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ORIGINAL RESEARCH

# Management and Outcomes of Pulmonary Embolism in the Oldest-Old

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**Background:** Treatment for pulmonary embolism has expanded to include Direct Oral Anticoagulants (DOACs). The incidence of pulmonary-embolism (PE) in "oldest-old" age group (≥85 years) is rapidly increasing, but there is limited research on its management and clinical outcomes.

**Aim:** To examine the differences in management and outcomes in those aged ≥85 years compared to other age groups.

**Methods:** We performed a retrospective cohort-study of 373 consecutive patients with pulmonary embolism confirmed on imaging by Computed Tomography Pulmonary Angiogram (CTPA) or Ventilation Perfusion (VQ) Scan at a principal referral hospital in Sydney, Australia. Data collected include clinical and demographic data, Charlson comorbidity index, treatment type and outcomes including complications, recurrent venous thromboembolism, and mortality.

**Results:** Across the age groups, DOACS were prescribed to 53.4% (n=199) of patients. In oldest-old patients with PE, LMWH bridging to warfarin was the most frequently prescribed treatment, used in 46.2% (n=18, 95% CI: 30.8%–61.5%, p=0.003) of these patients. The mortality rate for patients on LMWH was 13.9% (n=5, 95% CI: 4.2%–37.5%, p=0.553). Overall, major bleeding incidents were rare, occurring in just 1.7% (n=4, 95% CI: 0.4%–3.3%) of patients, with no significant differences in outcomes across age groups.

**Conclusion:** DOACs are increasingly used as the treatment modality of choice in atrial fibrillation but are less well studied in pulmonary embolism, particularly in oldest-old patients. We found that the safety and efficacy profile of DOACs in pulmonary embolism treatment is similar across the age groups. Our study does not support any change in treatment protocols of PE in the oldest old, but further studies are required to confirm our findings.

**Keywords:** oldest-old, pulmonary embolism, anticoagulation, treatment, adverse outcomes

## Introduction

The incidence of pulmonary embolism (PE) rises significantly with age.[1] The oldest-old (≥ 85 years) represent a disproportionately high proportion of patients admitted to hospital with PE.[2] The main treatment of PE for many years was Vitamin K Antagonists (VKA) bridged with Unfractionated Heparin (UFH) or Low Molecular Weight Heparin (LMWH).[3] Limitations of VKA such as wide inter dosing response, narrow therapeutic window and food/drug interactions apply to all age groups but are more pronounced in older age group, as is a higher incidence of major bleeding.[4] LMWH has largely replaced UFH in the treatment of PE, in the absence of severe kidney disease.[5]

Direct Oral Anticoagulants (DOAC), introduced ten years ago, such as Rivaroxaban, Apixaban, Edoxaban and Dabigatran, have now been shown to be effective in the management of PE, with lower mortality and major bleeding rate.[6] However, the oldest-old constitute a small proportion of study subjects in these studies, warranting caution in extrapolating results. While DOACs have fewer drug interactions, limitations with concurrent liver, gastrointestinal and chronic kidney disease are more common barriers to use in older patients.[7] There is evidence of favorable risk profile in the use of DOACs for atrial fibrillation.[8] A meta-analysis found that the use of DOACs in atrial fibrillation was associated with a lower pooled risk of thromboembolic stroke with no significant difference in major bleeding.[9]

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However, studies on the use of DOACs in VTE for the oldest old are lacking. Current guidelines recommend a reduction in DOAC dose for atrial fibrillation with increasing age, but do not have the same recommendation for acute PE.[10] More data is required to confirm that this treatment regimen in PE is applicable to the oldest old population.

There is growing evidence that outpatient treatment of PE is safe in selected patient groups.[11] Suitability is assessed using prognostic scores such as the Pulmonary Embolism Severity Index (PESI). Age is identified as a predictor for poor outcomes, but it is debatable if poorer outcomes are due to age as an independent risk factor or due to concomitant comorbidities, whether diagnosed or silent.[12] With a high hospitalization rate and risk of hospital acquired complications in the older person, there is a pressing need to explore this treatment modality.

There is limited clinical information in the literature on the safety and effectiveness of standard PE treatment regimens, particularly with the use of DOACs in the oldest-old age group. We have previously investigated the clinical features and diagnosis of PE in the oldest-old.[13] In this study, we review and analyze the management and outcomes of PE, comparing different anticoagulation treatments in the different age groups.

## Aims

To examine the management of pulmonary embolism in the oldest-old, in comparison with other age groups in an Australian context. We will also examine complications and outcomes in relation to the anticoagulant treatment used.

## Methodology

We performed a retrospective cohort study of consecutive PE patients admitted to Bankstown-Lidcombe Hospital (New South Wales, Australia) from March 2015 to October 2018. This study is an extension of a prior study which focused on clinical presentation and diagnosis and has been previously published.[13]

Consecutive patients with a confirmed discharge diagnosis of new PE during the above study dates were identified using the International Classification of Diseases-10th Revision codes. Patients included in this study had PE diagnosed on CTPA or high-probability VQ scan. Patients with a clinical diagnosis but not confirmed on imaging were excluded. Data collected included demographic, clinical and management data including type of anticoagulation used, duration and setting of treatment (inpatient or outpatient). Outcome data collected included major bleeding, recurrent VTE, and mortality within three months. For quality assurance, ten percent of the data was cross-checked by a separate senior investigator.

Major bleeding was defined according to the International Society on Thrombosis and Hemostasis (ISTH) criteria.[14] Recurrent VTE was defined as presence of another PE or form of VTE within 3 months of diagnosis of the initial PE. Chronic kidney disease was defined as per Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[15] The Charlson Comorbidity Index (CCI) and PESI were calculated from clinical data.[16,17]

Subjects were divided into 3 age groups for analysis – young (age <65), younger-old (65–84) and the oldest-old (≥85). Continuous variables were reported as mean and standard deviation or median and interquartile range, as appropriate. Categorical variables were reported as frequency counts, percentages with 95% bootstrap confidence intervals provided when applicable. Differences in continuous variables were analyzed using ANOVA and Chi-square test for categorical variables. Significance was set at a p-value of <0.05. Multiple comparisons were adjusted using Bonferroni correction. The significance threshold for each test is adjusted by dividing the pre-specified alpha level of 0.05 by the number of comparisons (28), resulting in an adjusted alpha of 0.002. All analyses were performed using SPSS version 24.

The Ethics Committee assessed this study as a negligible to low-risk retrospective study with no treatment intervention, with sufficient protection of privacy and no reporting of identifying information. The study was assessed to fulfil the conditions allowing a waiver of informed consent according to the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research.[18] This study was approved by the South-Western Sydney Local Health District Human Research Ethics Committee (SWSLHD HREC Reference Number 2019/ETH04478). This study complies with the Declaration of Helsinki and this research did not receive any specific funding.

## Results

A total of 373 consecutive patients from March 2015 to October 2018 were identified with our pre-defined criteria for diagnosis of PE. Overall, 149 (39.9%), 185 (49.5%) and 39 (10.5%) of subjects were aged <65, 65–84 and ≥85, respectively, with 58.2% being female.

The oldest-old age group had the highest rate of congestive cardiac failure, with n=11 (28.2%), and moderate-to-severe chronic kidney disease (CKD), with n=13 (33.3%), both showing statistically significant differences compared to younger age groups (p<0.001) for both conditions. Higher PESI scores were observed more frequently in older age groups, with the oldest-old having the highest proportion of high-risk PESI scores at n=23 (59%), demonstrating a statistically significant difference compared to younger groups (p < 0.001). CCI was significantly higher in the older age groups compared to the youngest population, with mean of 0.8 for those <65 years, 1.90 for those 65–84 year and 2.13 ≥85 years (p<0.001). A higher proportion of younger patients were treated out of hospital, with 64.4% (n=96) of those <65 years, 51.9% (n=96) of those 65–84 years, and 35.9% (n=14) of those ≥85 years, showing a statistically significant difference across age groups (p=0.003) (Table 1).

**Table 1** Clinical Characteristics and Clinical Management of Pulmonary Embolism by Age Group

| Variable | Age < 65 | Age 65–84 | Age ≥ 85 | P-value |
|---|---|---|---|---|
| **Number of Patients n (%)** | 149 (39.9) | 185 (49.6) | 39 (10.5) | |
| **Gender n (%, 95% CI)[a]** | | | | 0.277 |
| Female | 82 (55.0, 50.0–63.1) | 108 (58.4, 51.9–65.9) | 27 (69.2, 53.8–82.1) | |
| Male | 67 (45.0, 37.0–53.0) | 77 (41.6, 35.1–49.2) | 12 (30.8, 17.9–46.2) | |
| **Comorbidities, n (%, 95% CI)[a]** | | | | |
| Heart Failure | 4 (2.7, 0.7–5.4) | 8 (4.3, 1.6–7.6) | 11 (28.2, 15.4–41.0) | <0.001 |
| Myocardial Infarction | 8 (5.4, 2.0–9.4) | 34 (18.4, 13.0–24.3) | 8 (20.5, 10.3–33.3) | 0.001 |
| Malignancy | 8 (5.4, 2–9.4) | 37 (20.0, 25.0–25.9) | 1 (2.6, 0–7.7) | <0.001 |
| Chronic Lung Disease | 7 (4.7, 1.3–8.1) | 25 (13.5, 8.6–18.9) | 3 (7.7, 0–18.0) | 0.021 |
| Severe CKD | 8 (5.4, 2.0–9.4) | 31 (16.8, 11.9–22.2) | 13 (33.3, 17.9–48.7) | <0.001 |
| **Treatment Modality n (%, 95% CI)[a]** | | | | |
| UFH + Warfarin | 8 (5.4, 2.7–10.1) | 15 (8.1, 4.3–12.4) | 4 (10.3, 2.6–20.5) | 0.519 |
| LMWH only | 11 (7.4, 3.4–12.1) | 30 (16.2, 11.4–21.6) | 1 (2.6, 0-7.7) | 0.007 |
| LMWH + Warfarin | 29 (19.5, 13.4–26.2) | 50 (27.0, 20.5–33.5) | 18 (46.2, 30.8–61.5) | 0.003 |
| DOAC only | 100 (67.1, 59.1–74.5) | 86 (46.5, 39.5–53.5) | 13 (33.3, 17.9–48.7) | <0.001 |
| **PESI Score n (%, 95% CI)[a]** | | | | |
| Low Risk | 118 (79.2, 72.5–85.2) | 108 (58.4, 51.4–65.4) | 16 (41.0, 25.6–56.4) | < 0.001 |
| High Risk | 31 (20.8, 14.8–27.5) | 77 (41.6, 34.6–48.6) | 23 (59.0, 43.6–74.4) | |
| **Site of Treatment n (%, 95% CI)[a]** | | | | |
| Inpatient | 53 (35.6, 30.2–46.3) | 89 (48.1, 43.8–57.8) | 25 (64.1, 48.7–79.5) | 0.003 |
| **Charlson Comorbidity Index, mean (SD)** | 0.8 (±1.5) | 2.1 (±2.8) | 1.9 (±1.9) | <0.001 |

**Notes**: [a]95% bootstrap percentile confidence interval.
**Abbreviations**: CI, Confidence Interval; CKD, Chronic Kidney Disease; UFH, Unfractionated Heparin; LMWH, Low Molecular Weight Heparin; DOAC, Direct Oral Anticoagulants; PESI, Pulmonary Embolism Severity Index; SD, Standard Deviation.

Overall, DOAC was the most prescribed treatment modality, used in 53.4% (n=199) of patients, followed by LMWH with warfarin used in 26.0% (n=97) of patients. In the oldest-old, LMWH with warfarin was the most common 46.2% (n=18) followed by DOAC 30.8% (n=12). LMWH only was more commonly prescribed in the 66–84-year-old group, where 14.6% (n=27) of these patients had malignancy; however, this was not a statistically significant association.

Major bleeding within 3 months occurred in 1.7% (n=4, 95% CI: 0.4%–3.3%) of patients. Of these, three were in patients <65 years old, and one was in the 65–84 years age group. The bleeding episodes were associated with different treatments: two on DOAC, one on LMWH with warfarin and one on UFH and warfarin. The incidence of recurrent VTE was low at 0.27% (n=1), occurring in one patient treated with DOAC under the age of 65. Overall mortality within 3 months was 6.45% (n=16, 95% CI: 3.6%–9.6%). Among those who died, the most common treatment modality was LMWH only, used in 13.9% (n=5, 95% CI: 4.2%–37.5%, p=0.533) of patients, whereas DOAC was the least common with 8.3% (n=2). There were no statistically significant differences in major bleeding, recurrent VTE and mortality among the age groups (Table 2).

## Discussion

Comparing census data of local demographics[19] with demographics in our study, 88.9%, 9.5% and 1.6% of the population were aged <65, 65–84 and ≥85, respectively, versus 39.9%, 49.6% and 10.5% of study subjects. The discordance reflects the predominance of older patients with PE, consistent with the literature.[13,20] Previous studies on treatment and management of PE have only compared patients older and younger than 65 or 70 or focused on patients aged ≥90 or 100 without comparing other age groups.[21] By comparing the three age groups, <65, 65–84 and ≥85, we were able to demonstrate differences in treatment and outcomes more clearly.

**Table 2** Outcomes and Complications

| Variable | Age < 65 | Age 65–84 | Age ≥ 85 | P-value |
|---|---|---|---|---|
| **Major Bleeding, n (%, 95% CI[b])** | 3 (3.2, 0–7.5) | 1 (0.8) | 0 (0.0) | 0.435 |
| UFH + Warfarin | 0 (0.0) | 1 (8.3) | 0 (0.0) | 1.000 |
| LMWH only | 0 (0.0) | 0 (0.0) | 0 (0.0) | - |
| LMWH + Warfarin | 1 (5.9) | 0 (0.0) | 0 (0.0) | 0.475 |
| DOAC only | 2 (3.2) | 0 (0.0) | 0 (0.0) | 0.572 |
| **Recurrent VTE, n (%)** | 1 (0.27) | 0 (0.0) | 0 (0.0) | 0.488 |
| UFH + Warfarin | 0 (0.0) | 0 (0.0) | 0 (0.0) | - |
| LMWH only | 0 (0.0) | 0 (0.0) | 0 (0.0) | - |
| LMWH + Warfarin | 0 (0.0) | 0 (0.0) | 0 (0.0) | - |
| DOAC only | 1 (1.6) | 0 (0.0) | 0 (0.0) | 1.000 |
| **Mortality within 3 Months, n (%, 95% CI[b])** | 4[a] (4.3, 1.1–8.7) | 8 (6.3, 2.4–11.0) | 4[a] (14.0, 3.5–27.6) | 0.194 |
| UFH + Warfarin | 1 (17.0) | 1 (8.3) | 0 (0.0) | 1.000 |
| LMWH only | 0 (0.0) | 5 (21.0, 4.2–37.5) | 0 (0.0) | 0.553 |
| LMWH + Warfarin | 1 (5.9) | 1 (3.1) | 2 (17.0) | 0.232 |
| DOAC only | 1 (1.6) | 1 (0.5) | 0 (0.0) | 1.000 |

**Notes**: [a]Three patients died before treatment. [b]95% bootstrap percentile confidence interval. Confidence interval not calculated for counts less than 3. Major bleeding defined as per International Society on Thrombosis and Haemostasis (ISTH) criteria.[13] Recurrent VTE defined as presence of VTE within 3 months of initial PE diagnosis.

**Abbreviations**: CI, Confidence Interval; CKD, Chronic Kidney Disease; UFH, Unfractionated Heparin; LMWH, Low Molecular Weight Heparin; DOAC, Direct Oral Anticoagulants; PESI, Pulmonary Embolism Severity Index; SD, Standard Deviation.

DOACs are increasingly used as initial and sole therapy in the treatment of PE. LMWH is considered to have more predictable efficacy and clinical trials have excluded patients with relative contraindications to DOACs.[22] There was a decrease in use of DOACs with increasing age (67.1% to 46.5% to 33.3%), likely due to higher frequency of CKD. Consequently, there is an increase in use of UFH with increasing age as seen in some literature which recommends UFH in patients with a creatinine clearance of <30mL/min.[23] LMWH with anti-Xa monitoring have been used with caution in patients with Stage 4 CKD.[23] For longer term anticoagulation Warfarin was most frequently used in the older population in our study. In the group of patients between 65 and 84 years of age, a cluster of malignancy occurred, which likely affected the therapeutic approach between the age groups. The peak incidence of malignancy in this age group has been noted previously.[24]

Major bleeding episodes were low overall at 1.7%, consistent with current literature of 2% at three months.[25] We did not find a lower bleeding rate with DOAC compared to other studies.[26] The absence of major bleeding episodes with LMWH may be due to the small number of patients compared to other treatment modalities. The comparative absence of major bleeding in the oldest-old age group in our cohort, while not statistically significant, does suggest that judicious use of DOAC is safe.

The rate of recurrent VTE on anticoagulation, alternatively termed treatment failure, was 0.27% in our study. While a higher rate of 2% was reported elsewhere[27] treatment failure is uncommon but poses a challenging management issue. Further research may be required to see if improvement in management of PE and anticoagulation regimens has resulted in a lower rate of treatment failure. This was unexpected, and a higher rate may be detectable with a larger population sample. It is possible that in our cohort recurrent episodes are associated with minimal symptoms and managed by primary care without presenting to the hospital system. There were no episodes of recurrent VTE in the twelve patients on DOAC.

Mortality was lowest with DOACs across all age groups including the oldest-old. Expectedly the highest incidence of mortality occurred in the oldest-old age groups, but this difference was not statistically significant. A higher mortality rate was associated with the use of LMWH, though this was not statistically significant. Lower rates of mortality have been found with use of DOACs compared with warfarin,[28] though these studies did not specifically examine the oldest-old age groups.

The main limitation of our study was its retrospective nature. Some data relied on the accuracy of physician documentation, and under-reporting of comorbidities and complications may have occurred. However, the main data were objectively defined and less subject to interpretation. Confounding factors such as the high cancer prevalence may have affected mortality results but are unlikely to have a significant impact on the rates of major bleeding. The low rate of adverse outcomes are limitations inherent in the current study scope and larger studies are required to confirm our results. The examination of anticoagulation treatment according to CKD severity is limited by the small numbers, and this can also be addressed in a future larger study.

We have previously found that the clinical presentation of PE in the older age group differs from the younger population.[13] However, with PE treatment, while the anticoagulation practice is cautiously different, we found that the safety profile of anticoagulants in the older age group does not differ with that of the younger population. We also found that DOACs used within current guidelines and in the management of VTE clinical practice were not associated with worse outcomes compared to other anticoagulation treatment modalities. This favorable profile of the use of DOACs in the oldest old is consistent with findings from other studies on atrial fibrillation.[8,9] It should be noted that the use of DOACs is not universally appropriate for all older patients and further refining of treatment protocols specific for different DOACs may be required.[29,30]

## Conclusion

In this study, we found the safety and efficacy profile of anticoagulation treatment including DOACs for PE is similar across the age groups. Our study does not recommend any changes to the management of PE in the oldest old as compared to the younger age groups currently. With the increasing incidence of PE and advent of new treatments, it is critical that we review clinical management and outcomes in the oldest-old who are often neglected in clinical trials and

literature. Further studies are required to confirm our findings. More specific research on the management of patients with CKD and multi-morbidity where the incidence of poor outcomes is highest is also required.

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## Disclosure

The authors report no conflicts of interest in this work.

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