Paclitaxel and Mortality in Patients With Claudication and De Novo Femoropopliteal Lesions: A Historical Cohort Study

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Abstract

Objective: To compare the mortality rates of patients with claudication and de novo femoropopliteal lesions treated with and without paclitaxel coated devices (PCD).

Background: A recent meta-analysis, mostly including patients with claudication and de novo femoropopliteal lesions but also with recurrent stenoses and critical limb ischemia, has shown a significant excess mortality in patients treated with PCD.

Methods: Comparison of two historical cohorts of patients presenting with claudication and de novo femoropopliteal lesions treated with and without PCD at our institution between 2008 and 2018.

Results: After review of 5219 arteriograms in patients presenting with peripheral artery disease, 700 consecutive patients were included consisting in 72.6% of male (n=508). Mean age was 68.1±8.5 years. 45.7% of the patients (n=320) had a treatment including a PCD. Mean femoropopliteal lesion length was 123±91mm including 44.6% of occlusions. Patients of the control group were censored at crossover to paclitaxel when applicable. Mortality rates at 1, 2 and 5 years were 4.6%, 7.5%, 19.4% and 1.6%, 6.2%, 16.6% in the non-PCD and PCD groups respectively. The relative risks of death when using PCD were 0.35 (p=0.03), 0.83 (p= NS) and 0.86 (p= NS) at 1, 2 and 5 years respectively.

Conclusion: There was no excess mortality in patients with claudication and de novo femoropopliteal lesions treated with paclitaxel coated devices at 1, 2 and 5 years of follow-up. The current study suggests that additional prospective randomized studies properly powered to study mortality are necessary.

Introduction

The development of paclitaxel-coated devices (PCD) has allowed physicians to increase the proportion of patients treated with primary balloon angioplasty without the need of secondary stenting as this new approach was associated with a dramatic improvement in long term patency(1). A meta-analysis published by Katsanos et al in 2018 has had a profound impact upon the vascular community(2). In that study, the authors reported a significant absolute increase of 3.4% of all cause death at 2 years and 6.6% at 5 years in comparison to the control group when using PCD. Following this publication, the multidisciplinary VIVA physician group did an impressive work in close collaboration with industry. They comprehensively re-analyzed the data of 8 prospective randomized clinical trials (3). After this thorough reanalysis, they demonstrated a signal of excess mortality at 5 years in the PCD group. It is of importance to note that both meta-analyses were based upon studies that included patients with de novo claudication, recurrent stenoses and critical limb ischemia.

Following this so-called Paclitaxel controversy, the FDA recommended to consider alternative treatment options to PCD and to continue diligent monitoring of patients who have been treated with paclitaxel-coated balloons and paclitaxel-eluting stents (4). Given our large use of this very promising technology, we chose to review our database to compare two historical treatments. Our study aimed at comparing the 1 year, 2 years and 5 years mortality rates of patients with claudication and de novo femoropopliteal lesions treated endovascularly with PCD in comparison to a historical cohort treated without PCD at our institution.

Material And Methods

Study Population:

The study was approved by the local institutional ethics committee of the *Centre Intégré Universitaire de Santé et de Services Sociaux de l'Estrie - Centre Hospitalier Universitaire de Sherbrooke* (CIUSSS de l'Estrie-CHUS). This study was a single-center observational retrospective review of consecutive patients treated with plain old balloon ± bare metal stent (POBA) or Paclitaxel Coated Device (PCD) including Drug Coated Balloon (DCB) and Drug Eluting Stents (DES) for the treatment of disabling intermittent claudication at the University Hospital of Sherbrooke from January 2008 to December 2018. The written

consent to participate in the study was waived due to its retrospective character. Following the institutional and local regulatory policies, all patients signed written informed consent before undergoing the procedure.

A review of the entire database of patients treated endovascularly at our institution during the 2008–2018 period was performed. Consecutive patients who presented with lifestyle limiting claudication and have had an endovascular treatment of de novo femoropopliteal disease were included.

Inclusion criteria were as follows: 1- patients older than 18y-o; 2- presenting with disabling intermittent claudication (*Rutherford stage 2 and 3*); 3- referred for endovascular revascularization of de novo femoropopliteal artery lesions. Exclusion criteria were as follows: 1-Past history of femoropopliteal bypass graft; 2- Past history of endovascular revascularization of ipsilateral or contralateral femoropopliteal artery lesion(s); 3- Past or current history of critical limb ischemia (Rutherford class 4, 5 and 6).

Detailed demographic, clinical, and procedural informations were gathered for each patient from their electronic medical record. Patients treated with a DCB and/or DES were enrolled in the PCD group. Patients treated with a POBA and/or BMS were enrolled in the POBA group. It was imperative for patients in the POBA group not to have been in contact with a paclitaxel-coated device neither before the index procedure nor during the follow-up. When a patient initially in the POBA group was subsequently treated with PCD, the follow-up was censored at the date of this crossover to paclitaxel treatment.

Study Endpoints

The primary endpoint of this study was the difference in all-cause mortality rates after POBA and PCD angioplasty at 1, 2 and 5-years of follow-up. Secondary endpoints included the relationship between paclitaxel dose and mortality, and search for mortality predictors, including type of treatment (POBA vs. PCD), age, sex, dyslipidemia, diabetes mellitus, tobacco use, renal insufficiency, cancer, chronic obstructive pulmonary disease, coronary artery disease and heart failure.

Data Collection

Since 1995, all clinical and biological files of the patients treated at our institution are systematically and comprehensively gathered in an Electronic Health Record system. Since 2000, all the imaging files are archived in a PACS system. Paclitaxel Coated Devices are used as a standard of practice for the treatment of femoropopliteal artery lesions since 2014 at our institution(4). A systematic review of the entire database of lower limb arteriograms performed from 2008 to December 2018 was conducted. After careful review and analysis of the clinical indications and treatments, 700 patients were included (cf. flow chart Fig. 1). The clinical characteristics and risk factors of the patients were extracted from their numerical files. The reported baseline clinical characteristics were those present at the time of treatment. The corresponding 700 DSA were carefully analyzed to determine arterial lesion lengths, locations and quality (stenosis or occlusion). When applicable, the date of death of the patients were retrieved from a registry held by the Régie de l'Assurance Maladie du Quebec, the organism responsible for the management of public health in the province of Québec. All the death occurring in the province are gathered in this database. The interrogation date of this mortality registry for the current study was the 14th of October 2020.

Statistical Analysis:

Continuous variables were expressed as means ± standard deviation (SD). Dichotomous and categorical variables were expressed as counts and percentages. Continuous variables were compared using the Mann-Whitney or Student's t-tests. Categorical data were compared using the chi-squared or Fisher's exact tests. Survival was evaluated using Kaplan-Meier analysis; the survival curves were compared using the log-rank test. Between-group comparisons were

made with a time-dependent multivariable Cox regression model in order to adjust group hazard mortality ratios with known confounding factors. This time-varying model allowed to consider the patients included in the POBA group that were subsequently treated with PCD without censoring them. The Cox model was adjusted for age, sex, active tobacco use, diabetes, cancer, hyperlipidemia, arterial hypertension, Charlson score and heart failure. The level of statistical significance was set at $p < 0.05$. The software used was IBM SPSS Statistics, v.24, Armonk, NY.

Results

Patients characteristics:

From 2008 to 2018, a total of 700 consecutive patients presenting with lifestyle limiting claudication and treated for de novo femoropopliteal artery disease were included. The cohort included 72.6% of male (n=508). Mean age was 68.1±8.5years.

All baseline demographics and clinical characteristics were summarized on a patient-basis (cf. Table 1). Cardiovascular risk factors were highly prevalent, including arterial hypertension in 51.3%, hyperlipidemia in 50%, smoking in 19.4%, and diabetes in 27.4% of patients. Several baseline characteristic differences were statistically significant between the POBA and DCB groups, respectively: Diabetes mellitus [31.1% and 23.1% (p=0.02)], Dyslipidemia [59.2% and 39.1% (p<0.001)]; Coronary Artery Disease [44.2% and 34.3% (p=<0.001)], Tobacco use [24.3% and 14.7% (p=0.004)]; Arterial Hypertension [58.9% and 42.2% (p<0.001)], COPD [15% and 9.4% (p=0.03)], and Charlson score [0.44±0.98 and 0.31±0.9 (p=0.04)].

Treatments:

The mean dose of paclitaxel delivered per intervention in the PCD group was 12.3±9.4 mg. Details regarding the paclitaxel coated devices used are reported in Table 2. 140 patients had same day bilateral femoropopliteal treatments. There were 44.8% of femoropopliteal occlusions (n=376/840). Mean length of treated lesions were 123±91mm. Details regarding the femoropopliteal lesions are reported in Table 3.

Mortality study:

Mortality rates at 1, 2 and 5 years in the POBA and PCD groups were 4.6% CI [2.1-7.1], 7.5% [4.4-10.5], 19.4% [14.5-24] and 1.6% [0.2-2.9], 6.2% [3.5-8.9], 16.6% [10.2-22.6] respectively (p=0.03 at 1 year and NS at 2 and 5 years). In comparison to the POBA group, the relative risks of death in the PCD group were 0.35, 0.83 and 0.86 at 1, 2 and 5 years. Kaplan Meier survival curves are presented in Figure 2 and Figure 3.

The multivariable Cox regression analysis showed that age (p<0.0001), Tobacco use (p=0.0003) and a Charlson score ≥1 (p<0.02) were independent predictors of all-cause mortality. There were also trends for cancer (p=0.053) and male sex (p=0.052) (cf. Table 4). When adjusting for potential confounders and accounting for cross-over, PCD didn't show any significant association with all-cause mortality. There was no correlation between DCB length or paclitaxel dose with mortality. Neither were there any correlation between treated lesion length and mortality.

Discussion

The current study, comparing two historical cohorts of patients with claudication and de novo femoropopliteal artery lesions treated with and without paclitaxel coated devices (PCD), failed to show any excess mortality with the use of PCD. On the contrary, there was a statistically significant excess mortality at one year of follow-up in the non PCD group. This excess mortality was not maintained over time at 2 and 5 years of follow-up. Those results are consistent with two recent studies that also failed to show any significant increase in mortality when using paclitaxel coated devices(5,6).

Despite its retrospective design, this work has several strengths. The availability of a national mortality registry limited the potential lost to follow-up bias. This allowed to draw reliable conclusions regarding the mortality of the patients included in this work. Furthermore, it was chosen to only include the patients who presented for their very first endovascular treatment of femoropopliteal artery related disabling claudication. It is important to note that the patients in the POBA group had significantly higher cardiovascular risk factors such as tobacco use, hypertension, dyslipidemia and diabetes. Nevertheless,

after adjustment for potential confounders and accounting for cross-over, PCD didn't show any significant association with all-cause mortality.

On the other hand, patients in the PCD group had significantly longer lesions and more occlusions. These differences are very likely explained by the fact that our institutional technology evaluation unit recommended the use of PCD for TASC C and D femoropopliteal lesions but the choice between POBA and PCD was left at the operator's discretion for TASC A and B lesions (4).

The question of how a supposedly local treatment may be responsible for an excess mortality 2 years and 5 years later is currently a conundrum. Several factors influence the fraction of drug released into the arterial wall and the fraction released in the systemic circulation, such as the drug carrier and the arterial lesion complexity(8,9). Though there is an initial burst of serum paclitaxel following DCB or some of the DES delivery, this is a transient phenomenon with the drug being cleared during the following days(10,11). The rest of paclitaxel is receptor bound, and there is no evidence for a paclitaxel reservoir in the organism(12). A dose-effect relationship had been initially suspected but never confirmed in accordance with the current study. Performance and detection biases had been suspected since interventional studies are difficult to blind(13). One of the hypothesis was that the patients in the control arm, with more restenosis, might have had more visits with study investigators at which secondary prevention medical therapies could have been properly adjusted. Another hypothesis could be that the patients treated with PCD having a better ambulatory capability could have been more active, raising the risk of stress-induced myocardial infarction. Nevertheless, as of today, no study has demonstrated a significant increase in cardiovascular events in the paclitaxel group. It is also important to realize that the mechanism of action, if mechanism there is, could impact the way we should analyze the mortality. If the phenomenon precipitates some already preexisting conditions that were about to decompensate in the near future, then this premature death will be noticed only during a certain period of time. This mortality displacement or "harvesting effect" implies that after some periods with excess mortality, there is a decrease in overall mortality during a subsequent period of time(14). On the other hand if this is a toxic phenomenon, occurring randomly in patients or without regard to the underlying conditions, then the excess mortality should be maintained over a longer period of time. The current study refutes both hypotheses with on the contrary an excess mortality in the POBA group at 1 year of follow-up and almost no difference at 2 and 5 years of follow-up.

Patients with claudication are expected to benefit the most from drug coated devices. The longer patency rates associated with PCD are synonym with a better ambulatory capability and better quality of life. Both Katsanos et al and Rocha-Singh et al studies included mostly patients with claudication but also 11.4% and 6.1% of patients with CLI respectively. It is important to note that patients with critical ischemia have a higher mortality rate than patients with claudication. When combined together, the mortality rate of patients with claudication and critical ischemia does not follow a normal distribution, but a bimodal distribution since mortality has been reported to be up to 36% at two years in CLI (7) while ranging between 4 and 10% in patients with claudication (2,5). Combining both groups together may have an important impact on mortality studies. The probability of death has a binomial distribution (dead or alive). The standard deviation of a binomial distribution is estimated to be $\sqrt{\frac{pq}{n}}$, with p: probability to be dead at two years, q: probability to be alive at two years and n: number of patients. Following this definition, the closer the probability of an event is to 50%, the larger is its standard deviation and its confidence interval. If it is assumed that the respective mortality rates of patients with claudication and CLI are 4% and 36%, using a similar number of patients as in the meta-analysis by Katsanos et al (4133 patients with claudication and 530 with CLI), the standard deviation of the mortality rates at two years is 0.3% in patients with claudication and 2.08% in patients with CLI. The respective confidence intervals are then [3.41 - 4.59] (4±1.96x0.3) and [31.9 - 40.1] (36±1.96x2.08). Among the 4133 patients with claudication, at two years the 95% confidence interval of deaths ranges between 141 and 190 patients while it could vary between 169 and 213 for the 530 patients with CLI. This example shows how an apparently small proportion of patients with CLI may have a huge impact on mortality rates. On a same note, to show an excess mortality rate of 3.4%, as reported by Katsanos et al at 2 years, 1618 patients are necessary (809 per arm) when using a mortality risk of 4%, a risk alpha of 5% and a risk beta of 20%. This number becomes 7192 (3596 per arm) when using a mortality risk of 36%. Consequently, both groups

of patients with claudication and CLI should rather be studied separately as in the study by Nordanstig et al. It could be relevant for both the VIVA group and Katsanos et al to report the respective mortality rates of patients with de novo claudication, recurrent disease and critical limb ischemia to better appreciate the impact of each group on their mortality analyses.

Given our large use of this very promising technology with excellent patency rates, the study by Katsanos et al has had a profound impact upon our practice. Although claudication may be a severely debilitating disease with dire consequences for the quality of life of patients, the possibility of increasing the risk of death dramatically lowered its benefit to risk ratio. On the other hand, given the lack of physiopathological mechanism, and knowing that the meta-analysis combined studies that were not powered to study mortality, it was very difficult to offer a second class treatment with all its limitations instead of drug eluting devices that would provide improved patency rates, lower reinterventions and better quality of life. In order to help us with this ethically demanding task, the FDA recently asked the Multi-Specialty and Multi-Society Coalition for Patient Safety with Paclitaxel Technologies to develop a set of talking points concerning the risks and benefits of using paclitaxel devices(15). Among others, the committee indicated that in individual patients judged to be at particularly high risk for restenosis and repeat femoropopliteal interventions, clinicians may determine that the benefits of using a paclitaxel-coated device may outweigh the risk of late mortality. The results of the current study, that failed to show any increase in mortality in patients with de novo claudication treated with paclitaxel coated devices, support the need for additional prospective randomized studies properly powered to study mortality.

Conclusion

The paclitaxel controversy has cast doubts over the safety profile of paclitaxel for the management of peripheral artery disease in patients with claudication and de novo femoropopliteal lesions. The current study, including a large group of patients with claudication and de novo femoropopliteal lesions didn't show any excess mortality with the use of paclitaxel up to 5 years of follow-up and support the need for additional prospective randomized studies properly powered to study mortality.

Limitations

This was a retrospective study comparing two historical cohorts with the potential biases related to this methodology.

Though one strength of our study was the availability of a provincially held register of patients' death, limiting the potential lost to follow-up patients, the specifics regarding the causes of death weren't available.

Abbreviations

CLI: Critical Limb Ischemia

DCB: Drug Coated Balloon

DES: Drug Eluting Stent

PCD: Paclitaxel Coated Devices

POBA: Plain Old Balloon Angioplasty

Declarations

Acknowledgements: Not applicable.

Authors' contributions: GG, SB, MNL, FB, BB, MAD performed the interventions and followed-up the patients. GG and JFV wrote the manuscript. SCP, MC, AB, MB, KM, PF, BYD, MB, CA collected and organized the data. All the authors revised and approved the final manuscript.

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Availability of data and materials: N/A

Ethics approval and consent to participate: This work was approved by the Institutional Review Board of Sherbrooke University Hospital. Approval number is 2020-3139. All procedures reported herein were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Consent for publication: N/A.

Competing interests: Gerald Gahide is medical consultant for Boston Scientific. The other authors declare that they have no competing interests.

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Tables

Due to technical limitations, table 1-4 is only available as a download in the Supplemental Files section.

Figures

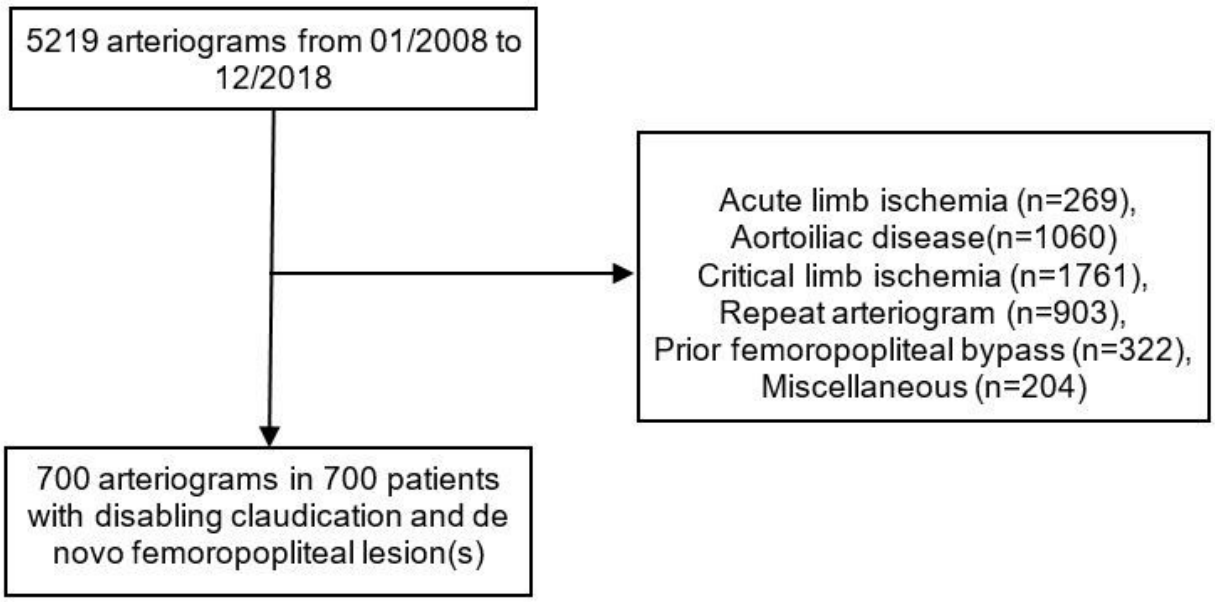

Figure 1

Flow chart of the selection of the patients included in the study.

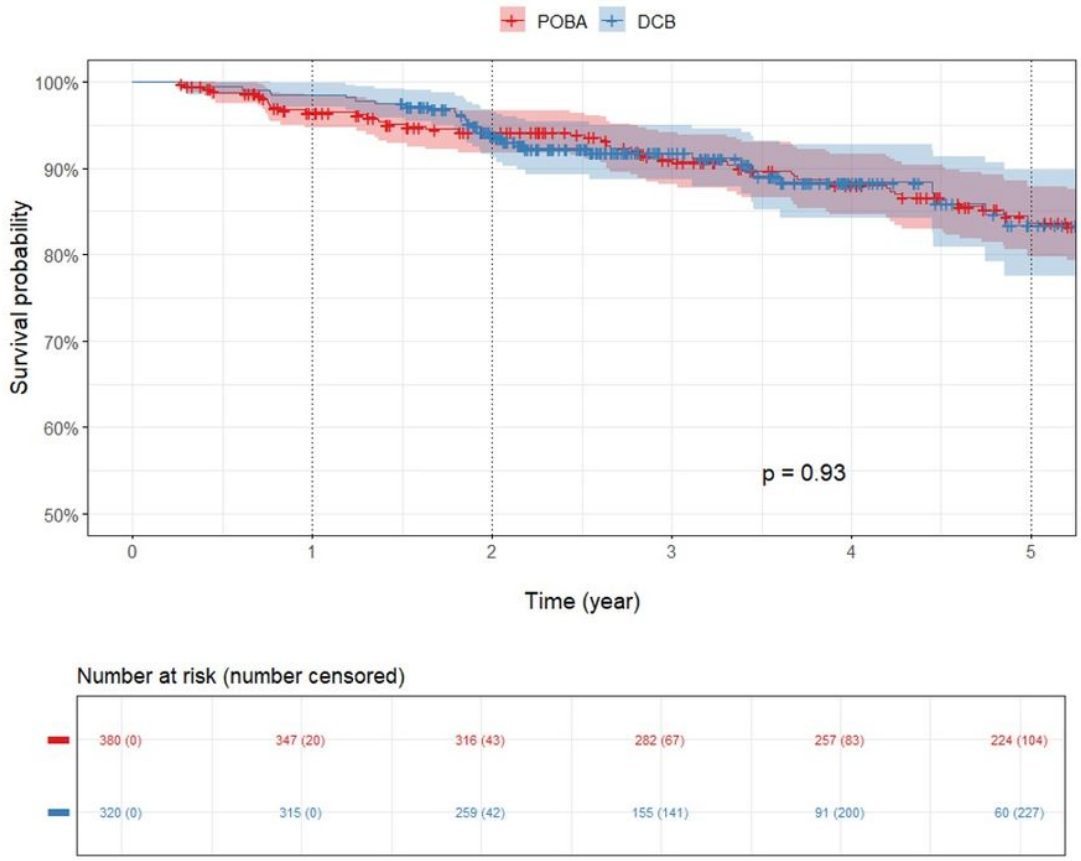

Figure 2

Kaplan-Meier estimates of survival of the entire cohort for the POBA and DCB group through 5 years including the interval of confidence. (PCD: Paclitaxel Coated Devices; POBA: Plain Old Balloon Angioplasty).

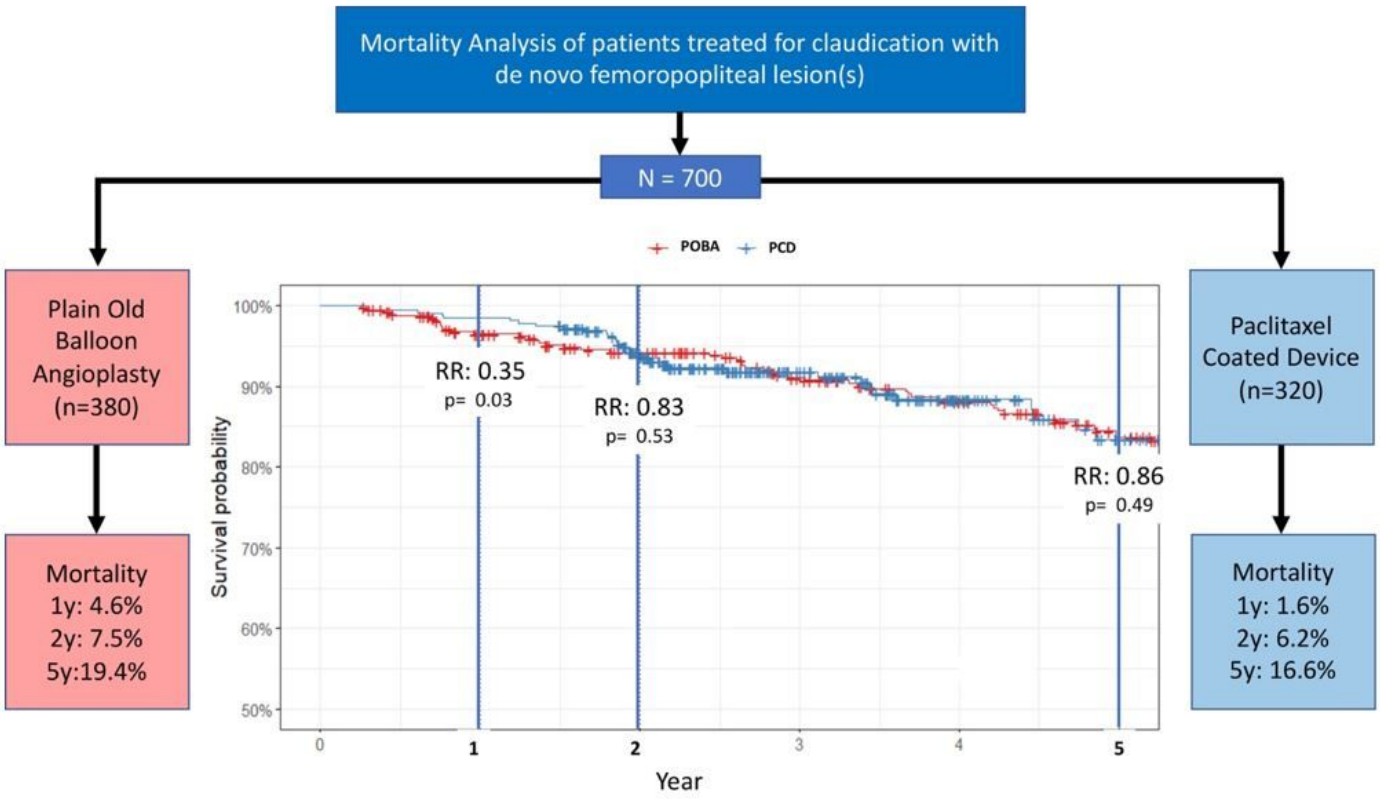

Figure 3

Annotated Kaplan-Meier survival analysis with the relative risk-ratio (RR) at 1, 2 and 5 years of follow-up. (PCD: Paclitaxel Coated Devices; POBA: Plain Old Balloon Angioplasty)

Supplementary Files

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- Table1.docx