Update of the Preventive Antibiotics in Stroke Study (PASS):

Statistical Analysis Plan

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ABSTRACT

Background Infections occur in 30% of stroke patients and are associated with unfavourable outcome. Preventive antibiotic therapy lowers the infection rate after stroke, but the effect of preventive antibiotic treatment on functional outcome in patients with stroke is unknown. This paper presents in detail the statistical analysis plan (SAP) of the Preventive Antibiotics in Stroke Study (PASS) and was submitted while the investigators were still blinded for all outcomes

Methods The PASS is a multicentre, prospective, phase three, randomised, open-label, blinded end-point (PROBE) trial of preventive antibiotic therapy in acute stroke. Patients are randomly assigned to either ceftriaxone at a dose of 2 g, given every 24 h intravenously for four-days, in addition to standard stroke-unit care, or standard stroke-unit care without preventive antibiotic therapy. Aim of the study is to assess whether preventive antibiotic treatment improves functional outcome at 3 months by preventing infections. The primary outcome is the score on the modified Rankin Scale (mRS), assessed by ordinal logistic regression analysis according to a proportional odds model. Secondary analysis of the primary outcome is the score on the mRS dichotomized as a favourable outcome (mRS 0–2) *vs.* unfavourable outcome (mRS 3–6). Secondary outcome measures are death rate at discharge and three-months, infection rate during hospital admission, length of hospital admission, volume of post stroke care, use of antibiotics during hospital stay, quality-adjusted life years and costs. Complications of treatment, Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported as safety outcomes.

Conclusion The data from PASS will establish whether preventive antibiotic therapy in acute stroke improves functional outcome by preventing infection; and will be analysed according to this pre-specified SAP.

Keywords stroke, infection, antibiotics, randomised clinical trial, statistical analysis plan

UPDATE

Introduction

Stroke is a leading cause of death worldwide.[1] Infections occur in 30% of stroke patients and are associated with unfavourable outcome.[2,3] Preventive antibiotic therapy lowers infection rate in patients after stroke, but the effect of preventive antibiotic treatment on functional outcome after stroke has not yet been investigated.[4,5] The Preventive Antibiotics in Stroke Study (PASS) is a phase three randomised clinical trial investigating whether the preventive use of the antibiotic ceftriaxone improves functional outcome in acute stroke patients by preventing infections. We previously published the trial protocol and an update of this protocol; we now present the statistical analysis plan (SAP).[6,7] This SAP was drafted without knowledge of any of the outcomes by the investigators and randomisation code will not be broken before acceptation for publication of the current paper.

Summary study protocol

PASS is a multicentre prospective, randomised, phase III, open-label, blinded end-point superiority trial (PROBE) of standard care with preventive ceftriaxone treatment compared to standard care without preventive ceftriaxone. Adult patients with stroke (both ischaemic and haemorrhagic), a score ≥1 on the National Institutes of Health Stroke Scale (NIHSS) and stroke onset within 24 hours were included.[8] Patients were excluded in case of infection at admission, use of antibiotics within 24 hours before admission, previous hypersensitivity of anaphylaxis to cephalosporins or penicillin, subarachnoid haemorrhage, pregnancy or when death seemed imminent. Patients were randomly assigned to either ceftriaxone at a dose of 2 g, given every 24 h intravenously for four days, in addition to stroke-unit care, or standard stroke-unit care without preventive antibiotic therapy. Randomisation was performed through ALEA (online software for randomised trials) and is based on a uniform distribution; weight of the arms is equal (1:1). Randomisation is stratified according to study centre (academic hospital, large non-academic hospital, small non-academic hospital) and stroke severity (score on NIHSS 1-9 or >9) and performed by using random blocks with a maximum block size of 6; blocks of 2, 4 and 6 are made per stratum combination.[9] The study has a PROBE design, which implies that blinding is lost, but only as to treatment. Patient and physician were aware of treatment allocation, however, the assessors of outcome were not. Data was collected on admission, during hospital stay, and at three months by standardized case record forms. The primary outcome is functional outcome at 3 months follow-up, as assessed on the modified Rankin Scale (mRS) during a structured telephone interview by a trained assessor blinded for treatment allocation. Secondary

outcomes are death rate at discharge and at 3 months, infection rate during hospital admission, length of hospital admission, volume of post-stroke care, use of antibiotics during hospital stay, quality adjusted life years (QALYs) and costs. Safety outcomes are complications of treatment, Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs). In the initial trial protocol we presented a binary logistic regression analysis on the dichotomized mRS (0-2 vs 3-6) as primary outcome, requiring a sample size of 3200 patients, and a proportional odds model in a secondary analysis of the primary end point.[9] Blinded for any of the outcomes, we have changed the primary analysis in PASS from a binary logistic to ordinal logistic regression on the original mRS, enhancing statistical power. The adapted power analysis showed that with identical assumptions on the clinical effect, using a 0·05 two-sided significance level and 80% study power, 2550 patients were needed.[9] The analysis of dichotomized mRS data will now be the secondary analysis of the primary end point.

On the 23rd of March 2014 all patients were included and the last follow-up is expected in June 2014. For the complete study protocol and update we refer to previous publications.[6,10]

Protocol developments

PASS is registered at current controlled trials (www.controlled-trials.com; ISRCTN: 66140176; date of registration: 6-4-2010). The medical-ethical board of the Academic Medical Center, Amsterdam, approved the protocol on 5-5-201, and 29 Dutch participating centres were added in the course of the study. Due to a change in primary analysis of primary outcome, from a binary logistic approach to an ordinal logistic regression analysis, and an expected rate of patients lost to follow-up and/or patients with incomplete data of 5%, total sample size was reduced from 3200 patients to 2550 patients in 2014.[10] Importantly, no changes were made regarding the primary outcome measurement, i.e. the assumed size of the effect on the mRS. This update of the protocol was recently published in this journal.[10]

Statistical analysis plan

General analysis principles

The code of the database will not be broken until all efficacy and safety data up to the last patient is included in the database, after data verification and validation are performed, and the SAP has been accepted for publication. Analysis will be performed by the investigators of the PASS study group (see acknowledgement section) assisted by a biostatistician of the Academic Medical Centre in Amsterdam .

Patients flow diagram

The flow of participants will be displayed in the Consolidated Standards of Reporting Trials CONSORT Flow diagram (figure 1). Due to the pragmatic design of the study the total number patients assessed for eligibility has not been assessed.

Definition of intention-to-treat and per-protocol population

Main analysis will be performed according to the intention to treat (ITT) principle. The safety analysis will be performed in a per protocol (PP) analysis. If a patient was by fault randomised more than once the first randomisation outcome was used. Patients who withdrew consent directly after randomisation (i.e. before treatment was initiated in those randomised for ceftriaxone in addition to standard care, or within 6 hours after randomisation in those randomised for standard care) will be excluded from analysis. Patients with protocol deviations in eligibility are included in the ITT analysis and will be tabulated (table 1: number and type of protocol violations in eligibility). Patients not receiving their allocated treatment due to instantaneous cross-over are considered protocol violations, these patients will be included in the ITT population. PP analysis will exclude patients in whom protocol deviations in treatment and eligibility were made (see protocol deviations in eligibility and protocol deviations in treatment).

Handling of missing data

If outcome data could not be obtained at the 3 month evaluation we will firstly check the municipal council to ensure that patient is not deceased. All other patients are considered lost to follow-up and will be tabulated, including the percentage of missing outcome data and the association with treatment. Missing outcome data will be obtained by imputation, using the coefficients of five rounds of imputation to obtain the final estimates. We will perform sensitivity analysis. First, we will use single imputation by Last Observation Carried Forward (LOCF). An observer blinded for treatment allocation will obtain the last observational score on the mRS using medical charts and the letters of discharge of the stroke episode. All patients with LOCF will be tabulated with explanation for the loss-to-follow-up (table 2: assessment of follow-up according to treatment allocation).
We will also perform a sensitivity analysis of baseline characteristics of the group of patients not lost-to-follow-up *vs.* all patients included in PASS. In addition, we will also perform a joint model analysis of the loss-to-

follow-up and the mRS change during follow-up.[11] Missing values of baseline characteristics will not be included or imputed in the display of baseline characteristics. When values are missing for dichotomous variables, the actual denominator will be stated. In case of continuous variables, a footnote will be made showing the number of patients of whom the variable was missing.

Protocol deviations in eligibility, consent procedure, treatment

When a patient was randomised but did not adhere to inclusion or exclusion criteria this was considered a protocol deviation regarding eligibility. Patients with protocol deviations in eligibility were included in the ITT analysis, but excluded from PP analysis.

In each centre the local investigator obtained written informed consent from patient or its representative according to the PASS study protocol. Patients who withdrew consent directly after randomisation were excluded from further analysis. The flow of patients is displayed in the CONSORT flow-chart (figure 1)

Treatment allocation was regarded as carried out according to the study protocol, when a patient randomised for ceftriaxone in addition to standard care received ceftriaxone 2 gram each 24 hours for 4 days. Patients were also considered as treated PP when treatment was terminated within 4 days due to discharge, death, a palliative care policy, an allergic reaction without anaphylaxis or a previous allergic reaction in medical history (see inclusion and exclusion criteria and protocol deviation in eligibility), other side effects of treatment or when treatment with ceftriaxone was changed into treatment with another antibiotic because of an infection - because these situations and what to do were all defined and described in the initial protocol.[6] In patients allocated to standard care, treatment was carried out according to the study protocol when patients did not receive preventive antibiotic therapy.

Baseline characteristics

Baseline characteristics of all patients will be outlined per treatment allocation in a baseline table describing the following variables: age, male sex, medical history (atrial fibrillation/flutter, stroke, hypercholesterolaemia, hypertension, myocardial infarction, cardiac valve insufficiency/stenosis/replacement, peripheral vascular disease, obstructive pulmonary disease, immunocompromised), current smoking, specific medication (anticoagulants, antiplatelet, statin, ACE-inhibitor, ß-blocker, proton pump inhibitor) prior to stroke, disability

prior to stroke on mRS, stroke severity on NIHSS, performance of a screening test for swallowing function, dysphagia, acute treatment (IV thrombolysis, anticoagulant antagonist therapy) and diagnosis at discharge (infarct, haemorrhage, TIA, or other). Outline of the table is displayed at the 'outline of figures and tables'-section (table 3: baseline characteristics). All variables will be presented categorised by treatment arm. Dichotomous variables will be displayed in percentage with number of patients divided by total number of evaluated patients. Continuous variables will be reported in means, with standard deviations when normally distributed, and in medians with interquartile ranges, when they do not meet the criterion of being normally distributed, as assessed by the Kolmogorov-Smirnov test. For continuous variables the number of patients evaluated will be presented in a footnote of table 3.

Assessment of primary outcome

A structured telephone interview with each patient was held at three months by one of three trained research nurses, blinded for treatment allocation, to assess the primary outcome on the mRS. This structured telephone interview has been validated in an earlier study.[12]

Assessment of secondary outcomes

1) Infection rate during hospital admission: the total number of patients diagnosed with one or more infection(s) during hospital admission will be reported, as well as the total number of infections. Infections will be reported according to subtypes pneumonia, urinary tract infection and other infection. Infection will be assessed in two ways. First, infection will be diagnosed in the clinical setting as judged by the treating physician and registered as pneumonia, urinary tract infection or other infection. The clinical diagnosis of infection will be used for the primary analysis. Suspected infections without diagnostics being performed are also recorded and reported as such (for example in a patient with a palliative care policy). Second, infection will be categorized by two infectious disease specialists who are blinded for treatment allocation, using the modified criteria of the Centers for Disease Control and Prevention (CDC criteria).[13] For this second categorization, patients with fever, new onset delirium or clinical diagnosis of infection during hospital admission will be reviewed. For this purpose, data on the diagnostic procedures during admission as recorded in the CRF will be used. For the diagnosis of pneumonia and urinary tract infection pre-specified algorithms will be used based on the CDC-criteria (figure 2 and 3: diagnosis of pneumonia and urinary tract infection). Patients with a positive blood culture or a positive culture from the presumed site of infection, other than the lungs or urine, with a clinically relevant pathogen will

be diagnosed as ‘other infection’. Patients will be categorized as having confirmed pneumonia, urinary tract infection, or other infection. Solely bacterial infections will be assessed since preventive antibiotic therapy aims to reduce these infections. Infection with *Clostridium difficile* is reported as a treatment complication. Case definition of this infection is diarrhoea plus a positive *C. difficile* toxintest. Clostridium infection was diagnosed by the treating physician and is reviewed by the expert panel.

2) Death rate at discharge and at 3 months: death during hospital admission was recorded in the CRF by the treating physician and notified as SAE to the trial office. Death was also registered at the 3 months follow-up. If needed, survival status at 3 months is evaluated though contact with general practitioners and the municipality register.

3) Length of hospital stay: day of admission and discharge was recorded in the CRF by the treating physician. Length of hospital admission is measured in days.

4) Total use of antibiotics during hospital stay: use of antibiotics other than preventive antibiotic therapy will be recorded in the case record form. Total antibiotic use will be recorded in units of the ‘Defined-daily-dosis’ (DDD), and number of days of use. For definitions of the DDD the classification according to the World Health Organization (WHO) will be used for each antibiotic.[14]

5) Volume of post-stroke care, cost-effectiveness analysis: cost-effectiveness will be measured by an economic analysis conducted alongside the study. This analysis is not included in the publication to which this analysis plan applies to.

Assessment of safety outcomes

Safety outcomes are complications of treatment, SAEs and SUSARs. All SAEs and SUSARs during hospital stay are recorded in case record forms by the treating physician and notified to the trial office. SAEs and SUSARs occurring after discharge are recorded during the follow-up interview at 3 months. The physician records treatment complications in the CRF (diarrhoea caused by *C. difficile*, allergic reaction that caused cessation of ceftriaxone, infection with ceftriaxone resistant micro-organism, phlebitis on place of IV-catheter, elevation of liver enzymes, oliguria or elevation of serum creatinine).

Cause of death will be reviewed by two independent observers. They will use information from the hospital discharge letter or the medical correspondence received by the general practitioner in case the patient died after discharge. Discrepancies will be reviewed in a consensus meeting in presence of a third investigator. Outcome parameters were derived from three recent cardiovascular trials and were modified for expected outcomes in our study.[15-17] A distinction will be made between a cardiovascular cause (brain infarction, brain haemorrhage, myocardial- or pulmonary embolism or another cardiovascular cause), an infection (pneumonia, sepsis or another infection), death by any type of malignancy, death by any other cause (*e.g.*, traffic accident), withdrawal of treatment due to a poor prognosis or unknown cause of death.

Analysis of primary outcome

An ordinal regression model on the total range of the mRS will be performed as first analysis of primary outcome, under the assumption of proportional odds.[7] The distribution of primary outcome (*e.g.*, functional outcome on the mRS) in both treatment groups will be expressed in a histogram (figure 4: histogram of primary outcome). Both adjusted and unadjusted analysis will be performed and reported. In clinical trials, adjusting for prognostic covariates improves statistical power, can correct for imbalances in baseline prognostic variables and can reduce variability in data.[18,19] The choice of prognostic covariates is mostly based on either imbalances across treatment groups, prognostic factors that are related to the primary outcome, or a combination of both.[18] As the investigators are blinded for all outcome data until the statistical analysis plan is accepted for publication, we chose to use the most important prognostic factors for outcome after stroke: age, stroke severity on the NIHSS, history of stroke, history of diabetes, prior disability as defined on mRS, and stroke type.[20] Stratification of randomisation was performed according to both study centre and stroke severity, so we will also include study centre as a covariate. The second analysis of the primary endpoint, *i.e.*, the dichotomized score on the mRS (*e.g.*, favourable *vs.* unfavourable, mRS 0-2 *vs.* mRS 3-6) will be expressed as OR with 95% confidence intervals (CI; table 4: secondary outcomes). In the discussion section the results of the dichotomized approach will be compared to the results of the primary analysis of primary outcome.

Analysis of secondary outcomes

The number of patients with one or more in hospital post-stroke infection(s) will be presented as numbers with event of numbers evaluated and analysed using the Chi-square test, and OR estimates with 95%CI. Infection

rates will be reported as “judged by treating physicians” and “infectious diseases panel”. Death rate at discharge and at 3 months will also be analysed using the Chi-squared test and presented as OR estimates and 95% CI; use of antibiotics in defined-daily-doses and length of hospital admission will be analysed using the two group t-test or Mann-Whitney test where appropriate (table 4: secondary outcomes). The analysis of volume of post-stroke care, use of antibiotics during 3 months follow-up and the cost-effectiveness analysis will be analysed using a separate analysis protocol and presented in a subsequent paper and is therefore not discussed here.

Safety outcomes

Complications of treatment, SAE’s and SUSAR’s per patient will be tabulated according to treatment group, and analysed using the Chi-squared test (table 5: complications of treatment).

Subgroup analysis of primary and secondary outcomes

We will perform the following sub-group analyses for the primary outcome: stroke type (infarction or haemorrhage), stroke severity (NIHSS 1-9 or NIHSS 10-30), and time between stroke symptoms and start of the antibiotic treatment (0-12 h vs. 12-24 h) and age. For the subgroup analysis of primary analysis of primary outcome, the single OR from the proportional odds model will be calculated for each subgroup separately. For the subgroup analysis of secondary analysis of primary outcome we will tabulate the results and analysed using the Chi-squared test and presented as OR and 95% CI (table 3: subgroup analyses of secondary analysis of primary outcome). In addition to these predefined subgroup analyses, we will perform a larger set of exploratory additional analyses. For secondary outcomes we will perform all the previous mentioned subgroup analyses (stroke type, severity, time to treatment, age). In addition we will perform analysis on presence of a swallowing disorder, respiratory tract infections, and the presence of a urinary catheter.

Authorships

Two PhD students (WFW and J-DV) of this project will have shared first authorship; the two principle investigators (PIs) of this project will have shared last authorship (DvdB and PJN; DvdB corresponding author); local investigators who included at least 100 patients will be co-author; PASS study group members, and physicians in expert panels for outcome-scoring will be co-author; all local investigators who included less than 100 patients in PASS will be explicitly listed in the PASS investigators list.

DISCUSSION

The aim of our study is to investigate whether preventive antibiotic therapy improves functional outcome by reducing the number of infections in acute stroke patients. With this SAP we present the analyses that will be published in the primary publication. By publishing the statistical analysis plan before knowledge of any outcome, we stimulate transparency of scientific conduct and allow others to add timely suggestions for additional analyses.

Patients in the acute phase of stroke are at risk for infections. In a systematic review and meta-analysis of 87 studies was shown that infections complicate stroke in 30% of all stroke patients. Pneumonia was associated with mortality with an OR of 3.62 (95%CI 2.80-4.68). [3] The effect of preventive antibiotic therapy on outcome in stroke patients has been investigated in few studies. Two meta-analyses of these studies showed that preventive antibiotic therapy reduced the number of infections.[4,5] The proportion of patients who died and the number of disabled patients were not significantly reduced but numbers of included patients were small.

The PROBE design with open-label preventive antibiotics might introduce detection bias for infection. Physician are aware of the treatment allocation which potentially influences decisions on non-scheduled treatment, i.e., the detection and treatment of patients with infection. This might influence the outcome measure of infection rate. To control for this bias we will provide a secondary judgement of infection diagnosis by a blinded expert panel, according to CDC-criteria. The CDC criteria are restrictive and use ancillary investigation such as blood test, chest X-ray and culture results to confirm the diagnosis of infection. In clinical practice, a physician will often not wait for culture results, or refrain from treating pneumonia when a chest X-ray does not (yet) show a consolidation, in stroke patient with fever, a cough and abnormalities on auscultation.

Preventive treatment with ceftriaxone after stroke might improve outcome by preventing infections. A potential beneficial effect on functional outcome might be caused by a direct effect of prevention of infections in patients after stroke, most commonly pneumonia, but also by the result of decreased length of stay on the stroke unit of even in the hospital. A recent study individual patient data meta-analysis of randomized trials of ventilator-associated pneumonia prevention showed an overall attributable mortality of ventilator-associated pneumonia is 13%, which was mainly caused by prolonged exposure to the risk of dying due to increased length of ICU stay.[21] Ceftriaxone also has neuroprotective properties, at least in animal studies of stroke, which may be

mediated by increased expression and activity of the glutamate transporter.[22]

Antibiotics may induce overgrowth of antibiotic resistant pathogens in individual patients.[23] In the general population, selective antibiotic pressure is an important determinant of emergence and dissemination of antibiotic resistance.[24,25] Previous clinical trials on preventive antibiotic therapy in stroke, antibiotic resistance patterns of bacteria cultured from patients with or without preventive antibiotics were similar, but numbers of patients were low.[26] Previous work has showed that implementation of preventive antibiotics in the ICU did not increase resistance rates in an environment with low levels of antibiotic resistance.[27] We will compare total antibiotic use in both treatment groups during hospital stay and collect stool specimens in a nested case control study including 300 patients.

During the course of the study we changed the analysis of primary outcome on the mRS from a dichotomised analysis towards an ordinal regression analysis. The ordinal regression analysis is increasingly used in stroke trials because of its higher efficiency.[28] Importantly, our primary outcome, *e.g.*, functional outcome on the mRS, was not changed, and the assumptions used in the initial sample size calculation were maintained. By using ordinal regression analysis, the total sample size was lowered from 3200 patients to 2550 patients. Using this method enables us to reduce the number of patients without changing the assumptions on the magnitude of the effect on the primary outcome scale from the original sample size calculation.

Abbreviations

CONSORT: Consolidated Standards of Reporting Trials; ITT: intention to treat; LOCF: Last Observation Carried Forward; mRS: modified Rankin scale; OR: Odds Ratio; PASS: Preventive Antibiotics in Stroke Study; PP: Per Protocol; SAE: Serious Adverse Event; SUSAR: Suspected Unexpected Serious Adverse Reaction; VAP: ventilator-associated pneumonia.

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Outline of figures and tables

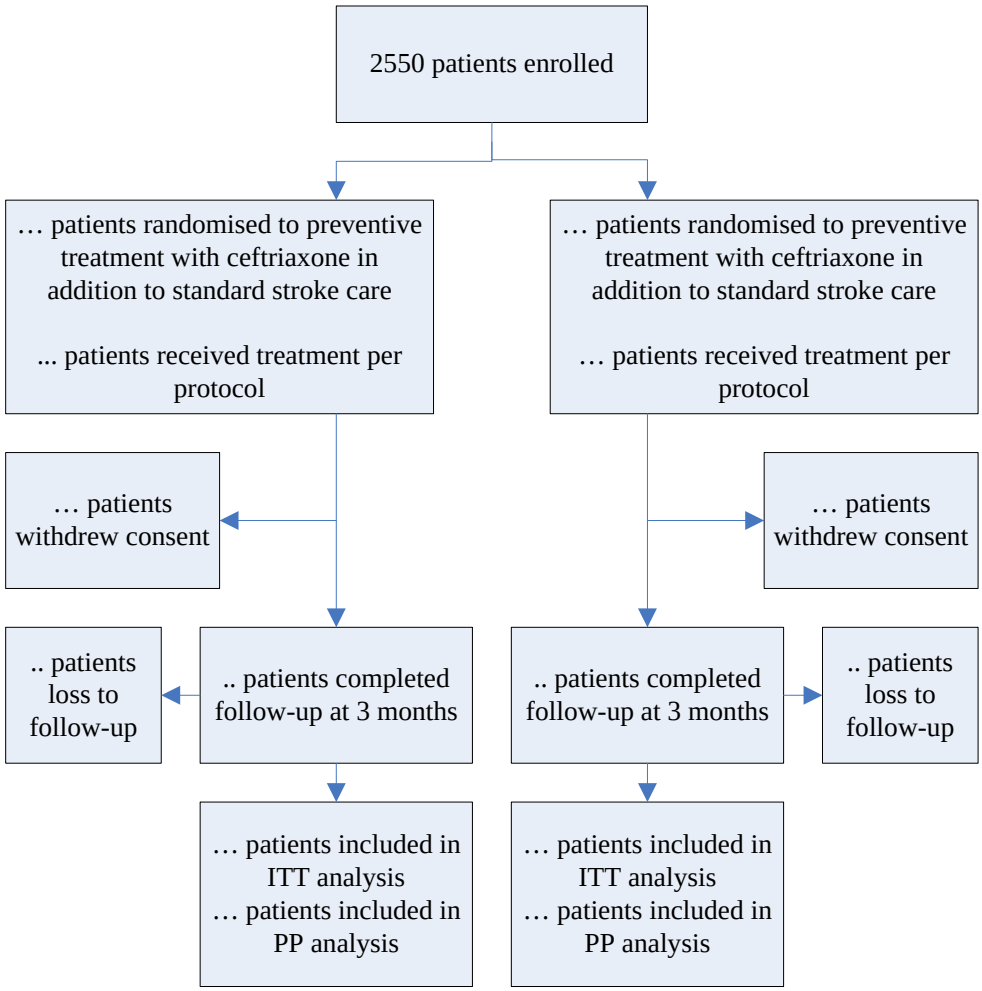

Figure 1. Flow-chart of patients

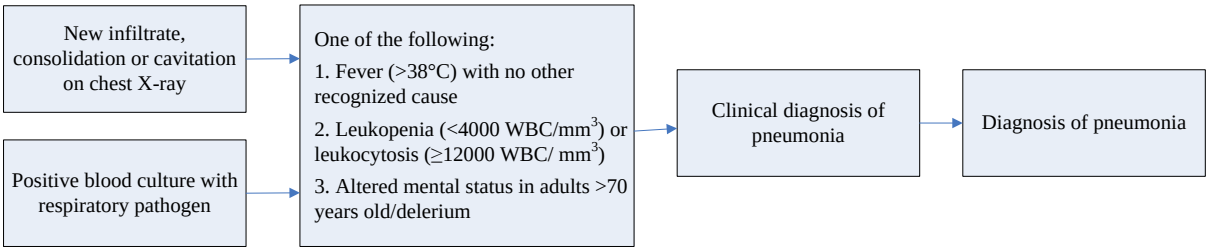

Figure 2. Diagnosis of pneumonia

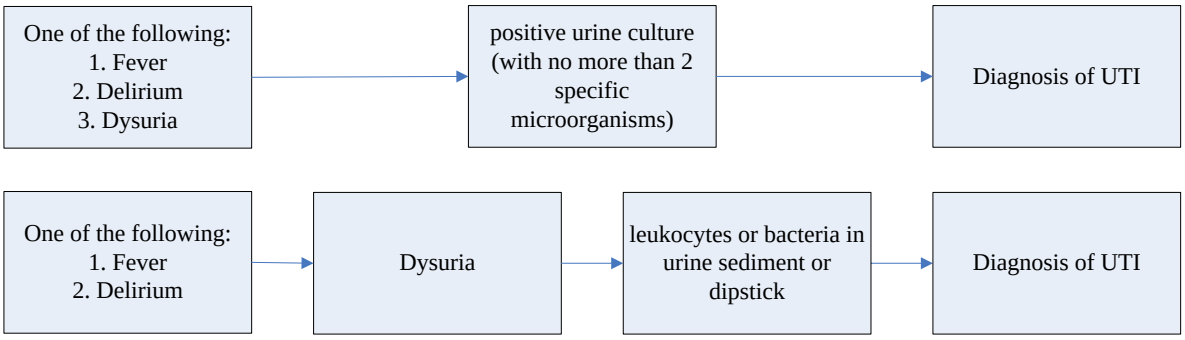

Figure 3. Diagnosis of urinary tract infection

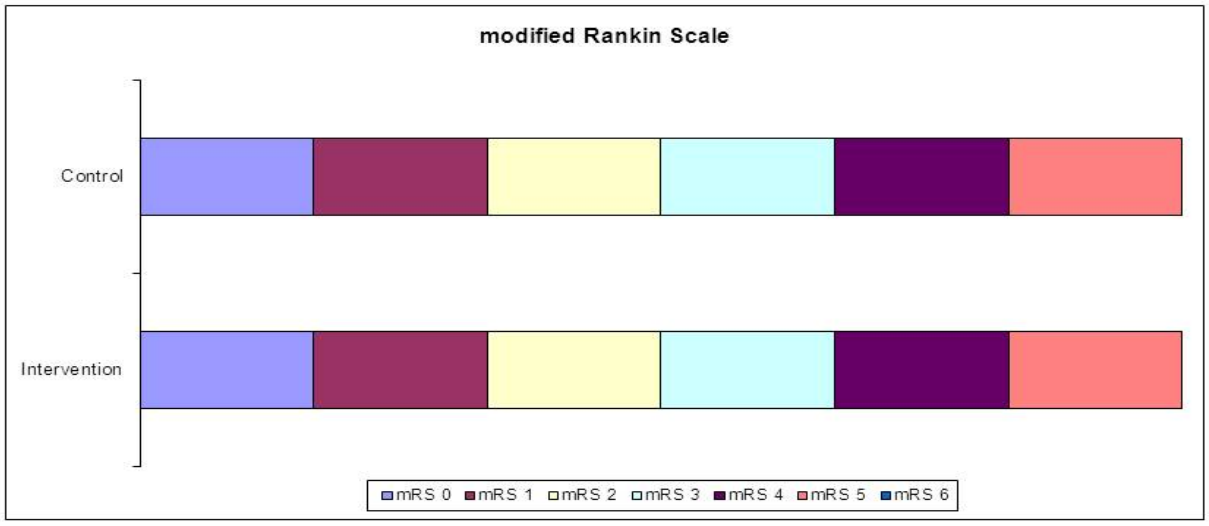

Figure 4. Graphic display of primary outcome

	Ceftriaxone + standard care (n=…)	**Standard care (n=…)**
Follow-up ascertained at telephone interview at 3 months Follow-up was ascertained by LOCF Follow-up by worst-case scenario		

Table 1. Number and type of protocol violations in eligibility

Patient number	**Explanation**	**Treatment allocation**

Table 2. Assessment of follow-up according to treatment allocation

Baseline characteristics	**Ceftriaxone + standard care** **(n=…)**	**Standard care** **(n=…)**
Age – year */**		
Male sex - % n/N		
Medical history - % n/N - Atrial fibrillation/flutter - Stroke - Hypercholesterolaemia - Hypertension - Myocardial infarction - Cardiac valve insufficience/stenosis/replacement - Peripheral vascular disease - Obstructive pulmonary disease - Immunocompromised		
Current smoker - % n/N		
Medication prior to stroke - % n/N - Anticoagulants - Antiplatelet - Statin - ACE-inhibitor - Bèta-blocker - Protonpompinhibitor		
Disability prior to stroke - mRS */**		
Stroke Severity - NIHSS */**		
Swallowing screening performed - % n/N Dysphagic patients - % n/N		

Acute treatment - % n/N - IV Thrombolysis - Coagulant therapy		
Diagnosis at discharge - % n/N - Infarction - Haemorrhage - TIA - Other		

Table 3: Baseline characteristics

	Ceftriaxone + standard care (n=…)	**Standard care (n=…)**	***p***	**OR 95%**
Secondary analysis of primary outcome Favourable outcome - % n/N *Secondary outcomes:* Clinical diagnosis of infection during admission - n - Pneumonia - Urinary tract infection - Other Diagnosis of infection based on expert panel – n - Pneumonia - Urinary tract infection - Other Mortality - % n/N - At discharge - At 3 months Length of hospital stay – days				

Table 4. Secondary outcomes

	Ceftriaxone + standard care (n=…)	**Standard care (n=…)**	***p***	**OR 95%**
Favourable outcome (mRS 0-2) - % n/N - Ischemic stroke - Haemorrhagic stroke - TIA - Other				
Favourable outcome (mRS 0-2) - % n/N - NIHSS 1-9 - NIHSS 10-30				
Favourable outcome (mRS 0-2) - % n/N - time to treatment 0-6 h - time to treatment 6-12 h - time to treatment 12-24 h				

Table 5. Subgroup analysis of primary outcome

Type of SAE - % n/N	**Ceftriaxone + standard care (n=…)**	**Standard care (n=…)**	***p***	**OR 95%**
- Death - Life-threatening event - New hospitalisation - Prolongation of existing hospitalisation - Persistent of significant disability or incapacity				
Total number of SAE's				

Table 6. Number and type of serious adverse events

Adverse reaction - % n/N	Ceftriaxone + standard care (n=…)	Standard care (n=…)	*p*	OR 95%
- Diarrhoea caused by C. difficile - Allergic reaction that caused cessation of ceftriaxone - Infection with ceftriaxone resistant micro-organism - Flebitis on place of IV-catheter - Elevation of liver enzymes - Oliguria or elevation of serum creatinin				
Total number of adverse reactions - no.%				

Table 7. Complications of treatment

Type of protocol violation in eligibility	Ceftriaxone + standard care (n=…)	Standard care (n=…)
Age < 18 year Stroke No neurological symptoms (NIHSS = 0) Onset of stroke > 24 hours ago Admission Infection at admission Use of antibiotics < 24 hours before admission Pregnancy Known hypersensitivity to cephalosporins Previous anaphylaxis for penicillin derivates Subarachnoidal haemorrhage Death is imminent		
Total number of protocol violations in eligibility		

Table 8. Patients with a protocol violation in eligibility

Reference List

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