A multicenter study of anticoagulation in operable chronic thromboembolic pulmonary hypertension

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Short Title: Anticoagulation in chronic thromboembolism

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Essentials:

- Life-long anticoagulation is recommended in thromboembolic pulmonary hypertension (CTEPH)
- We provide the largest evaluation of anticoagulation outcomes and complication rates in CTEPH
- Bleeding rates were similar but recurrent thromboembolism higher with Direct Oral Anticoagulants
- We provide a strong rationale for further prospective study of anticoagulation in CTEPH

Abstract:

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is an uncommon complication of acute pulmonary emboli necessitating lifelong anticoagulation. Despite this, little data exists on the safety and efficacy of Vitamin K Antagonists (VKAs) in CTEPH and none for Direct Oral Anticoagulants (DOACs).

Objectives: To evaluate outcomes and complication rates in CTEPH following Pulmonary Endarterectomy (PEA) for individuals receiving VKAs or DOACs.

Methods: Consecutive CTEPH patients undergoing PEA between 2007 and 2018 were included in a retrospective analysis. Post-operative outcomes, recurrent venous thromboembolism (VTE) and bleeding events were obtained from patient medical records.

Results: 794 individuals were treated with VKAs and 206 with DOACs following PEA. Mean observation period was 612 (SD: 702) days. Significant improvements in haemodynamics and functional status were observed in both groups following PEA ($p < 0.001$). Major bleeding events were equivalent ($p = 1$) in those treated with VKAs (0.67%/person-year) and DOACs (0.68%/person-year). VTE recurrence was proportionately higher ($p = 0.008$) with DOACs (4.62%/person-year) than VKAs (0.76%/person-year), although survival did not differ.

Conclusions*:* Post-PEA functional and haemodynamic outcomes appear unaffected by anticoagulant choice. Bleeding events were similar, but recurrent VTE rates significantly higher in those receiving DOACs. Our study provides a strong rationale for prospective registry data and/or studies to evaluate the safety of DOACs in CTEPH.

Keywords: Anticoagulant, complications, pulmonary hypertension, venous thromboembolism, warfarin

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is an uncommon complication of acute pulmonary embolism [1]. It is characterised by the elevation of mean pulmonary artery pressure in the presence of organised occlusive thromboemboli in the pulmonary arteries following at least three months of effective anticoagulation [1]. Pulmonary endarterectomy (PEA) is the treatment of choice in those with surgically accessible thrombi [2,3]. Lifelong anticoagulation is recommended in all [2,3].

Conventionally, Vitamin K antagonists (VKAs) have been used in the treatment of CTEPH [2]. Although these compounds have proven to be safe and effective in the management of acute venous thromboembolism (VTE) limited data exists in CTEPH [4,5]. Henkens *et al* (2014) reported a major bleeding rate of 2.4%/person-year and Jujo-Sanada *et al* (2017) major bleeding and VTE recurrence rates of 5% and 1.2%/person-year, respectively in CTEPH patients treated with VKAs [4,5].

In recent years, four direct oral anticoagulants (DOACs) have been approved for the treatment of acute VTE in the UK (Edoxaban, Rivaroxaban, Dabigatran and Apixaban) [6,7,8,9]. Large-scale studies in acute VTE indicate DOACs to be as effective in preventing VTE and with fewer major bleeding complications than VKAs [10,11,12]. Given the similar efficacy, potential lower side-effect profile and administrative convenience of DOACs over VKAs, the number of patients on DOACs presenting to CTEPH centres is rising and in some regions now supersedes VKA use [13]. Given limited data regarding the safety and efficacy of VKAs in CTEPH and the evolving use of DOACs, an evaluation of anticoagulation in CTEPH is warranted.

Methods

Patient Selection

Consecutive CTEPH patients undergoing PEA at the UK National PEA Centre (Royal Papworth Hospital) between 1 August 2007 and 30 June 2018 were included in a retrospective analysis. Follow-up was included up to 1 March 2019. Paediatric cases, those with chronic thromboembolism without pulmonary hypertension (mpap $\leq$ 20mmHg) [14] and individuals with CTEPH mimicking conditions (eg. vasculitis and sarcoma) were excluded from analysis. The diagnosis of CTEPH was based on international criteria [1]. Suitability for PEA was determined by a multidisciplinary team comprised of pulmonary hypertension physicians, specialist cardiothoracic radiologists and pulmonary endarterectomy surgeons. PEA was based on surgical technique as previously described [15]. Follow-up was for a minimum of one year at Royal Papworth Hospital and up to five years under the care of one of the eight UK specialist pulmonary hypertension centres following PEA. This study was deemed to be research without requiring ethics by the Royal Papworth Hospital R&D department.

Study Design

Demographic, functional and haemodynamic data at pre-operative baseline and first follow-up within one year of PEA were collected prospectively in dedicated databases at Royal Papworth Hospital. Patient-reported outcomes were assessed the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), a pulmonary hypertension specific health-related outcome measure comprising three scales evaluating symptoms, activity levels and quality of life. Symptom and Quality of Life scales are both scored out of 25 with Activities having a maximum score of 30. Each CAMPHOR scale is negatively weighted so that a higher

score reflects worse quality-of-life and greater functional limitation [16]. Longitudinal data regarding anticoagulation and complications was retrospectively assessed from review of patient medical records. Thrombophilia was deemed if there was a history of Factor V Leiden, Prothrombin gene mutation, Protein C, S or Antithrombin III deficiency or Antiphospholipid Syndrome. International Normalised Ratio (INR) management for VKAs was undertaken by local anticoagulation services with the exception of inpatient admission to Royal Papworth Hospital.

Anticoagulation management

Standard surgical practice at Royal Papworth Hospital is for oral anticoagulation to be discontinued at the time of PEA. VKAs are stopped five days and DOACs 24-72 hours prior to PEA dependent on the agent's half-life. Subcutaneous treatment dose low molecular weight heparin (LMWH) is commenced Day 2 post-operatively and continued until oral anticoagulation is stabilised. VKAs are recommenced at maintenance dose on patient discharge from the Intensive Care Unit with a standard target International Normalised Ratio (INR) range of 2 - 3. DOACs were recommenced at an individual's usual dose at time of hospital discharge. Given the alteration to anticoagulation regimes and the additional contribution of the surgical procedure including cardiac bypass in the perioperative period, mortality and complication rates during the period between PEA and recommencement of oral anticoagulation were excluded from analysis.

Life-long anticoagulation is recommended in all following PEA. The management of long-term anticoagulation after PEA hospital discharge was undertaken by the patient's General Practice or local anticoagulation clinic with oversight from a specialist Pulmonary Hypertension centre.

Those treated with VKAs were maintained with an INR in the target range of 2 to 3, unless otherwise indicated by Haematology services. Should the INR fall beneath the target range, patients were recommended treatment with concomitant treatment dose subcutaneous low molecular weight heparin until the INR returned to the required range, as per standard UK CTEPH practice.

As access to primary care data was not available, INR measurements from patient review at Royal Papworth Hospital were collated as a measure of compliance/adherence. Samples taken at the 3-6 month visit following PEA were excluded. This visit involves a routine right heart catheter and historical practice has been to stop VKAs and cover with treatment dose subcutaneous LMWH when undertaking invasive procedures

Bleeding events and VTE recurrence

Bleeding events were identified and categorised into 'major bleeding' or 'clinically relevant non-major bleeding' using International Society on Thrombosis and Haemostasis criteria [17]. Major bleeding was defined as symptomatic events which resulted in the transfusion of ≥ 2 red cell units, involved a critical site or were fatal; critical sites being the central nervous system, retroperitoneum, pericardium, intraocular and respiratory tract. Clinically relevant non-major bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with medical intervention, unscheduled contact with a physician, interruption of anticoagulation, or discomfort or impairment of activities of daily life.

VTE recurrence was recorded for all episodes of acute pulmonary thromboembolism (PE) or deep vein thromboembolism (DVT) documented in medical records following PEA and after

re-stabilisation of oral anticoagulation. As all patients routinely undergo CT Pulmonary Angiogram (CTPA) imaging in the year following PEA, imaging reports were also text-mined using phrases associated with recurrent VTE to enhance event capture. All identified episodes of recurrent PE were confirmed by a sub-specialised CTEPH Radiologist during departmental MDT.

Survival

Post-PEA survival was calculated using a censoring date of last review or 1 March 2019 whichever was latest. The NHS summary care record tracking system was used for survival status (searched 1 March 2019).

Statistical analysis

Baseline characteristics and outcome variables were expressed as numbers and percentages for categorical data and mean +/- standard deviation or median (interquartile range) for continuous variables according to data distribution. Variable missingness was calculated and reported (Supplemental Table 1). Missingness rates for key outcome variables of recurrent VTE, bleeding events and survival for those receiving VKA or DOACs was 1.6%, 1.6% and 0% respectively. Complete cases data was used in analyses. Between-group and within group comparisons were made using parametric and non-parametric tests as appropriate. A p-value of < 0.05 was considered significant. Multiple comparisons where corrected for, where necessary, using a false discovery rate and adjusted p-values reported. Statistical analysis was performed using R version 3.5.1 (wwww.r-project.org) [18].

Results

Cohort characteristics

During the study period 1322 individuals underwent PEA. There were 90 deaths prior to first post-operative follow-up. Mean follow-up duration was 612 +/- 702 days. Pre-operative patient characteristics and post-operative outcomes at first follow-up within one year of PEA are summarised in Table 1.

The median age was 62 (22) years and 54% were male. 8.4% had a history of malignancy, although only 0.4% had active malignancy, or were receiving treatment for malignancy at the time of PEA (all were warfarinised). An additional two patients were diagnosed with malignancy after PEA but prior to first follow-up. Pre-operative mPAP was 44 (16) mmHg, pulmonary vascular resistance 651 (493) dynes$\cdot s^{-1} \cdot cm^{-5}$ and cardiac index 2.12 (0.8) $l \cdot min^{-} \cdot m^{2}$. Prior to PEA 85% of patients were in NYHA functional class III or IV and six-minute walk distance was 310 (200) m. Significant improvements in haemodynamics, functional status and self-reported outcomes were seen following PEA ($p < 0.001$).

Anticoagulation group characteristics at time of PEA

Anticoagulation data prior to PEA was available for 1078 individuals. 808 were treated with VKAs (75%) and 204 with DOACs (19%). 60 individuals were anticoagulated with subcutaneous or intravenous heparins (6%) and three patients were on Fondaparinux (< 1%). Three patients were not anticoagulated prior to PEA.

The most common pre-operative VKA was Warfarin (99%) with Acenocoumarol used in 0.7% and Phenindione in 0.1%. Rivaroxaban was the most frequently prescribed DOAC (76%) with Apixaban, Dabigatran and Edoxaban prescribed in 19%, 4% and 1% respectively. One additional individual was on dual DOAC therapy pre-operatively (Apixaban with Dabigatran). The proportion of patients prescribed DOACs steadily increased over time from < 1% in 2007 – 2008 to 55% in 2017-2018.

Prescribed anticoagulant was not dependent on patient demographics (Table 2). Age, sex and body mass index did not differ between anticoagulation groups. Although the incidence of Antiphospholipid Syndrome (4.0% vs 1.5%) and indeed any underlying thrombophilia (7.2% vs 3.9%) was higher in those receiving VKAs compared to DOACs, the difference failed to reach statistical significance. The exclusion of those with APS from analysis did not alter findings (Supplemental Table 2), nor did the presence, or absence, of Inferior Vena Cava filters (Supplemental Table 3).

Post-operative anticoagulation

Post-operative anticoagulation was documented for 1,057 patients (Table 2). 794 were treated with VKAs and 206 with DOACs. Warfarin remained the most popular VKA (99%) and Rivaroxaban the most popular DOAC (77%).

Change in anticoagulant class following PEA was recorded for 71 individuals. A move from heparin-based regimes to oral anticoagulation accounted for the majority of changes occurring prior to first follow-up (n = 27). Changes occurring during longer term follow-up

were most commonly from VKA to DOAC due to the administrative convenience of DOACs or difficulty in maintaining INR control.

INR measurements from post-operative review at Royal Papworth Hospital were collated. A total of 2054 INR measurements were obtained of which 1039 (51%) had an INR above a threshold of 2.

Post-PEA outcomes

Improvements in haemodynamics, functional status and self-reported outcomes were seen with PEA in those receiving both VKAs and DOACs ($p < 0.001$). Outcomes were unaffected by anticoagulation class ($p > 0.05$). Significant residual pulmonary hypertension (mPAP $\geq$ 38mmHg) was observed in 113 (14%) with VKAs and 20 (9.7%) with DOACs.

Recurrent VTE

There were 22 episodes of recurrent VTE across 20 individuals post-PEA (1.17%/person-year). All events were pulmonary thromboemboli with the exception of one lower limb deep vein thrombosis (Table 3). Thrombophilia status for all VTEs was known. No events occurred in association with underlying malignancy. Median time to VTE recurrence following PEA was 5.8 (5.4) months. Seven PEs were incidental findings on routine post-operative imaging in asymptomatic individuals.

Twelve VTEs occurred with VKA use (0.76%/person-year). Warfarin was the VKA in all instances. Four episodes were associated with INRs beneath target range. Two events occurred with INRs within the target range in the context of underlying thrombophilia

(Antiphospholipid Syndrome). One individual underwent bilateral lung transplantation and one balloon pulmonary angioplasty for residual CTEPH following VTE recurrence. Rates of recurrent VTE with VKAs did not differ between those with (pre-2014), and without (post-2014), Inferior Vena Cava filters in-situ (p = 0.585).

Ten VTE events were associated with DOACs (4.62%/person-year). Four events occurred in the context of subtherapeutic dosing. One individual had underlying thrombophilia (Antiphospholipid Syndrome) with recurrent VTE resulting in urgent re-do PEA following a period of anticoagulation non-compliance.

Rates of VTE recurrence were significantly higher in those treated with DOACs compared to VKAs (p = 0.008). Statistical significance remained even with the removal of those with prothrombic Antiphospholipid Syndrome (p = 0.011)

Bleeding events

There were 12 bleeding events during follow-up, of which 8 were classified as major (Table 3). Major bleeding in VKA (0.67%/person-year) and DOAC (0.68%/person-year) groups did not differ significantly (p-value = 1). Bleeding events were not associated with significant hepatic disease or concomitant antiplatelet therapy. Two individuals were treated pulmonary vasodilators (Riociguat) at the time of bleeding event.

Ten bleeding events occurred with VKA use (7 major, 3 clinically relevant non-major), all of whom were warfarinised. Mortality resulted from three major bleeding events; one ruptured abdominal aortic aneurysm, one traumatic intracranial haemorrhage and one gastrointestinal

haemorrhage secondary to gastric adenocarcinoma. Of the four remaining major bleeding events, two were subdural haematomas (one associated with a labile INR) and two were associated with underlying malignancy (gastrointestinal and bladder). There were three clinically relevant non-major bleeding events; two diffuse subcutaneous haematomas (one of which occurred following a fall) and one episode of epistaxis requiring hospital attendance in the context of a supratherapeutic INR.

Two bleeding events occurred with DOACs; both of which were gastrointestinal. The one major bleeding event was massive haematemesis secondary to erosive oesophagitis in the context of Riociguat therapy. The one recorded clinically relevant non-major bleeding event was rectal bleeding which resulted in the patient self-downtitrating their DOAC dose with recurrent VTE diagnosed thereafter.

Survival

A total of 115 deaths occurred between the post-operative reinstitution of oral anticoagulation and five-years post-PEA. 106 deaths occurred in those treated with VKAs and 9 with DOACs. One, three and five-year survival was 94%, 90%, 84% in the VKA group and 96%, 96% and 92% in the DOAC group. Given the propensity for DOAC prescribing in the latter part of the cohort and that survival rates following PEA are known to have improved over time (learning curve with respect to patient selection, surgical technique and post-operative management), Cox Proportional Hazards modelling was performed with year of PEA as a co-variate amongst others selected from prior regression analyses. Independent predictors of survival were age at PEA and post-operative PVR, mPAP, cardiac index and six-minute walk distance (Supplemental Table 4). Anticoagulation class was not an independent predictor of

survival and its addition to the Cox Proportional Hazards model failed to improve model fit (likelihood ratio p-value = 0.295; Figure 1).

Discussion

Whilst the efficacy and safety of VKAs has been well established in atrial fibrillation and acute VTE, their risk/benefit profile in CTEPH is largely unknown. Moreover, no CTEPH-specific data exists to support the emerging use of DOACs, despite superseding VKA use in many CTEPH centres.

This study is the largest evaluation of oral anticoagulation in operable CTEPH to-date, and the first to directly compare VKAs and DOACs. As anticipated, there was an increasing predilection for DOACs during the study period. Significant improvements in haemodynamics and functional status were observed following PEA with post-operative outcomes unaffected by anticoagulant class (p-value > 0.05). Recurrent VTE was proportionally higher with DOACs than VKAs (p-value = 0.008) yet the incidence of bleeding events did not differ (p-value = 1)

In line with UK prescribing trends, the use of DOACs rose steadily following licensing in 2008. By 2017-2018 55% of the cohort were treated with DOACs, comparative to UK primary care anticoagulant prescribing rates (DOACs, 57%) and that of other CTEPH centres [13,19]. Warfarin was the most commonly used VKA (99%) and Rivaroxaban the most frequent DOAC (76%) as per national data [19]. Age, sex and body mass index did not influence anticoagulant choice (adjusted p-values 0.60). Those with underlying thrombophilias, including antiphosphoplid syndrome were more likely to be treated with VKAs than DOACs, though differences failed to reach statistical significance (adjusted p-values 0.34).

Consistent with previous publication from this cohort, we report significant improvements in haemodynamic and functional status following PEA [20]. Outcomes were unaffected by anticoagulant class. Although other studies have suggested quality-of-life to be better in VTE treated with DOACs rather than VKAs [21] we failed to show any significant difference pre- and post-PEA on a patient-reported quality-of-life outcome measure (p-values: pre-PEA 0.34, post-PEA 0.76). This suggests that despite the administrative convenience of DOACs, quality-of-life when assessed using a pulmonary hypertension specific outcome is comparable.

Major bleeding events associated with VKAs was 0.67%/person-year, lower than that of prior studies in CTEPH with Henken's et al reporting an incidence of 2.4%/person year and Jujo-Sanada of 5.1%/person-year [4,5]. Major bleeding was however comparable to that reported from VTE meta-analyses of extended anticoagulation [22]. Whilst our classification of bleeding events was similar to that adopted by other CTEPH-specific VKA studies, our concomitant use of pulmonary vasodilators was lower. All participants in Henken's and two-thirds in Jujo-Sanada *et al's* analyses were treated with vasodilators compared to 12% in our study. As indicated by the results of the CHEST-1 trial, pulmonary vasodilators, particularly soluble guanylate stimulators, may be associated with increased VKA bleeding risk; indeed Jujo-Sanada et al reported a clinically relevant bleeding rate of 21% in those treated with VKAs and Riociguat [5,23]

Bleeding risk associated with DOACs in CTEPH has not previously been explored. In this first evaluation we demonstrate major bleeding with DOACs to be equivalent to VKAs (p-value = 1). Our finding contradicts that of VTE trials where DOACs are generally associated with lower

major bleeding rates [11]. Recent meta-analysis of extended anticoagulation in VTE however suggests the superiority of DOACs over VKAs with regard to bleeding risk is significant only for Apixaban 5mg [22]. Given the majority of our DOAC cohort are anticoagulated with Rivaroxaban, this may in part explain our lack of discrepancy in bleeding rates between anticoagulation classes.

VTE recurrence was uncommon (1.17%/person-year). Overall VTE rates were similar to Jujo-Sanada et al's CTEPH cohort (1.2%/person-year), although this applied to anticoagulation with VKAs only [5]. VTE recurrence was significantly higher in those treated with DOACs (4.62%/person-year) compared to VKAs (0.76%/person-year; p = 0.008), though no VTE associated deaths occurred in either group. Whilst the efficacy of DOACs in acute VTE is comparable to VKAs [11], network meta-analysis of extended anticoagulation in VTE suggests standard-dose VKA to have the highest probability of being the best treatment for VTE reduction [22]. Higher VTE recurrence rates associated with DOACs in our cohort may therefore reflect the extended duration of anticoagulation follow-up post-PEA in the context of an increased frequency of incidental cases identified through the routine screening of asymptomatic individuals. APS incidence was also noted to be lower in our population compared to previous and in light of the findings suggesting higher VTE recurrence in APS treated with DOACs compared to VKAs, the possibility that thrombophilia was underdiagnosed in our cohort needs to be considered [24,25]. From a pharmokinetic perspective, Rivaroxaban the most commonly prescribed DOAC in our cohort has the shortest half-life of all Factor Xa inhibitors and its bioavailability known to be affected by its consumption with food [26].

Median time from PEA to VTE recurrence was 5.8 (IQR 5.4) months suggesting the first six months following PEA to be the most crucial with regard to mode of anticoagulation. Higher VTE recurrence rates in DOACs theoretically may reflect the inability to easily quantify in-vivo DOAC activity and hence the capacity to identify and pre-emptively act upon low treatment adherence. VKA compliance by contrast is monitored by frequent INR measurement undertaken by an individual's General Practitioner or local anticoagulation clinic. Despite this, our data suggests that time-in-therapeutic range for the CTEPH cohort is at best comparable to established VTE data, or possibly worse.

Little data exists as to the implicated costs of life-long anticoagulation in VTE for VKAs versus DOACs. Whilst DOACs currently account for around half of anticoagulant prescriptions for VTE in the UK they are responsible for >90% of anticoagulant expenditure [19,28]. Data from life-long anticoagulation in atrial fibrillation indicates a cost saving with VKAs (Warfarin) compared to DOACs, even when INR monitoring is accounted for [29]. In the NHS in England Warfarin (the most common VKA in use) costs £0.78 per month (based upon a 5mg daily dose) compared to the average cost of DOACs at £50-60 per month [30]. The combined cost of Warfarin prescription and INR monitoring, whether delivered centrally or using self-testing is ~£300 per year compared to the annual cost of life-long DOAC anticoagulation of ~£800 excluding renal function checks [29,31]. Extrapolated to our post-PEA prevalent population the cost of treating all individuals with DOACs would equate to an additional ~£506,000 per year over VKAs. Whilst cost savings are presently in favour of VKAs, the costs associated with DOAC use are likely to fall considerably once patents expire in 2022.

In conclusion, major bleeding risk in CTEPH appears similar with VKAs and DOACs. Although VTE recurrence following PEA was uncommon, rates were significantly higher in those treated with DOACs. We acknowledge the limitation of this retrospective case review. Although all CTPAs are reviewed in MDT by subspecialised CTEPH radiologists and clinicians, the gold standard in determining the non-inferiority of DOACs would be prospective evaluation. Given previous experiences with valvular heart disease there are grounds for caution in assuming DOACs are safe [27].

Addendum:

Katherine Bunclark & Michael Newnham collected and curated the data. Katherine Bunclark performed the analysis and wrote the manuscript. Yi-Da Chiu and Sofia S Villar were involved in reviewing statistical methods. Nicholas Screaton and Alessandro Ruggiero reviewed CT imaging for recurrent thromboembolism. Mark Toshner provided guidance and support on data collection, data analysis and interpretation and drafting of the manuscript. John E Cannon, Gerry Coghlan, Paul A Corris, Luke Howard, David Jenkins, Martin Johnson, David G Kiely, Choo Ng, Karen Sheares, Dolores Taboada, Steven Tsui, S John Wort and Joanna Pepke-Zaba critically revised the manuscript. All authors approved the final version.

Conflict of Interest Statement

K.B, Y-D.C, A.R, S.V, J.C, G.C, M.J, C.N, N.S & S.T have no conflicts of interest to declare. M.N has received educational grants from MSD and GSK. P.C has served on speakers bureau and advisory boards of Actelion, Bayer and MSD and received institutional grant/research support from Actelion and Bayer. L.H has received personal fees and institutional grants/research support from Bayer and personal fees from MSD, Daichii Sayo and Pfizer. D.J has received

teaching honoraria and institutional grant/research support from Bayer and personal fees from Actelion. D.K has received speakers fees, institutional grant/research support and educational funding from Bayer. K.S has received educational funding from Actelion, Bayer, GSK and MSD and served on an advisory board for Actelion. D.T has received speakers fees and educational funding from Actelion, Bayer, GSK, Lilley, MSD and Pzier. S.J.W has received personal fees from Actelion, GSK, MSD and Bayer and institutional grant/research support from Actelion and Bayer. J.P.Z has served on advisory boards of, and received personal fees, institutional grant/research support from Actelion, Bayer, MSD and GSK. M.T has received personal fees from Actelion, GSK and Bayer and institutional grant/research support from Actelion, Roche and Bayer.

References

1. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, Delcroix M, Pruszczyk P, Mairuhu ATA, Huisman MV, Klok FA. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. *Eur Respir J* 2017; **49**:1601792.

2. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *European heart journal* 2016; **37**: 67-119.

3. Kim NH, Delcroix M, Jenkins DP, Channick R, Dartevelle P, Jansa P, Lang I, Madani MM,

Ogino H, Pengo C, Mayer E. Chronic Thromboembolic Pulmonary Hypertension. *J Am Coll Cardiol* 2013;**62**:92-99.

4. Henkens IR, Hazenoot T, Boonstra A, Huisman M V., Vonk-Noordegraaf A. Major bleeding with vitamin K antagonist anticoagulants in pulmonary hypertension. *Eur Respir J* 2013; **41**: 872-8

5. Jujo-Sanada T, Tanabe N, Sakao S, Sugiura T, Sekine A, Nishimura R, Suda R, Naito A, Miwal H, Yamamoto K, Sasaki A, Matsumura A, Ema R, Kasai H, Kato F, Tatsumi K.The anticoagulant effects of warfarin and the bleeding risk associated with its use in patients with chronic thromboembolic pulmonary hypertension at a specialist center in Japan: A retrospective cohort study. *Pulm Circ* 2017; **7**: 684–691.

6. National Institute for Health and Care Excellence. Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. *Guidance and Guidelines. NICE* 2012; TA261

7. National Institute for Health and Care Excellence. Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. *Guidance and Guidelines. NICE* 2015; TA341

8. National Institute for Health and Care Excellence. Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. *Guidance and Guidelines. NICE* 2014; TA327.

9. National Institute for Health and Care Excellence. Edoxaban for treating and for preventing deep vein thrombosis and pulmonary embolism. *Guidance and Guidelines. NICE* 2015; TA354.

10. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, Christiansen AV, Friedman J, Le Maulf F, Peter N, Kearon C; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled

analysis. *Circulation* 2014;**129**:764-772.

11. Van Es N, Coppens M, Schulman S, Middeldorp S, Büller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: Evidence from phase 3 trials. *Blood* 2014;**124**:1968-1975.

12. Hokusai-VTE Investigators, Büller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwocho L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism. *N Engl J Med* 2013;**369**:1406-1415.

13. Kramm T, Wilkens H, Fuge J, Schafers HJ, Guth S, Wiendenroth CB, Weingard B, Huscher D, Pittrow D, Cebotari S, Hoeper MM, Mayer E, Olsson KM. Incidence and characteristics of chronic thromboembolic pulmonary hypertension in Germany. C*lin Res Cardiol* 2018; **107**:548-553.

14. Frost A, Badesch D, Gibbs JSR, Gopalan D, Khanna D, Manes A, Oudiz R, Satoh T, Torres F, Torbicki A. Diagnosis of pulmonary hypertension. *Eur Respir J* 2019;**53**:1801904.

15. Madani MM, Jamieson SW. Pulmonary Endarterectomy for Chronic Thromboembolic Disease. *Oper Tech Thorac Cardiovasc Surg* 2006;**11**:264-274.

16. McKenna SP, Doughty N, Meads DM, Doward LC, Pepke-Zaba J. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): A measure of health-related quality of life and quality of life for patients with pulmonary hypertension. *Qual Life Res* 2006;**15**:103-115.

17. Schulman S, Kearon C, the SUBCOMMITEE ON CONTROL OF ANTICOAGULATION OF THE SCIENTIFIC AND STANDARDIZATION COMMITTEE OF THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEDMOSTASIS. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Scientific and Standardization Committee Communication. *J Thromb Haemost* 2005;**3**:692-694

18. R Core Team. R. *R Core Team*. 2017.

19. Loo S, Dell'Aniello S, Huiart L, Renoux C. Trends in the prescription of novel oral antiocagulants in UK primary care. *Br J Clin Pharmacol* 2017;**83**:2096–2106

20. Cannon JE, Su L, Kiely DG, Page K, Toshner M, Swietlik E, Treacy C, Ponnaberanam A, Condliffe R, Sheares K, Taboada D, Dunning J, Tsui S, Ng C, Gopalan D, Screaton N, Elliot C, Gibbs S, Howard L, Corris P, Lordan J, Johnson M, Peacock A, MacKenzie-Ross R, Schreiber B, Coghlan G, Dimopoulos K, Wort SJ, Gaine S, Moledina S, Jenkins DP, Pepke-Zaba J. Dynamic Risk Stratification of Patient Long-Term Outcome After Pulmonary Endarterectomy: Results From the United Kingdom National Cohort. *Circulation* 2016: **133**: 1761-1771.

21. Keita I, Aubun-Auger I, Lalanne C, Aubert JP, Chassany O, Duracinsky, Mahé. Assessment of qulaity of life, satisfaction with anticoagulation therapy and adherence to treatment in patients receiving long-course vitamin K antagonists or direct oral anticoagulants for venous thromboembolism. *Patient Prefer Adherence* 2017;**25**: 1625-1634

22. Mai V, Bertoletti L, Cucherat M. Extended anticogulation for the secondary prevention of venous thromboembolic events: An updated network meta-analysis. *PLoS One* 2019; **14**: e0214134

23. Ghofrani H-A, D'Armini AM, Grimminger F, Hoeper M, Jansa P, Kim NH, Mayer E, Simonneau G, Wilkins MR, Fritsch A, Neuser D, Weimann G, Wang C for the CHEST-1 Study Group. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2013;**369**:319-329.

24. Wolf M, Boyer-Neumann C, Parent F, Eschwege V, Jaillet H, Meye D, Simonneau G. Thrombotic risk factors in pulmonary hypertension. *Eur Respir J* 2000;**15**:395-399.

25. Pengo V, Denas G, Zoppellaro G, Jose SP, Hoxha A, Ruffatti A, Andreoli L, Tincani A, Cenci C, Prisco D, Fierro T, Gresele P, Cafolla A, De Micheli V, Ghirarduzzi, A., Tosetto, A, Falanga A, Martinelli I, Testa S, Barcellona, D, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood* 2018; **132**:1365-1371.

26. Stampfuss J, Kubitza D, Becka M, Mueck W. The effect of food on the absorption and pharmacokinetics of rivaroxaban. *Int J Clin Pharmacol Ther* 2013;**51**:549-561.

27. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, Blatchford J, Devenny K, Friedman J, Guiver K, Harper R, Khder Y, Lobmever MT, Maas H, Voigt JU, Simoons ML, Van de Werf F for the RE-ALIGN Investigators. Dagibatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013; **369**:1206-1214.

28. Burn J, Pirmohamed M. Direct oral anticoagulants versus warfarin: is new always better than old? *Open Heart* 2018; **5**: e000712

29. National Institute for Health and Care Excellence. Costing Report: atrial fibrillation. Implementing the NICE guidance on atrial fibrillation. *Putting NICE guidance into practice* 2014; CG180

30. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press <http://www.medicinescomplete.com> [Accessed on [01/08/2019]

31. National Institute for Health and Care Excellence. Costing Statement. Implementing the NICE guidance on apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. *Putting NICE guidance into practice* 2015; TA341

Tables and Figures

	Preoperative	**Postoperative**	*Adjusted p*
Patients, n	1322	1232	-
Age at PEA, yrs	62 (22)	-	-
Sex (male:female), %	54:46	-	-
BMI, kg/m^2	29 (8)	-	-
Active malignancy,%	0.4	0.6	-
NHYA Functional Class			
Patients, n	1224	985	-
1/2/3/4, %	0/15/74/11	30/43/26/1	< 0.001
Haemodynamics			
Patients, n	1322	1070	-
Mean PAP, mmHg	44 (16)	24 (12)	< 0.001
PVR, dynes·s^{-1}·cm^{-5}	651 (493)	240 (209)	< 0.001
P_{awp} , mmHg	11 (6)	10 (5)	< 0.001
Cardiac Index, l·min^{-}·m^2	2.12 (0.8)	2.31 (0.7)	< 0.001
6-minute walk test			
Patients, n	827	988	-
Distance, metres	310 (200)	368 (162)	< 0.001
CAMPHOR scale score			
Patients, n	1242	897	-
Activity	11 (10)	6 (10)	< 0.001
Symptoms	12 (11)	4 (9)	< 0.001

Quality of Life	10 (11)	4 (11)	< 0.001

Table 1. Cohort baseline and postoperative patient characteristics

Baseline and first post-operative follow-up patient characteristics. Postoperative results are from first follow-up within one-year post-PEA. Values are median ± interquartile range unless otherwise indicated. P value adjusted for multiple comparisons by false discovery rate. BMI indicates Body Mass index.; NYHA, New York Heart Association functional class; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; P_{awp}, pulmonary arterial wedge pressure and CAMPHOR, Cambridge Pulmonary Hypertension Outcome Review Questionnaire.

	Preoperative			Postoperative		
	VKA	**DOAC**	*p*	**VKA**	**DOAC**	*p*
Patients, n	808	204	-	794	206	-
Age at PEA, yrs	62 (21)	63 (20)	0.64	-	-	-
Sex (m:f), %	56:44	53:47	0.69	-	-	-
BMI, kg/m^2	29 (8)	29 (8)	0.64	-	-	-
Thrombophilia, n	783	204	-	-	-	-
Incidence, %	7.2	3.9	0.44	-	-	-
APS, n	780	200	-	-	-	-
Incidence, %	4.0	1.5	0.44	-	-	-
NYHA FC , n	740	185	-	635	133	-
1/2/3/4, %	0/16/74/10	0/13/80/8	0.69	30/42/27/1	27/45/27/1	0.86
Haemodynamics, n	808	204	-	681	167	-
Mean PAP, mmHg	45 (17)	44 (16)	0.64	25 (13)	24 (12)	0.54
PVR, $dynes \cdot s^{-1} \cdot cm^{-5}$	649 (486)	660 (486)	0.87	243 (215)	239 (195)	0.75
P_{awp}, mmHg	11 (5)	11 (6)	0.44	10 (5)	10 (6)	0.54
CI, $l \cdot min \cdot m^2$	2.1 (0.8)	2.1 (0.7)	0.44	2.3 (0.7)	2.3 (0.8)	0.65
6MWD, n	538	176	-	625	142	-
Distance, m	312 (202)	330 (202)	0.64	368 (157)	384 (166)	0.54
CAMPHOR scale score, n	764	183	-	610	165	-
Activity	11 (11)	11 (11)	0.77	6 (10)	5 (9)	0.56
Symptoms	12 (12)	13 (13)	0.64	4 (9)	3 (8)	0.54
Quality of Life	10 (10)	12 (10)	0.44	4 (10)	3 (10)	0.71

Table 2 Anticoagulation groups: baseline and postoperative patient characteristics

Postoperative results from first follow-up within one-year of PEA. Values are median (IQR) unless otherwise indicated. P values reported have been adjusted for multiple

comparisons by false discovery rate. Percentages may not add to 100 due to rounding. VKA indicates Vitamin K Antagonist (Baseline: Warfarin 801, Acenocoumarol 6, Phenindione 1, Post-PEA: Warfarin, 787; Acenocoumarol, 5; Phenindione, 1; Warfarin + Fondaparinux,1) and DOAC, Direct Oral Anticoagulant (Baseline: Rivaroxaban,155; Apixaban, 38; Dabigatran, 8; Edoxaban, 2; Apixaban & Dabigatran,1**.** Post-PEA: Rivaroxaban ,158; Apixaban, 35; Dabigatran 10; Edoxaban, 2; Apixaban + Dabigatran, 1). BMI indicates Body Mass index; APS, Antiphospholipid Syndrome; NYHA, New York Heart Association functional class; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; P_{awp}, pulmonary arterial wedge pressure; CI, Cardiac Index; 6MWD, six-minute walk distance and CAMPHOR QoL, Cambridge Pulmonary Hypertension Outcome Review Questionnaire.

	VKA		DOAC	
	n	events	n	Events
Recurrent VTE	-	-	-	-
Pulmonary Embolism	11	11	10	10
Deep Vein Thrombosis	1	1	0	0
Major Bleeding	-	-	-	-
Fatal events	3	3	0	0
Central Nervous System	3	3	0	0
Retroperitoneal	1	1	0	0
Haemopericardium	0	0	0	0
Intraocular	0	0	0	0
Haemoptysis	0	0	0	0
Gastrointestinal	2	2	1	1
Haematuria	1	1	0	0
Clinically relevant non-major bleeding	-	-	-	-
Gastrointestinal	0	0	1	1
Large diffuse haematomas	2	2	0	0
Epistaxis	1	1	0	0

Table 3: Recurrent venous thromboembolism (VTE) and bleeding events following pulmonary endarterectomy

VKA indicates Vitamin K Antagonist, DOAC; Direct Oral Anticoagulant. Major bleeding was defined as symptomatic and resulting in the need for a transfusion of at least 2 units of red cells, involving a critical site or were fatal; critical sites

being the central nervous system, retroperitoneum, pericardium, intraocular and respiratory tract. Clinically relevant non-major bleeding was also documented and subcategorised accordingly.