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CLINICAL INVESTIGATION ARTERIAL INTERVENTIONS

Two-Year Mortality After Angioplasty of the Femoro-Popliteal Artery with Uncoated Balloons and Paclitaxel-Coated Balloons—A Pooled Analysis of Four Randomized Controlled Multicenter Trials

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Abstract
Purpose In view of a recent meta-analysis reporting increased mortality following angioplasty with paclitaxel-coated devices in peripheral arteries, we performed a patient-level 2-year mortality analysis based on pooled original data of four randomized controlled trials (THUNDER, FEMPAC, PACIFIER and CONSEQUENT).
Methods and Results Clinical data of four randomized controlled trial were pooled to assess 2-year mortality following paclitaxel-coated balloon (PCB) angioplasty compared to angioplasty without paclitaxel (control group). A logistic regression model was applied to identify potential predictors of mortality. At two years, 13 of 185 (7.0%) patients had died in the control group and 16/184 (8.7%) in the PBC group, $p = 0.55$. Kaplan–Meier analysis revealed no significant difference from all-cause death at 2 years (log rank $p = 0.54$). Causes of death were well balanced between the groups with no pattern or trend in favour of any specific causes in the PBC group. Logistic regression revealed that treatment groups (controls or PBC) were not a predictor of 2-year mortality. The only predictor for mortality was patient age $\geq$ 75 years. The delivered paclitaxel doses per patient were not significantly different in patients that died and those who did not die during the 24-month follow-up (5.300 ± 4.224 µg vs. 6.248 ± 4.629 µg, $p = 0.433$).
Conclusions Based on original patient-level data of four pooled randomized controlled trials, we found no increase in 2-year mortality in patients treated with PCB compared to control patients treated with uncoated balloons. Causes of death were well balanced between PCB and control patients.

Keywords Paclitaxel · Drug-coated balloon angioplasty · Femoro-popliteal lesions · Mortality · Pooled data analyses

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Introduction

In a recent meta-analysis of several randomized controlled trials (RCTs), Katsanos et al. [1] reported a significantly increased 2- and 5-year mortality following angioplasty of the femoro-popliteal artery with paclitaxel-coated devices (coated balloons and stents) compared to control groups without paclitaxel. Based on 12 studies, 2-year mortality was reported as 7.2% in the paclitaxel group as compared to 3.2% in the control group. Furthermore, based on three

studies five-year mortality was reported to be 14.7% (paclitaxel) versus 8.1% (controls).

One inherent limitation of the meta-analysis by Katsanos et al. is the lack of access to original patient data. Instead, published summaries of data were used. None of these publications focused on mortality, and neither was mortality of the primary endpoint of the included studies, nor were the studies designed or powered for long-term analysis of mortality. (Primary endpoints were usually late lumen loss or patency at 6 or 12 months.) Furthermore, for several included studies, the mortality data used in the meta-analysis were calculated based on the number of originally included patients and not on the number of patients with follow-up which was available at the relevant time points. In other words, patients lost to follow-up could not be appropriately considered. Last but not least, causes of deaths were not available to Katsanos and colleagues for most included studies, so that they could not provide any causative explanation, as to why more patients might have died after the use of paclitaxel-coated devices and what the underlying toxicological mechanism might be.

These limitations potentially challenge the results of Katsanos et al., and the authors acknowledge the urgent need for further investigation into the subject [1]. As a first and important step, a detailed review of the large body of available patient-level data from RCTs with focus on mortality and causes of death is required to shed more light on this important topic.

We recently published a pooled subgroup analysis of original patient data of four RCTs [2], i.e. THUNDER, FEMPAC, PACIFIER and CONSEQUENT [3–8] with regard to the influence of various patient and lesion characteristics on late lumen loss at 6 months, which was the common primary endpoint. The purpose of the current study is to use the same original patient database for an expanded and detailed pooled analysis of mortality at 2 years.

Methods

Study Design

Original patient data from the prospective THUNDER [3, 4], FEMPAC [5], PACIFIER [6] and CONSEQUENT [7, 8] RCTs were pooled and used for this analysis of mortality. Published results of two of these studies (FEMPAC and CONSEQUENT) [5, 8] were also included in the 2-year mortality analysis by Katsanos et al. [1], and one PCB study (THUNDER) was used in their 5-year mortality analysis [3].

All four studies were conducted by the same core research group. Patients were recruited between 2006 and 2016 in several German centres and had a minimum clinical follow-up period of 2 years. In all four studies, patients with steno-occlusive lesions of the femoro-popliteal artery were randomized to angioplasty using a paclitaxel-coated balloon (PCB) or an uncoated balloon (control group) on a 1:1 basis. Details of study designs, inclusion and exclusion criteria, patient demographics and lesion morphological details were described previously [2]. An overview of the key patient and lesion characteristics is provided in Table 1. Late lumen loss at 6 months was the primary endpoint of the four studies. Two-year clinical follow-up was conducted in all studies and used for mortality analysis. Definitions of the 2-year follow-up in the individual studies are shown in Table 2.

Double inclusions of the left and right legs were allowed by the study protocols as previously reported [3, 5, 6].

Study Devices and Paclitaxel Dose Measurement

In the first two studies (THUNDER and FEMPAC), a PCB with an early version of the Paccocath® coating (prototype catheter of Cotavance®, Bayer/Medtronic) was used. In the PACIFIER trial, the InPact® Pacific (Medtronic) PCB and, in the CONSEQUENT trial, the SeQuent® Please OTW device (B. Braun Melsungen AG) were used. A paclitaxel dose of 3.0 µg/mm^2 with different excipients was applied on all PCBs.

In all four studies, PBC catheters were returned to the sponsor to perform post-interventional measurements of the residual paclitaxel dose left on the catheter. These residual doses were subtracted from the nominal paclitaxel doses of the utilized PCB to determine the doses which were delivered to the patient. Individual patient doses were calculated by adding the doses of all balloons used in the patient, including those used in the contralateral leg in case of double inclusion in the PBC group.

Statistical Analysis

The number of deaths at 2 years in the control and PCB groups was compared using Chi-square statistics. Kaplan–Meier survival analyses were based on the last available follow-up date until the 2-year follow-up was reached. A logistic regression with all-cause mortality at two years as the dependent variable was conducted with the treatment group, i.e. PCB or plain old balloon angioplasty (POBA), patient characteristics and lesion characteristics as independent variables. Paclitaxel dose measurements in patient groups were compared with the unpaired *t* test. All analyses were performed using SPSS version 24.0 (IBM, Munich, Germany).

Table 1 Key patient and lesion characteristics (at enrolment) of the 4 pooled RCTs

Study name	THUNDER		FEMPAC		PACIFIER		CONSEQUENT	
Study group	Control	PCB	Control	PCB	Control	PCB	Control	PCB
Patients (N)	54	48	42	45	47	44	78	75
Age (years)	68 ± 9	69 ± 8	70	67	71 ± 7	71 ± 9	68 ± 9	68 ± 9
Female gender	37%	35%	40%	40%	36%	41%	24%	40%
Diabetes	46%	50%	55%	40%	28%	43%	39%	35%
Hypertension	83%	79%	81%	78%	66%	66%	80%	77%
Hypercholesterolaemia	63%	69%	59%	58%	47%	50%	52%	56%
History of smoking	22%	23%	36%	40%	60%	49%	49%	46%
Coronary artery disease	35%	31%	41%	38%	32%	32%	40%	42%
Cerebrovascular disease	35%	31%	41%	38%	11%	32%	5%	4%
Claudicants	98%	90%	98%	96%	96%	100%	100%	100%
Critical limb ischaemia	2%	10%	7%	4%	4%	0%	0%	0%
Occlusions	26%	27%	19%	13%	23%	38%	29%	23%
Lesion calcification	52%	50%	52%	53%	66%	64%	68%	53%
Mean lesion length (cm)	7.4	7.5	4.7	4.0	6.6	7.0	12.6	13.7

Table 2 Definitions of 2-year follow-up in individual studies

Study	Intervals of 2-year follow-up from date of inclusion
THUNDER	18–30 months
FEMPAC	22–36 months
PACIFIER	21–27 months
CONSEQUENT	21–27 months

Results

Patients Available for 2-Year Follow-Up

A total of 218 patients were originally included in the control group and 215 in the PCB group. Since in the earlier studies (THUNDER, FEMPAC and PACIFIER), double inclusions of the left and right legs were allowed by the study protocols as previously reported, 9 patients/limbs of the control group and 13 patients/limbs of the PBC group with double inclusions were excluded from the original patient base for this mortality analysis. This left 209 patients in the control group and 202 patients in the PCB group as the primary patient base. Of those, 24 patients were lost to follow-up before 2 years in the control group and 18 patients in the PCB group. The final patient base for the 2-year mortality analysis was therefore 185 (controls) and 184 (PCB) patients. Details are shown in Table 3.

Mortality at 2 Years and Causes of Death

At 2-year follow-up, 13 of 185 patients had died in the control group and 16 of 184 in the PCB group. Corresponding mortality rates were 7.0% and 8.7% of available patients, respectively ($p = 0.55$). Details of mortality in individual studies are provided in Table 4. Kaplan–Meier statistics for freedom from all-cause death also showed no difference between groups ($p = 0.54$, Fig. 1).

The causes of death are shown in Table 5. The most common causes were cardiac (6 patients in the control group and 4 after PCB) and malignancy (one lung cancer and one liver cancer in the control group and one lung cancer and two pancreatic cancers in the PCB group). Causes of death only seen in the PCB group were stroke, major amputation, thrombosis, multiple organ failure, brain haemorrhage and trauma (one patient each). Overall, causes of death were well balanced between the treatment groups with no obvious pattern or trend towards an increase in any specific causes of death in the PCB group.

Results of the logistic regression analysis revealed that patient age $\geq$ 75 years was the only significantly associated risk factor for 2-year mortality. All other tested patient and lesion variables had no significant association with mortality. This included treatment groups (uncoated balloon or PCB), which were not a predictor for mortality ($p = 0.53$) (Table 6).

Given that age had a negative impact on mortality, a Chi-square analysis was conducted to study patients who died during the 2-year follow-up. All-cause mortality rate was numerically higher ($p = 0.100$) in patients $\geq$ 75 years, i.e. 11.8% (11/93) vs 6.5% (18/276). Patients who passed

Table 3 Patient population and 2-year follow-up

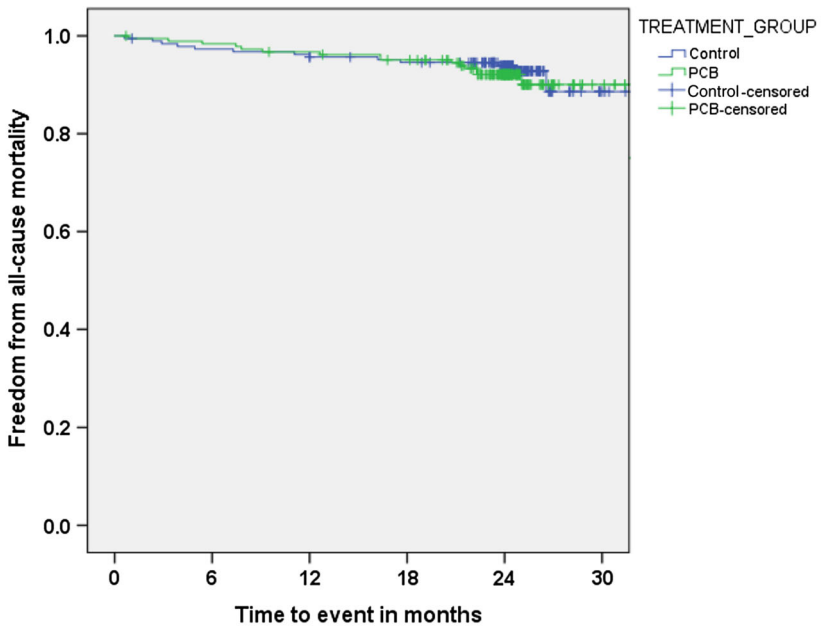
Study	Patients originally included		Patient base for mortality analysis (after exclusion of double entries)		Patients with 2-year follow-up	
	Control	PCB	Control	PCB	Control	PCB
THUNDER	54	48	54	46	49	43
FEMPAC	42	45	36	37	29	32
PACIFIER	47	44	44	41	42	39
CONSEQUENT	75	78	75	78	65	70
Pooled	218	215	209	202	185 (88.5%*)	184 (91.1%*)

*Percentages refer to the patient base for mortality analysis

Table 4 Mortality at 2 years with the number of dead patients and the number of patients for whom the survival status was known

Study	Control		PCB	
	Dead	Mortality (%)	Dead	Mortality (%)
THUNDER	5/49	10	6/43	14
FEMPAC	3/29	10	6/32	19
PACIFIER	4/42	10	2/39	5
CONSEQUENT	1/65	2	2/70	3
Pooled	13/185*	7.0	16/184*	8.7

*$p = 0.55$ (Chi-square test)



Patients at risk	0 months	3 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months
Control	185	182	179	176	173	170	167	164	161
PCB	184	181	178	175	172	169	166	163	160

Fig. 1 Kaplan–Meier curve for freedom from all-cause death (log rank $p = 0.542$)

Table 5 Causes of death at 2 years

	Control	PCB
Cardiac	6	4
	Heart failure (n = 3)	Heart failure (n = 2)
	Acute MI	Acute MI
	Cardiac arrhythmia	Cardiac arrhythmia
	Sudden cardiac death	
Malignancy	2	3
	Liver	Pancreas (n = 2)
	Lung	Lung
Sepsis	2	0
	Pneumonia	
	Perforated duodenal ulcer and peritonitis	
Other	1	6
	Chronic obstructive pulmonary disease	Stroke
		Major amputation
		Thrombosis
		Multiple organ failure
		Brain haemorrhage
		Trauma
Unknown	2	3
All	13	16

MI myocardial infarction

Table 6 Patient and lesion morphological risk factors in the binary logistic regression model

Variable in logistic regression model	*P* value
Treatment group DEB versus POBA	0.530
Age ≥ 75 years	0.030
Gender	0.115
Diabetes	0.864
Hypertension	0.270
Smoking	0.748
Hypercholesterolaemia	0.747
Coronary artery disease	0.704
Cerebrovascular disease	0.965
Critical limb ischaemia	0.179
Occlusion	0.333
Lesion calcification	0.498
Lesion length	0.941

away were numerically slightly older compared to patients who did not die (71.3 ± 9.2 vs 68.5 ± 8.7 years, p = 0.105).

Delivered Paclitaxel Doses

The mean delivered paclitaxel doses were 5.300 ± 4.224 μg in the patients that died during the 24-month follow-up and 6.248 ± 4.629 μg in those who did not die (p = 0.433).

Discussion

In this pooled analysis of original patient data of four RCTs, we found no relevant difference in 2-year mortality between patients with steno-occlusive lesions of the femoro-popliteal artery treated with PCBs and control patients without the use of paclitaxel. Mortality rates of available patients at 2 years were 7.0% for controls and 8.7% for the PCB group (p = 0.55). We could therefore not confirm the findings of significantly increased mortality after paclitaxel-coated devices in the recent meta-analysis by Katsanos et al. [1]. The only tested patient or lesion variable that affected 2-year mortality was patient age ≥ 75 years.

The causes of death were well balanced between the treatment groups in our study with no obvious pattern or trend towards an increase in any specific causes of death in the PCB group. Causes of death only seen in the PCB group were stroke, major amputation, thrombosis, multiple organ failure, brain haemorrhage and trauma (one patient each). Even if one assumed that these deaths might have been influenced by the use of PCB, it would be extremely difficult to explain what common toxicological mechanism

might have played a role in such very different diseases, especially if one considers the extremely low doses of paclitaxel on PCBs. Systemic side effects of paclitaxel such as neutropenia, peripheral neuropathy, hypersensitivity reactions and asymptomatic bradycardia have been reported in systemic therapy for cancer with plasma levels in the order of 100–1000 times higher than those observed after local intra-arterial administration [9].

Patients who underwent PCB angioplasty and died during the 24-month follow-up did not have a higher paclitaxel dose compared to those who did not die. Indeed, the mean dose per patient was numerically lower in patients who died (NS). We could therefore not confirm the finding by Katsanos et al. of a relationship between delivered paclitaxel dose and mortality. Their postulated causality was on the foundation of theoretically derived paclitaxel doses which in turn were based on a number of assumptions. These assumptions included the lesion length and vessel diameter representing the exposed tissue surface, irrespective of the used drug delivery platform (stent, balloon). Furthermore, precise procedural details such as the number of PCBs or the degree of balloon overlap were not available for their regression analysis, further contributing to the granularity of their data. In contrast, in our study paclitaxel doses delivered to individual patients were calculated based on measurements of the post-interventional residual paclitaxel dose on every balloon used. We did not find a significant differences in terms of the delivered paclitaxel doses in patients who died and those who did not (5.300 ± 4.224 µg vs. 6.248 ± 4.629 µg, $p = 0.433$) which is in agreement with the findings by Schneider et al. [10]. As compared to our dose levels, the reasons for the higher doses reported by Schneider and coworkers for patients who died $11.829.8 \pm 7.347.6$ µg vs. those who survived $11.419.6 \pm 7.414.8$ µg ($p = 0.529$) can probably be found in the longer lesions which constituted their database.

A major limitation of the meta-analysis of Katsanos et al. [1] is the assumptions made on the number of patients with available clinical follow-up at the relevant time points. For example, in the original publication of the FEMPAC study by Werk et al. [5], it was reported that at 2-year follow-up 3 and 6 patients had died in the control and PCB groups, respectively. Werk et al. did not specify how many patients were available for the 2-year follow-up. Katsanos et al. used the original number of recruited patients as the reference, i.e. 42 (controls) and 45 (PCB). However, our analysis of original patient data revealed that only 29 (controls) and 32 (PCB) were available for 2-year mortality analysis. Furthermore, Katsanos et al. used 7 deaths for the PCB group (Fig. 2 in their paper), instead of the correct number of 6 deaths reported by Werk et al. As a result, the assumed mortality rates by Katsanos et al. were 7% for controls and 16% for PCB. The mortality rates based on individual patient data analysis as per our study, however, were 10% and 19%, respectively. Similarly, Katsanos et al. reported the 5-year mortality rates of the THUNDER study based on the originally recruited patient numbers as 8 of 54 patients (15%) for controls and 12 of 48 patients (25%) for PCB (Fig. 3 in their paper). However, the 5-year follow-up paper of THUNDER by Tepe et al. [3] specifies that only 29 (controls) and 37 (PCB) patients were available for 5-year follow-up (Fig. 1 in their paper), resulting in mortality rates of 28% and 32%, respectively. These examples of substantial discrepancies cast a serious shadow of doubt on the validity of the results of the meta-analysis by Katsanos et al. and underline the importance of revisiting the original patient-based data.

A very recent post hoc analysis of four other PCB trials by Schneider et al. [10] consisted of 1837 patients treated with PCB and 143 patients treated with POBA. They reported no significant difference ($p = 0.399$) in terms of 5-year mortality between PCB (9.3%) and controls (11.2%) in their patient population, which is in good agreement with our pooled data.

Patients lost to follow-up are an important factor in mortality analysis. It is a likely assumption that deceased patients are over-represented among these patients. This assumption is supported by our results. Of the four analysed studies, the CONSEQUENT trial had the lowest 2-year mortality rates in both groups with 2% for controls and 3% for PCB and the highest number of patients was lost to follow-up (10 and 8 patients, respectively). Given that the overall number of patients lost to follow-up was higher in the control group than in the PCB group (24 versus 18), it appears possible that the true mortality rate in the control was somewhat underestimated.

The unaccounted number of patients lost to follow-up in the meta-analysis by Katsanos et al. [1] as discussed above is a further limitation of their study.

Our study has limitations. It is a post hoc subgroup analysis based on prospectively collected data over a considerable time span. However, due to similar protocols across the pooled studies, the data were quite homogenous. Despite pooling four RCTs, the overall number of patients that had died was relatively small. Our analysis refers to a lower number of studies and fewer patients than in the meta-analysis of Katsanos [1].

Conclusions

Based on pooled patient-level data of four RCTs, we found no increase in 2-year mortality in patients treated with PCB compared to POBA patients. Causes of death were well balanced between PCB and control patients. Paclitaxel

dose was not higher in patients who died at two years compared to those that did not die.

Given the well-proven clinical benefit of PCB for patients with steno-occlusive disease of the femoro-popliteal artery, no premature conclusions should be drawn from the paper by Katsanos and coworkers. Further in-depth patient-level mortality analysis of the large amount of available data from previous RCTs is required to further clarify the matter.

Compliance with Ethical Standards

Conflict of interest TA consults for B. Braun Melsungen AG. MWW is a full-time employee of the Medical Scientific Affairs department of B. Braun Melsungen AG.

Ethical Approval All studies were approved by the Federal Institute for Drugs and Medical Devices, by the Federal Agency for Radiation Protection and by all relevant ethics committees of participating centres.

Informed Consent Patients gave written informed consent prior to inclusion. An independent critical event committee was installed to adjudicate event rates. All trials were registered with the US National Institutes of Health prior to recruitment. This trial was conducted in accordance with the updated Declaration of Helsinki and other relevant guidance.

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