Outpatient treatment in low-risk pulmonary embolism patients receiving direct acting oral anticoagulants is associated with cost savings.

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Research

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Abstract

Background Direct oral anticoagulants (DOAC) are first line treatment for pulmonary embolism (PE). Treatment of acute PE is traditionally hospital based and associated with high costs, in spite of recent guidelines suggesting outpatient treatment for low-risk patients. The aims of this study were to evaluate potential cost savings with outpatient DOAC treatment of patients with low risk PE compared to DOAC treatment of low risk PE patients in hospital.

Methods A retrospective comparatory multicenter cohort study in patients with low risk PE (simplified pulmonary severity index [sPESI]) ≤ 1 admitted to the eight hospitals in Sweden´s southernmost healthcare region during 2013-2015, and treated with DOAC. Local criteria guiding outpatient treatment had been used, and sPESI was calculated retrospectively. Health care costs were analysed in the 223 (44%) patients treated as outpatients and the 287 (56%) treated in hospital.

Results Total cost per patient was 7334 EUR in the inpatient group, and 2088 EUR in the outpatient group ($p<0.001$). In multivariate analysis, type of treatment (in- or outpatient, $p=<0.001$) and sPESI group (0 or 1, $p=<0.001$) were significantly associated with total cost below or above median, whereas age ($p=0.565$) and gender ($p=0.177$) was not. Total cost for inpatients was higher ($p<0.001$) compared to outpatients in subgroups with sPESI 0 and 1.

Conclusion Better adherence to current guidelines recommending outpatient treatment with DOAC in patients with low risk PE would potentially lead to significant savings in healthcare expenditure.

Background

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) affects 5% of a western/world wide population during a lifetime [1]. PE is associated with a wide prognostic spectrum, ranging from prompt resolution to sudden death [2].

Anticoagulant (AC) therapy of acute PE [1–4] has traditionally been hospital based, with a mean hospital stay of 6 days [5]. Outpatient treatment of PE was suggested already in the 1990s [6], however, and both European [7] and American [8] guidelines recommend outpatient treatment for selected low-risk patients. In spite of the facts that different eligibility criteria for identification of low-risk patients suitable for outpatient treatment have been evaluated in prospective and retrospective studies [9–11], a recent prospective study has documented the safety of this approach [12], and another randomized study is ongoing [13], the proportion of patients selected for outpatient treatment is still low in most industrialized countries [14].

During recent years direct oral anticoagulants (DOAC) with a favorable risk profile have been introduced as an alternative to warfarin for VTE treament [15–21], and are now considered as first line treatment of PE [8]. As the need for monintoring of DOAC treatment is less than for warfarin [21, 22], outpatient

treatment of VTE is potentially facilitated by DOAC use. We have recently demonstrated that selected low-risk PE patients in our institution could be safely treated with DOAC on an outpatient basis [23].

In the United States PE is estimated to cause annual costs ranging from 8.5 to 19.8 billion US dollars [24]. Dasta et al reported that the daily cost for inpatient PE treatment started at 2034 US dollars and was highest during the first three days, and that the total mean daily cost for inpatient care of PE was 1735 US dollars [25].

Recently presented data indicate that outpatient treatment of low-risk PE (LRPE) is associated with potential savings [26, 27], however, as the economic burden incurred by PE is lower in patients with short length of stay (LOS). Furthermore, PE patients with short LOS also run a noticeable lower risk for hospital acquired conditions (HAC) [28].

The aim of this study was to evaluate whether outpatient treatment of patients with low risk PE with DOAC is associated with savings compared to treatment in hospital.

Methods

We performed a retrospective multicenter cohort study in consecutive patients diagnosed with acute PE in the emergency departments (ED) of all eight hospitals in Sweden´s southernmost health care region (1.3 million inhabitants) in 2013–2015, a period during which DOAC were gradually replacing warfarin as first line PE treatment. Patient data were extracted from the Swedish quality register for anticoagulation AuriculA [29], from digital patient files, and from imaging databases.

For selection of PE patients suitable for outpatient treatment, the eight hospitals in the region use a flow chart with pragmatic Criteria for Guiding Outpatient treatment (CGO, Fig. 1). Outpatients were offered an appointment or telephone appointment with a nurse in a vascular unit within 24 to 72 hours, and both outpatients and hospitalized patients were offered an appointment with a vascular physician within 4–6 weeks after diagnosis (Fig. 2). A previous study has documented that outpatient treatment based on the CGO-algorithm is safe and effective, although 48% of the patients were high risk PE patients according to the most validated risk stratification tool (Simplified Pulmonary Embolism Severity Index, sPESI ≥ 1) [23].

As factors such as compliance problems and social conditions might affect decisions on hospitalization, we restricted our comparison of out- and inpatients to low risk PE patients with sPESI 0 and 1 [31].

Digital patient files revealed that 223 (48%) of the 510 low risk PE (sPESI ≤ 1) patients had been selected for outpatient DOAC-treatment (Fig. 2), i.e. The treatment had been started already during an ED visit not exceeding 24 hours [23], whereas the remaining 287 (52%) patients had been treated on a hospital basis.

Symptoms and signs at presentation were retrospectively retreived from files and imaging databases, and the sPESI risk stratification score [31, 23] was calculated. Furthermore, we retrospectively assessed all other hospitalizations and scheduled and unscheduled appointments with nurses and doctors from

six months before to six months after the acute PE episode, together with mortality, recurrent VTE episodes, and bleeding complications.

Assessment of costs for health care 6-months pre and post diagnosis

Cost data were obtained from the central economic unit of the administrative body of our Health Care Region, and are those debited to an insurance company or an external region. The figures in SEK were converted to EUR (1 EUR = 9.3 SEK, currency year 2018). The daily cost for hospitalization is 554 EUR based on the average cost for room and staff, imaging, laboratory tests, and medication. We also inlcluded costs for outpatient visits to physicians (175 EUR) and nurses (131 EUR), both during the 6 months preceding hospitalization for PE and during the 6 months after discharge. As the costs for the initial ED visit (435 EUR) and CT-examination (255 EUR) were the same in both groups, these figures were not included in the calculations. Costs for telephone appointments are not debited in our region.

Data analysis

We performed a descriptive analysis with comparison of the in- and outpatient subgroups by Mann-Whitney tests. Results were also evaluated separately in subgroups with sPESI 0 and 1. Results are expressed as n (%), mean ± standard deviation (SD), or median and interquartile range (IQR) as indicated. Multivariate analysis was conducted to identify baseline variables significantly associated with a total cost below or above median for this variable. Analyses were performed using SPSS for Windows, version 23.0 (SPSS Inc, Chicago, IL).

Ethical considerations and permission

Ethical permission was obtained from the Ethics Committee in Lund, Sweden (dnr 2015/143).

Results

Among the 223 outpatients, 97 (43%) patients had sPESI score 0 and 126 (57%) sPESI score 1, whereas the proportions in those selected for inpatient treatment were 112 (39%) and 175 (61%) respectively. Age (p=<0.001, table 1), but not gender distribution differed significantly between out- and inpatients.

Inpatients had a mean stay of 7.4 days incurring a cost of 3626 EUR for the index PE but also a higher number of hospital days six months before the acute PE episode (table 1), leading to a cost difference in inpatients of 1186 EUR vs 645 EUR in outpatients (p=<0.001), and higher number of days at hospital also during six months after PE diagnosis, 1702 EUR versus 1275 EUR (p=<0.001).

The number of outpatient nurse- and physician visits during the six months before and six months after the acute PE episode were also higher in the inpatient group (p=<0.001, table 1),

leading to a significantly higher total cost in the inpatient group compared to PE patients treated on an out of hospital basis, 7334 EUR vs 2088 EUR (p=<0.001). In multivariate analysis, type of treatment (in- or outpatient, p=<0.001) and sPESI group (0 or 1, p=<0.001) was significantly associated with having a total cost below or above median for this variable, whereas age (p=0.565) and gender (p=0.177) was not (table 2).

No mortality, reccurent VTE, or major bleeding episodes were observed during six months of follow-up in either group.

sPESI 0

Among the 238 patients with sPESI 0, 112 (47%) patients were hospitalized and 126 (53%) were treated as outpatients (p=0.364). The age distribution between the in- and outpatient group were significantly older (p=0.007), whereas gender distribution did not differ (p=0.976, table 1).

Inpatients had a mean of 7 days of hospital stay for the index PE incurring a cost of 3483 EUR (p= <0.001), whereas the number of hospital days or physician appointments six months before or after the acute PE episode did not differ significantly between groups (table 1).

The costs for nurse appointments six months after PE diagnosis were higher in inpatients (p=0.113, table 1). Total cost in the inpatient group was higher compared to for outpatients, (5758 EUR vs 1815 EUR, p= <0.001).

sPESI 1

Among the 272 patients with sPESI 1, 175 (64%) patients was treated as inpatients and 97 (36%) as outpatients (p=<0.001). No significance in age nor gender distribution was noted betweent out- and inpatients (p=0.011, p=0.652, table 1).

Inpatients had a mean stay of 7.6 days, incurring a cost of 3715 EUR (p=<0.001) and also higher number of hospital days six months before and after the acute PE episode (table 1), to a cost of 1511 EUR vs 689 EUR (p=0.368) respectively 2229 EUR vs 768 EUR (p=0.002).

No significant cost differences were oberved for physician or nurse appointments six months before or after the acute PE episode (table 1). Total cost in the inpatient group was higher compared to for outpatients (8351 EUR vs 2558 EUR, p=<0.001).

Discussion

The numbers of hospitalized patients with PE, the third most common acute cardiovascular disease after myocardial infarction and stroke [2, 26] are increasing, as well as treatment costs [26]. Traditionally, patients with PE are treated in hospital with a mean LOS of 6 days [5]. As hospitalization is a major cost driver for total cost, any reduction in the number of inpatient days may translate into important cost savings [25].

In our retrospective study comparing medical cost in low-risk (sPESI ≤ 1) hospitalized PE patients with costs in outpatients, total costs for the outpatient group were 5246 EUR lower than for the inpatient group. By definition, this was mainly driven by the difference in the cost for hospital stay caused by the index acute episode of PE, but inpatients also spent slightly more time in hospital before and after the acute PE. This difference was probably due to the increased prevalence of comorbidities in hospitalized patients.

As 30-day survival after PE with or without DVT might be as low as 59.1% [26, 31], the use of risk stratification tools such as sPESI [30] or Hestia critera [10] is crucial [3] to guide decisions on treatment modality. Selection for outpatient treatment with DOAC treatment by using the CGO-criteria (Fig. 1) in our study was safe and efficient and associated with significant savings without mortality, reccurent VTE, or major bleeding episodes. Importantly, these results were demonstrated in a patient population in which a majority had sPESI 1, a group for which many guidelines recommend against outpatient treatment. In this context, it is of interest that the CGO-criteria recommends evaluations of safety aspects not included in the sPESI classification before the decision on in- or outpatient treatment.

Furthermore, as both the in- or outpatient treatment variable and the sPESI group variable were associated with total cost in multivariate analysis, it was of special interest to evaluate sPESI groups 0 and 1 separately documenting cost savings with outpatient treatment both in patients with sPESI 0 and sPESI 1 [23]. Our study therefore corroborates the results of Dasta et al [25], showing that LOS is a major cost driver in PE and that any reduction in LOS may translate into relatively important cost savings.

As DOAC have a more predictable dose response than warfarin and allow fixed dosage without need for routine laboratory monitoring, DOAC treatment in itself might potentially lead to shorter duration of hospitalization. Dobesh et al recently reported that such advantages could reduce the costs for the health care system by potentially preventing recurrent VTE and its complications [32].

To determine wether prolonged LOS is always caused by complications, or in itself might lead to complications is not always easy, however.

Wang et al [33] recently presented data from 1918 patients with LRPE, whereof 688 had a short LOS, defined as ≤ 2 days. They reported that patients with short LOS had both fewer hospital acquired conditions and less occurrence of pneumonia. Furthermore, costs in patients with short (≤ 2 days) and longer LOS total were 9056 and 12544 dollars, respectively, implying that LRPE patients with short LOS had a better net clinical outcome at a lower cost than matched LRPE patients with long LOS [33].

Among our patients selected for either out- or inpatient treatment, total costs were 2088 EUR and 7334 EUR, respectively. When comparing these figures with those previously published [34], it should be kept in mind that our patients had a higher mean age and a more balanced gender distribution compared to in Wang´s study [33], in which patients were younger and almost exclusively (> 90%) male. Furthermore, as sPESI scores were not presented by Wang et al [33], and as some of their patients underwent thrombolysis or placement of inferior vena caval filters, one might suspect that these patients had a more complicated course of PE than ours. Furthermore, there was no recurrent VTE or major haemorrhages in our material whereas Wang and colleagues reported 14 recurent DVT and 5 bleeds further supporting this assumption.

Dasta et al recently published a study [25] in which mean LOS was 5.4 days, mean age of PE patients 60 years, and gender distribution was equal. Both LOS and mean age in their material were thus slightly lower than in our study, whereas gender distribution was comparable. The mean daily cost per patient reported by Dasta was 1735 dollars, whereof the major part was room and board (accounting for 38–59% of the total), the main cost driver in our study as well. Mean total hospitalization cost per patient in Dasta ´s study was 11486 dollars, which of course is higher compared to outpatients (0 EUR), but also compared to hospitalized patients in our study (6514 EUR).

No data regarding mortality, reccurent VTE and other complications were reported by Dasta and co-workers, but in contrast to our material of patients with sPESI scores ≤ 1, 24% of their patients [25] underwent ICU treatment for their acute PE. The mean total hospitalization cost for patients in this subgroup was 19901 dollars, whereof surgery and supplies accounted for 1576 dollars. No such costs were incurred in our study, as our patients had a sPESI score ≤ 1, and did not require ICU facilities or surgical treatment.

Spyropoulus et al [34] reported a total hospitalization cost per PE patients treated with low molecular heparin (LMH) and warfarin of 14146 dollars. SPESI scores of their patients were not reported, however, but hospital readmission rate was between 5 and 14% whereof half occured within 90 days. Patients were excluded from the calculations if their age was > 65 years or if they were outside Medicare risk groups, which might have lead to selection effects indirectly influencing total costs.

A recent study showed that the use of LMH injections during institution of warfarin treatment was associated with prolonged hospital stay [35]. As this is not necessary for treatment with rivaroxaban or apixaban, use of these DOACs might potentially have further beneficial effects on costs. Coleman et al [36] showed that rivaroxaban use was associated with a 1.36-day shorter LOS and 2304 dollar reduction in total costs compared to parenteral bridging during institution of warfarin. Furthermore, this cost reduction was achieved without increasing the short-term risk of adverse events including readmission for VTE or major bleeding.

Similarly, Bookhart and colleagues [37] evaluated the impact of rivaroxaban on LOS among 321 hospitalized acute symptomatic PE patients recruited into EINSTEIN PE in North American sites. In these patients, rivaroxaban use resulted in a 1.7-day mean reduction in LOS compared with enoxaparin and

vitamin K antagonists, enabling a reduction of total hospital costs of 3000 dollars per patient. As the use of risk stratification tools such as sPESI or Hestia criteria was not reported, the results cannot be directly compared to ours. Mean patient age was slightly lower than in our study, however, 53.6 years [37].

Bookhart and collegues also highlighted that the data they used were obtained before rivaroxaban was widely used, and its efficacy fully understood [37].

Our patients were studied between 2013 and 2015, when DOAC treatment was gradually introduced in Sweden. Lack of familiarity with these new agents at the time of this study may thus have reduced the potential cost savings also in our study. As DOAC are now generally accepted as first line PE treatment [7, 8], potential savings might be even greater in the future. Coleman et al estimated that up to 50% of PE patients can be treated safely in an outpatient setting [36], and Peacock and colleagues subsequently [27] documented total savings of 2496 dollars per patient with rivaroxaban treatment and early discharge of low risk PE patients identified using Hestia criteria [10]. Mean age in these patients was nearly 20 years lower than in our material, however.

Our study is retrospective, not matched in terms of other comorbidities, and the selection of patients for in- and outpatient treatment was based upon clinical judgement guided by regional criteria (Fig. 1) and not randomized. Furtermore patients were not assessed after six months concerning long-term complications such as chronic thromboembolic pulmonary hypertension, a condition associated with high costs [30]. As this condition rarely occurs in patients with LRPE, however, this is probably not an important study limitation. A potentially important limitation, however, is the fact that we did not have the possibility to assess whether the number of sick-leave days differed between the groups.

In previous studies [34], outpatient visits were most frequently with internists, family physicians, or pulmonologists, whereas in our vascular unit outpatients are offered a nurse appointment within 72 hours and an appointment with an angiologist within 4–6 weeks (Fig. 2). Whether this approach leads to decreased risk for VTE reccurence, better compliance, and increased cost-effecitivity remains to be investigated.

Conclusion

Calculations of costs incurred by PE in different medical systems cannot be directly compared, but there seems to be a strong correlation between the economic burden of PE and LOS. Outpatient PE treatment with DOAC after careful selection of PE patients with validated risk stratification tools and comorbidities taken into account therefore seems to be a promising strategy to decrease the economic burden to society caused by this disease.

Abbreviations

AC Anticoagulant

CGO Criteria for Guiding Outpatient treatment

DOAC Direct acting oral anticoagulant

DVT Deep vein thrombosis

ED Emergency department

HAC Hospital acquired conditions

ICU Intensive care unit

IQR Interquartile range

LMH Low molecular heparin

LOS Length of stay

LRPE Low-risk pulmonary embolism

PE Pulmonary embolism

SD Standard deviation

sPESI Simplified pulmonary embolism severity index

VTE Venous thromboembolism

Declarations

Ethical approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standard of the institutional and/or national research committe and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Availability of data and supporting materials:

The unidentified dataset supporting the conclusions of this article is available upon request by contacting the corresponding author.

Competing interests

The authors state that they have no competing interests.

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Authors´ contribution

All authors contributed to the study concept and design. RG contributed to the acquisition of the data. RG, AG, and JE all contributed to data analysis and interpretation, and drafting. RG, AG, JE, JH, and SL contributed to critical revision of the manuscript. Statistical analysis was performed by RG.

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Tables

Due to technical limitations, tables are only available as a download in the supplemental files section

Figures

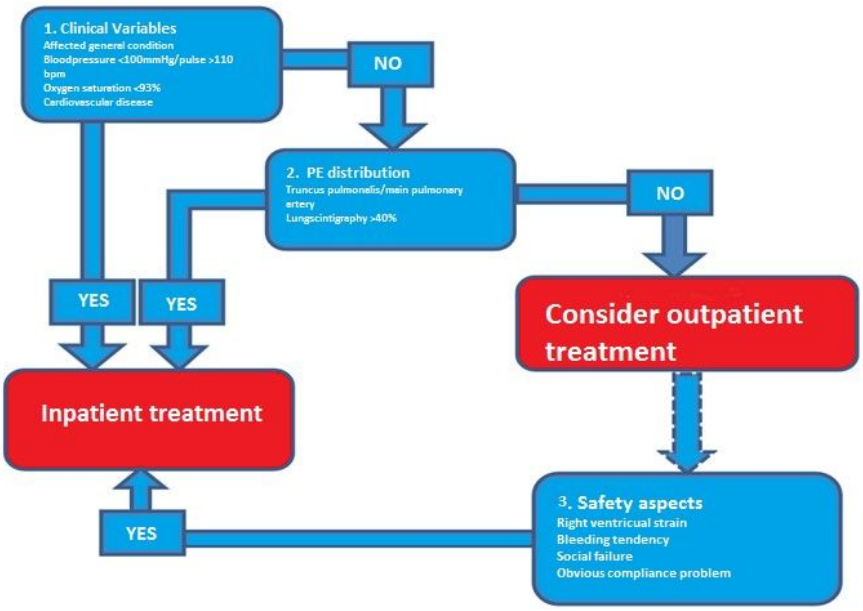

Figure 1

Selection criteria for outpatient treatment of low-risk patients with pulmonary embolism (PE) at the eight study hospitals in in Sweden´s southernmost health care region.

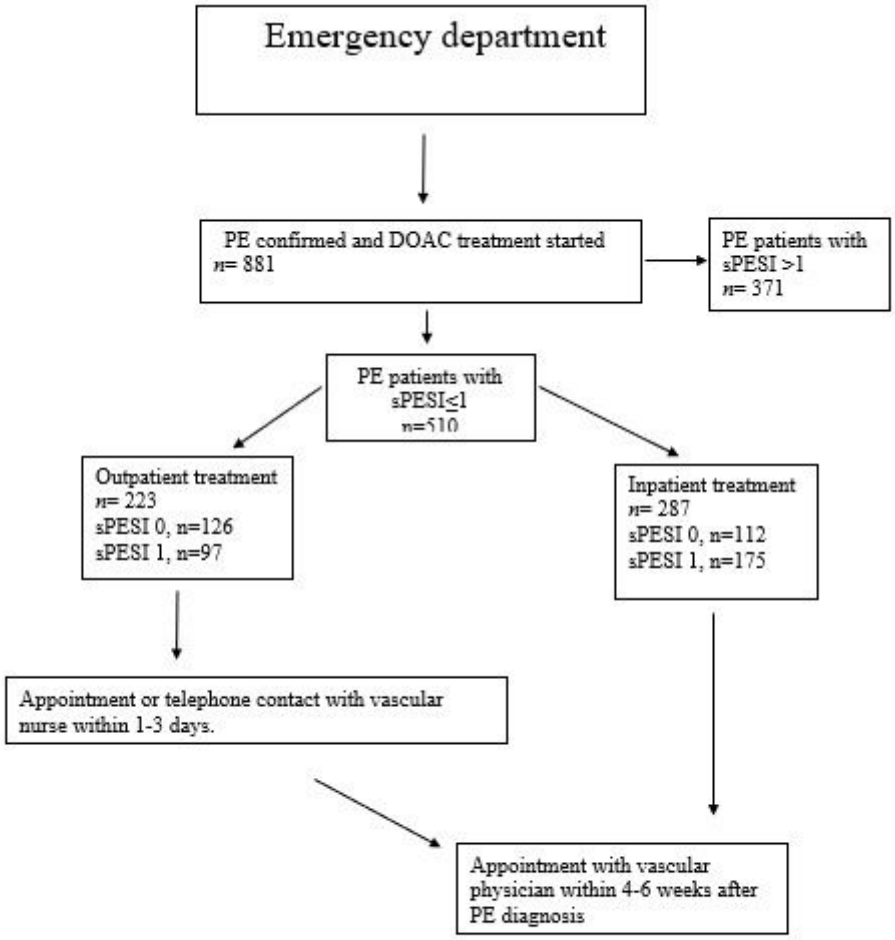

Figure 2

Flow chart depicting treatment and follow-up of 510 patients diagnosed with low risk (simplified pulmonary embolism severity score [sPESI] scores 0-1) PE in the emergency departments of the eight hospitals in Sweden´s southernmost healthcare region treated with direct oral anticoagulants (DOAC) during 2013-2015. DOAC treated PE patients with sPESI >1 (n = 371) are excluded.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- MSTHRJD1900068Table1.docx
- MSTHRJD1900068Table2.docx