Medtronic

IN.PACT ADMIRAL PACLITAXEL-COATED PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY (PTA) BALLOON CATHETER

SPONSOR PANEL SUMMARY FOR THE CIRCULATORY SYSTEM DEVICE PANEL ADVISORY COMMITTEE

MEETING DATE: 19-20 JUNE 2019

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1.0 Executive Summary

Key Points

Results from randomized studies up to 5 years support the remarkable effectiveness and overall safety profile of IN.PACT Admiral Drug Coated Balloon (DCB) for the treatment of patients with femoropopliteal artery disease.

Medtronic completed multiple analyses in response to the paclitaxel safety concern and the results demonstrate:

- No significant difference in mortality between IN.PACT DCB and uncoated percutaneous transluminal angioplasty (PTA) through 5 years
- No correlation between paclitaxel dose and mortality
- Superior, consistent and durable effectiveness across multiple randomized trials and in real-world use in hundreds of thousands of patients

The risk-benefit profile of IN.PACT Admiral DCB continues to support DCB as first line therapy for the treatment of femoropopliteal artery disease.

1.1 Introduction

A summary-level meta-analysis published in the Journal of the American Heart Association (JAHA) in December 2018 reported an increased risk of death, beyond one year, following treatment of lesions in the femoropopliteal artery in the lower limb with paclitaxel-coated balloons or paclitaxel-eluting stents when compared to non-drug controls. (1) The authors associated the higher delayed mortality rates to paclitaxel exposure, though a plausible mechanism was not hypothesized (1) Limitations of the research include:

- Use of summary-level data from published reports
- No access to patient-level data and thus no details on causes of death
- No plausible biological mechanism between paclitaxel toxicity and mortality established
- Incorrect assumption in drug exposure model which assumes constant dose over time (2)

The Food and Drug Administration (FDA) issued a letter to healthcare providers on March 15, 2019, reporting an “approximate 50% increased risk of mortality in patients treated with paclitaxel-coated products than patients treated with control devices” following preliminary analysis of three trials with 5-year follow up data. (3)

1.2 Medtronic Response to Safety Concern

Medtronic took a number of immediate steps to address the safety concerns within the context of IN.PACT Admiral DCB as listed below.

1.2.1 Literature Review on Mortality Rates

An in-depth review of published literature was conducted. Mortality rates across IN.PACT Admiral DCB studies are comparable to or lower than what would be expected in similar patient populations.(2)

1.2.2 Independent Patient-level Meta-analysis of IN.PACT Admiral DCB

An independent patient-level meta-analysis was conducted and accepted for publication in the Journal of the American College of Cardiology (JACC). (2) The authors evaluated data from four independently-adjudicated prospective studies of 1,980 patients with five-year follow-up involving IN.PACT Admiral DCBs. Extensive analyses of baseline, procedure, and follow-up data of individual patients were performed to explore a potential correlation between paclitaxel exposure and mortality. The results

showed no statistically significant difference in all-cause mortality between DCB and uncoated percutaneous angioplasty (PTA) through 5 years. A survival analysis stratified by nominal paclitaxel dose (low, mid, and upper terciles) showed no statistically significant difference in all-cause mortality between the three groups through 5 years.

Conclusion: This independent patient-level meta-analysis demonstrated that IN.PACT Admiral DCB is safe, showing no correlation between paclitaxel exposure from treatment with IN.PACT Admiral DCBs and mortality.

1.2.3 Collection of Vital Status Data on Patients Lost to Follow-up

Steps were taken to obtain vital status data on patients who were lost to follow-up (LTFU) from the studies in the IN.PACT Admiral clinical program. Vital status data collected from LTFU patients were shared with the FDA who also conducted their own analyses regarding the safety concern.

Using the additional vital status data that included vital status information on 96% of the total patients enrolled in the RCTs, Medtronic conducted multiple analyses to determine if a correlation existed between paclitaxel exposure and increased risk of mortality.

Results from these analyses demonstrate:

- No significant difference in mortality between IN.PACT DCB and uncoated PTA through 5 years
- No correlation between paclitaxel exposure and mortality
- No observed dose relationship with mortality
- No trends in adverse events suggesting systemic toxicity from paclitaxel exposure
- No relatedness between deaths and paclitaxel, as adjudicated by a newly convened independent Clinical Events Committee (CEC)

Collectively, the risk-benefit profile of IN.PACT Admiral DCB remains positive and supports DCB as a first line strategy for the treatment of femoropopliteal PAD.

1.2.4 Newly Convened Independent Clinical Events Committee

Medtronic convened a new independent CEC with paclitaxel toxicity expertise to review deaths from the superficial femoral artery IN.PACT IDE and Japan trials. The objective was to specifically assess causes of death for relatedness to known paclitaxel toxicities.

The new independent CEC members were licensed, board certified (or equivalent) vascular surgeons, interventional radiologists, interventional cardiologists, and oncologists. Each member had clinical expertise in the relevant therapeutic specialty, experience with clinical trial methodology, and previous experience on CECs, Data Monitoring Committee (DMCs) or was otherwise knowledgeable and familiar with safety reporting requirements for medical device or pharmaceutical clinical trials.

The new independent CEC assessed the cause of death of all patients in IN.PACT SFA and IN.PACT SFA Japan and adjudicated the relatedness of death to the procedure, to the device, and/or to paclitaxel. Any event that occurred 30 days or less after the index procedure was considered procedure-related. If there was a secondary procedure required through the duration of the trial, (e.g. a revascularization), any event that occurred 30 days or less after that secondary procedure was also considered procedure-related. If any event was adjudicated as related to the device, that event was reported as device-related, as device-relatedness supersedes procedure-relatedness, any event may also have been adjudicated as paclitaxel-related.

Patient deaths from the IN.PACT IDE and Japan randomized controlled trials were reviewed and adjudicated by the new independent CEC. None of the deaths were deemed related to the device or paclitaxel.

1.3 Risk / Benefit and Conclusion

Medtronic concludes no correlation exists between paclitaxel exposure and increased risk of mortality based on an extensive literature review on mortality rates, independent patient-level meta analyses, the results of the additional IN.PACT clinical data analyses, and findings from a new independent CEC with paclitaxel toxicity expertise that reviewed all deaths from the IN.PACT IDE and IN.PACT Japan trials and concluded that there was no relatedness between causes of deaths and paclitaxel.

IN.PACT Admiral has also demonstrated consistent, superior and durable effectiveness over PTA and the lowest clinically-driven TLR (CD-TLR) rates reported across multiple trials, geographies, and lesion morphologies, with 3 out of 4 patients treated remaining reintervention-free through 5 years. (4,5)

The risk-benefit profile of IN.PACT Admiral DCB remains positive and supports the continued use of DCBs as a first line strategy for the treatment of femoropopliteal PAD.

2.0 IN.PACT Admiral DCB Overview

Key Points

- Indicated to treat de novo, restenotic, or in-stent restenotic lesions with lengths up to 360 mm in the superficial femoral artery (SFA) or popliteal arteries with reference vessel diameters of 4-7 mm.
- Used as a first line therapy to treat SFA disease effectively
- Received FDA approval December 2014
- Approved in the European Union, Japan, and 87 countries around the world
- Treated over 375,000 patients worldwide

2.1 Prevalence and Treatment Options for PAD

Lower extremity Peripheral Artery Disease (PAD) is a significant health problem affecting between 8-12 million people are in the United States. (6,7) Risk factors for PAD include smoking, diabetes, hypertension, hyperlipidemia, and impaired kidney function. Treatment options include aggressive risk factor modification, medical therapy, endovascular revascularization, supervised exercise regimens and surgical intervention. (7)

Percutaneous transluminal angioplasty (PTA) is associated with high rates of restenosis when used to treat long, complex lesions in the SFA. Restenosis is the most common cause for the lack of durability of revascularization procedures in the SFA segment.

The advent of paclitaxel devices has significantly changed the landscape for SFA revascularizations, showing improved patency and lower restenosis rates compared with PTA in randomized controlled trials. (4,5,8,9)

The IN.PACT Admiral Drug Coated Balloon demonstrated consistent and durable outcomes out to five years, as shown in the IN.PACT IDE clinical trial.

2.2 Description of Device

The IN.PACT Admiral DCB is intended for PTA of the superficial femoral and popliteal arteries. The IN.PACT Admiral DCB's primary mode of action is mechanical dilatation of *de novo*, restenotic, and in-stent restenotic lesions by means of PTA, with a secondary inhibition of restenosis (caused by the proliferative response to the PTA) through the application of paclitaxel (the product's Active Pharmaceutical Ingredient [API]) to the vessel wall. The IN.PACT Admiral DCB is coated with FreePac™, a proprietary paclitaxel coating with a nominal drug dose density of 3.5 µg of paclitaxel per 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 wall. The IN.PACT Admiral DCB is approved for diameters 4.0, 5.0, 6.0, and 7.0mm and lengths, 20, 40, 60, 80, 120, 150, 200, and 250mm

2.3 Indication for Use

The IN.PACT Admiral paclitaxel-coated PTA balloon catheter is indicated for percutaneous transluminal angioplasty, 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. (10)

2.4 Product History

Around the world, IN.PACT Admiral DCB is used as a first line therapy to effectively treat patients with PAD in the superficial femoral and popliteal arteries. The IN.PACT Admiral DCB enables physicians to treat long, complex lesions with longer balloon lengths, which helps reduce procedure time and costs. IN.PACT Admiral DCB has 10 years of proven experience and has been used to treat over 375,000 patients.

2.5 Regulatory History

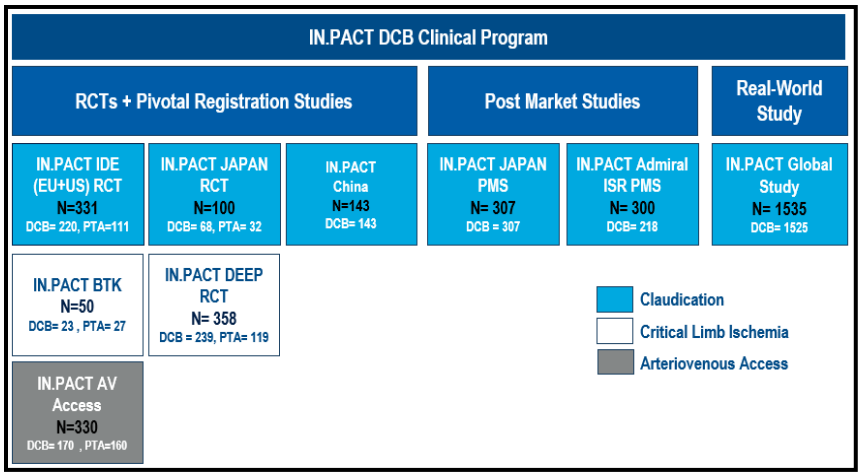
IN.PACT Admiral DCB received CE Mark approval in March 2009. Since that time, Medtronic received regulatory approval in over 87 countries worldwide. In September 2017, Medtronic received approval from the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan for IN.PACT Admiral DCB. In the United States, Medtronic worked with the FDA from the start of the IN.PACT IDE Trial (reference IDE G110200) through PMA approval. IN.PACT Admiral DCB was FDA approved in December 2014 (reference PMA P140010).

3.0 Clinical Program

Medtronic developed and conducted one of the most comprehensive clinical programs for evaluating drug coated balloons. The safety and effectiveness of paclitaxel in the IN.PACT DCB[1] has been studied in more than 3,000 patients across 9 Medtronic sponsored trials which includes both randomized controlled trials (RCT) and single-arm trials.

Figure 3-1 below shows the list of the studies under the IN.PACT DCB Clinical program including studies for multiple indications (claudication, critical limb ischemia and arteriovenous access). IN.PACT Admiral DCB is the only DCB from the IN.PACT family approved in the United States (claudication indication).

Figure 3-1: IN.PACT DCB Clinical Program Overview



For all the analysis performed and presented in this document, Medtronic will focus on the two key trials IN.PACT IDE and IN.PACT Japan. These two trials studied the IN.PACT Admiral DCB in femoropopliteal arteries for treatment of claudication and are randomized control trials which enable us to analyze and compare the results of DCB and PTA devices. A summary of these two RCTs is provided below.

3.1 Study Synopsis

Table 3-1 provides a high-level overview of two Medtronic sponsored RCTs namely the IN.PACT IDE and IN.PACT Japan trials. These trials evaluated the IN.PACT Admiral DCB in femoropopliteal arteries of patients with claudication. Both trials had identical inclusion/exclusion criteria except for the maximum lesion length (18cm for IDE vs 20cm for Japan), and used the same independent CEC, angiographic, and duplex core-labs. It is important to note that these trials were not powered to analyze long-term mortality.

[1] The studies included the following devices: IN.PACT Admiral DCB, IN.PACT Amphirion (not commercially available) and IN.PACT AV DCB(Currently not approved)

Table 3-1: Study Synopsis for Medtronic Sponsored RCTs

Study	IN.PACT IDE*: Study Complete	IN.PACT Japan**: Study Complete
Device	IN.PACT Admiral DCB	IN.PACT Admiral DCB
Design	RCT (2:1), prospective, global, multicenter, single-blind	RCT (2:1), prospective, multicenter single-blind
No. of Patients	SFA I (Europe) **DCB: n =99 PTA: n=51** SFA II (US) **DCB n = 121 PTA: n= 60**	**DCB: n = 68 PTA: n = 32**
Primary Safety Endpoint	Freedom from device- and procedure-related death through 30 days and freedom from target limb major amputation and clinically-driven target vessel revascularization (CD-TVR) at 12 months.	Freedom from device- and procedure-related death through 30 days and freedom from target limb major amputation and clinically-driven target vessel revascularization (CD-TVR) at 12 months.
Primary Effectiveness Endpoint	Primary patency at 12 months, defined as freedom from clinically-driven TLR (CD-TLR) and freedom from restenosis as determined by duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) ≤ 2.4.	Primary patency at 12 months, defined as freedom from clinically-driven TLR (CD-TLR) and freedom from restenosis as determined by duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) ≤ 2.4.
Follow-up Duration	In-clinic follow up: -30 days, 6 months, 12 months, 24 months and 36 months post procedure. Telephone follow up: 48 and 60 months	30 days, 6 months, 12 months, 24 months and 36 months post procedure

* IN.PACT SFA IDE includes SFA I (Europe) and SFA II (US)
**The Japan SFA randomized trial was conducted as a confirmatory study in Japanese patients in order to obtain regulatory approval in Japan.

4.0 Paclitaxel Safety

Key Points

Results from the IN.PACT DCB randomized trials and multiple analyses demonstrate:

- No mortality signal observed:
  - No significant difference in mortality between IN.PACT Drug Coated Balloon (DCB) and percutaneous transluminal angioplasty (PTA) through 5 years
  - No trends in adverse event profiles that would indicate any systemic toxicity from paclitaxel exposure
  - No causes of death were deemed related to paclitaxel as adjudicated by the newly convened Independent Clinical Events Committee (CEC) with paclitaxel toxicity expertise
- No dose relationship observed:
  - No correlation between paclitaxel exposure and mortality
  - No observed dose relationship with mortality
  - In a multivariate analysis, paclitaxel dose was not a predictor of increased risk for mortality through 5 years

4.1 Medtronic Analyses to Support IN.PACT Admiral DCB Clinical Safety

Given this safety concern, Medtronic did a rigorous examination of the data available from 2 Randomized Controlled Trials (RCTs) involving the INPACT Admiral device i.e. IN.PACT IDE and IN.PACT Japan.

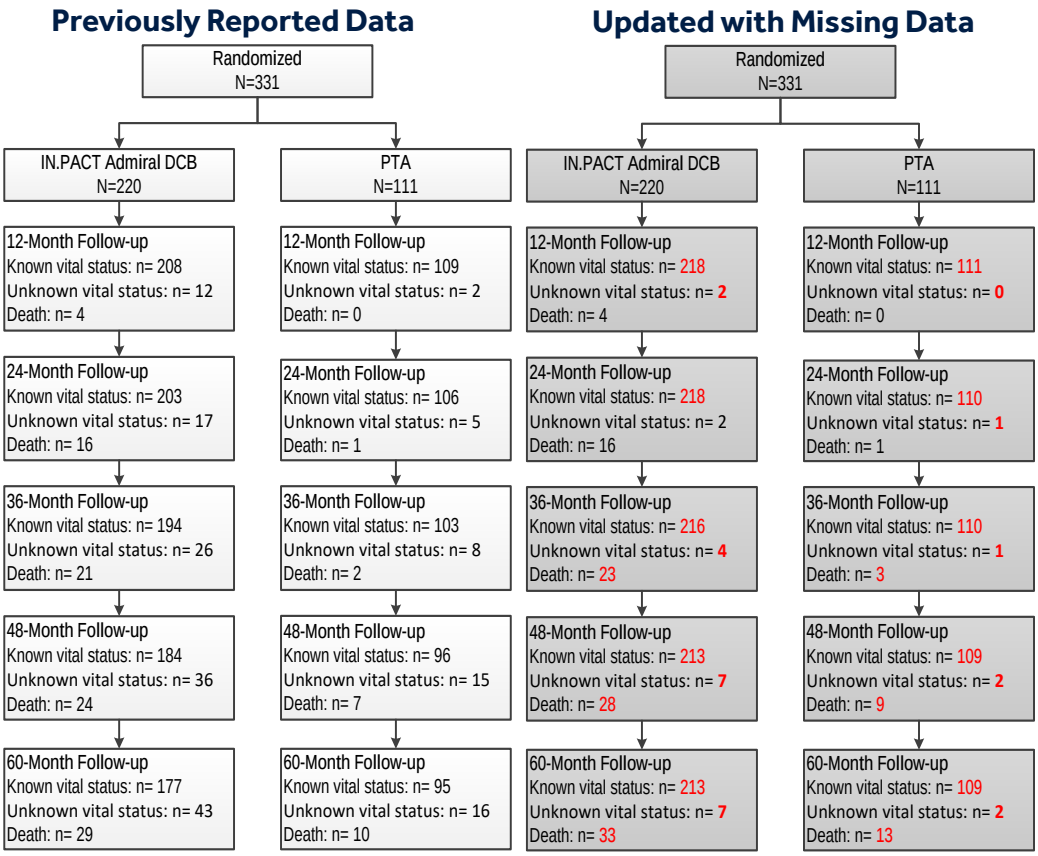
- Medtronic undertook a significant effort to collect vital status information on patients lost to follow-up (LTFU) in the IN.PACT IDE trial, to help create a more complete picture of the overall mortality. 97% of vital status data in the DCB Arm and 98% in the PTA arm were collected **Figure 4-1**.
- Medtronic convened a new independent CEC with paclitaxel toxicity expertise to review causes of death from the RCT trials for any relatedness to paclitaxel toxicity. Details regarding the process of establishing the Independent CEC and its findings is presented in **Section 5.2**.

4.2 Patient Accountability

4.2.1 IN.PACT IDE Study

One limitation of the RCTs conducted in the peripheral space is that the trials were not powered for long-term mortality. As a result, emphasis was placed on the completeness of data for assessment of the one-year primary endpoints and not on long term mortality. Following an effort to get this information, the updated known vital status rate at 5 years for the DCB arm is now 96.8% (213/220) and 98.2% for the PTA (109/111) arm. The overall known vital status for the IDE study at 5 years is 97.3%. The figure below provides a pictorial overview of the previously collected data and the updated data after obtaining lost to follow-up information.

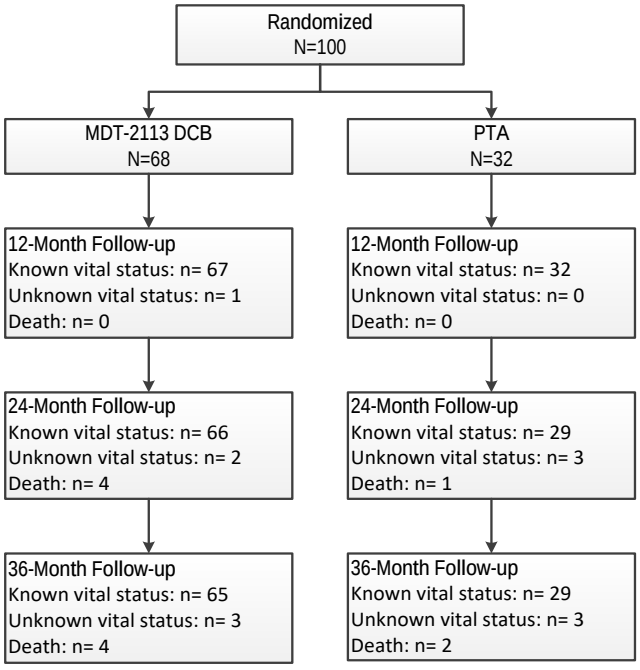
Figure 4-1: Vital Status of Patients LTFU in the IN.PACT IDE Trial



4.2.2 IN.PACT Japan

The known vital status rate for the Japan trial at three years is 95.6% (65/68) for the DCB arm and 90.6% (29/32) for the PTA arm. No additional vital status was obtained for the lost-to-follow-up patients in the Japan trial. Overall known vital status at three years for the Japan trial is 94%.

Figure 4-2: Vital Status of Patients in IN.PACT Japan Trial



4.3 Baseline Characteristics

The IN.PACT IDE and Japan pooled baseline and lesion characteristics are provided in **Table 4-1**. Of note, patients in the IN.PACT Japan trial were older and were more likely to present with hyperlipidemia and diabetes.

Table 4-1: IN.PACT IDE Key Baseline & Procedural Characteristics

IN.PACT IDE	IN.PACT IDE n = 331 Patients n = 334 Lesions	IN.PACT Japan n = 100 Patients n = 100 Lesions	P-value*
Age, Y ± SD	67.6±9.4	73.6±7.0	**<0.001**
Male Gender, % (n)	65.9% (218/331)	76.0% (76/100)	0.066
Obesity (BMI ≥ 30 kg/m^2)	26.9% (89/331)	3.0% (3/100)	**<0.001**
Hyperlipidemia	83.7% (277/331)	73.0% (73/100)	**0.020**
Diabetes, % (n)	43.2% (143/331)	58.0% (58/100)	**0.012**
Insulin Dependent Diabetes Mellitus (%)	17.5% (58/331)	16.0% (16/100)	0.880
Carotid Artery Disease	33.9% (105/310)	17.7% (17/96)	**0.002**
Current smoker, % (n)	37.8% (125/331)	28.0% (28/100)	0.075
Renal insufficiency, % (n)	7.7% (25/326)	10.0% (10/100)	0.532
Lesion length (cm ± SD)	8.88±4.96	9.07±5.88	0.771
Total Occlusion, % (n)	23.7% (79/334)	16.0% (16/100)	0.129
Severe calcification, % (n)	7.5% (25/334)	8.0% (8/100)	0.832

*For categorical variables, Fisher's Exact test is used for binary variables; Cochran–Mantel–Haenszel test is used for multi-level variables. T-test is used for all continuous variables.

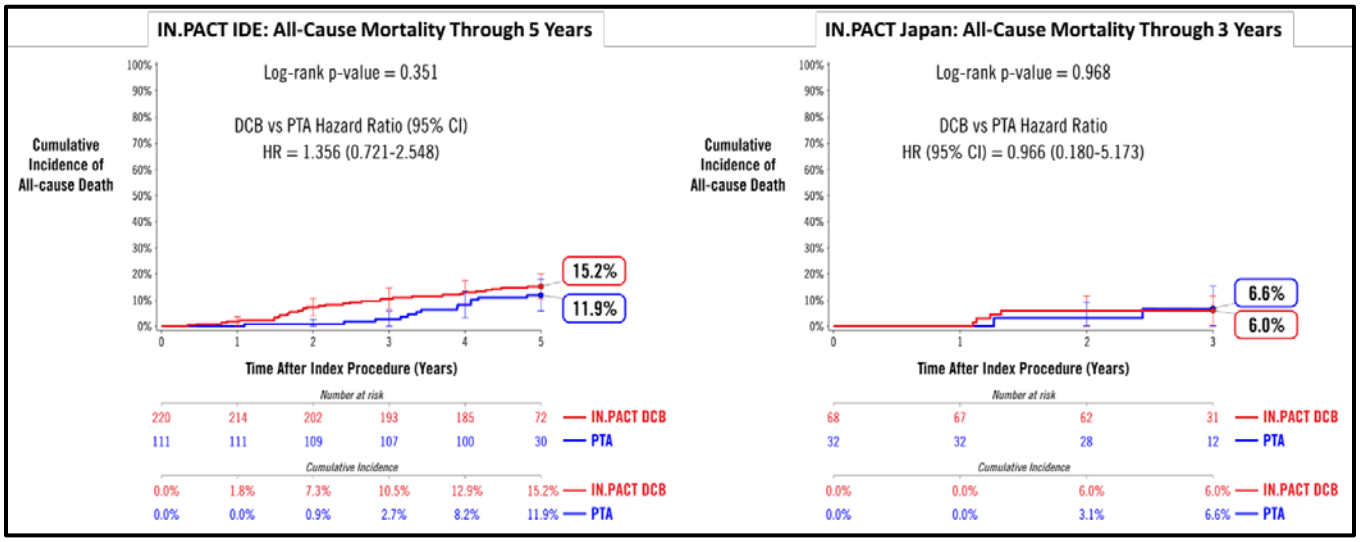
4.4 All-Cause Mortality and Paclitaxel-Related Adverse Events

4.4.1 All-cause Mortality: IN.PACT IDE Trial and IN.PACT Japan Trial

The Kaplan-Meier plot for cumulative incidence of all-cause mortality for IN.PACT IDE and IN.PACT Japan is presented in **Figure 4-3**. While a numerical difference is observed between the two groups in the IN.PACT IDE trial, it's important to note that the all-cause mortality rate in the PTA group was unusually low for this patient population. (2)

Conclusion: There was no statistically significant mortality difference between the two groups for both RCTs over their respective study follow-up periods.

Figure 4-3: All-Cause Mortality: IN.PACT IDE and IN.PACT Japan

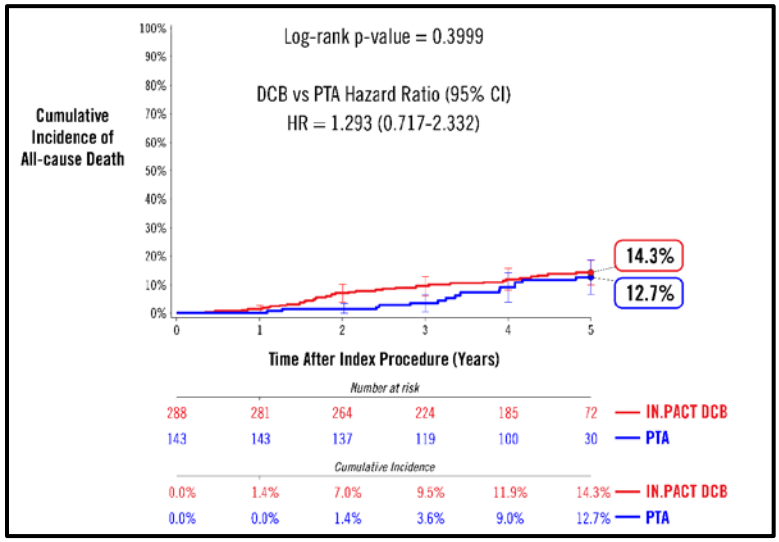


4.4.2 All-cause Mortality: Pooled IN.PACT IDE and Japan

Since the individual RCTs (IN.PACT IDE and IN.PACT Japan) were not powered to analyze long-term mortality, Medtronic performed a pooled analysis of the patients in both trials. The Japan trial was designed to be poolable with the US IDE cohort to show that consistent treatment effects can be demonstrated within the cohorts. As shown in **Table 4-1**, the baseline characteristics of the patients enrolled in these two RCTs are similar, therefore allowing for these two datasets to be pooled.

Conclusion: There was no statistically significant mortality difference between the two groups over the five-year study follow-up period.

Figure 4-4: IN.PACT IDE and Japan Pooled All-Cause Mortality



4.5 Potential Paclitaxel-related Adverse Events

Adverse events were reviewed for possible paclitaxel relatedness, as described by Markam, et al (11) All adverse events were classified according to these known paclitaxel-related adverse events. Overall, no differences were exhibited across all event types between the DCB and PTA arms with the exception of peripheral neuropathy in IN.PACT IDE, which was statistically higher in the PTA arm. Furthermore, no specific trends or patterns were seen to suggest any specific relationship to paclitaxel.

Conclusion: This analysis demonstrates that there are no trends in adverse event profiles that would suggest any systemic toxicity from paclitaxel. Additionally, there are no patterns of non-fatal adverse events that can indicate any mechanistic link between mortality and paclitaxel.

Table 4-2: IN.PACT IDE Potential Paclitaxel-Related Adverse Events

Bradycardia	**1-Year**	**3-Years**	**5-Years**
DCB (n=220)	1.0% (2/206)	1.7% (3/177)	3.3% (5/153)
PTA(n=111)	0.9% (1/109)	2.0% (2/101)	2.3% (2/86)
Bradycardia (transient, asymptomatic, reversible). P-value=1.000 at 1-year, 3-years, and 5-years			
Hematologic	**1-Year**	**3-Years**	**5-Years**
DCB (n=220)	3.4% (7/207)	7.1% (13/182)	10.7% (17/159)
PTA(n=111)	4.6% (5/109)	5.9% (6/101)	6.9% (6/87)
Hematologic toxicities include Leukopenia, Neutropenia, Thrombocytopenia, and Anemia. P-value=0.785 at 1-year, 0.807 at 3-years, and 0.370 at 5-years			
Neurotoxicity	**1-Year**	**3-Years**	**5-Years**
DCB (n=220)	0% (0/206)	0% (0/176)	0% (0/151)
PTA(n=111)	3.7% (4/109)	3.9% (4/102)	4.6% (4/87)
Peripheral neuropathy (p-value=0.014 at 1-year, 0.017 at 3-years, and 5-years)			
Myalgia	**1-Year**	**3-Years**	**5-Years**
DCB (n=220)	0.5% (1/206)	0.6% (1/176)	0.7% (1/52)
PTA(n=111)	0% (0/109)	0% (0/101)	0% (0/111)
P-value=1.000 at 1-year, 3-years, and 5-years			

Table 4-3: IN.PACT Japan Potential Paclitaxel-Related Adverse Events

Hematologic	**1-Year**	**3-Years**
DCB (n=68)	4.5% (3/67)	4.9% (3/61)
PTA(n=32)	0% (0/32)	0% (0/27)
Hematologic toxicities include Leukopenia, Neutropenia, Thrombocytopenia, and Anemia. (p-value=0.549 at 1-year and 0.550 at 3-years)		

Conclusion: There were no trends in adverse events suggesting systemic toxicity from paclitaxel.

4.6 Clinical Events Committee (CEC) Adjudicated Causes of Death

The newly convened independent CEC reviewed 45 deaths in the RCTs (33 DCB + 12 PTA) that were previously reported, looking for possible paclitaxel correlation to mortality. No deaths through five years for IN.PACT IDE and three years for Japan were deemed to be device, procedure, or paclitaxel-related as shown in **Table 4-4**.

Parameters assessed by the Independent CEC included: confirmation of date of death, cause of death (the cause of death was assigned based on “2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials,” Hick et.al), device-, procedure-, and paclitaxel-relatedness.

Table 4-4: Summary of Relatedness of Device, Procedure, or Paclitaxel through 5-years – IDE and Japan Pooled

Relatedness	IN.PACT DCB (N=33 Deaths in 288 Patients)	PTA (N=12 Deaths in 143 Patients)	Log-Rank P-value
Device-Related	0.0% (0)	0.0% (0)	NA
Index Procedure-Related	0.0% (0)	0.0% (0)	NA
Second Procedure-Related	0.0% (0)	0.0% (0)	NA
Paclitaxel-Related	0.0% (0)	0.0% (0)	NA
Notes: Numbers are Kaplan-Meier Estimate (number of patient with event) 7 additional deaths identified through the vital status data collection were not adjudicated due to the limited source documentation available			

Causes of death through 5-years for the IN.PACT IDE and Japan pooled are provided in **Table 4-5**. There was no clustering of specific causes of death between DCB and PTA. The identified causes of death are typical for this patient population.

Table 4-5: Cause of Death Through 5-years- IDE and Japan Pooled

CV Type/Cause	IN.PACT DCB (N=33 Deaths in 288 Patients)	PTA (N=12 Deaths in 143 Patients)	Log-Rank P-value
Cardiovascular (CV) Deaths	4.0% (10)	3.2% (3)	0.376
Acute Myocardial Infarction[a]	0.4% (1)	0.0% (0)	0.470
Sudden Cardiac Death[b]	1.1% (3)	1.0% (1)	0.682
Heart Failure[c]	1.2% (3)	0.0% (0)	0.210
Stroke[d]	0.8% (2)	0.0% (0)	0.311
CV Procedure[e]	0.0% (0)	0.0% (0)	NA
CV Hemorrhage[f]	0.0% (0)	1.1% (1)	0.182
CV Disease	0.0% (0)	0.0% (0)	NA
Other CV Cause[g]	0.6% (1)	1.1% (1)	0.676
Unknown-CV Cause	0.0% (0)	0.0% (0)	NA
Non-CV Death	8.4% (19)	5.7% (6)	0.250
Pulmonary	0.4% (1)	0.0% (0)	0.469
Renal	0.6% (1)	0.0% (0)	0.455
Gastrointestinal	0.4% (1)	0.0% (0)	0.474
Pancreatic	0.0% (0)	0.0% (0)	NA
Hepatobiliary	0.0% (0)	0.0% (0)	NA
Infection/Sepsis[h] (includes inflammatory)	2.0% (5)	1.8% (2)	0.737
Hemorrhage (Excluding CV bleed or stroke)	0.0% (0)	0.0% (0)	NA
Non-CV procedure or surgery	0.0% (0)	0.0% (0)	NA
Trauma (includes homicide)	0.0% (0)	0.0% (0)	NA
Suicide	0.0% (0)	1.1% (1)	0.186
Neurological (non-CV)[i]	1.0% (2)	0.0% (0)	0.294
Drug reaction or overdose (may include anaphylaxis)	0.0% (0)	0.0% (0)	NA
Other Non-CV	0.0% (0)	0.0% (0)	NA
Non-CV Unknown	0.0% (0)	0.0% (0)	NA
Malignancy	4.3% (9)	2.9% (3)	0.466
Lung	1.6% (3)	2.2% (2)	0.832
Gastrointestinal	0.8% (2)	0.7% (1)	0.974
Prostate	0.0% (0)	0.0% (0)	NA
Breast	0.0% (0)	0.0% (0)	NA
Brain	0.0% (0)	0.0% (0)	NA
Bone (Primary)	0.0% (0)	0.0% (0)	NA

CV Type/Cause	IN.PACT DCB (N=33 Deaths in 288 Patients)	PTA (N=12 Deaths in 143 Patients)	Log-Rank P-value
Undetermined Neoplasm	0.0% (0)	0.0% (0)	NA
Bladder	1.0% (2)	0.0% (0)	0.299
Ovarian	0.0% (0)	0.0% (0)	NA
Uterine/Cervical	0.0% (0)	0.0% (0)	NA
Renal	0.6% (1)	0.0% (0)	0.452
Sarcoma	0.0% (0)	0.0% (0)	NA
Hepatic	0.0% (0)	0.0% (0)	NA
Pancreatic	0.0% (0)	0.0% (0)	NA
Throat, nasopharyngeal	0.4% (1)	0.0% (0)	0.471
Other	0.0% (0)	0.0% (0)	NA
Undetermined Cause[j]	1.8% (4)	2.7% (3)	0.661

Note: Numbers are Kaplan-Meier Estimate (number of patient with event)
2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials," Hick et.al (JACC publication)
a: Death by any CV mechanism (e.g.: arrhythmia, sudden death, HF, stroke, PE, PAD) ≤30 days after an MI, related to the immediate consequence of the MI. For simplicity, if a CV death occurs ≤30 days of the MI, it will be considered a death due to MI. Death resulting from procedure to treat MI (PCI, CABG) or treat complication resulting from MI, should also be considered death due to acute MI. Death resulting from elective coronary procedure to treat myocardial ischemia (chromic stable angina)or death due to MI that is a direct consequence of a CV procedure/operation should be considered as death due to CV procedure.
b: Unexpected death not within 30 days of acute MI Death that is:
• Witnessed w/o new or worsening symptoms
• Witnessed w/in 60 minutes of onset of new or worsening cardiac symptoms (unless symptoms suggest acute MI)
• Witnessed and attributed to an identified arrhythmia (captured on ECG, witnessed on monitor, or unwitnessed but found on ICD review)
• After unsuccessful resuscitation from cardiac arrest
• After successful resuscitation from cardiac arrest and w/o identification of specific cardiac or non-cardiac etiology
• Unwitnessed in subject seen alive and clinically stable ≤24 hours prior to being found w/o evidence of specific non-CV cause of death o If subject was not observed alive within 24 hours of death, undetermined cause of death should be recorded
c: Clinically worsening symptoms and/or signs of HF regardless of HF etiology
d: Death as direct consequence of stroke or complications of stroke
e: Death due to immediate consequence of cardiac procedure
f: Death related to hemorrhage such as non-stroke intracranial hemorrhage (i.e. subdural hematoma), non-procedural/non-traumatic vascular rupture (i.e. aortic aneurysm) or hemorrhage causing cardiac tamponade
g: CV deaths not included in above categories but with a specific known cause (e.g. pulmonary embolism or peripheral arterial disease)
h: e.g. Systemic Inflammatory Response Syndrome (SIRS)/Immune (including autoimmune), may include anaphylaxis from environmental (e.g. food allergies)
i: excludes CV death from ischemic stroke, hemorrhagic stroke, or undetermined cause of stroke or CV hemorrhage of central nervous system
j: refers to a death not attributed to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death
Note: 7 additional deaths identified through the vital status data collection were not adjudicated due to the limited source documentation available

Conclusion

No mortality signal observed with no events reported related to paclitaxel toxicity

4.7 Paclitaxel Dose Analysis

4.7.1 Patient-level Pooled Analyses (IDE and Japan): Paclitaxel Dose Analysis

An analysis was performed to determine if there was any difference in the paclitaxel dose received by the patients who died compared to those that survived in the two RCTs. As shown in **Table 4-6** below, the overall mean nominal dosage of paclitaxel received was similar between patients that died compared to patients that survived in the DCB group (7.9 mg vs 7.8 mg, p=0.914). Therefore, showing no difference in dose in DCB patients by survival status.

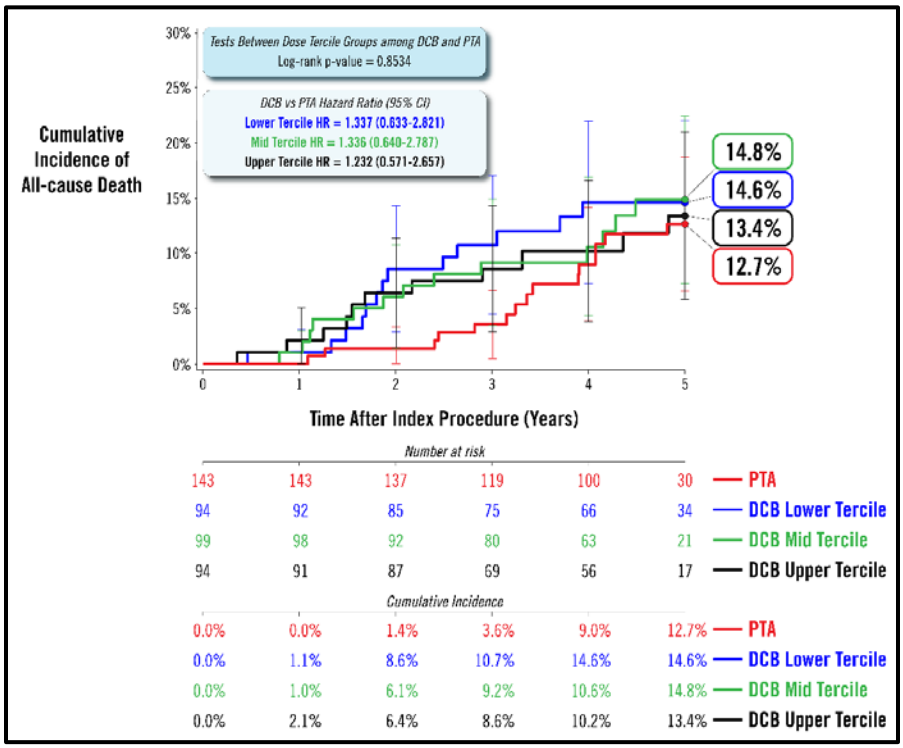
Table 4-6: Nominal Paclitaxel Dose in Patients that Died vs Survived

Nominal Delivered Paclitaxel Dose* (mg)	Death (N=37 Patients)	Survival (N=251 Patients)	P-value
Mean	7.9	7.8	0.914

Additionally, to assess the association of the paclitaxel nominal dose received by each patient during the index procedure and mortality over time, the DCB group was segmented into three terciles based on the amount of paclitaxel received: a low-dose group shown in blue, a mid-dose group shown in green, and an upper-dose group shown in black. PTA was included as the reference group of paclitaxel dose zero. Mean dosages for the three groups were 4.0, 7.3, and 12.3 mg, respectively. There was no significant difference in mortality between groups, demonstrating no direct impact of levels of nominal paclitaxel dose exposure at the index procedure and survival status in the DCB patients through 5 years (p=0.8534) as presented in the Kaplan Meier curve in **Figure 4-5**.

Conclusion: There is no observed dose relationship with mortality.

Figure 4-5: IN.PACT IDE and Japan Pooled Survival Status by Dose Tercile



4.7.2 Multivariate Analysis

A multivariate analysis of baseline demographic, lesion, and procedural characteristics was performed for all IDE and Japan patients to identify predictors of increased risk (**Table 4-7**).

Conclusion: Paclitaxel dose was not selected by the model selection process. Even when forced into the model, dose was not identified as a predictor of mortality. Similarly, lesion or procedure characteristics were not identified as predictors of mortality.

Table 4-7: Multivariate Analysis - Death through 5 Years - All ITT Patients from IN.PACT IDE and Japan Trials

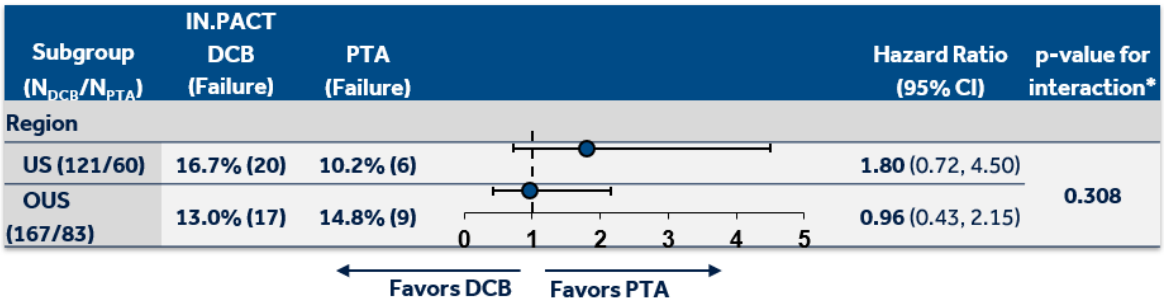
Predictors of Death though 5 Years	Hazard Ratio [95% CI]*	P-value*
Age (yrs)	1.047 [1.011, 1.083]	0.009
Renal Insufficiency (baseline serum creatinine >= 1.5 ng/dl) (Y vs. N)	2.466 [1.169, 5.202]	0.018
Insulin Dependent Diabetes Mellitus (Y vs. N)	2.683 [1.076, 6.691]	0.034
Smoking (Current/Previous vs. Never)	1.729 [0.891, 3.355]	0.105
Diabetes Mellitus (Y vs. N)	0.539 [0.246, 1.182]	0.123
PTX Dose Tercile in DCB (Mid vs. PTA)	1.465 [0.691, 3.105]	0.319
PTX Dose Tercile in DCB (Lower vs. PTA)	1.444 [0.681, 3.064]	0.338
PTX Dose Tercile in DCB (Upper vs. PTA)	1.099 [0.500, 2.418]	0.814
*Frailty Cox model with geography (EU, US, Japan) as random effect was conducted to calculate the hazard ratio and p-value.		

Conclusion
No observed dose relationship with mortality

4.8 Cumulative Incidence of Mortality and Follow-up Compliance By Region: US vs OUS (IN.PACT IDE and IN.PACT Japan)

Medtronic conducted a forest plot analysis on cumulative incidence of mortality by region. A difference in cumulative incidence mortality was observed between the US and Outside the US (OUS), although, not statistically significant (p-value = 0.308). The analysis showed that the numerical difference in all - cause mortality between the DCB and PTA arms occurred in the US only. Japan and EU showed comparable rates at all time points. This could potentially be linked to the lower follow-up visit compliance in the US.

Figure 4-6: Representation of Numerical Difference between DCB and PTA



*p-value is derived from Cox Proportional Hazard model by testing the interaction term
OUS: Outside the US-included Europe and Japan

Preliminary findings suggest follow-up visit compliance, a surrogate for repeat touch points with the healthcare system, is associated with a lower mortality risk. The follow-up schedule was pre-defined by respective study protocols. PTA compliance rates were higher at all time points compared to DCB as shown in **Table 4-8**.

Table 4-8: IN.PACT IDE and Japan Follow-up Visit Compliance

	IN.PACT IDE SFA I (Europe) (n=150)			IN.PACT IDE SFA II (US) (n=181)			IN.PACT Japan (n=100)		
	DCB (n=99)	PTA (n=51)	P-value	DCB (n=121)	PTA (n=60)	P-value	DCB (n=68)	PTA (n=32)	P-value
1-Year	94.2%	97.4%	0.149	92.6%	96.1%	0.153	98.5%	99.0%	0.767
2-Years	91.8%	93.5%	0.548	90.4%	94.5%	0.165	98.4%	100%	0.103
3-Years	89.9%	91.0%	0.753	89.1%	94.1%	0.102	98.0%	100%	0.057
4-Years	88.4%	89.5%	0.786	87.9%	94.6%	0.024	Study Completed		
5-Years	87.1%	87.3%	0.895	87.2%	96.0%	0.003			

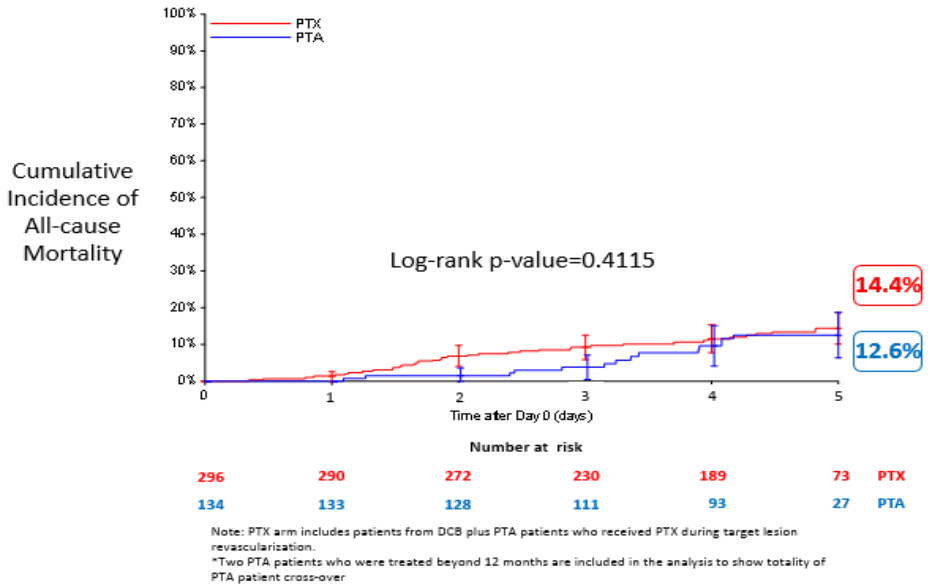
Note: Follow-up visit compliance was defined as number of completed visits over number of expected visits through the follow-up periods

4.9 Modified As-Treated Analysis

IN.PACT IDE and IN.PACT Japan trials did not allow cross-over or treatment of the target lesion with a drug-coated device within one year of the index procedure. Medtronic collected limited information about use of drug-coated devices for treatment of target lesions beyond the index procedure. As such, an additional 'modified as-treated' (mAT) analysis was performed by evaluating patients in the PTA arm who received drug-coated treatment for target lesion revascularization beyond the index procedure. These patients were then included in the 'paclitaxel' cohort and compared to the PTA arm. There were eight PTA patients (seven in IN.PACT IDE and one in IN.PACT Japan) who crossed-over to the paclitaxel cohort in the modified as treated analysis. Six of the eight patients in this cohort received drug-coated treatment within one year of the index procedure and protocol deviations were collected. The remaining two PTA patients who were treated beyond 12 months are included in the analysis to show totality of PTA patient cross-over. This analysis is limited to target lesion revascularizations and does not include treatment in contralateral limbs.

Conclusion: Similar to intent-to-treat analysis, the modified as-treated analysis showed no statistically significant mortality difference between the two groups over the five-year study follow-up period.

Figure 4-7: All-cause Mortality: Modified As Treated Patients in IN.PACT IDE And IN.PACT Japan



4.10 Conclusion

Based on the collection of additional survival data and the results of the additional data analyses for IN.PACT IDE and Japan, and findings from a new independent CEC that reviewed all deaths from IN.PACT IDE and Japan trials, Medtronic concludes that IN.PACT Admiral DCB is a safe device and no correlation between paclitaxel exposure and mortality can be established. The data show no observed dose relationship with mortality or any trends in adverse event profiles that would suggest any systemic toxicity from paclitaxel.

5.0 Effectiveness

Key Points

Results from independent core-lab adjudications demonstrate:

- Superior and durable patency results seen in IN.PACT Drug Coated Balloon (DCB) relative to percutaneous transluminal angioplasty (PTA)
- Superior clinically-driven target lesion revascularization (CD-TLR) rates in the DCB arm vs PTA arm in both IN.PACT IDE and Japan trials
- Superior results which allow patients fewer repeat hospital visits and higher quality of life

5.1 IN.PACT IDE Effectiveness

The IN.PACT Admiral DCB IDE study was an independently adjudicated, blinded, randomized trial demonstrating superior effectiveness of DCB through five years relative to PTA. When looking at the primary effectiveness endpoint, which was defined as primary patency within 1 year post-index procedure, IN.PACT Admiral demonstrated superior patency at one, two, and three years compared to PTA (**Figure 5-1**). (12) As shown in **Figure 5-2**, more patients in the IN.PACT DCB arm experienced less need for reintervention at all time points, including out to five years. The time to first reintervention is delayed almost two times in the DCB arm by 2.2 years compared to 1.3 years in the PTA arm (**Table 5-1**). This allows patients fewer repeat hospital visits and higher quality of life.

Figure 5-1: IN.PACT IDE Patency and Freedom from CD-TLR through 5 years

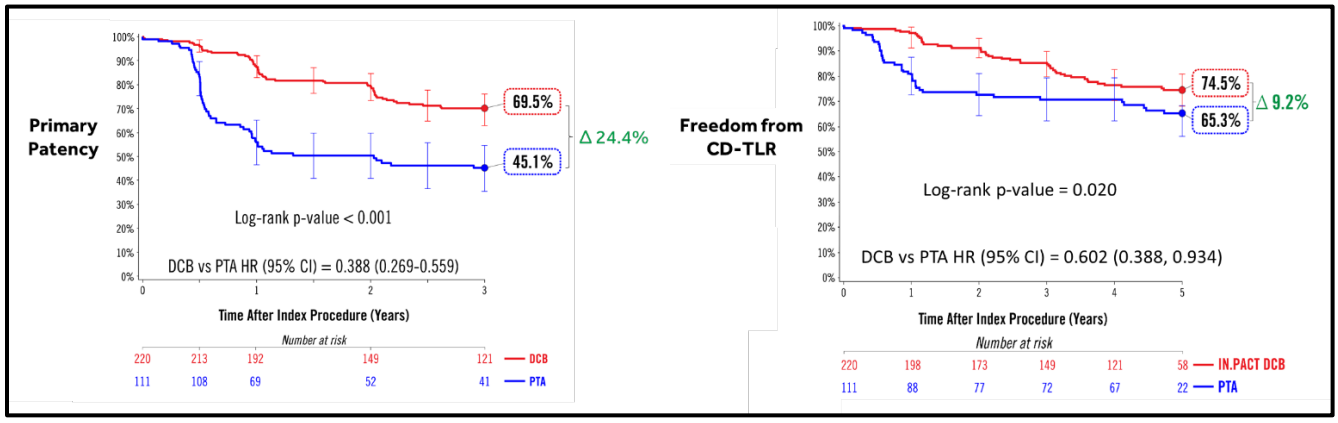


Table 5-1: IN.PACT IDE Time to First CD-TLR

	IN.PACT DCB (47 CD-TLRs in 220 Patients)	PTA (37 CD-TLRs in 111 Patients)	P-value
Time to first CD-TLR within 5 years	2.2 years	1.3 years	< 0.001

5.2 IN.PACT Japan Effectiveness

The superior and durable patency results seen in IN.PACT IDE were also seen in IN.PACT Japan (**Figure 5-2**). Similarly, superior results with regards to CD-TLR rates were also observed in the Japan trial. (**Figure 5-2**). The time to first CD-TLR was more delayed with DCB than with PTA, 1.6 versus 0.5 years, respectively (**Table 5-2**).

Figure 5-2: IN.PACT Japan Patency and Freedom from CD-TLR through 3 years

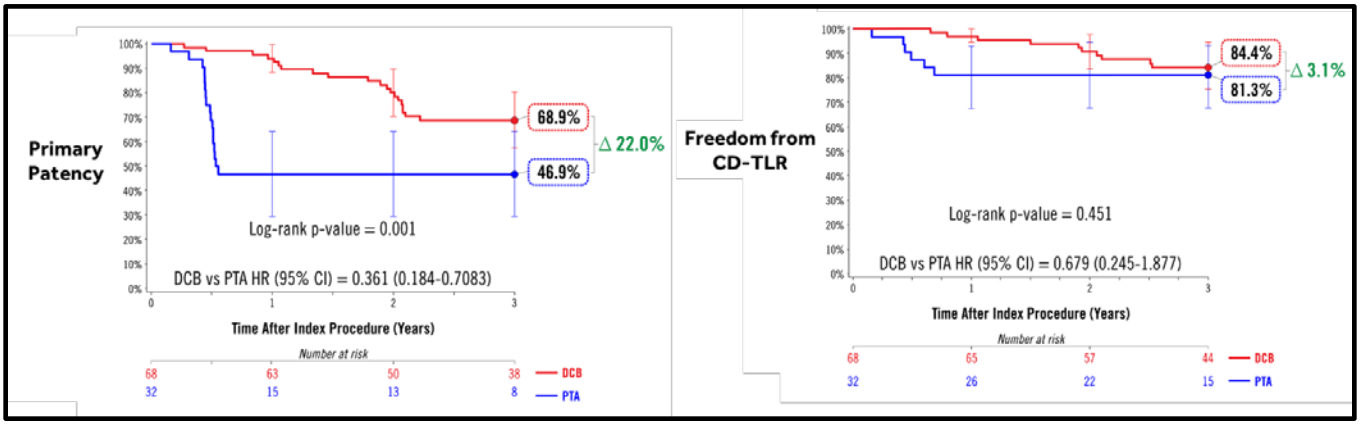


Table 5-2: IN.PACT Japan Time to First CD-TLR rates within 3 years

	MDT-2113 DCB (n=68 Patients)	PTA (n=32 Patients)	p-value
Time to first CD-TLR within 3 years	1.6 years	0.5 years	<0.001

Conclusion: IN.PACT DCB demonstrates superior and durable patency results seen in the IDE and Japan trials. Additionally, superior CD-TLR revascularization rates are seen in the DCB arm versus the PTA arm in both trials along with increased time to first CD-TLR with DCB arm for both RCTs.

6.0 Conclusion

Key Points

Results from randomized studies up to 5 years support the remarkable effectiveness and overall safety profile of IN.PACT Admiral Drug Coated Balloon (DCB) for the treatment of patients with femoropopliteal artery disease.

Medtronic completed multiple analyses in response to the paclitaxel safety concern and the results demonstrate:

- No significant difference in mortality between IN.PACT DCB and uncoated percutaneous transluminal angioplasty (PTA) through 5 years
- No correlation between paclitaxel dose and mortality
- Superior, consistent and durable effectiveness across multiple randomized trials and in real-world use in hundreds of thousands of patients

The risk-benefit profile of IN.PACT Admiral DCB continues to support DCB as first line therapy for the treatment of femoropopliteal artery disease.

7.0 Next Steps

Medtronic acknowledges the mortality signal seen in the Katsanos et al. meta-analysis. The meta-analysis concluded the signal was caused by paclitaxel, with higher doses increasing the magnitude of the signal.

Data from multiple IN.PACT clinical studies demonstrate no safety signal through 5 years and no correlation between paclitaxel dose and mortality. Importantly, preliminary findings suggest follow-up visit compliance is associated with a lower mortality risk, and lesion or procedure characteristics were not identified as predictors of mortality.

Mortality rates and causes following the use of paclitaxel-coated devices are comparable to those observed in un-coated device clinical trials used for lower extremity PAD treatment in similar patient populations.

IN.PACT Admiral DCB demonstrated superior and durable patency and less need for reintervention out to five years. The time to first reintervention is delayed almost two times for patients treated with IN.PACT Admiral DCB (2.2 years vs. 1.3 years PTA). This allows patients fewer repeat hospital visits and provides higher quality of life.

Therefore, proposed recommendations for next steps include the following:

1. **Guideline Enhancement:** Review and update as needed to clarify the appropriate follow-up for PAD patients to optimally manage the overall complexity and range of co-morbidities found in this patient population.
2. **Future PAD studies:** Ensure consistent follow-up and visit compliance in both control and treatment arms, as appropriate. Ensure detailed reporting of contralateral limb revascularization and pharma regimen used. Provide additional guardrails to minimize loss to follow-up, in particular for mortality outcomes.
3. **Large datasets:** Industry supports partnering with key stakeholders (physician societies, FDA, etc.) to further interrogate large observational datasets to confirm lack of a mortality signal over an extended period (through 5 years).

8.0 References

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