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Risk stratification of outpatient management in acute venous thromboembolism

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Current practice patterns of outpatient management of acute pulmonary embolism: a post-hoc analysis of the YEARS study

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ABSTRACT

Background: Studies have shown the safety of home treatment of patients with pulmonary embolism (PE) at low risk of adverse events. Management studies focusing on home treatment have suggested that 30% to 55% of acute PE patients could be treated at home, based on the HESTIA criteria, but data from day-to-day clinical practice are largely unavailable.

Aim: To determine current practice patterns of home treatment of acute PE in the Netherlands.

Method: We performed a post-hoc analysis of the YEARS study. The main outcomes were the proportion of patients who were discharged <24 hours and reasons for admission if treated in hospital. Further, we compared the 3-month incidence of PE-related unscheduled readmissions between patients treated at home and in hospital.

Results: Of the 404 outpatients with PE included in this post-hoc analysis of the YEARS study, 184 (46%) were treated at home. The median duration of admission of the hospitalized patients was 3.0 days. The rate of PE-related readmissions of patients treated at home was 9.7% versus 8.6% for hospitalized patients (crude hazard ratio 1.1 (95%CI 0.57-2.1)). The 3-month incidence of any adverse event was 3.8% in those treated at home (2 recurrent VTE, 3 major bleedings and two deaths) compared to 10% in the hospitalized patients (3 recurrent VTE, 6 major bleedings and fourteen deaths).

Conclusions: In the YEARS study, 46% of patients with PE was treated at home with low incidence of adverse events. PE-related readmission rates were not different between patients treated at home or in hospital.

INTRODUCTION

Over the last decade, there has been a trend towards treating patients with pulmonary embolism (PE) at low-risk of early adverse events at home. The safety and feasibility of home treatment in selected patients with PE has already been shown in several large trials, although the optimal method for selecting relevant patients is still debated.¹⁻¹⁰ The severity of the PE and risk of adverse outcomes largely determine clinical decision making with regard to initial home treatment. Other factors such as locoregional cultural and patient preferences, the (financing of the) healthcare system and corresponding infrastructure also play a role. These latter greatly differ between countries, as was recently demonstrated in a post-hoc analysis of the Hokusai VTE study: the vast majority of Canadian patients was treated at home in contrast to only a quarter of the patients from the United States.¹¹ Same differences were observed between countries in Europe, as more than half of all patients were treated at home in Germany and the United Kingdom, whereas the majority of patients in Spain or France were initially hospitalized.

It has been suggested that as much as 30% to 55% of patients with acute PE could be selected for home treatment.^{10,12,13} These numbers were found in prospective outcome studies focusing on home treatment, but detailed data from day-to-day clinical practice is currently largely unavailable. We therefore aimed to evaluate current practice patterns and outcome of home treatment of patients with confirmed PE in Dutch Hospitals.

METHODS

Design

The current study was a post-hoc analysis of the YEARS study. The YEARS study was a prospective, multicenter, diagnostic management study conducted in 12 university or community hospitals in the Netherlands between October 2013 and July 2015 in patients with suspected acute PE. The YEARS study aimed to validate the diagnostic YEARS algorithm, consisting of three Wells criteria (clinical signs of deep vein thrombosis, haemoptysis, and assessment whether PE is the most likely diagnosis) with simultaneous assessment of the D-dimer concentrations.¹⁴ According to the algorithm, PE is excluded in patients without YEARS items and D-dimer less than 1000 ng/mL, or in patients with one or more YEARS items and D-dimer less than 500 ng/mL. Patients were eligible for inclusion if they were aged 18 years or older, with the main exclusion criteria of initiated therapeutic doses of anticoagulants 24 hours or more before eligibility assessment. Furthermore, a life expectancy less than 3 months, an expected inability to achieve the required 3-month follow-up, pregnancy and allergy to intravenous contrast agent were exclusion criteria. Patients were followed for three months to assess the occurrence of symptomatic venous thromboembolism (VTE).

For the present analysis, all outpatients who were diagnosed with acute PE at baseline were eligible for inclusion. Eleven of 12 hospitals were able to provide additional data. In the participating hospitals, decision for hospitalization or home treatment was mainly based on the Hestia criteria. However this was not part of the study protocol and was left to the discretion of the treating physician. The Hestia rule contains eleven pragmatic parameters to select PE patients who do not require in-hospital care (**Appendix**).¹⁰

Study objectives

The primary aim of this study was to determine current patterns of home treatment in patients with confirmed acute PE in the Netherlands, i.e. the proportion of patients with symptomatic PE who were treated at home, defined as discharged from the hospital within 24 hours after diagnosis. Furthermore, reasons for admission if treated in hospital were evaluated.

The secondary aims were 1) to evaluate the 3-month incidence of unscheduled PE-related readmissions in both home treated or hospitalized patients and 2) to evaluate the duration of hospitalization if treatment started initially in hospital, i.e. the median duration of admission; and 3) to compare the clinical outcome of PE patients treated at home or in hospital. This latter endpoint includes all-cause mortality, recurrent VTE and major bleeding during a 3-month follow-up period.

Study definitions

Acute PE was defined as an intraluminal filling defects of the subsegmental or more proximal pulmonary arteries confirmed by computed tomographic pulmonary angiography (CTPA). Recurrent VTE was defined as a new intraluminal filling defect on CTPA or confirmation of a new PE at autopsy. Recurrent lower extremity DVT was defined as new non-compressibility by ultrasonography or as an increase in vein diameter under maximal compression, as measured in the abnormal venous segment, indicating an increase in thrombus diameter (≥ 4 mm) or by a positive signal on magnetic resonance direct thrombus imaging (MRDTI) indicative of fresh thrombus in the proximal veins of the leg.¹⁵

Major bleeding was defined as any bleeding resulting in death; symptomatic bleeding in a critical organ (intracranial, intra spinal, intraocular, retroperitoneal, intra articular and pericardial bleeding and muscle bleeding resulting in compartment syndrome) or symptomatic bleeding resulting in a decrease in the hemoglobin concentration of at least 2g/dL or resulting in the transfusion of at least two packs of red blood cells, following the ISTH criteria.¹⁶

In case of death, information was obtained from the hospital records. Deaths were classified as caused by PE when confirmed by autopsy, shown by objective testing shortly before death, or if it could not be confidently excluded as a cause of death.

PE-related readmission was defined as any unscheduled visit to the outpatient clinic, emergency room or readmission in hospital due to PE-related complications, such as thoracic pain, dyspnea, major bleeding, clinically relevant non-major bleeding or (suspected) recurrent VTE.

An independent adjudication committee assessed and adjudicated all (suspected) adverse events occurring during follow-up.

Statistical analysis

Categorical data are presented as percentages and continuous variables as means \pm standard deviation. The proportion of patients who were discharged within 24 hours after diagnosis and reasons for admission are provided as frequencies with corresponding 95% confidence intervals (95%CI). Also, frequencies with corresponding 95%CI will be provided to assess the 3-month incidence of PE-related unscheduled readmissions.

In order to describe the natural course of PE in patients treated at home or hospitalized (secondary outcomes), crude Odds Ratios are provided with corresponding 95%CI which allows for providing the relevant perspective. Because patients treated at home or hospitalised are inherently different (hospitalized patients have a different risk profile for adverse outcome), we did not perform multivariate analysis to formally compare the outcomes of the two patient cohorts. The cumulative incidence of PE-related unscheduled readmission according to initial treatment management were compared with a hazard ratio. SPSS version 25.0.0 (SPSS, IBM) was used to perform all analyses.

RESULTS

Study patients

A total of 456 patients were diagnosed with acute PE in the YEARS study. Of these, 52 were excluded for this current analysis because PE was diagnosed during hospitalization or patients were included in the one hospital that could not provide additional data for this sub study. The baseline characteristics of the 404 remaining study patients are summarized in **Table 1**. Their mean age was 59 years (standard deviation (SD) 16), 52% was female and 13% had active malignancy at time of diagnosis. Patients initially treated at home were younger with a mean age of 56 years compared to 62 of those initially hospitalized (mean difference 6.1 years (95%CI 2.9-9.3)) and had less renal insufficiency, 13 % vs 23% (OR 0.49 (95%CI 0.29-0.85)). In this cohort, the majority of patients was treated with vitamin K antagonists while only 4.2% were treated with a direct oral anticoagulants (DOAC).

Table 1: Baseline characteristics of outpatients with acute pulmonary embolism of the YEARS study

| | Home treatment (n=184) | Initial hospitalization (n=220) | Total (n=404) |
|-------------------------|---------------------------|------------------------------------|------------------|
| Age, mean (SD) | 56 (16) | 62 (16) | 59 (16) |
| Male sex, no (%) | 92 (50) | 100 (47) | 195 (48) |
| Weight in kg, mean (SD) | 85 (17) | 86 (19) | 86 (18) |

Table 1: Baseline characteristics of outpatients with acute pulmonary embolism of the YEARS study (continued)

| | Home treatment (n=184) | Initial hospitalization (n=220) | Total (n=404) |
|---|---------------------------|------------------------------------|------------------|
| Body Mass Index, mean (SD) | 28 (5.4) | 28 (5.8) | 28.1 (5.6) |
| Creatinine clearance < 60 ml/min* — no. (%) | 23 (13) | 48 (23) | 73 (18) |
| COPD (%) | 7 (3.8) | 14 (6.6) | 21 (5.2) |
| Heart failure (%) | 2 (1.1) | 8 (3.8) | 11 (2.7) |
| Mean duration of symptoms in days (SD) | 8.6 (17) | 8.2 (18) | 8.3 (17) |
| Previous VTE — no. (%) | 51 (28) | 44 (21) | 95 (24) |
| DVT | 21 (11) | 14 (6.6) | 35 (8.7) |
| PE +/- DVT | 26 (14) | 30 (14) | 57 (14) |
| Estrogen Use (%) | 25 (14) | 19 (8.9) | 44 (11) |
| Active malignancy no. (%) | 21 (11) | 31 (15) | 53 (13) |

Abbreviations: PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism; DVT, Deep vein thrombosis; COPD, chronic obstructive pulmonary disease

* estimated GFR calculated by the abbreviated MDRD equation

Primary outcome

Of the 404 patients, 184 (46%, 95%CI 41-50) were treated at home whereas the remaining 220 patients (54%) were treated in hospital. The median duration of admission of those initially hospitalized was 3.0 days (interquartile range 2.0-5.0). In 1.7% of patients, the duration of admission could not be retrieved. Reasons for hospitalization are shown in **Table 2** and consisted mainly of need for oxygen administration (37%) and “medical or social reasons” (47%; **Table 3**). Of note, relevant inter hospital differences were observed in the proportion of patients treated initially at home treatment with percentages ranging from 13% to 83% (**Figure 1**).

Table 2: Reasons for hospitalization after diagnosis PE*

| Reasons for hospital admission | Frequency n= 261 | Proportion |
|---|---------------------|------------|
| 1. Hemodynamically unstable | 15 | 7.0% |
| 2. Need for thrombolysis or embolectomy | 1 | 0.5% |
| 3. Active bleeding or high bleeding risk | 10 | 4.7% |
| 4. > 24 hour oxygen supply | 78 | 37% |
| 5. Need for intravenous pain medication > 24 hr | 21 | 9.9% |
| 6. Medical or social reasons | 100 | 47% |
| 7. Renal insufficiency (< 30 ml/min) | 5 | 2.3% |
| 8. Severe liver impairment | 2 | 1.0% |
| 9. New PE during anticoagulant treatment | 3 | 1.4% |
| 10 No risk stratification scheme such as Hestia applied | 26 | 12% |

* Multiple Hestia criteria for admission could be scored in one patient

Abbreviations: PE, pulmonary embolism

Table 3: Reasons for awarding the subjective Hestia criterion ‘social or medical reason for admission’

| Reasons for hospital admission | Frequency n=100 | Proportion |
|---|--------------------|------------|
| 1. Concomitant infection | 16 | 16 % |
| 2. Malignancy | 9 | 9 % |
| 3. Concomitant acute condition, e.g. electrolyte disorders | 14 | 14 % |
| 4. Extensive PE | 13 | 13 % |
| 5. PE related cardiac problems | 5 | 5 % |
| 6. Outpatient treatment not feasible because of comorbidities or social reasons | 16 | 16 % |
| 7. Need for pain medication (not i.v.) | 5 | 5 % |
| 8. Contrast allergy | 1 | 1 % |
| 9. Other | 21 | 21 % |

Abbreviations: PE: Pulmonary embolism; i.v., intravenously, Extensive PE: saddle embolus, large thrombus load, RV dilatation; PE related cardiac problems: rhythm alterations, syncope

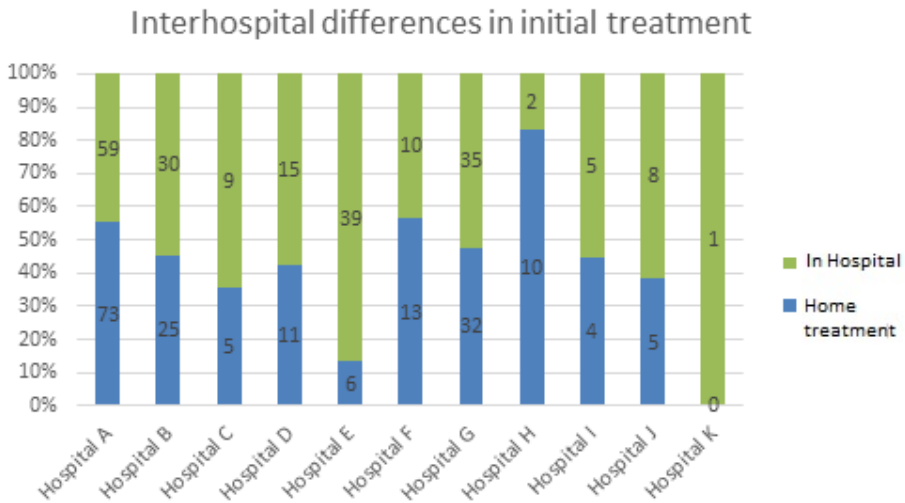


Figure 1: Inter hospital differences in initial treatment policy

Secondary outcome

The 3-month cumulative incidence of any adverse event was 3.8% (95% confidence interval (CI) 1.5% - 7.7%) in those treated at home (2 recurrent VTE, 3 major bleedings and two deaths) versus 10% (95% CI 6.7% - 15.3%) in the initially hospitalized patients (3 recurrent VTE, 6 major bleedings and fourteen deaths). Specifications of the adverse events of patients with PE treated at home are described in **Table 4**. In those patients treated at home, none of the major bleeding or recurrent VTE events were fatal. The two deaths were adjudicated not to be associated to VTE: one occurred in the setting of progressive non-small cell lung carcinoma and the other

patient died of progressive non-specified interstitial pneumonia requiring increasing amounts of oxygen suppletion.

Table 4: Details of adjudicated adverse events in all outpatient treated at home.

| Patient | Sex | Age | Adverse event | Specification |
|---------|-----|-----|-------------------------|---|
| No. 1 | M | 50 | Major bleeding | Subdural bleeding during anticoagulant therapy with low-molecular weight heparin. |
| No. 2 | F | 51 | Major bleeding | Spontaneous liver bleeding: subcapsular haematoma with multiple active bleeding foci treated with a coiling procedure. An inferior vena cava filter was placed and removed two months later; anticoagulation with vitamin K antagonist was stopped and switched to LMWH |
| No. 3 | F | 95 | Major bleeding | Decrease in hemoglobin concentration > 2g/dL due to severe spontaneous m. rectus sheath hematoma, treated with transfusion of 2 packs red blood cells. Anticoagulation was stopped indefinitely and replaced by aspirin. |
| No. 4 | F | 43 | Recurrent VTE and Death | Recurrent VTE during LMWH treatment with new thrombus load in superior vena cava in patient with advanced non-small cell lung carcinoma. Patient died thirteen days later due to progressive vena cava superior syndrome. |
| No. 5 | M | 42 | Death | Death not adjudicated to PE. History of severe non-specific interstitial pneumoniae with increasing oxygen requirement. |
| No. 6 | F | 50 | Recurrent VTE | New symptomatic DVT after initial diagnosis of PE during VKA treatment. LMWH was temporarily added on top of the VKA. |

Abbreviations: SD, standard deviation; PE, pulmonary embolism; VTE, venous thromboembolism; VKA, vitamin K antagonists; LMWH, low-molecular weight heparin

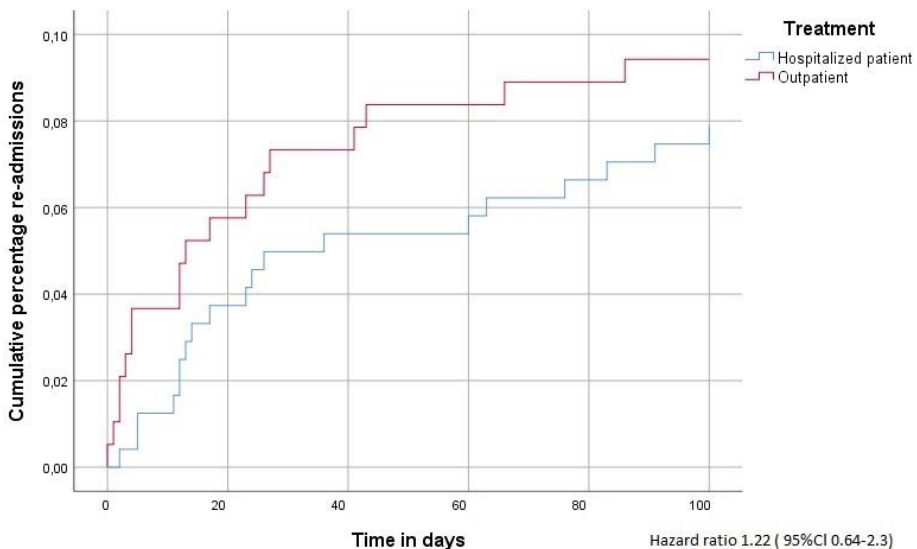


Figure 2: Cumulative incidence of PE-related unscheduled readmissions to the hospital.

The rate of PE-associated unscheduled readmissions in patients treated at home was 9.7% versus 8.6% for initially hospitalized patients, for a crude hazard ratio of 1.1 (95%CI 0.57-2.1; **Figure 2**). The main reason for readmission was thoracic pain (n=16, 43%). Specification of all reasons for an unscheduled readmission are provided in **Table 5**. The PE-associated unscheduled readmissions of patients initially hospitalized consisted of nine admissions, eight emergency room visits and two unscheduled visits to the outpatient clinic, whereas unscheduled PE-associated readmissions of patients treated at home consisted of nine admissions and nine emergency room visits.

Table 5: Reasons for readmission

| | Home treatment n (%) | Initial Hospitalization n (%) | Median Time until readmission in days n (IQR) |
|--|-------------------------|----------------------------------|--|
| 1. Thoracic pain | 8 (4.3) | 8 (3.6) | 9 (2-34) |
| 2. Dyspnea (without any other explanation than PE) | 2 (1.0) | 3 (1.4) | 7 (7-68) |
| 3. Major bleeding | 2 (1.0) | 3 (1.4) | 12 (8-39) |
| 4. Clinically relevant non-major bleeding | 3 (1.6) | 4 (1.8) | 25 (23-62) |
| 5. Recurrent VTE | 2 (1.0) | 1 (0.5) | 26 (14-34) |
| 6. Total | 18 (9.7) | 19 (8.6) | 29 (13-84) |

Abbreviations: IQR interquartile range; PE, pulmonary embolism; VTE, venous thromboembolism

DISCUSSION

This post-hoc analysis of the YEARS study showed that 46% of all outpatients with confirmed PE were treated at home in Dutch daily clinical practice. The incidence of adverse outcome for those treated at home was low and PE-associated unscheduled readmission rates were not different between patients treated at home or initially managed in hospital.

Although we observed relevant inter hospital differences regarding the proportion of home treatment with percentages ranging from 13% to 83%, the overall proportion of patients treated at home in this analysis is very much in line with numbers suggested in prospective outcome studies focusing on home treatment. In the Hestia study 297 (51%) of the initially screened 581 patients were treated at home, while this was 152/351 (43%) and 516/1102 (47%) in two other studies.^{3,6,10} Limited data are available from practice based studies in other countries. Published literature from three countries showed lower rates of home treatment, with numbers varying from 10 to 33%.^{13,17-19} This 33% was observed in a large Italian prospective cohort comparing different risk stratification scores.¹³ In that study, the Hestia criteria identified a higher proportion (42%) of PE patients eligible for early discharge (within 48 hours) than the PESI (24%) and sPESI (18%) scores.

Where the introduction of DOACs has likely lowered the threshold for treating a PE patient at home, it may also lead to a decrease in the mean duration of hospitalization. The

median duration of admission in the hospitalized patients in our cohort was 3.0 days, with the vast majority of all patients in this cohort treated with low-molecular weight heparin followed by vitamin K antagonists. Notably, this was shorter than found in a large study comprising mainly European hospitals showing a mean duration of 13.6 days in 2001 and 9.3 days in 2013.^{7,20} This decrease in length of stay was also observed in recent published data from the United States showing a decrease to 6 days of hospitalization in 2015.²¹ Notably, the mean duration of admission in the current study may thus decrease even further with more extensive use of DOACs than the observed proportion of 4.2%. The main reasons for in-hospital care were oxygen administration (37%) and “medical or social reasons” (47%); these frequencies are very comparable to those shown in dedicated outpatient management studies.^{6,10}

The incidence of adverse events in the patients treated at home was low. These low adverse event rates were very much comparable to those observed in the Vesta and Hestia studies, in which patients were treated at home in the absence of any Hestia criteria.^{6,10} This low rate of events was also found in the HoT-PE trial, in which patients were selected by the majority of the exclusion criteria correspond to the items of the Hestia criteria in combination with the mandatory absence of right ventricular dysfunction.²² In current literature, data regarding unscheduled readmissions in PE patients after initial home treatment is only sparsely available. To our surprise, we could not demonstrate a difference between patients treated at home or in hospital. Notably, the proportion of patients with a readmission or prolonged initial hospitalization in the HoT-PE study was 10% as well. Slightly higher readmission rates (+/-15%) were reported in a large retrospective cohort study in the United States using international classification of diseases (ICD) codes for the identification of PE.^{21,22}

Strong points of this study include the novelty of our data, the completeness of follow-up, the multicentric design and the practice based setting. Main limitation of this study is the post-hoc design. Data concerning major bleeding and the Hestia criteria was not prospectively collected in the YEARS study, but were extracted from the medical charts. Also, as the YEARS study was a management study, underrepresentation of high-risk subgroups is possible, including but not limited to pregnant patients or hemodynamically unstable patients. Even so, as the YEARS algorithm was implemented as standard diagnostic strategy in all participating hospitals, the vast majority of all potential PE patients participated in the original study, underlying the validity of our conclusions.

In conclusion, forty-six percent of all outpatients with acute PE participating in the YEARS study were treated at home. Rates of adverse events were low and PE-related unscheduled readmission rates were not different between patients treated at home or in hospital. This supports the widespread trend to treat PE patients more often at home.

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Appendix Hestia Criteria

| | |
|---|--------|
| Is the patient hemodynamically unstable? ^a | Yes/No |
| Is thrombolysis or embolectomy necessary? | Yes/No |
| Active bleeding or high risk of bleeding? ^b | Yes/No |
| More than 24 hour of oxygen supply to maintain oxygen saturation > 90%? | Yes/No |
| Is pulmonary embolism diagnosed during anticoagulant treatment? | Yes/No |
| Severe pain needing intravenous pain medication for more than 24 h? | Yes/No |
| Medical or social reason for treatment in the hospital for more than 24 h (infection, malignancy, no support system)? | Yes/No |
| Does the patient have a creatinine clearance of < 30 ml/min? ^c | Yes/No |
| Does the patient have severe liver impairment? ^d | Yes/No |
| Is the patient pregnant? | Yes/No |
| Does the patient have a documented history of heparin-induced thrombocytopenia? | Yes/No |
| If the answer to one of the questions is 'yes', the patient cannot be treated at home | |

^a Include the following criteria, but are left to the discretion of the investigator: systolic blood pressure < 100mmHg with heart rate > 100 beats per minute; condition requiring admission to an intensive care unit.

^b Gastrointestinal bleeding in the preceding 14 days, recent stroke (less than 4 weeks ago), recent operation (less than 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count < 75 9 10⁹/L), uncontrolled hypertension (systolic blood pressure > 180mm Hg or diastolic blood pressure > 110mm Hg).

^c Calculated creatinine clearance according to the Cockcroft-Gault formula.

^d Left to the discretion of the physician.