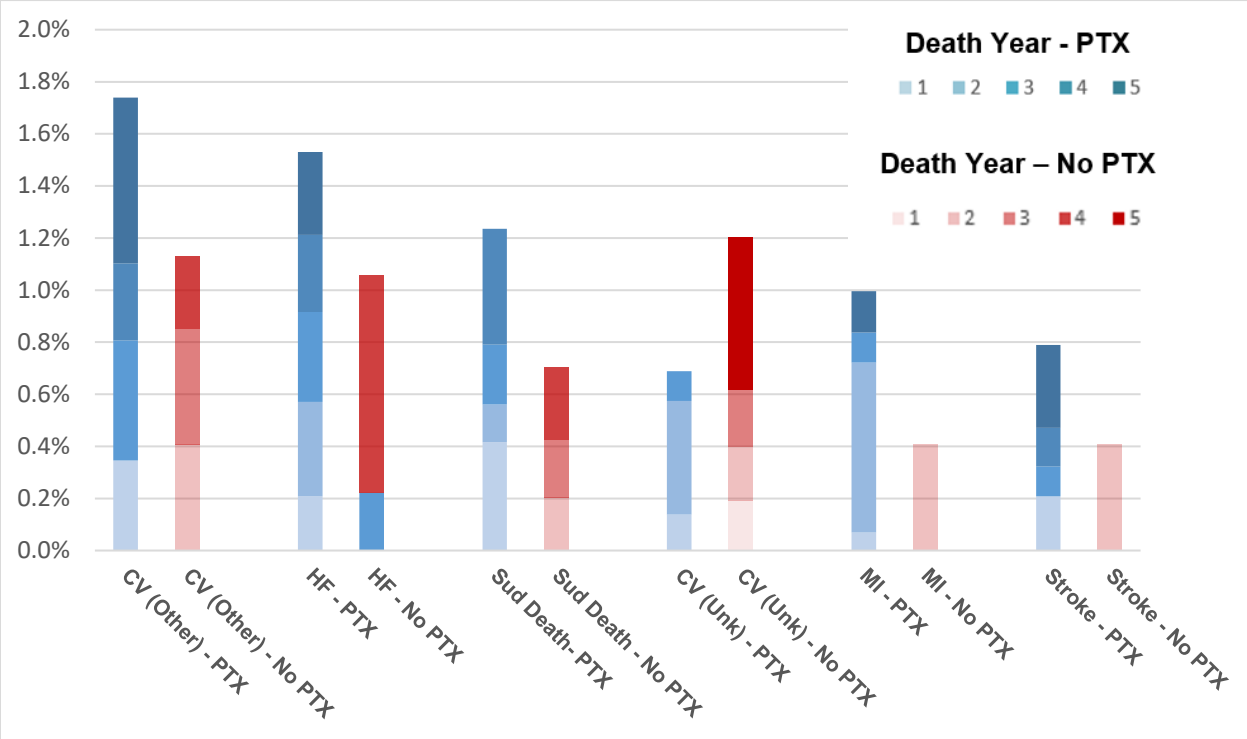
**Table 14. Cardiovascular Death Subtypes (AT Population)**

| Year<br>#Evaluated (PTX/No-PTX) | 1<br>(1444/517) | 2<br>(1378/491) | 3<br>(869/451) | 4<br>(674/360) | 5<br>(629/342) | Cumulative Rate |
|---|---|---|---|---|---|---|
| **CV (Other) - PTX** | 0.3% | | 0.5% | 0.3% | 0.6% | 1.7% |
| **CV (Other) - No PTX** | | 0.4% | 0.4% | 0.3% | | 1.1% |
| **HF - PTX** | 0.2% | 0.4% | 0.3% | 0.3% | 0.3% | 1.5% |
| **HF - No PTX** | | | 0.2% | 0.8% | | 1.1% |
| **Sud Death- PTX** | 0.4% | 0.1% | 0.2% | 0.4% | | 1.2% |
| **Sud Death - No PTX** | | 0.2% | 0.2% | 0.3% | | 0.7% |
| **CV (Unk) - PTX** | 0.1% | 0.4% | 0.1% | | | 0.7% |
| **CV (Unk) - No PTX** | 0.2% | 0.2% | 0.2% | | 0.6% | 1.2% |
| **MI - PTX** | 0.1% | 0.7% | 0.1% | | 0.2% | 1.0% |
| **MI - No PTX** | | 0.4% | | | | 0.4% |
| **Stroke - PTX** | 0.2% | | 0.1% | 0.1% | 0.3% | 0.8% |
| **Stroke - No PTX** | | 0.4% | | | | 0.4% |
| **CV Hem - PTX** | | 0.1% | | | | 0.1% |
| **CV Hem - No PTX** | | | | | | |
| **CV Procedure - PTX** | | 0.1% | | | | 0.1% |
| **CV Procedure - No PTX** | | | | | | |

1. Shaded cells represent 0.0% values.
2. See Table 12 for definitions of cause of death codes.

3. The paclitaxel (PTX) group includes DES/DCB devices, and the No PTX group includes BMS/PTA devices. Both DES arms of the IMPERIAL Trial are included in the PTX group.

**Figure 32. Most Common CV Death Sub-types (AT Population)**




1. The paclitaxel (PTX) group includes DES/DCB devices, and the No PTX group includes BMS/PTA devices. Both DES arms of the IMPERIAL Trial are included in the PTX group.
2. Events with a ≤0.1% cumulative mortality rate are not shown. For the PTX group, there was one death associated with CV hemorrhage and one death associated with a CV procedure, which were excluded from the chart.

Specific sub-types for non-CV death are shown in **Table 15** and **Figure 33**. Cumulative deaths related to malignancies had the largest difference in mortality rates between the paclitaxel-coated device group (5.1%) and the control group (3.2%), and all non-CV subtypes occurred at a higher rate in the combined PTX group compared to the non-PTX group. The only exception was that the death rate due to infection was higher in the control group.

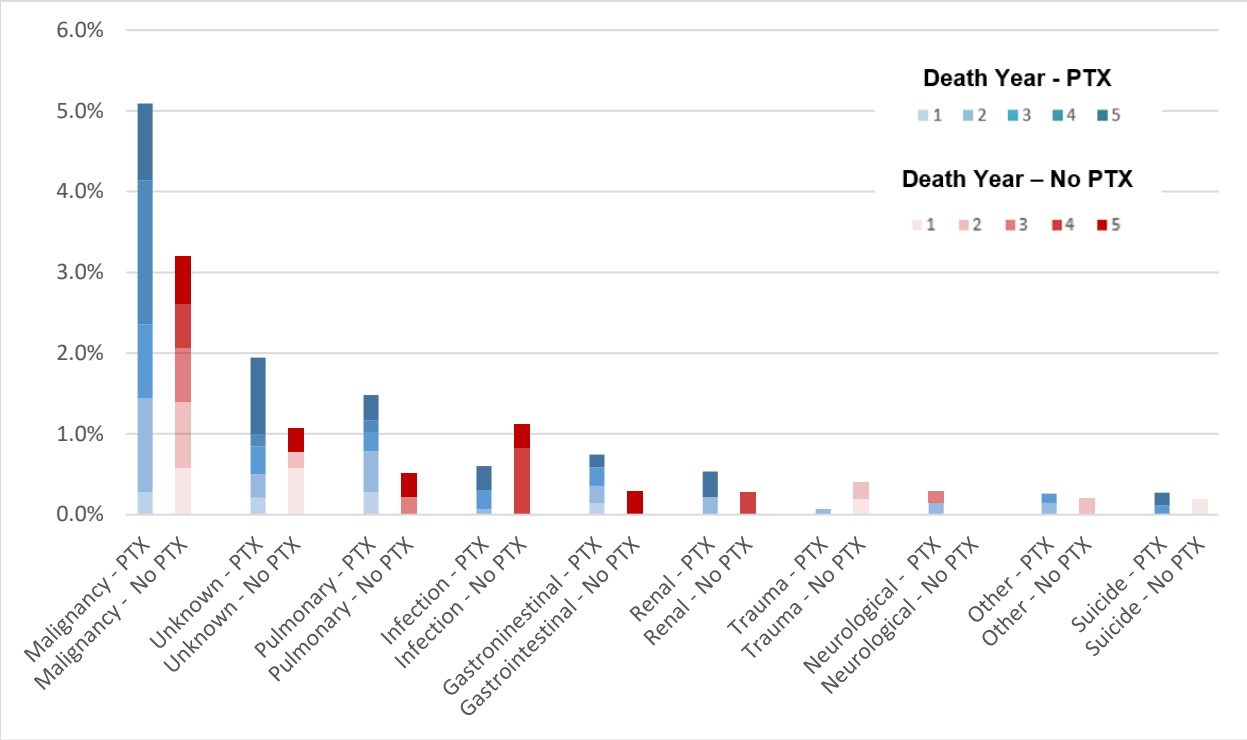
**Table 15. Non-Cardiovascular Death Sub-types (AT Population)**

| Year<br>#Evaluated (PTX/No-PTX) | 1<br>(1444/517) | 2<br>(1378/491) | 3<br>(869/451) | 4<br>(674/360) | 5<br>(629/342) | Cumulative Rate |
|---|---|---|---|---|---|---|
| **Malignancy - PTX** | 0.3% | 1.2% | 0.9% | 1.8% | 1.0% | 5.1% |
| **Malignancy - No PTX** | 0.6% | 0.8% | 0.7% | 0.6% | 0.6% | 3.2% |
| **Unknown - PTX** | 0.2% | 0.3% | 0.3% | 0.1% | 1.0% | 1.9% |
| **Unknown - No PTX** | 0.6% | 0.2% | | | 0.3% | 1.1% |
| **Pulmonary - PTX** | 0.3% | 0.5% | 0.2% | 0.1% | 0.3% | 1.5% |
| **Pulmonary - No PTX** | | | 0.2% | | 0.3% | 0.5% |
| **Infection - PTX** | | 0.1% | 0.2% | | 0.3% | 0.6% |
| **Infection - No PTX** | | | | 0.8% | 0.3% | 1.1% |

| Year<br>#Evaluated (PTX/No-PTX) | 1<br>(1444/517) | 2<br>(1378/491) | 3<br>(869/451) | 4<br>(674/360) | 5<br>(629/342) | Cumulative Rate |
|---|---|---|---|---|---|---|
| **Gastrointestinal - PTX** | 0.1% | 0.2% | 0.2% | | 0.2% | 0.7% |
| **Gastrointestinal - No PTX** | | | | | 0.3% | 0.3% |
| **Renal - PTX** | | 0.2% | | | 0.3% | 0.5% |
| **Renal - No PTX** | | | | 0.3% | | 0.3% |
| **Trauma - PTX** | | 0.1% | | | | 0.1% |
| **Trauma - No PTX** | 0.2% | 0.2% | | | | 0.4% |
| **Neurological - PTX** | | 0.1% | | 0.1% | | 0.3% |
| **Neurological - No PTX** | | | | | | |
| **Other - PTX** | | 0.1% | 0.1% | | | 0.3% |
| **Other - No PTX** | | 0.2% | | | | 0.2% |
| **Suicide - PTX** | | | 0.1% | | 0.2% | 0.3% |
| **Suicide - No PTX** | 0.2% | | | | | 0.2% |
| **Hem - PTX** | | 0.1% | | | | 0.1% |
| **Hem - No PTX** | | | | | | |
| **Drug Reaction/OD - PTX** | | | | 0.1% | | 0.1% |
| **Drug Reaction/OD - No PTX** | | | | | | |
| **HepatoBil - PTX** | 0.1% | | | | | 0.1% |
| **HepatoBil - No PTX** | | | | | | |
| **NonCV Proc - PTX** | | | | | | |
| **NonCV Proc - No PTX** | | | | | | |
| **NonCV (Unknown) - PTX** | | | | | | |
| **NonCV (Unknown) - No PTX** | | | | | | |

1. Shaded cells represent 0.0% values.
2. See Table 12 for definitions of cause of death codes.
3. The paclitaxel (PTX) group includes DES/DCB devices, and the No PTX group includes BMS/PTA devices. Both DES arms of the IMPERIAL Trial are included in the PTX group.

**Figure 33. Most Common Non-CV Death Sub-types (AT Population)**




1. The paclitaxel (PTX) group includes DES/DCB devices, and the No PTX group includes BMS/PTA devices. Both DES arms of the IMPERIAL Trial are included in the PTX group.
2. Events with a ≤0.1% cumulative mortality rate are not shown. For the PTX group, there was one death associated with CV hemorrhage and one death associated with a CV procedure, which were excluded from the chart. There was one death associated with Non-CV hemorrhage, one death associated with drug reaction/OD, one death associated with hepatobiliary causes, and no deaths related to non-CV procedures or unknown non-CV causes.

Given the frequency of malignancy-related deaths and pulmonary-related deaths, specific sub-types were also assessed (**Figure 34** and **Figure 35)**. Note that the results reflect sponsor-reported definitions, which are not uniform across trials and therefore limit interpretation. For example, for pulmonary deaths, sub-categories such as “respiratory insufficiency,” “respiratory failure,” and “pulmonary disease” may or may not reflect the same disease process.

**Figure 34. Malignancy Death Sub-Type as a Percentage of Total Deaths in Group (AT Population)**

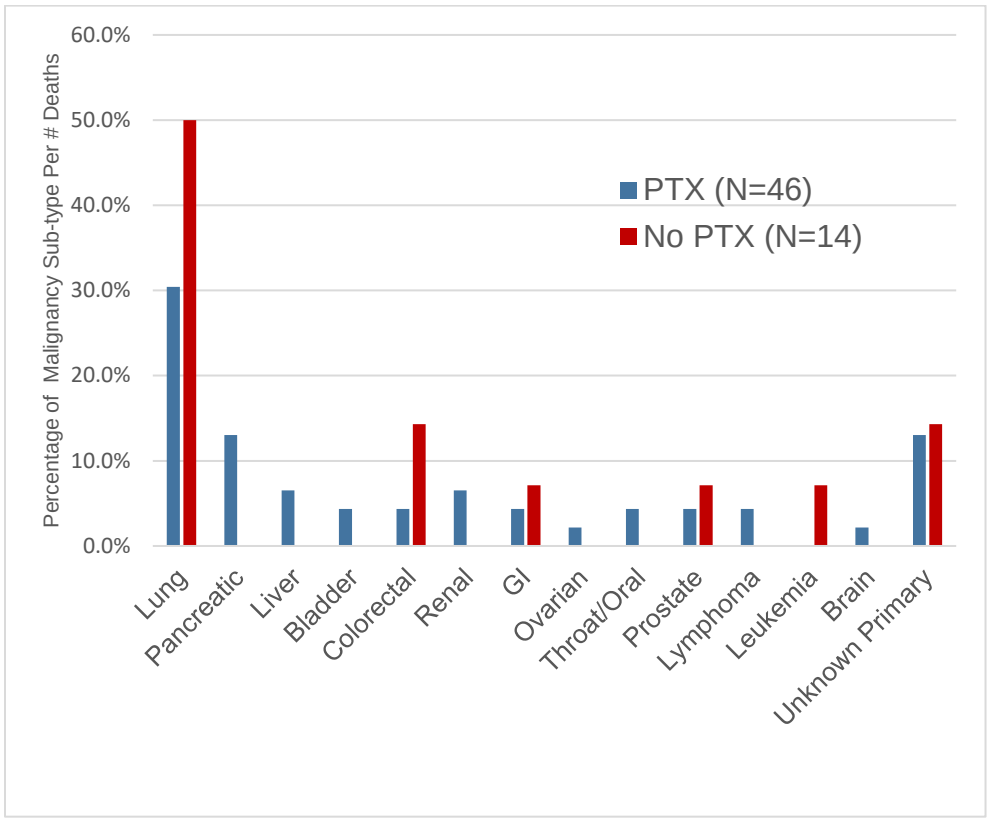
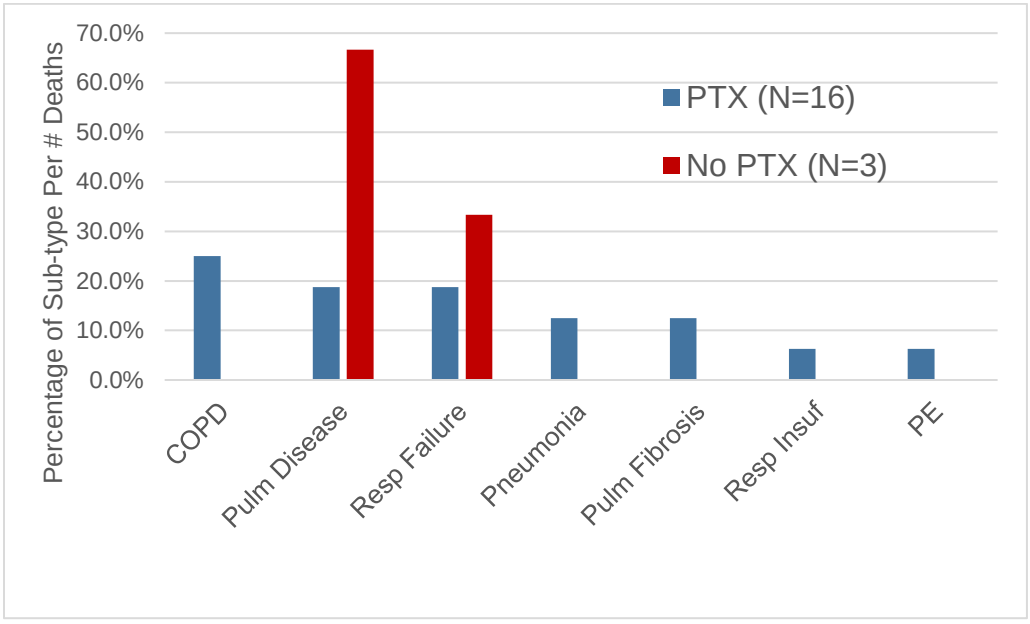



**Figure 35. Pulmonary Death Sub-Type as a Percentage of Total Deaths in Group (AT Population)**



The leading causes of CV death were "other" and heart failure, and the leading causes of non-CV death were malignancies, unknown, and pulmonary deaths (with the subtypes of lung cancer and chronic obstructive pulmonary disease being the most common). Overall, patients treated with paclitaxel-coated devices had higher rates of all death types vs. patients treated with uncoated devices (except for infection-related deaths, which trended higher in the control group). However, there is no clear signal that treatment with paclitaxel-coated devices was associated with an excess rate of a *specific CV or non-CV death sub-type*. It should be noted that a substantial portion of CV deaths and non-CV deaths were categorized as "other" or "unknown," respectively, which limits the interpretation of these data.

### 5.1.1 *Baseline Mortality/Survival Comparisons*

Baseline comparisons were conducted between patients that died and patients remaining alive at the end of available follow-up period for the pivotal trials based on the AT populations (5 years for ZILVER PTX RCT, LEVANT 2 RCT, and IN.PACT SFA I & II; and 3 years for ILLUMENATE RCT). In general, continuous variables are presented as Mean ± SD and were compared using Wilcoxon rank sum test. Categorical variables are presented as %(n/N) and were compared using an Exact test. The identified differences in baseline characteristics in each of the four pivotal studies with a p-value <0.10 are listed in **Table 16** with full results shown **Appendix J**.

**Table 16. Baseline Variable Comparisons Between Patients (Mortality vs Survival)**

| | **Dead** | **Alive** | **p-value** |
|---|---|---|---|
| **ZILVER PTX RCT** | N=64 | N=232 | |
| Age (years) | 71.8 ± 10.1 | 67.1 ± 9.1 | 0.0019 |
| Total Target Lesion Length (mm) | 67.0 ± 52.3 | 53.5 ± 40.1 | 0.0459 |
| Region (% US) | 85.9% (55/64) | 70.7% (164/232) | 0.0153 |
| Diabetes Mellitus | 56.3% (36/64) | 39.7% (92/232) | 0.0223 |
| History of Heart Failure | 20.3% (13/64) | 9.9% (23/232) | 0.0310 |
| Hyperlipidemia | 79.7% (51/64) | 67.7% (157/232) | 0.0656 |
| Rutherford Category above 3 | 15.6% (10/64) | 7.4% (17/231) | 0.0513 |
| | | | |
| **LEVANT 2** | N=71 | N=332 | |
| Total Target Lesion Length (mm) | 70.1 ± 38.7 | 61.3 ± 41.4 | 0.0359 |
| Smoking | | | 0.0547 |
| Active | 28.2% (20/71) | 35.2% (117/332) | |
| Previous | 60.6% (43/71) | 45.2% (150/332) | |
| Never | 11.3% (8/71) | 19.6% (65/332) | |
| Renal Insufficiency (% Baseline Serum creatinine ≥ 1.5 ng/dl | 14.1% (10/71) | 3.8% (12/312) | 0.0026 |
| History of CABG | 22.5% (16/71) | 13.3% (44/332) | 0.0644 |
| Statins | 66.2% (47/71) | 80.4% (267/332) | 0.0116 |
| | | | |
| **IN.PACT SFA I & II** | N=39 | N=233 | |
| Renal Insufficiency (% Baseline Serum creatinine ≥ 1.5 ng/dl) | 17.9% (7/39) | 6.6% (15/229) | 0.0259 |
| | | | |

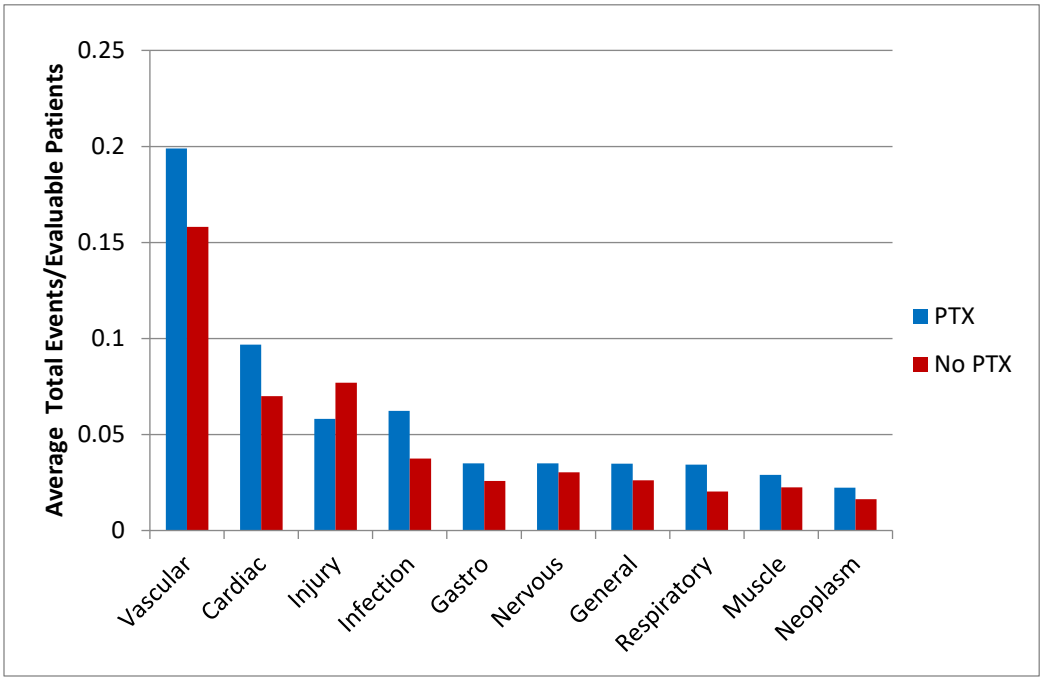
| | Dead | Alive | p-value |
|---|---|---|---|
| **ILLUMENATE RCT** | N=27 | N=206 | |
| Age (years) | 72.8 ± 7.9 | 68.4 ± 9.8 | 0.0221 |

In general, patients who died were older, had more co-morbidities, had longer lesions, and less frequently used statins vs. surviving patients. However, there was no consistent pattern of specific baseline characteristics that could be used to identify patients who may be at a particularly increased risk of mortality following treatment with a paclitaxel-coated device.

## 5.2 *Adverse Events Analyses*

To further investigate possible causes or trends in mortality, FDA analyzed adverse event (AE) data for the five pivotal RCTs. Adverse events were classified into 27 different categories (see Appendix H.1). The sum of adverse events for each classification was reported over the sum of evaluable patients for the completed follow-up of each pivotal RCT. These ratios were stratified by treatment group for each study to look for trends in the types of AEs reported (AppendixH.2). Unfortunately, AE reporting (both frequency and classification) was not consistent across trials. Some trials reported only approximately 200 AEs in 5 years, while other similarly sized trials with similar enrollment criteria reported >1000 AEs for the identical time period. Additionally, some AE definitions (e.g., procedural complications) were subject to judgement, and interpretation may not have been uniform across trials. These inconsistencies made it challenging to compare AEs across studies (Appendix H). The data were also averaged for PTX (DCB and DES) and No PTX (BMS and PTA) devices. These results suggest a higher percentage of patients treated with paclitaxel-coated device group had AEs in almost all categories except injury. **Figure 36** shows the average ratio for the most common AEs for paclitaxel-coated devices vs. uncoated devices for the maximum follow-up period for the five pivotal RCTs.

**Figure 36. Ratio of the Most Frequently Reported AEs**




1. The paclitaxel (PTX) group includes DES/DCB devices, and the No PTX group includes BMS/PTA devices. Both DES arms of the IMPERIAL Trial are included in the PTX group

Because the mortality signal was identified for timepoints beyond two years following the index procedure, adverse events were also separated into year one (Appendix H.3.1) and year two through five (Appendix H.3.2). The trends were similar to those noted in Figure 26, with paclitaxel-coated devices demonstrating a greater average ratio of all events except for "injury." The only noted difference was that control devices reported slightly more vascular adverse events in the first year compared to paclitaxel-coated devices. Overall, the incidence of AEs was consistent with the trends observed for the death-subtypes described above; patients treated with paclitaxel-coated devices reported higher numbers of adverse events across the majority of classifications. There was no evidence of specific adverse events at any timepoint that may suggest a mechanism for late term mortality. It is important to note that there are inconsistencies in the reporting of adverse events that limit the conclusions that can be drawn from these data.

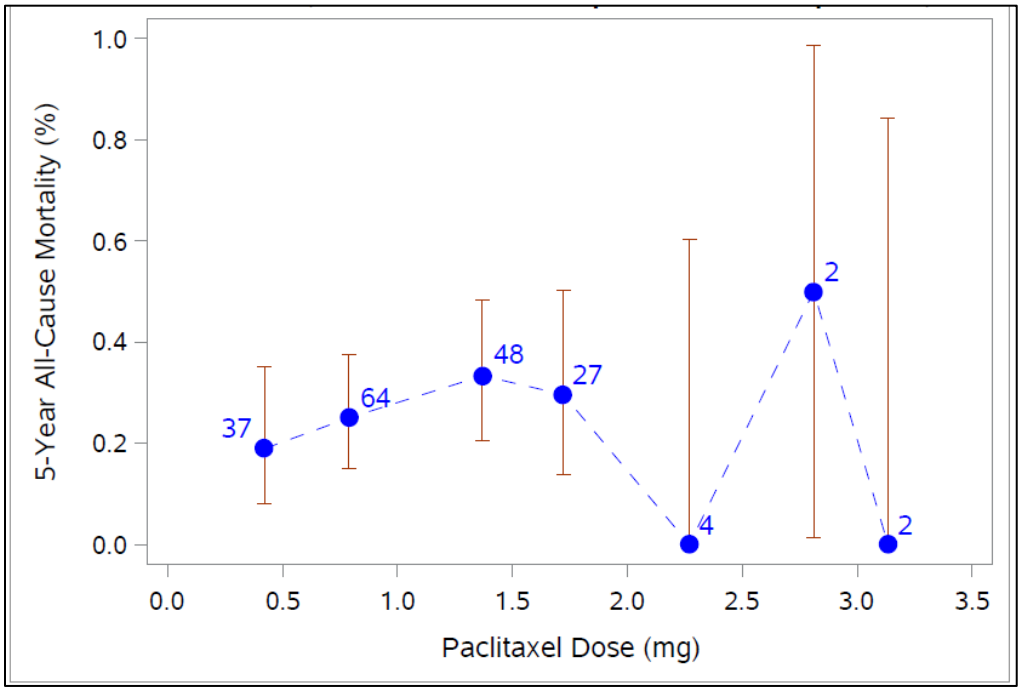
## 5.3 *Paclitaxel Dosage*

An evaluation of the association between paclitaxel dose and all-cause mortality for each pivotal trial was conducted based on the AT population of patients treated with paclitaxel-coated devices. Patients with known 5-year mortality status were separated into dose groups based on the total paclitaxel dose received. The 5-year mortality rate vs. mean dose for each dose group was plotted for each trial with the corresponding 95% confidence interval and the number of patients included. For the ILLUMENATE RCT, the dose analyses were based on patients with known 3-year mortality status.

To further assess the potential effect of paclitaxel dose on survival time, a univariate Cox proportional hazard (PH) model for all-cause mortality was conducted with dose as the only exploratory variable.

*Cook ZILVER PTX RCT*. Patients treated in the Zilver PTX DES group received a mean total paclitaxel dose during the index procedure of 1.1 ± 0.5 mg (range of 0.3-3.2 mg). In **Figure 37**, the scatter plot shows no evident trend between the dose and 5-year mortality. The lack of an association is supported by the univariate Cox PH model analysis (p-value for Dose = 0.5155).

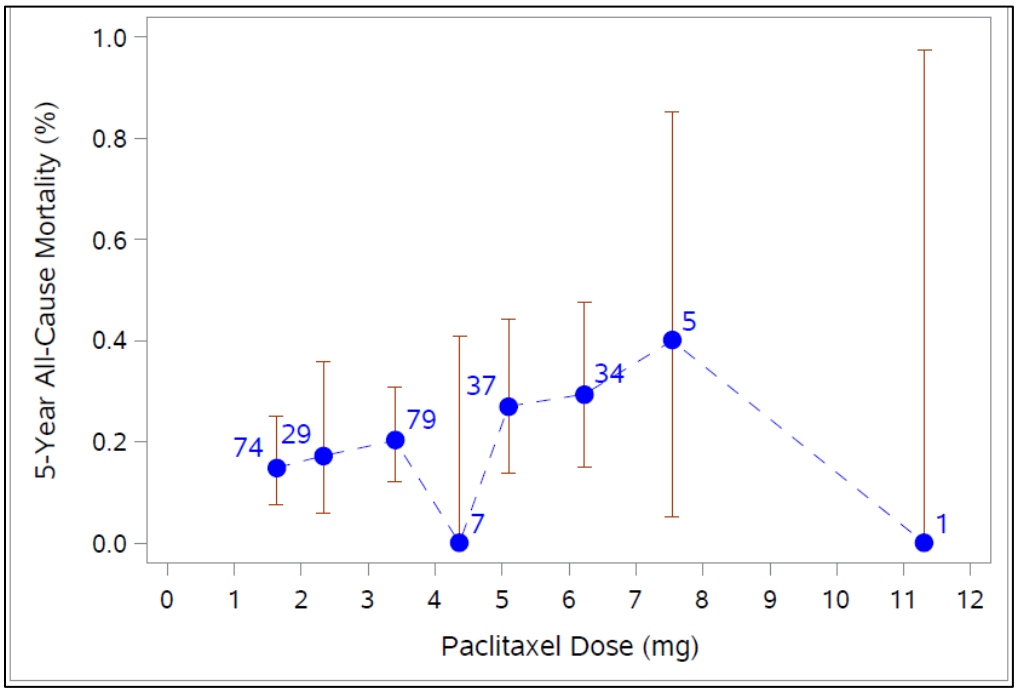
**Figure 37. Five-Year All-Cause Mortality Rate for Paclitaxel Dose Groups: ZILVER PTX RCT (AT Population)**




*Patients were separated into 7 dose groups based on the following dose range cutoffs (in mg): [0.3, 0.5), [0.5, 1.0), [1.0, 1.5), [1.5, 2.0), [2.0, 2.5), [2.5, 3.0), and [3.0, 3.5]. Numbers in blue indicate the number of patients included in the specific dose group. The red line indicates the 95% confidence intervals for the group mortality rate.

*LUTONIX LEVANT 2 RCT*. Patients treated in the Lutonix 035 DCB group received a mean total paclitaxel dose during the index procedure of 3.5 ± 1.8 mg (range 1.0-11.3 mg). In **Figure 38**, the scatter plot suggests a trend of increased 5-year mortality as a function of increased paclitaxel dose, but there is overlap in the 95% CIs. The possible association between the dose and survival time is supported by the univariate Cox PH model (p-value = 0.0382).

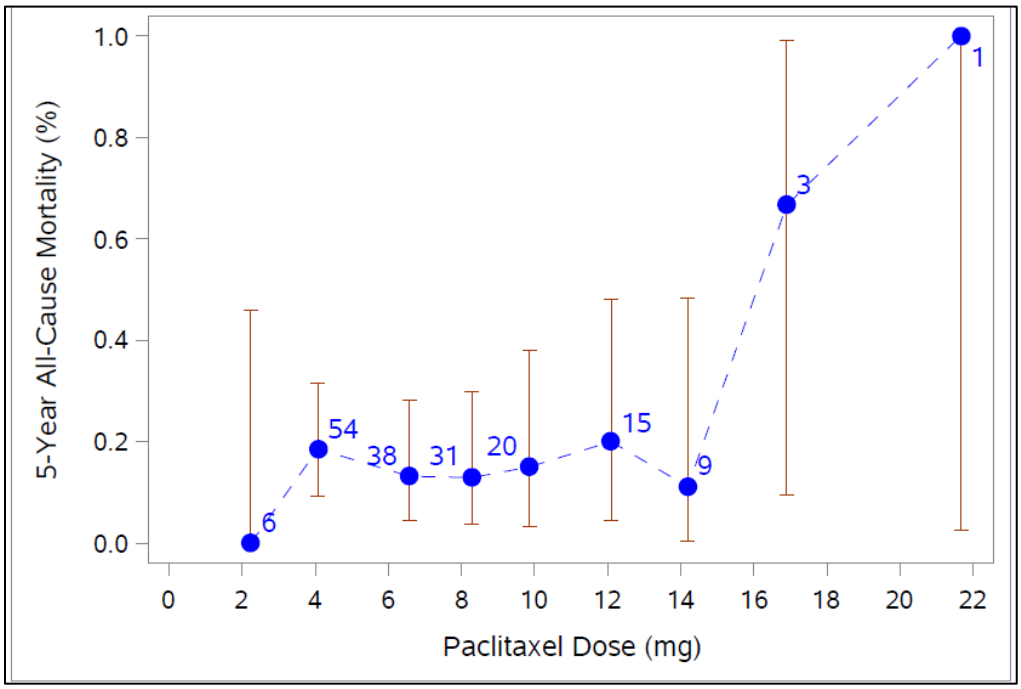
**Figure 38. Five-Year All-Cause Mortality Rate for Paclitaxel Dose: LEVANT 2 RCT (AT Population)**




*Patients were separated into 8 dose groups based on the following dose range cutoffs (in mg): [1.0, 2.0), [2.0, 3.0), …, [11.0, 12.0]. Numbers in blue indicate the number of patients included in the specific dose group. The red line indicates the 95% confidence intervals for the group mortality rate.

IN.PACT SFA I & II RCT. Patients treated in the IN.PACT Admiral DCB group received a mean total paclitaxel dose during the index procedure of 7.5 ± 3.7 mg (range 1.9-21.7 mg). In **Figure 39**, the scatter plot suggests no clear trend of the 5-year all-cause mortality by dose (p-value = 0.0869 based on the univariate Cox PH model).

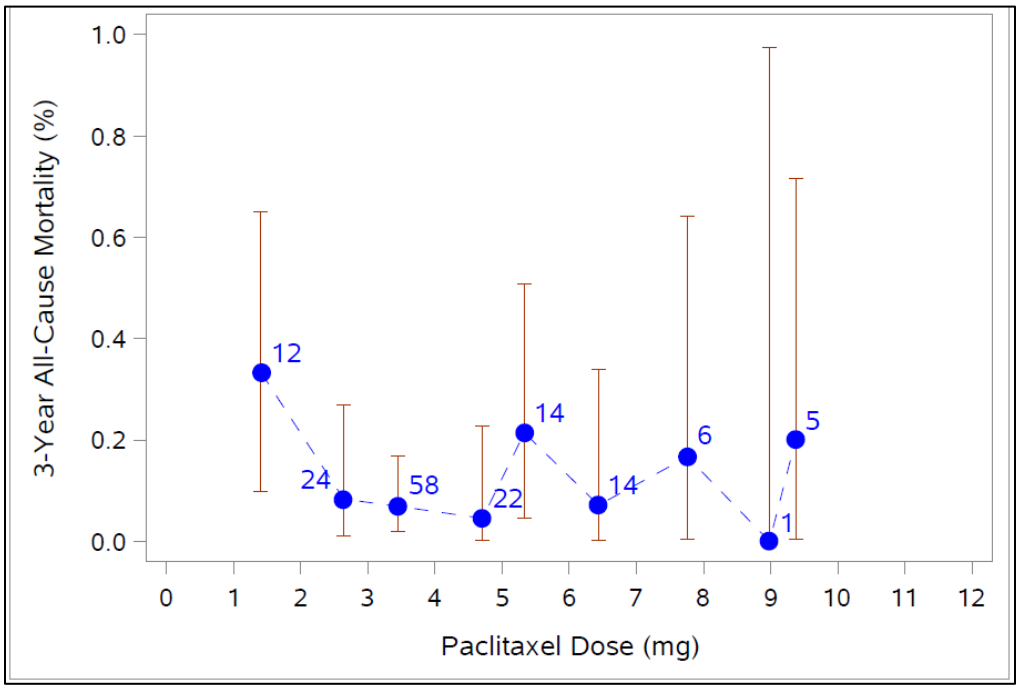
**Figure 39. Five-Year All-Cause Mortality Rate for Paclitaxel Dose: IN.PACT SFA I & II (AT Population)**




*Patients were separated into 9 dose groups based on the following dose range cutoffs (in mg): [1, 3), [3, 5), [5, 7), …, [21, 23]. Numbers in blue indicate the number of patients included in the specific dose group. The red line indicates the 95% confidence intervals for the group mortality rate.

*Philips ILLUMENATE RCT*. Patients treated in the Stellarex DCB group received a mean total paclitaxel dose during the index procedure of 4.2 ± 1.8 mg (range 1.3-9.4 mg). In **Figure 40**, the scatter plot shows no evident trend between paclitaxel dose and 3-year mortality. The p-value of the univariate Cox PH model is 0.8013.

**Figure 40. Three-Year All-Cause Mortality Rate for Paclitaxel Dose: ILLUMENATE RCT (AT Population)**




*Patients were separated into 9 dose groups based on the following dose range cutoffs (in mg): [1, 2), [2, 3), [3, 4), …, [9, 10]. Numbers in blue indicate the number of patients included in the specific dose group. The red line indicates the 95% confidence intervals for the group mortality rate.

There was no consistent association between dose and mortality detected across studies. The LEVANT 2 RCT suggested possible increased mortality with increased dose, while no clear relationship between dose and mortality was identified in ZILVER PTX RCT, IN.PACT SFA I & II, and ILLUMENATE RCT. The sample size was small for many of the dose range groups, which limited the interpretation of the data in some cases.

## 5.4 *Pre-clinical Safety and Pharmacology/Toxicology Evaluations*

Data from all pre-clinical safety, safety margin, and pharmacokinetic (PK) animal studies were evaluated in FDA's review of the initial marketing applications for each of the five FDA-approved devices. As part of FDA's evaluation of the late mortality signal observed in the clinical trials, a CDRH veterinary pathologist and a CDER pharmacologist/toxicologist reevaluated these pre-clinical studies, focused on potential biological mechanisms for the late mortality observed in clinical trial patients.

### 5.4.1 *Large Animal Safety Studies*

Across all applications, there were 23 separate vascular safety studies conducted between 2004 and 2018 at various animal study facilities. A total of 566 animals were exposed to the test and/or control devices (either uncoated PTA catheter balloons or bare metal stents). All studies were conducted in either non-diseased domestic crossbred or Yucatan mini-swine. Study designs

differed (e.g., presence or absence of a control article; control and test articles in the same animal). Each device was tested at both nominal and safety margin (generally 3-4X) paclitaxel doses in the healthy iliofemoral arteries of the animals. For each device, an average of 6 to 10 animals were exposed to the test and control devices for varying lengths of time post-implantation, generally 1-7 days, 30 days, 90 days, and 180 days prior to sacrifice. One study also included a 210-day cohort. Study endpoints included acute device delivery and handling, general animal health and in life clinical observations, comprehensive gross pathological evaluation, downstream and major systemic organ histopathological evaluation, and target tissue histomorphologic and histomorphometric analysis. As the sample size of large animal safety studies are traditionally small by design, statistical analyses were not performed other than in conjunction with target tissue arterial semi-quantitative or histomorphometric analysis.

Regarding animal health and in life clinical observations through 180 days, the results were similar across all paclitaxel DCB and DES studies, with extremely low animal mortality and relatively low morbidity rates. There was no unexpected device-related animal mortality and only one death attributed to a procedural complication at the vascular access site. Overall, there was no overt evidence of potential device-related safety concerns in any study animal.

Clinical pathology assessment for all study animals included hematology with differential, clinical chemistry, and coagulation assessments at baseline and sacrifice, or less often, at intervals throughout the study. The most commonly observed abnormalities across almost all studies included hyperglycemia and elevated creatine phosphokinase values. These findings are frequently noted in large animal vascular safety studies and are typically attributed to stress and/or procedural handling. Many animals exhibited a transient leukocytosis 1-2 weeks following the procedure (if interim blood work was performed), which typically resolved. There was no evidence of device-related bone marrow suppression or hepatic or renal toxicity.

A systemic necropsy was performed on all test animals which included gross examination of target tissues, downstream musculoskeletal structures, all major organs, and body cavities (generally excluding the cranial vault, brain and spinal cord). There were no reports of extensive gross vessel trauma such as hemorrhage, perforation, dissection or thrombus at treatment sites in either the drug coated balloon or peripheral stent studies. In addition, there were no descriptions of gross downstream thromboemboli or thromboembolic lesions associated with tissue ischemia, such as skeletal muscle swelling, edema, discoloration, or atrophy. The most commonly reported pathologic findings were renal cysts and gastric mucosal erosions, which are commonly seen in commercially raised swine. There were no reports of malignancy or unusual gross findings in any of the reviewed animal studies.

Gross and histopathological pulmonary findings were relatively common across all studies, in both test and control groups, and at all survival timepoints. Gross findings included multifocal parenchymal discoloration, firmness, and pleural adhesions. Pulmonary nodules or gross evidence of pneumonia or bronchopneumonia were uncommon and were found in approximately 25 animals in total. Pulmonary histology in all studies showed minimal to moderate multifocal

atelectasis, congestion, interstitial or peribronchial chronic inflammation, and/or focal areas of fibrosis. These microscopic changes are often related to endotracheal intubation, anesthesia, and stress in swine used in biomedical research studies. More significant but less common microscopic findings were consistent with acute necrotizing abscesses or organizing bronchopneumonia with bacterial colonization, but these findings did not appear to be treatment-specific. There was no crystalline foreign material consistent with drug and or excipient reported in any pulmonary section examined in any study.

Histopathology of target iliofemoral arterial tissues was performed for all study animals. There were no reports of loss of patency due to thrombosis, or findings of aneurysmal dilation due to arterial wall attenuation. The most common finding associated with target arteries treated with paclitaxel versus controls was (as expected) medial smooth muscle loss with replacement proteoglycan and collagen deposition; this finding was more pronounced in safety margin treated arteries, and more severe at early versus later timepoints. Delayed arterial healing, characterized by fibrin deposition and mild inflammation, was also present to a greater degree in arteries treated with safety margin paclitaxel doses and at earlier timepoints, generally resolving by 180-days. Luminal fibrin deposition was also frequently noted at the acute or subacute timepoints, sometimes with embedded crystalline material consistent with drug material but was very rarely present at 90 days. Luminal endothelialization was typically incomplete at acute timepoints but was generally complete in both the DCB and DES device studies by 30 to 90 days. Overall, there were no reported histopathological findings in any of the paclitaxel-treated arteries that would be expected to increase animal mortality or morbidity risks.

Histopathology of musculoskeletal structures in the runoff region of the treated iliofemoral arteries were examined in almost all studies, and generally included the gluteal, gastrocnemius, semimembranosus, and semitendinosus muscle groups. Coronary beds, bone marrow and regional lymph nodes were less frequently examined. Reported microscopic vascular changes associated with paclitaxel effect included intramuscular small artery-fibrinoid necrosis with small muscle cell loss, focal vasculitis, and rarely, the presence of embedded crystalline drug material. These findings were generally most prominent in the gastrocnemius muscles. When examined, similar vascular changes were also rarely noted in the bone marrow with crystalline drug material possibly present in one animal. These changes were generally more severe in the safety margin animals at early timepoints and varied in intensity among the DCB device studies. Comparison of these findings among devices was difficult as the method of tissue sampling and microscopic quantification was not standardized across studies. However, no regionally extensive areas of muscle necrosis or infarct were detected in any study, and there were no in-life clinical symptoms observed in any of the studies. Downstream findings associated with drug or particulate effects were reported only in the DCB studies and were generally absent in the DES studies.

A histopathological examination of systemic organs, including lung, liver and kidney, was performed in most studies. In addition to the pulmonary findings noted above, kidney and liver sections frequently exhibited occasional mild chronic inflammatory changes and congestion, which is considered within normal limits for the species. The bone marrow, when examined, did

not demonstrate suppression of any cell line at any drug dosage or at any timepoint. Generally, there were no systemic pathologic changes which appeared to be device or drug-related or indicative of systemic toxicity.

Overall, animal mortality and morbidity were low across all studies to 210 days post-exposure, and there was no distinct pattern or data trends suggestive a potential mechanism for increased late mortality observed in human study subjects. Longer term preclinical safety studies may be considered to further investigate the mortality signal.

### 5.4.2 *Pre-clinical Pharmacokinetic and Toxicity Analysis*

In the healthy pig studies, the initial drug concentration in the target artery was relatively high. However, drug deposition did not appear to be associated with necrosis, thrombosis, aneurysm, neutropenia, or other evidence of severe toxicity. The adverse effects noted were mostly local, characterized by vascular smooth muscle cell loss, medial hypocellularity, inward remodeling, and delayed vascular healing.

Paclitaxel detected in the tissues and organs for several months is in a solid formulation, which is not available for intracellular uptake. The deposited drug is sequestered within the extracellular matrix, which gradually undergoes dissolution to release unbound active drug. The free drug partitions between tissues and plasma compartments, where it is subsequently cleared. Despite the differences in drug load and type of excipient, the drug effect at the local vascular site was generally similar between studies and devices. For some DCB, only a fraction of the load drug (15%) was transferred into the target vessel wall, and as much as 70% may be lost into the systemic circulation. In addition, paclitaxel's plasma half-life is short, with clearance typically around 24 hours.

Paclitaxel was detected in the organs of elimination, including the lung, liver and kidney, but the concentrations were generally low. In one study, the peak concentration was within the cytostatic potency of paclitaxel in the lungs.

It should be noted that the preclinical studies were not designed to address the cellular effects of paclitaxel retained in non-target organs for a prolonged duration. In addition, the young and healthy pig arterial model is different from human atherosclerotic arteries, which contain resident chronic inflammatory cells (particularly monocytes/macrophages) which produce inflammatory mediators such as cytokines and chemokines. Evidence gaps remain regarding potential concentration-dependent cellular effects (proinflammatory or pro-oncogenic) of residual paclitaxel retained in tissues (see Section 2.3.4).

## 6. Benefit-Risk Determination

FDA considers both the benefits and risks of a given therapy in its regulatory decision-making. Factors that are considered include: the extent of the probable benefits and risks, including the type, magnitude/severity, probability, and duration; the uncertainty associated with these factors;

whether alternative treatments exist; patient perspectives on benefits and risks; and the public health need. Benefit-risk assessments early during device development can help to guide selection of the intended patient population and clinical trial design.

FDA's original approval of these devices was based on the available data, which consisted of one-year follow-up (the time of primary endpoint assessment) supplemented with some longer-term data. FDA determined that the probable benefits outweighed the probable risks of these devices. However, because of the current potential late mortality signal, it is necessary to re-evaluate the benefit-risk profile of this device class. The late mortality signal has been discussed above in this Executive Summary. To help in the re-assessment of benefit-risk, FDA examined the benefits of these devices (i.e., a decreased rate of clinically-driven target lesion revascularization). Risk ratios for repeat revascularization were estimated at each year. In Question 8, the Panel will be asked to discuss the current benefit-risk profile of paclitaxel-coated DCB and DES.

## 6.1 *Benefit-Risk of Clinically-Driven Target Lesion Revascularization (CDTLR)*

Relative risk (RR) forest plots and the meta-analysis results for clinically-driven TLR (CDTLR) based on the AT and ITT populations at each time point are provided in Appendix F. The same meta-analytic techniques described in Section 4.2.5 were used for the CDTLR analysis. In this section, the results for 1, 2 and 5-year CDTLR based on the AT population are shown in **Figure 41-Figure 43**.

**Figure 41. Meta-analysis for CDTLR for Pivotal RCTs based on 1-year Data (AT population)**

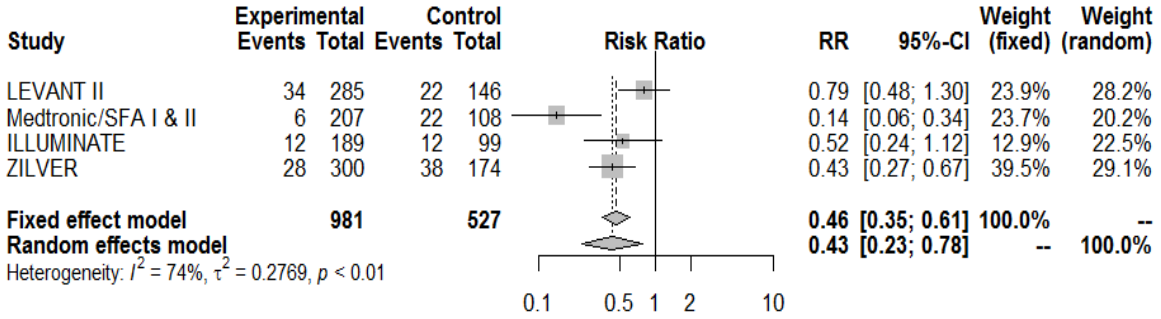


**Figure 42. Meta-analysis for CDTLR for Pivotal RCTs based on 2-year Data (AT population)**

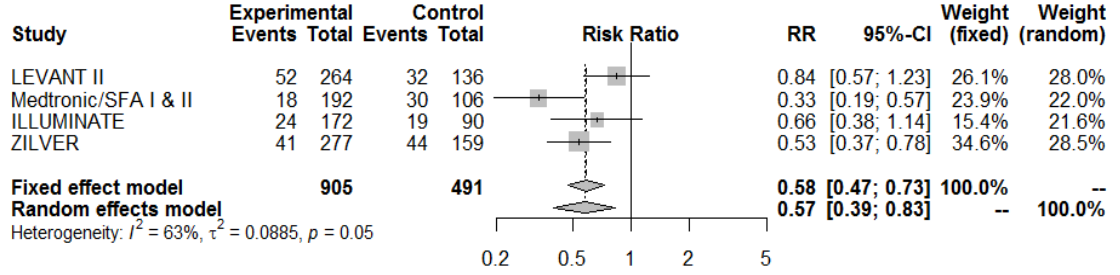
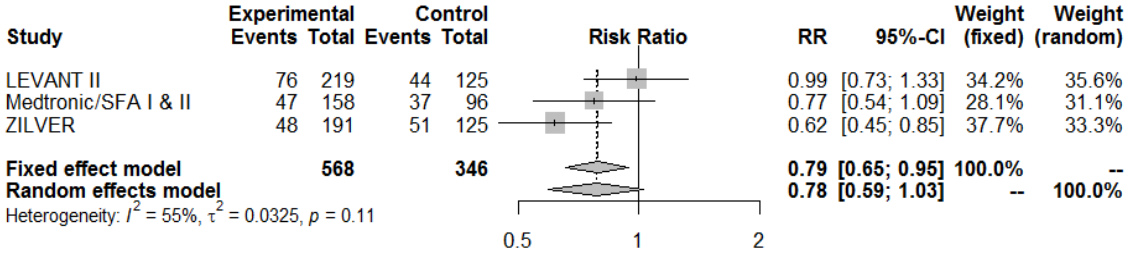



**Figure 43. Meta-analysis for CDTLR for Pivotal RCTs based on 5-year Data (AT population)**




The RR of CDTLR varies among the RCTs for each time point. However, the RR values are always <1 favoring the paclitaxel-coated device group compared to non-coated device group. The RR point estimate at year 1, 2 and 5 based on the fixed effects model are similar to the random effects model, although the 95% confidence intervals for RR based on the random effects model are wider.

The RR point estimates suggest that the risk of CDTLR for patients treated with paclitaxel-coated devices is less than treatment with uncoated devices group. Up to two years, the risk of CDTLR appears to be significantly less for the paclitaxel device group compared to the control group. However, at 5 years, the CDTLR treatment effect for paclitaxel-coated devices appears less evident. At 5 years, the RR is approximately 0.8 (i.e., an approximate 20% decreased risk of CDTLR in patients treated with paclitaxel-coated devices. Note that the associated 95% CI based on the random effects model crosses 1.

# 7. Limitations of Currently Available Data

As noted above, there are limitations to the currently available data and FDA analyses. These limitations include missing data at the longer-term follow-up time points, missing data regarding potentially important covariates (e.g., concomitant medications, repeat procedures with paclitaxel-coated devices), limited clinical information to support the adjudication process focused on potential paclitaxel effects, and limitations in the amount of data and statistical methods utilized for the analyses. In addition, if industry efforts to collect missing data are successful, further analyses of the late mortality signal may be useful. The Panel will be asked to comment on the impact of these limitations in their overall conclusions and recommendations for future studies and device labeling.

## 7.1 *Sample Size and Availability of Long-Term Data*

There are currently five approved paclitaxel-coated devices to treat stenosis in the femoropopliteal arteries available in the US. Additional devices are approved OUS, but FDA lacks access to patient-level data for these products. For the US-approved devices, modest-sized pivotal RCTs were conducted, typically enrolling approximately 300-500 total patients. Though follow-up is scheduled to 5 years for all pivotal trials, only three trials have reached 5-years following the index procedure (totaling fewer than 1000 patients). Approval of these devices was based on 1-year data and any available data beyond 1-year. Therefore, the data analyzed to assess this safety signal may not be sufficient to definitively determine the presence, magnitude, and causality for the increase in late mortality.

## 7.2 *Missing Data*

In addition to small sample sizes available for assessment, the analyses were also limited by missing data. Though the missing data rates were generally similar for the treatment and control groups in the pivotal RCTs, there were many clinical trial patients for whom data were missing due to withdrawn consent or loss to follow-up. As detailed in **Table 4, Table 8** and **Table 10**, the pivotal trials had approximately 14.4-38.3% missing data at 5 years, with as much or more missing data noted in the OUS RCTs and registries at 3 years and beyond. Attempts are on-going to acquire missing mortality information for the pivotal RCTs. Although no clinically-relevant differences were noted between baseline characteristics of subjects with or without missing data, the amount of missing data reduces the robustness of the statistical analyses and introduces greater uncertainty.

## 7.3 *Additional Unknown Treatments*

Another limitation of the available data is the ambiguity associated with any additional paclitaxel treatments patients may have received. Most of the clinical trials discussed did not allow for treatment with an additional paclitaxel-coated device in the ipsilateral limb within the first 12-months after the index procedure. However, subjects may have received a paclitaxel-coated device in the contralateral limb within the first 12 months or in either limb after 12 months. Of note, other paclitaxel-coated devices were available for US use during most of the clinical trials

(except for the Zilver PTX DES, which was the first device approved), and paclitaxel-coated devices were also available for use OUS. Most of the trials did not capture detailed information regarding additional paclitaxel-coated device use following the index procedure. Therefore, there is a chance that some study patients received additional paclitaxel-coated devices or paclitaxel for cancer treatment. If a significant number of patients did receive additional doses of paclitaxel, this could potentially affect the outcome of these analyses.

### 7.4 *Death Adjudication and Categorization*

As noted above in Section 5.1, another major limitation of the available data was how deaths were adjudicated and categorized. In the pivotal RCTs, no deaths were adjudicated to be device- or drug-related. However, the information available to adjudicators may not have been sufficiently granular to fully assess potential paclitaxel-related adverse effects. Furthermore, in many cases, adjudication and categorization of deaths lacked precision. Many deaths were categorized as "other" or "unknown." Patients with PAD typically have numerous comorbidities, and the death categorization may not have fully captured all events that led to death. As a result, there are important challenges in identifying trends associated with increased mortality in the various cause of death categories.

## 8. Post Approval Data Collection

Considering FDA's least burdensome principles approach, it may not be possible at the time of device approval to fully predict long-term safety and effectiveness. Therefore, FDA expects that post-approval studies (PAS) continue to collect important safety and effectiveness information. In such circumstances, product labeling can indicate the limits of currently available data and state that further safety and effectiveness data is being obtained through a PAS. Product labeling can be updated following PAS completion. FDA requested that for paclitaxel-coated devices, the pivotal study subjects be followed for up to five years as part of a condition of PMA approval, because these products represented a novel combination product therapy to treat stenoses in the peripheral vasculature. Assessment during the final two years is typically limited to an assessment of adverse events.

Based on the review of available data, there appears to be a trend of increased mortality 3-5 years following treatment with a paclitaxel-coated stent or balloon in the femoropopliteal arteries. However, there are limitations with the currently available clinical data, and a mechanism responsible for late mortality is not evident. The Panel will be requested to comment if additional clinical studies should be considered to address questions related to the late mortality signal. There are numerous approaches that can be taken to gather additional clinical data including a new PAS or a 522 Postmarket Surveillance Study. The collection of real-world evidence (RWE) may also be considered.

*New Enrollment PAS.* Individual manufacturers or an industry consortium can proactively design a new clinical study to evaluate specific clinical outcomes (e.g., adverse events, mortality) in a selected patient population. Alternatively, under Section 522 of the FD&C Act, FDA can require

a manufacturer to conduct postmarket surveillance of a class II or class III device that meets any of the following criteria:

- its failure would be reasonably likely to have serious adverse health consequences;
- it is expected to have significant use in pediatric populations;
- it is intended to be implanted in the body for more than one year; or
- it is intended to be a life-sustaining or life-supporting device used outside a device user facility.

*Real-World Evidence.* FDA recognizes the wealth of existing real-world data available from clinical experience derived from electronic health records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including in home-use settings, and data gathered from other sources. The data available in these sources may help to streamline collection of real-world experience of these devices to generate robust and meaningful evidence to support the safety and effectiveness of devices in the general population. Several registries and consortia capture data from peripheral interventional procedures, such as the Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI), the American College of Cardiology (ACC) National Cardiovascular Registry (NCDR), and the International Consortium of Vascular Registries (ICVR). However, there are potential limitations that may discourage use of RWE as a primary source of clinical evidence, which may include sub-optimal data quality and reliability, lack of follow-up, and selection bias. Some limitations to obtaining late mortality information in RWE can be overcome with the use of social security numbers or Medicaid/Medicare identification information. However, because of the many confounding factors, the use of RWE should be carefully considered when used to support regulatory and clinical decisions.

## 9. Other Indications for Use

Paclitaxel-coated devices are approved or under study for other vascular beds and indications for use, such as to treat stenosis in AVF or BTK PAD. Limited long-term data exist for paclitaxel-coated DCB or DES for these indications. Different patient populations may have different tolerances for the probable risks given the anticipated benefits. Therefore, the Panel will be asked to discuss whether concerns regarding paclitaxel-coated devices used in femoropopliteal PAD should be considered when these devices are used for other indications.

*Arteriovenous dialysis fistulae.* Only the LUTONIX DCB is currently approved for use in arteriovenous (AV) hemodialysis access circuits (FDA 2017a). It is indicated for treatment of stenotic lesions in dysfunctional native arteriovenous dialysis fistulae that are 4-12 mm in diameter and up to 80 mm in length. FDA approval was based on data from the LUTONIX AV RCT of 285 patients randomized to either the LUTONIX DCB or POBA. The primary effectiveness endpoint, Target Lesion Primary Patency at 180 days, was 71.4% in the LUTONIX DCB group and 63.0% in the Standard PTA group (p=0.0562). Although statistical significance was not achieved to meet the primary endpoint, the overall results demonstrated a numerically higher patency rate in the LUTONIX DCB group compared to conventional angioplasty through 12 months. An additional clinical benefit was the reduction in the number of target lesion reinterventions (31% reduction at 6 months, 26% reduction at 9 months, and 17% reduction at 12

months) in patients treated with the LUTONIX DCB. The primary safety endpoint, freedom from serious adverse events (SAEs) directly involving the AV access circuit through 30 days, was met. The proportion of subjects that did not have an SAE involving the access circuit through Day 30 was 94.9% in the LUTONIX DCB arm, and 95.8% in the Standard PTA arm (p = 0.004). Additionally, freedom from primary safety events by Kaplan Meier estimates at 12 months was 39.5% for the LUTONIX DCB group and 31.0% for the control group. All-cause mortality at 12 months was 12.8% for the LUTONIX DCB group and 9.7% for the POBA group.

Note that patients with renal failure on hemodialysis have high mortality rates. According to the United States Renal Data System (USRDS) report, once dialysis is initiated, patients are expected to have a lifespan of approximately 4-8 years. In addition, in contrast to femoropopliteal PAD patients, renal failure patients are typically treated with larger devices, undergo many repeat procedures, have different downstream organs (i.e. lungs versus lower limbs), and may experience different downstream effects (Collins et al. 2010).

*Below-the-knee.* DCB and DES used in the BTK vasculature are intended to improve luminal diameter to increase blood flow to the feet. In patients with critical limb ischemia, improved blood flow may promote wound healing, reduce the need for amputation, and improve patient quality of life. These patients typically have multiple comorbidities with a 20% mortality rate within 6 months after diagnosis and a 50% mortality rate at 5 years, regardless of treatment (Uccioli et al. 2018). In the Swedvasc registry, which collected data on patients following revascularization, there was an approximately 50% incidence of death or amputation at 3 years (Baubeta Fridh et al. 2017). No devices are currently approved in the US for BTK PAD. However, a number of studies are currently being conducted under FDA approved IDEs for this indication.

*Coronary artery disease.* The FDA-approved Boston Scientific Corp. (BSC) TAXUS family of drug-eluting stents (DES) are paclitaxel-eluting devices indicated for improving luminal diameter for the treatment of de novo lesions in native coronary arteries. TAXUS stents share the same amorphous paclitaxel formulation and drug delivery mechanism as the BSC ELUVIA stent, and TAXUS stents have a higher paclitaxel dose-density (10 $\mu g/mm^2$) versus Eluvia stents (0.167 $\mu g/mm^2$). Considered first generation coronary DES, TAXUS stents are no longer in use in the US, as newer generation -limus-eluting DES demonstrated lower rates of repeat revascularization and stent thrombosis.

TAXUS stents were evaluated in several RCTs (TAXUS I, II, IV, and V and HORIZONS AMI) vs. bare metal stents (BMS). These studies demonstrated a consistent reduction in target lesion revascularization in the TAXUS DES group vs. the BMS group. Within these individual TAXUS Program trials, there was no signal of increased mortality at 5-years follow-up among subjects treated with TAXUS stents. A meta-analysis of the TAXUS I, II, IV, and V RCTs (Stone et al. 2011) showed an 9.8% Kaplan-Meier all-cause mortality rate at 5-years in patients treated with TAXUS stents versus 9.1% in BMS subjects (HR 1.08, 95% CI 0.84-1.39, p = 0.53). However, a landmark analysis of results from year 1 to year 5 showed the following increased event rates in

TAXUS stent versus BMS subjects: a significant increase in cardiac death or MI (6.7% versus 4.5%, 95% CI 1.08-2.13, p=0.01); a significant increase in MI (3.8% versus 2.3%, p = 0.03); a nonsignificant increase in cardiac death (3.5% versus 2.5%, p = 0.15); and a nonsignificant increase in Academic Research Consortium-defined definite or probable stent thrombosis (1.4% versus 0.9%, HR 1.65, 95% CI 0.78-3.50, p = 0.18).

## 10. Conclusions

FDA analyses of available data from FDA-approved devices show an increase in late mortality (between two and five years) associated with paclitaxel-coated devices intended to treat femoropopliteal disease. However, causality for the late mortality rate increase 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 sub-groups that may be at greater risk, and to update benefit-risk considerations of this device class.

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