Effect of landiolol on organ failure in patients with septic shock

A Randomized Clinical Trial

Tony Whitehouse, MD[1;2]; Anower Hossain, PhD[3]; Gavin D Perkins, MD[1;3]; Anthony C Gordon, MD[4]; Julian Bion, MD[1;5]; Duncan Young, MD[6]; Danny McAuley, MD[7;8]; Mervyn Singer, MD[9]; Janet Lord, PhD[2]; Simon Gates, PhD[10]; Tonny Veenith, MD[1;2]; Niall S MacCallum, PhD[11]; Joyce Yeung, MD[1;3]; Richard Innes, MD[12]; Ingeborg Welters, MD[13]; Nafisa Boota, MSc[3] ; Emma Skilton, BSc[3]; Belinder Ghuman, BSc[3]; Maddy Hill, MPH[3]; Scott E Regan, BA[3]; Dipesh Mistry, PhD[3]; Ranjit Lall, PhD[3]; for the STRESS-L collaborators

1 University Hospitals of Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Birmingham, UK

2 Institute of Inflammation and Ageing, University of Birmingham, UK

3 Warwick Clinical Trials Unit, University of Warwick, Coventry, UK

4 Division of Anaesthetics, Pain Medicine & Intensive Care, Faculty of Medicine, Imperial College London, London, UK

5 Institute of Clinical Sciences, University of Birmingham, UK

6 Kadoorie Centre for Critical Care Research, Nuffield Division of Anaesthesia, University of Oxford, Oxford, UK

7 Regional Intensive Care Unit, Royal Victoria Hospital, Belfast Health and Social Care Trust, Belfast, UK

8 The Wellcome Wolfson Institute for Experimental Medicine, Queens University Belfast, Belfast, UK

9 Centre for Intensive Care Medicine, Department of Medicine and Wolfson Institute for Biomedical Research, University College, London, UK

10 Cancer Research UK Clinical Trials Unit, University of Birmingham, Birmingham, UK

11 University College London Hospitals NHS Foundation Trust, Gower Street, London, UK

12 Musgrove Park Hospital, Taunton and Somerset NHS Foundation Trust, Taunton, UK

13 Royal Liverpool University Hospital, Liverpool, UK

Corresponding Author: Tony Whitehouse, MD, Department of Critical Care, University Hospitals Birmingham NHS Trust, Mindelsohn Way, Edgbaston, Birmingham, B15 2GW, United Kingdom (Tony.Whitehouse@uhb.nhs.uk)

Date of Revision: 13th September 2023

Word Count: 3470

Key Points

Question: Among critically ill patients with septic shock, tachycardia, treated with high dose norepinephrine for 24hrs, does beta blockade for up to 14 days with landiolol improve organ as measured by the Sequential Organ Failure Assessment (SOFA) score?

Findings: In this randomized clinical trial enrolling 126 patients with established septic shock (treated with norepinephrine for > 24hours) and a tachycardia, the administration of landiolol intravenously to reduce heart rate to below 95 beats per minute compared with standard care did not significantly decrease organ failure as measured by the mean SOFA score (8.8 (SD 3.9) vs. 8.1 (SD 3.2), respectively) in the 14 days following randomization.

Meaning: These results do not support the use of landiolol in the management of tachycardic patients on norepinephrine undergoing treatment for established septic shock.

Abstract

IMPORTANCE: Patients with septic shock undergo adrenergic stress which affects cardiac, immune, inflammatory and metabolic pathways. Beta-blockade may attenuate the adverse effects of catecholamine exposure and has been associated with reduced mortality.

OBJECTIVES: To assess the efficacy and safety of landiolol in patients with established septic shock requiring prolonged (>24 hours) vasopressor support and tachycardia.

DESIGN, SETTING, PARTICIPANTS: An open-label, multi-center, randomized trial in 40 NHS UK Intensive Care Units which randomized adult patients with septic shock after 24 hours of continuous norepinephrine with tachycardia of 95 beats per minute (bpm) or more and norepinephrine requirement >= 0.1mcg/kg/min.

INTERVENTION: 126 Patients randomized to receive standard care (n=63) or landiolol infusion (n=63).

MAIN OUTCOMES AND MEASURES: The primary outcome was the mean Sequential Organ Failure Assessment (SOFA) score from randomization to 14 days. Secondary outcomes included mortality at day 28 and 90 and the number adverse events in each group.

RESULTS: The trial was stopped prematurely on the advice of the independent Data Monitoring Committee as it was unlikely to demonstrate benefit, and for possible harm. Of a planned 340

participants, 126 were enrolled (37%) (mean age, 55.6 years, [95% CI, 52.7 to 58.5]); 58.7% male). The mean SOFA score was 8.8 (SD 3.9, landiolol) compared with 8.1 (SD 3.2, standard care) (mean difference (MD), 0.75 [95% CI: -0.49 to 2.0], P=0.24). Mortality at day 28 after randomization was 37.1% (23/62) for landiolol and 25.4% (16/63) for standard care (difference, 11.7% [95% CI: -4.4% to 27.8%], P=0.16). Mortality at day 90 after randomization was 43.5% (27/62) in the landiolol group and 28.6% (18/63) in the standard care group (absolute difference, 14.9% [95% CI: -1.7% to 31.5%], P=0.08). There were no differences in numbers of patients having at least one adverse event.

CONCLUSION AND RELEVANCE: In patients with septic shock treated with norepinephrine for more than 24 hours and tachycardia, an infusion of landiolol did not improve organ failure measured by the SOFA score over 14 days from randomization. These results do not support the use of landiolol in the management of tachycardic patients on norepinephrine undergoing treatment for established septic shock.

TRIAL REGISTRATION: EU Clinical Trials Register EudraCT: 2017-001785-14; ISRCTN12600919

INTRODUCTION

Autonomic dysfunction and tachycardia are associated with poor outcomes in septic shock[1] with reported mortality more than 70%[2] in some studies. Norepinephrine is recommended for the maintenance of blood pressure in septic shock[3] but has been associated with a variety of adverse effects including immunosuppression[4] and myocardial damage[5]. Bradycardia provides relative protection[6] and interest has grown in the potential of beta-adrenergic blockade to protect from the possible harmful effects of catecholamines.

The mechanisms by which beta blockade may produce benefits are unknown. Immunomodulation by reducing pro-inflammatory cytokines and prolonged survival times have been demonstrated in animals using beta1 antagonism[7,8]. Morelli[9] reported the safety of a short-acting beta blocker, esmolol, in septic shock patients in a randomized trial and noted a markedly reduced adjusted hazard ratio mortality of 61% but as a non-primary outcome and with a high mortality in the control group of >80%. A recent meta-analysis of eight randomized studies using esmolol[10] suggested 32% risk ratio decreased 28-day mortality and a meta-analysis of seven studies using either esmolol or landiolol in patients with sepsis and septic shock was associated with a 32% lower 28-day mortality. Landiolol (Rapibloc®, AOP Orphan Pharmaceuticals, Vienna, Austria) is a very short acting beta blocker and is approximately 8 times more selective for the beta1 receptor than esmolol[11]. We hypothesized that additional beta1 receptor specificity would bring about myocardial protection and immunomodulation to confer benefits to a high-risk population. To address this, we conducted a pragmatic randomized trial planned to recruit 340 patients with established septic shock treated with high dose norepinephrine in 40 centers with the UK National Health Service (NHS)

METHODS

The methods for this study were published previously[12] and online supplements (Supplement 1 & 2). The trial was conducted in full conformance with the principles of the Declaration of Helsinki[13] and to ICH Good Clinical Practice (GCP) guidelines. Full details of the Blinding, Randomization, Sample Size calculations and Study Procedures can be found in the Study Protocol[12].

Trial Design and Oversight

The STRESS-L trial was an investigator initiated, parallel group, multi-center, randomized open label phase IIb trial designed to assess the efficacy and safety of a continuous infusion of intravenous landiolol compared with standard care in adults with established septic shock and tachycardia.

It was conducted in 40 acute care National Health Service (NHS) hospitals in the UK. The trial protocol[12] was approved by the East of England, Essex Research Ethics Committee (Reference: 17/EE/0368). Interim analyses were undertaken prior to each independent Data Monitoring Committee (DMC) meeting which occurred every three months. There were no formal stopping rules for futility or benefit.

Trial Participants

The study recruited adult patients (≥ 18 years) on an intensive care unit (ICU) diagnosed with septic shock as defined by consensus criteria (Sepsis-3)[14] who, having received adequate fluid resuscitation, were being treated with ≥ 0.1mcg/kg/min norepinephrine (for >24 hours but <72 hours) at the time of randomization and were tachycardiac with a Heart Rate (HR) of 95 beats per minute (bpm) or more. Sepsis-3 criteria were met if the patient had known or suspected infection, a Sequential Organ Failure Assessment (SOFA) score change of ≥ 2 from baseline, a blood lactate > 2mmol/l at any point during shock resuscitation and vasopressor therapy to maintain a mean arterial pressure either

predefined by the clinician or ≥ 65mmHg. Patients were excluded if they had a tachycardia because of pain/discomfort, or any non-infective form of vasodilatory shock (see Supplement 1: Trial Protocol for extended inclusion and exclusion criteria).

Interventions

The intervention was open-label as the landiolol dose was titrated to achieve a target HR. Investigators remained blinded to all group data during the trial.

Landiolol

The continuous intravenous infusion of landiolol was started at 1.0 mcg/kg/min, increasing every 15 minutes by a step change of 1.0 mcg/kg/min to reach the target HR of 80-94 bpm with the expectation that this should be within 6 hours. Whilst the patient was receiving vasopressor agents (norepinephrine and/or vasopressin), the landiolol infusion was adjusted by step changes of 1.0 mcg/kg/min to maintain the target HR. The infusion was reduced by step change, and if necessary, ultimately stopped, if the HR fell below 80 bpm; the infusion was deliberately weaned once all the vasopressor agents had been discontinued for 12 hours (which we defined as the End of Norepinephrine Treatment).

It was recommended that the landiolol infusion be stopped for at least 12 hours before the patient was discharged from the ICU. (See Supplement 3: eFigure 1 and eTable 1 for Cardiovascular Management and Infusion protocols; eFigure 2, for vasopressor infusion weaning protocol. eFigure 3, for timing and weaning of the study drug).

Standard care

The control group received standard care but did not receive any beta blockade for the duration of their ICU stay. Management of the patient was based on the latest guidance from the Surviving Sepsis Campaign[15]. They recommend that all patients receive timely source control, prompt and

appropriate empiric antibiotic treatment modified according to culture results and appropriate fluid resuscitation to correct hypovolemia. The use of cardiac output monitoring was at the discretion of the local investigator. Three large international randomized trials [16-18] and the subsequent patient-level meta-analysis[19] had found that cardiac output monitoring did not improve outcomes and the Trial Steering Committee was of the opinion that to mandate it would be a severe barrier to recruitment.

Compliance

Compliance with the drug infusion protocol was closely monitored and reviewed in monthly trial management meetings. A patient was said to not comply if (i) landiolol was not started ,(ii) landiolol was not started at correct dose, (iii) HR was below 80 bpm and landiolol infusion was not reduced, (iv) HR was above 94 and landiolol infusion was not increased, and (v) landiolol was not stopped after the End of Norepinephrine Treatment. The compliance criteria are stipulated in Supplement 3: eTable 2 and the analysis criteria are stipulated in the statistical analysis plan (Supplement 2).

Procedure

Detailed descriptions of the trial procedures are given in the published protocol[12] and the online supplements 1 and 3. Patients in ICU with septic shock were screened for eligibility upon initiation of norepinephrine so that there was a 24-hour window during which patient/legal representative written consent was sought. Ethical approval included approaching patients during this window even though our scoping data suggested that 90% would fall outside the inclusion criteria at the 24-hour timepoint and would not be randomized. This was usually because the heart rate or the norepinephrine dose had improved below the rates needed for inclusion (Figure 1).

Outcomes

All outcomes were pre-specified and outlined in the published protocol[12]. We report no *post-hoc* analyses.

Primary outcome

The primary outcome was the mean SOFA score[20] over the first 14 days from entry into the trial and whilst in ICU. A modified version of the SOFA score was used (using respiratory, cardiovascular, hepatic, coagulation and renal, each scored 0-4) which excludes the neurological domain as therapeutic sedation markedly alters the Glasgow Coma Scale. The score ranged from 0-20, where a higher score reflects a higher degree of organ dysfunction.

Secondary outcomes

There were twelve secondary outcomes: mortality at day 28 and 90 after randomization, length of hospital and ICU stay, mean infusion rate and duration of norepinephrine (over 14 days), dose and duration of inotropes (first 5 days), in/out and balance of total fluids (over 14 days), HR (over the 14 days), blood glucose (mmol/L) and blood lactate (mmol/L) (day 1, 2, 4, 6 and end of norepinephrine treatment) and mean arterial pressure (over the 5 days) (See eTable 3).

There were an additional five safety outcomes included pre-specified adverse events including bradycardia (HR <50 bpm), bradycardia with hypotension requiring intervention (not including temporarily stopping the infusion), heart block, arrhythmia and arrhythmia hypotension requiring intervention.

Statistical Analysis

The statistical analysis plan[21] is provided in Supplement 2. All analyses used an intention to treat principle.

As used in previous sepsis studies[22-24], the mean modified SOFA during the ICU stay was calculated by adding the SOFA scores in ICU (up to a maximum of 14 days) and dividing by the number of days the patient was in ICU. Patients who died or were discharged from the ICU before 14 days had only the days from randomization to death or discharge counted.

For continuous outcomes, linear mixed effects regression models were fitted to estimate the treatment difference, 95% confidence interval and p-value using bootstrapping (10,000 bootstrapped samples). Both unadjusted and adjusted (for age, gender, recruiting site (random effect) and baseline norepinephrine dose) estimates were obtained.

Categorical outcomes were assessed using mixed effects logistic regression models and a fixed-effect logistic regression model was used to report absolute difference (Risk Difference). For data collected over time, longitudinal models were used to estimate the treatment difference. For mortality outcomes at day 28 and 90, Kaplan-Meier plots give a visual representation of the time to death (univariate survival analysis). The proportional odds assumption was also checked in these survival models.

Pre-specified sub-group analyses were undertaken for baseline shock severity (norepinephrine 0.1mcg/kg/min - 0.3mcg/kg/min vs. >0.3 mcg/kg/min) and use of beta blockers on ICU admission prior to randomization (Yes/No) using formal statistical tests for interaction for the primary outcome using logistic regression models.

Missing data were imputed only for the primary outcome (see Statistical Plan). Three sensitivity analyses were carried out using different imputation techniques assessing average SOFA score over 14 days and mortality as a composite outcome using the Pocock's win-ratio method[25] and an instrumental mean model[26] to assess the effect of non-compliance.

The number and percentage of adverse events and serious adverse events from randomization to 90-day follow-up were summarized by treatment group and analyzed using the Fisher's exact test.

Steroid doses were converted to hydrocortisone equivalents using the standard factors of 1 mg Dexamethasone = 26.7 mg Hydrocortisone; 1 mg methylprednisolone = 5.0 mg Hydrocortisone; 1 mg prednisolone = 4.0 mg Hydrocortisone.

The diagnosis of Acute Respiratory Distress Syndrome (ARDS) was based on the observation at randomization of infiltrates on chest radiography and the ratio of the arterial oxygen tension (PaO2) to the fraction of inspired oxygen (FiO2) (the P/F Ratio) according to the accepted Berlin Consensus Criteria[27].

Trial Termination

The DMC recommended that the trial be stopped on the basis that the intervention was unlikely to demonstrate benefit and there was a signal for possible harm.. The decision to stop was not based on a formal calculation of futility but based on the opinion of the DMC using all available information including outcome data from the interim analysis, analysis of lactate and norepinephrine and feasibility of future recruitment.

RESULTS

STRESS-L was terminated prematurely by the trial sponsor on 15 December 2021 based on the advice of the independent DMC that landiolol was unlikely to demonstrate benefit should recruitment have continued to full sample size and there was a signal of possible harm in relation to mortality in the intervention group.

Patient recruitment

Between 19 April 2018 and 15 December 2021, 126 patients were randomized in 40 centers. The trial was paused to recruitment from 18 March 2020 to 21 August 2020 due to COVID-19. A total of

4137 patients were screened and 348 (8.4%) patients were potentially eligible (Figure 1). Of these, 126 (36.2%) gave informed written consent and were randomized: 63 to landiolol and 63 to standard care; no patients withdrew from the study. Patient characteristics were similar in the two treatment groups at baseline (Table 1; also eTable 4). The mean age was 55.6 years ([95% CI, 52.7 to 58.5]), 58.7% were male.

Primary outcome

The mean SOFA score over the 14 days was 8.8 (SD 3.9) on landiolol compared with 8.1 (SD 3.2) on standard care. There was no evidence of a statistical difference between the interventions (MD, 0.75 [95% CI: -0.49 to 2.0], P=0.24: Table 2, see also Figure 2). The sensitivity analyses and the composite Pocock's win ratio test did not suggest evidence of a difference in the intervention group compared to the standard care (see Supplement 3: eTable 5).

Secondary outcomes

The secondary outcomes are presented in Table 2 and Supplement 3: eFigure 4, eFigure 5a/b, eTable 6.

Mortality at day 28 was 37.1% (23/62) in the landiolol group and 25.4% (16/63) for those receiving standard care (absolute difference, 11.7% [95% CI: -4.4% to 27.8%], P=0.16). Cox Proportional Hazards model from day 0 to day 28 demonstrated no difference in survival between the treatment groups (HR: 1.64 [95% CI: 0.87 to 3.10], P=0.13). Additional Cox Proportional Hazard modelling at day 90 was 43.5% (27/62) for landiolol and 28.6% (18/63) for standard care (absolute difference, 14.9% [95% CI: -1.7% to 31.5%], P=0.08). Supplement 3 eFigure 5b illustrates the Kaplan-Meier curve for mortality from day 0 to day 90 (Cox Proportional HR: 1.73 [95% CI: 0.95 to 3.15], P=0.07).

There was lower mean heart rate over 14 days in the landiolol group (MD over time: -6.46 bpm [95% CI: -10.46 to -2.46], P=0.002: Table 2, see also Figure 3(b)). There was a difference in the mean

arterial pressure over 5 days with average values lower in the landiolol group (MD over time, -2.67 mmHg [95% CI: -5.06 to -0.29], P=0.03: Table 2, see also Figure 3(a)).

The average norepinephrine infusion rate was greater in the landiolol group (mcg/kg/min MD, 0.10 [95% CI: 0.002 to 0.20], P=0.05: Table 2). Having adjusted for pre-defined covariates, requirements in the landiolol group remained greater (MD, 0.07 [95% CI: -0.003 to 0.15], P=0.06: Table 2).

Patients in the landiolol group had a numerically higher mean lactate over the course of the study (mean (SD), 32.5 mg/dL (SD 31.2) compared with 24.5 mg/dL (SD 15.6) in the standard care group) (MD over time: 6.48 mg/dL [95% CI: -1.12 to 14.08], P=0.10: Table 2.

For all the other clinical outcomes and comparisons, there was no evidence of a difference between the treatment groups.

Sub-group analyses

Among three subgroups evaluated, there was no evidence of statistical difference between treatment groups (see Supplement 3: eTable 7). For example, among the subgroup defined by baseline shock severity (norepinephrine 0.1mcg/kg/min - 0.3mcg/kg/min vs. >0.3 mcg/kg/min), the treatment by subgroup effect was not statistically significant (P=0.47).

Adverse events (see Supplement 3, eTable 8)

The proportion of patients with at least one adverse event did not differ significantly between the intervention groups: this was 17.5% (10/63) for those receiving landiolol and 12.7% (8/63) for those receiving standard care (P=0.80). However, a higher proportion of landiolol patients experienced serious adverse events (landiolol: 25.4% (16/63); standard care: 6.4% (4/63); P=0.006, Fisher's exact test).

In total there were 5/63 (7.9%) non-compliers in the landiolol group. Details of those patients are outlined in Supplement 3: eTable13. Further information about Protocol non-compliance may be

found in eTables 9-15. Further details of Site Screening and Recruitment may be found in Supplment 3: eFigure 6 and eTables 16-19.

DISCUSSION

In a trial of landiolol in tachycardic patients with septic shock, treated with high dose norepinephrine, there was no difference in mean SOFA score during the 14 days following randomization. The trial was stopped after recruiting 126 of its expected 340 patients as it was considered unlikely to demonstrate benefit should recruitment have continued to full sample size and there was a signal of possible harm in relation to mortality in the intervention group. Although landiolol use in critically ill patients has been reported in cases studies[28] and a previous randomized study[29], these reported only the safety of landiolol and efficacy in heart rate reduction. We believe that STRESS-L is the first study to report a clinical outcome - the effect of landiolol in organ failure in critically ill patients with septic shock.

STRESS-L was designed to replicate a previous study by Morelli[9] who reported a dramatic reduction in 28-day mortality with the use of esmolol in a similar cohort (control 80.5% to esmolol 49.4% adjusted hazard ratio, 0.39; 95% CI, 0.26 to 0.59; P<0.001). When designing the study, it was felt that there was not enough information to provide powering for a study based on 28-day mortality. The outcome SOFA score over 14 days was used as this has been demonstrated to have a good correlation with ICU mortality, its predictive value is similar regardless of length of stay[30] and was used in other trials of cardiovascular interventions in sepsis, most notably LeoPARDs (Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis)[22]. In contrast to Morelli, STRESS-L used landiolol rather than esmolol; study sites were unfamiliar with beta blockade in this group of

critically ill patients and the ultra-short-acting properties of landiolol provided additional safety in the event of cardiovascular instability.

Morelli also used the non-adrenergic calcium sensitizer levosimendan to improve systemic oxygen delivery where mixed venous saturation concentrations decreased or arterial lactate concentrations increased. This was not the case in STRESS-L. We found that the patients receiving landiolol had a higher mean lactate and norepinephrine requirements which may indicate a reduction in cardiac output.

Morelli included a mixed venous oxygen saturation higher than 65% as one of their inclusion criteria. The use of cardiac output monitoring and the decision to add a positive inotrope such as dobutamine (as suggested by the Surviving Sepsis Campaign[3]) or levosimendan (as used by Morelli) was left to the discretion of the clinical team which was a pragmatic reflection of septic shock resuscitation in the UK but may present a limitation. Many patients with septic shock treated with norepinephrine experience some degree of septic cardiomyopathy[5] and may be dependent on a tachycardia to maintain cardiac output. A recent post hoc analysis[31] of 45 patients with septic shock with persistent tachycardia and treated with esmolol, showed those with a less vigorous arterial trace (as measured by the change in pressure with time, dP/dtmax), were more likely to decrease their cardiac output during esmolol treatment.

Our results suggest that there is no benefit of landiolol used for short durations initiated during severe critical illness. There is an association with improved survival in patients already treated with longer-acting, non-specific beta blockers prior to ICU admission[32,33] and in ICU patients with septic shock[34]. Kuo reported premorbid beta1-selective (but not non-selective) beta blockade reduced ICU mortality [adjusted hazard ratio, 0.40; 95% confidence interval (CI), 0.18–0.92; P=0.030][35]. If there is

a benefit to beta blockade in critical illness, it may be only seen with longer-term use. This should be tested in a prospective clinical trial.

The mortality in our control group was much lower than expected. Validation of the Sepsis-3 definition for septic shock[36] analyzed 28150 participants in the Surviving Sepsis Campaign database demonstrated that the patient group requiring vasopressors to maintain mean BP 65 mm Hg or greater and having a serum lactate level greater than 2 mmol/L (18 mg/dL) after fluid resuscitation had a mortality of 42.3% [95% CI, 41.2%-43.3%]. Mortality for septic shock was 38% in a recent Cochrane Systematic Review[37]. Whilst it is satisfying that the mortality from such severe septic shock continues to fall, we cannot explain why the mortality in the standard care group in STRESS-L was 28.6% at day 90 in these otherwise high-risk patients.

LIMITATIONS

There were several limitations to our study. First, we are unable to comment on whether outcomes would have been different if the landiolol administration had been started before or after the 24-hours treatment with norepinephrine timepoint, at a different dose of norepinephrine or whether patient sub-phenotypes exist. It is not possible to infer whether our findings are a class effect, applicable to all beta blocking drugs or due to the high specificity for the beta1 receptor of landiolol. Second, although the primary outcome was selected as it had been previously used in other septic shock trials [22-24], it does not deal well with deaths and discharges from ICU. Third, decisions around withdrawal of life-sustaining measures leading to patient death or timing of discharge from ICU were not controlled for over the course of the study and may have impacted the primary outcome. Fourth, although a pragmatic study, we lack data on cardiac function (either through cardiac output monitoring or echocardiography), this hinders our ability to identify patient groups who may have

benefitted or been harmed by the intervention. Finally, by stopping prematurely, the trial may not have sufficient power to describe clinically important effects and further post-hoc subgroup analysis may have too few patients to reveal clinically important differences.

CONCLUSIONS

STRESS-L was stopped after recruiting 126 of 340 patients as it was unlikely to demonstrate benefit should recruitment have continued and there was a signal of possible harm in the intervention group. In patients with septic shock treated with norepinephrine for more than 24 hours and tachycardia, an infusion of landiolol did not improve organ function as measured by the SOFA score over 14 days from randomization. These results do not support the use of landiolol in the management of tachycardic patients on norepinephrine undergoing treatment for established septic shock.

ARTICLE INFORMATION

Author Contributions: Prof Lall and Dr Hossain had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and Design: Whitehouse, Bion, Perkins, McAuley, Singer, Gordon, Young and Gates.

Acquisition of data: Veenith, MacCallum, Yeung, Innes, Welters, Ghuman, Boota, Skilton.

Statistical analysis: Lall, Hossain, Gates, Mistry.

Drafting of the manuscript: Lall, Whitehouse, Hossain.

Critical revision of the manuscript for important intellectual content: Bion, Perkins, McAuley, Singer, Gates, Gordon, Lord, Young, Veenith, MacCallum, Yeung, Innes, Welters.

Obtained Funding: Whitehouse, Bion, Perkins, McAuley, Singer, Gates, Gordon, Lord, Young.

Administrative, technical, or material support: Ghuman, Boota, Skilton.

Supervision: Whitehouse, Boota, Skilton, Ghuman, Lall, Regan, Smith, Kaur.

Conflict of Interest Disclosures: Prof Whitehouse reports grants from National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) for the funding of STRESS-L (Project Number: EME-14/150/85) and during the conduct of the study; personal fees and non- financial support from AOP Orphan, manufacturer of landiolol, outside the submitted work. Prof Singer has received travel expenses from AOP Orphan for delivering lectures. Prof Singer also reports grants and other from NewB, grants from the UK Defence Science and Technology Laboratory, other from Amormed, Biotest, GE, Baxter, Critical Pressure, Apollo Therapeutics, Roche, Bayer, Shionogi, outside the submitted work. Prof Gordon reports receiving grants from the NIHR and the NIHR Research Professorship (RP-2015-06-018); non-financial support from the NIHR Clinical Research Network and the NIHR Imperial Biomedical Research Centre during the conduct of the study; and personal fees from AstraZeneca, Janssen and Novartis outside the submitted work. Prof McAuley reports a grant from the NIHR EME Programme for this study. He also reports personal fees from consultancy for

GlaxoSmithKline, Boehringer Ingelheim, Bayer, Novartis and Eli Lilly. In addition, his institution has received funds from grants from the NIHR, Wellcome Trust, Innovate- UK and others. In addition, Prof McAuley has a patent issued to his institution for a treatment for ARDS. Prof McAuley is the Director of the NIHR Efficacy and Mechanism Evaluation (EME) Programme. Prof Perkins is supported by NIHR academic research collaboration West Midlands and reports grants from the NIHR, during the conduct of the study. Profs Bion, Gates, Lord and Young were also named applicants on the grant from the NIHR EME and their Universities received payments for their participation. All other authors declare they have neither competing interests nor received additional compensation for the conduct of the trial.

FUNDING/SUPPORT: Funding was provided by the National Institute for Health Research Efficacy and Mechanism Evaluation (NIHR EME reference number: 14/150/85). University of Hospitals of Birmingham (UHB) NHS Foundation Trust was the sponsor for the study. STRESS-L was conducted and managed (data collection, management, data analysis and preparation of the manuscript) by Warwick Clinical Trials Unit. AOP Orphan, Vienna, Austria, for provided landiolol without cost. National study infrastructure was provided by the National Institute of Health Research (NIHR) Critical Care Specialty Group of the Comprehensive Clinical Research Network.

Role of the Funder/Sponsor: The funder (NIHR EME) approved the protocol. Neither the NIHR nor AOP Orphan had a role in the design, study conduct, data collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Neither AOP Orphan nor the sponsor had the right to veto publication or to control the decision regarding to which journal the paper was submitted.

Disclaimer: The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Data Sharing Statement: See Supplement 5, .

Additional Contributions

We are grateful to all the patients and families who supported the trial, together with the physicians, nurses, pharmacists, and allied health professionals across all participating hospitals who supported both trial recruitment and delivery of trial interventions in extremely challenging conditions.

We also thank the members of the Trial Steering Committee (Prof Tim Walsh (Chair), Professor of Intensive Care Medicine, University of Edinburgh; Prof Charles Hinds, Emeritus Professor of Intensive Care Medicine, Queen Mary University of London; Prof Claire Hulme, Head of Department – Health & Community Sciences, University of Exeter; Karen Keates, Keith Young and Matthew Robinson (PPI representatives)) and the independent Data Management Committee (Prof Paul Harrison, Head Statistician, Intensive Care National Audit and Research Centre (ICNARC), London, UK; Prof Rupert Pearse, Professor of Intensive Care Medicine, Queen Mary University of London, UK; Prof Paul Dark, Chair in Critical Care Medicine, University of Manchester, UK) for their time, mentoring, guidance and thoughtful input into STRESS-L.

Figure Legends:

Figure 1: Recruitment: Screening, randomization, and outcome assessment in the STRESS-L trial.

Figure 2: Median and Interquartile Range (Box and whisker) and mean Summary (unfilled circles) of SOFA scores. Filled circles represent outliers.

Figure 3: Median and Interquartile Range (Box and whisker) and mean Summaries (unfilled circles) of (a) MAP over 5 days, and (b) HR rate over 14 days

Figure 3a (Footnote): *Statistically significant difference in the interventions is noted at day 2 (MD, -4.53 [95% CI: -7.69 to -1.36], P=0.005).

Figure 3b (Footnote): **Statistically significant difference in the interventions was noted at day 1 (MD, -8.66 [95% CI: -13.20 to -4.12], P<0.001) and day 4 (MD, -8.68 [95% CI, -14.73 to 2.62], P=0.003) "

Table 1: Baseline patient characteristics[a].		
	No. (%)	
	Landiolol (N=63)	Standard Care (N=63)
Age, mean (SD), y	55.9 (16.2)	55.3 (17.1)
Male	37 (58.7)	37 (58.7)
Female	26 (41.3)	26 (41.3)
Main site of the infection		
Lungs	28 (44.4)	27 (42.9)
Abdomen	21 (33.3)	22 (34.9)
Other	8 (12.7)	13 (20.6)
Urine	4 (6.3)	1 (1.6)
Blood	2 (3.2)	0 (0.0)
Where was the infection acquired:		
Community / Hospital	46 (73.0) / 17 (27.0)	45 (71.4) / 18 (28.6)
Patient met ARDS criteria[b]	20 (31.7)	13 (20.6)
Patient has concomitant illnesses	57 (90.5)	55 (87.3)
Received beta-blockers 2 weeks prior to ICU admission	5 (14.3)	6 (16.7)
Received beta-blockers during ICU admission prior to randomization	3 (8.3)	5 (13.9)
Steroid (Hydrocortisone equivalent dose) (mg), mean (SD) [N]	170.6 (94.4) [33]	176.7 (100.8) [37]
Laboratory Values at randomization		
PaO_2, median (IQR) [N], mmHg	78.8 (67.5-91.5)	74.3 (66.0-84.0) [62]
$PaCO_2$, median (IQR) [N], mmHg	46.1 (41.3-57.0) [62]	44.3 (34.5-51.8) [62]
Glucose, mean (SD) [N], mg/dL	138.1 (56.0)	144.1 (51.4) [62]
Lactate, mean (SD) [N], mg/dL	41.0 (25.6)	40.9 (28.4) [62]
MAP, mean (SD) [N], mmHg	73.0 (9.1) [62]	72.3 (7.6)
HR, mean (SD), beats/min	110.6 (13.0)	114.1 (16.8)
Atrial Fibrillation at Randomization	7 (11.1)	8 (12.7)
Norepinephrine dose, mean (SD) (mcg/kg/min)	0.37 (0.30)	0.36 (0.22)
SOFA Score[c], mean (SD)	10.1 (3.3)	10.3 (2.4)

Abbreviations: MAP; mean arterial pressure, HR; HR, AF; atrial fibrillation

[a] N=63 unless it is stated

[b] Berlin Criteria[27] of PaO_2/FIO_2 ratio<300mmHg and Bilateral Infiltrates on Chest Radiograph

[c] STRESS-L used a 5-item SOFA score (respiratory, coagulation, cardiovascular, liver, and renal). Each item scores from 0 (best – normal function) to 4 (worst – most abnormal function). SOFA score is the mean of the 5 scored. Values in the table represent the results recorded at or closest prior to randomization

484

Table 2: Primary and secondary outcomes, and routinely collected data (landiolol vs standard care)[a,b]								
	Landiolol (N=63)	Standard care (N=63)		Unadjusted			Adjusted[c]	
				Effect estimate (95%)	P-value		Effect estimate (95%)	P-value
Primary outcome								
SOFA score, mean (SD)	8.8 (3.9)	8.1 (3.2)		MD, 0.75 (-0.49 to 2.0)	.24		MD, 0.63 (-0.47 to 1.73)	.26
Secondary outcomes								
28-day mortality, n/N (%)	23/62 (37.1)	16/63 (25.4)		OR, 1.76 (0.77 to 4.03) RD, 11.70% (-4.43% to 27.83%)	.18 .16		OR, 1.75 (0.73 to 4.22) RD, 9.65% (-5.03% to 24.33%)	.21 .20
90-day mortality, n/N (%)	27/62 (43.5)	18/63 (28.6)		OR, 2.04 (0.91 to 4.57) RD, 14.98% (-1.66% to 31.6%)	.08 .08		OR: 2.13 (0.88 to 5.16) RD, 12.77% (2.00% to 27.54%)	.09 .09
Length of stay in ICU (survivors), mean (SD) [N], d	21.3 (31.7) [42]	19.6 (19.3) [47]		MD, 1.72 (-8.94 to 12.39)	.75		MD, 0.63 (-9.82 to 11.07)	.12
Length of stay in hospital (survivors), mean (SD) [N], d	49.1 (56.8) [38]	52.2 (42.6) [42]		MD, -3.17 (-24.77 to 18.42)	.77		MD, -3.88 (-24.66 to 16.88)	.71
Duration of norepinephrine, mean (SD) [N], d	5.3 (4.3) [61]	4.3 (1.9) [59]		MD, 0.98 (-0.23 to 2.20)	.11		MD, 1.05 (-0.16 to 2.27)	.09
Total cumulative dose of norepinephrine (mcg/kg/min), mean (SD) & median [Q1, Q3]	0.34 (0.33) 0.24 [0.16, 0.37]	0.24 (0.23) 0.17 [0.10, 0.27]		MD, 0.10 (0.002 to 0.20)	.05		MD, 0.07 (-0.003 to 0.15)	.06
Duration of Landiolol, Mean (SD) [N], d & median [Q1,Q3]	3.4 (4.0) [60] 2.0 [0.8,3.9]	-						
Total cumulative dose of Landiolol (mcg/kg/min), mean (SD) [N] & median [Q1, Q3]	10.9 (10.2) [60] 6.7 [3.3, 15.0]	-						
Routinely Collected Data								
Cardiovascular								
MAP (over 5 day), mean (SD), mmHg	73.2 (7.6)	76.0 (6.5)		MD, -2.67 (-5.06 to -0.29)	.03		MD, -2.64 (-4.94 to -0.33)	.002
HR (over 14 days), mean (SD), beats/min	92.4 (10.4)	98.6 (12.2)		MD, -6.46 (-10.46 to -2.46)	.002		MD, -6.46 (-10.42 to -2.49)	.001

Glucose and Lactate								
Glucose (mg/dL), mean (SD) [N] & median [Q1, Q3],	136.5 (34.5) 134.2 [112.3, 152.1]	148.3 (38.0) [62] 140.1 [122.9, 176.3]		MD, -10.58 (-23.21 to 2.05)	.10		MD, -10.70 (-23.37 to 1.97)	.10
Lactate[a] (mg/dL), mean (SD) [N], & median [Q1, Q3],	32.5 (31.2) 21.3 [14.9, 31.5]	24.5 (15.6) [62] 19.7 [15.7,25.7]		MD, 6.48 (-1.12 to 14.08)	.10		MD, 6.31 (-0.76 to 13.40)	.08
Arterial Blood Gases								
PaO_2, mean (SD), mmHg	79.8 (14.4)	81.6 (21.1)		MD, -1.66 (-7.96 to 4.64)	.61		MD, -1.55 (-7.83 to 4.72)	.63
$PaCO_2$, mean (SD), mmHg	46.5 (10.2)	44.8 (10.4)		MD, 1.38 (-1.95 to 4.72)	.42		MD, 1.40 (-1.99 to 4.79)	.42
Steroid								
Steroid (Hydrocortisone equivalent dose) (mg), mean (SD) [N] & median [Q1,Q3]	167.9 (72.1) [43] 180.0 (133.3, 200.0)	182.8 (112.8) [44] 166.7 (137.5, 200.0)		MD, -15.43 (-52.59 to 21.73)	.42		MD, -21.0 (-56.32 to 14.31)	.24

Abbreviations: MD, mean difference; OR, Odds Ratio; RD, Risk Difference

[a] *N=63 unless it is stated*

[b] *The value of unadjusted mean difference may not be the same as the difference in means presented between the groups (Landiolol vs. standard care). This is because the model was fitted to the observed values for each timepoint. Whereas the means are calculated by first calculating mean for each patient over time and then mean of the means over all patients in each group.*

[c] *Adjusted for age, gender, and baseline norepinephrine value*

REFERENCES

1. Schwartz A, Brotfain E, Koyfman L, Klein M. Cardiac Arrhythmias in a Septic ICU Population: A Review. *J Crit Care Med (Targu Mures)*. Oct 2015;1(4):140-146. doi:10.1515/jccm-2015-0027

2. Schmidt H, Muller-Werdan U, Hoffmann T, et al. Autonomic dysfunction predicts mortality in patients with multiple organ dysfunction syndrome of different age groups. *Crit Care Med*. Sep 2005;33(9):1994-2002. doi:10.1097/01.ccm.0000178181.91250.99

3. Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Critical Care Medicine*. 2021;49(11):e1063-e1143. doi:10.1097/ccm.0000000000005337

4. Singer M. Catecholamine treatment for shock--equally good or bad? *Lancet*. 8/25/2007 2007;370(9588):636-637. doi:S0140-6736(07)61317-8 [pii];10.1016/S0140-6736(07)61317-8 [doi]

5. Rudiger A, Singer M. Mechanisms of sepsis-induced cardiac dysfunction. *Crit Care Med*. 6/2007 2007;35(6):1599-1608. doi:10.1097/01.CCM.0000266683.64081.02 [doi]

6. Beesley SJ, Wilson EL, Lanspa MJ, et al. Relative Bradycardia in Patients With Septic Shock Requiring Vasopressor Therapy. *Crit Care Med*. Feb 2017;45(2):225-233. doi:10.1097/CCM.0000000000002065

7. Ackland GL, Yao ST, Rudiger A, et al. Cardioprotection, attenuated systemic inflammation, and survival benefit of beta1-adrenoceptor blockade in severe sepsis in rats. *Crit Care Med*. 2/2010 2010;38(2):388-394. doi:10.1097/CCM.0b013e3181c03dfa [doi]

8. Ibrahim-Zada I, Rhee P, Gomez CT, Weller J, Friese RS. Inhibition of sepsis-induced inflammatory response by beta1-adrenergic antagonists. *J Trauma Acute Care Surg*. 2/2014 2014;76(2):320-327. doi:10.1097/TA.0000000000000113 [doi];01586154-201402000-00010 [pii]

9. Morelli A, Ertmer C, Westphal M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. *JAMA*. 10/23/2013 2013;310(16):1683-1691. doi:1752246 [pii];10.1001/jama.2013.278477 [doi]

10. Zhang J, Chen C, Liu Y, Yang Y, Yang X, Yang J. Benefits of esmolol in adults with sepsis and septic shock: An updated meta-analysis of randomized controlled trials. *Medicine*. 2022;101(27):e29820. doi:10.1097/md.0000000000029820

11. Iguchi S, Iwamura H, Nishizaki M, et al. Development of a highly cardioselective ultra short-acting beta-blocker, ONO-1101. *Chem Pharm Bull (Tokyo)*. 6/1992 1992;40(6):1462-1469.

12. Lall R, Mistry D, Skilton E, et al. Study into the reversal of septic shock with landiolol (beta blockade): STRESS-L Study protocol for a randomised trial. *BMJ Open*. Feb 16 2021;11(2):e043194. doi:10.1136/bmjopen-2020-043194

13. Association WM. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

14. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2/23/2016 2016;315(8):801-810. doi:2492881 [pii];10.1001/jama.2016.0287 [doi]

15. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2/2013 2013;39(2):165-228. doi:10.1007/s00134-012-2769-8 [doi]

16. A Randomized Trial of Protocol-Based Care for Early Septic Shock. *New England Journal of Medicine*. 2014;370(18):1683-1693. doi:10.1056/NEJMoa1401602

17. Goal-Directed Resuscitation for Patients with Early Septic Shock. *New England Journal of Medicine*. 2014;371(16):1496-1506. doi:10.1056/NEJMoa1404380

18. Mouncey PR, Osborn TM, Power GS, et al. Trial of Early, Goal-Directed Resuscitation for Septic Shock. *New England Journal of Medicine*. 2015;372(14):1301-1311. doi:10.1056/NEJMoa1500896

19. Rowan KM, Angus DC, Bailey M, et al. Early, Goal-Directed Therapy for Septic Shock - A Patient-Level Meta-Analysis. *N Engl J Med*. Jun 8 2017;376(23):2223-2234. doi:10.1056/NEJMoa1701380

20. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 7/1996 1996;22(7):707-710.

21. Accessed 26th June 2023, https://warwick.ac.uk/fac/sci/med/research/ctu/trials/stressl/public/

22. Gordon AC, Perkins GD, Singer M, et al. Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis. *N Engl J Med*. 10/27/2016 2016;375(17):1638-1648. doi:10.1056/NEJMoa1609409 [doi]

23. Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. *Crit Care Med*. Apr 1999;27(4):723-32. doi:10.1097/00003246-199904000-00025

24. Brunkhorst FM, Oppert M, Marx G, et al. Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction in patients with severe sepsis: a randomized trial. *Jama*. Jun 13 2012;307(22):2390-9. doi:10.1001/jama.2012.5833

25. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J*. 1/2012 2012;33(2):176-182. doi:ehr352 [pii];10.1093/eurheartj/ehr352 [doi]

26. Baiocchi M, Cheng J, Small DS. Instrumental variable methods for causal inference. *Stat Med*. Jun 15 2014;33(13):2297-340. doi:10.1002/sim.6128

27. The ARDS Definition Task Force. Acute Respiratory Distress Syndrome: The Berlin Definition. *JAMA*. 2012;307(23):2526-2533. doi:10.1001/jama.2012.5669

28. Mizuno J, Yoshiya I, Yokoyama T, Yamada Y, Arita H, Hanaoka K. Age and sex-related differences in dose-dependent hemodynamic response to landiolol hydrochloride during general anesthesia. *Eur J Clin Pharmacol*. 3/2007 2007;63(3):243-252. doi:10.1007/s00228-006-0249-1 [doi]

29. Kakihana Y, Nishida O, Taniguchi T, et al. Efficacy and safety of landiolol, an ultra-short-acting β1-selective antagonist, for treatment of sepsis-related tachyarrhythmia (J-Land 3S): a multicentre, open-label, randomised controlled trial. *Lancet Respir Med*. Sep 2020;8(9):863-872. doi:10.1016/s2213-2600(20)30037-0

30. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 10/10/2001 2001;286(14):1754-1758. doi:jce00056 [pii]

31. Morelli A, Romano SM, Sanfilippo F, et al. Systolic-dicrotic notch pressure difference can identify tachycardic patients with septic shock at risk of cardiovascular decompensation following pharmacological heart rate reduction. *Br J Anaesth*. Dec 2020;125(6):1018-1024. doi:10.1016/j.bja.2020.05.058

32. Macchia A, Romero M, Comignani PD, et al. Previous prescription of β-blockers is associated with reduced mortality among patients hospitalized in intensive care units for sepsis. *Crit Care Med*. Oct 2012;40(10):2768-72. doi:10.1097/CCM.0b013e31825b9509

33. Christensen S, Johansen MB, Tonnesen E, et al. Preadmission beta-blocker use and 30-day mortality among patients in intensive care: a cohort study. *Crit Care*. 2011 2011;15(2):R87. doi:cc10085 [pii];10.1186/cc10085 [doi]

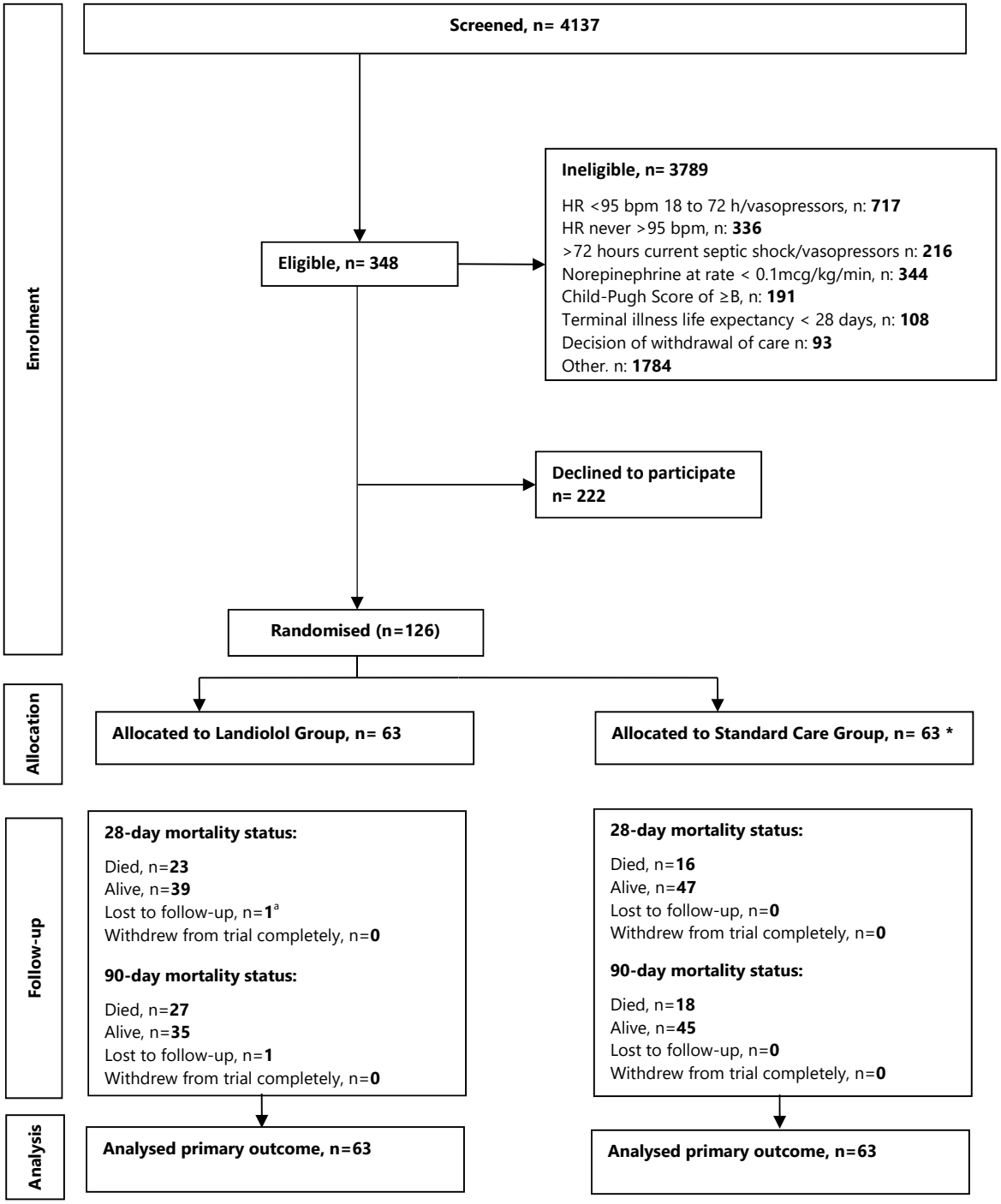
34. Fuchs C, Wauschkuhn S, Scheer C, et al. Continuing chronic beta-blockade in the acute phase of severe sepsis and septic shock is associated with decreased mortality rates up to 90 days. *Br J Anaesth*. Oct 1 2017;119(4):616-625. doi:10.1093/bja/aex231

35. Kuo M-J, Chou R-H, Lu Y-W, et al. Premorbid β1-selective (but not non-selective) β-blocker exposure reduces intensive care unit mortality among septic patients. *Journal of Intensive Care*. 2021/05/13 2021;9(1):40. doi:10.1186/s40560-021-00553-9

585 36. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a New Definition and Assessing New
586 Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and
587 Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):775-787. doi:10.1001/jama.2016.0289
588 37. Gamper G, Havel C, Arrich J, et al. Vasopressors for hypotensive shock. *Cochrane Database*
589 *Syst Rev*. Feb 15 2016;2(2):Cd003709. doi:10.1002/14651858.CD003709.pub4

590

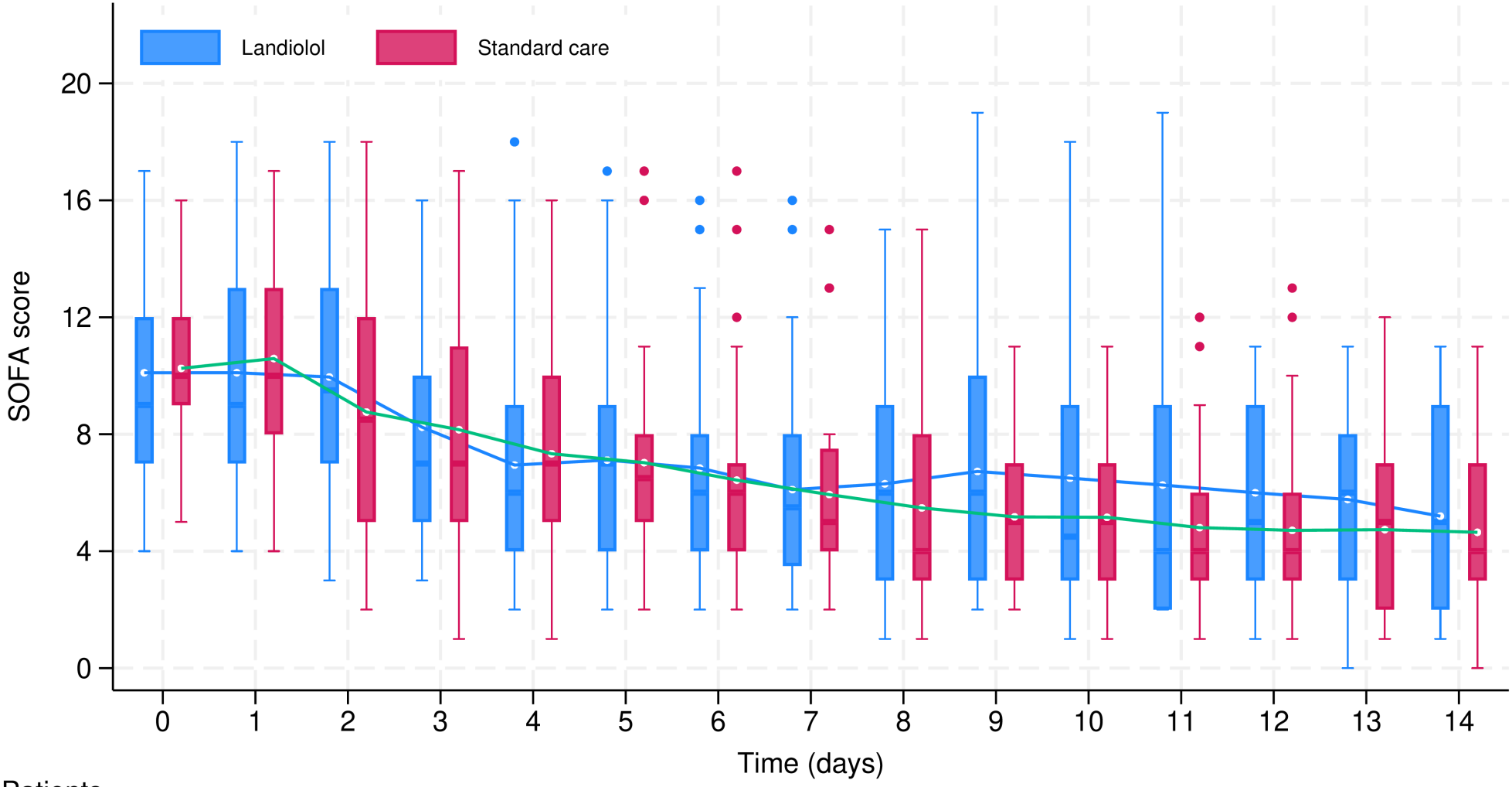
Figure 1: Recruitment: Screening, randomization, and outcome assessment in the STRESS-L trial.



*One patient was randomized in error- the patient had a heart rate of 84bpm at the point of randomization and thus this patient did not satisfy the eligibility criteria. However, the patient remained in the trial, on an intention to treat basis and their routine data were collected.

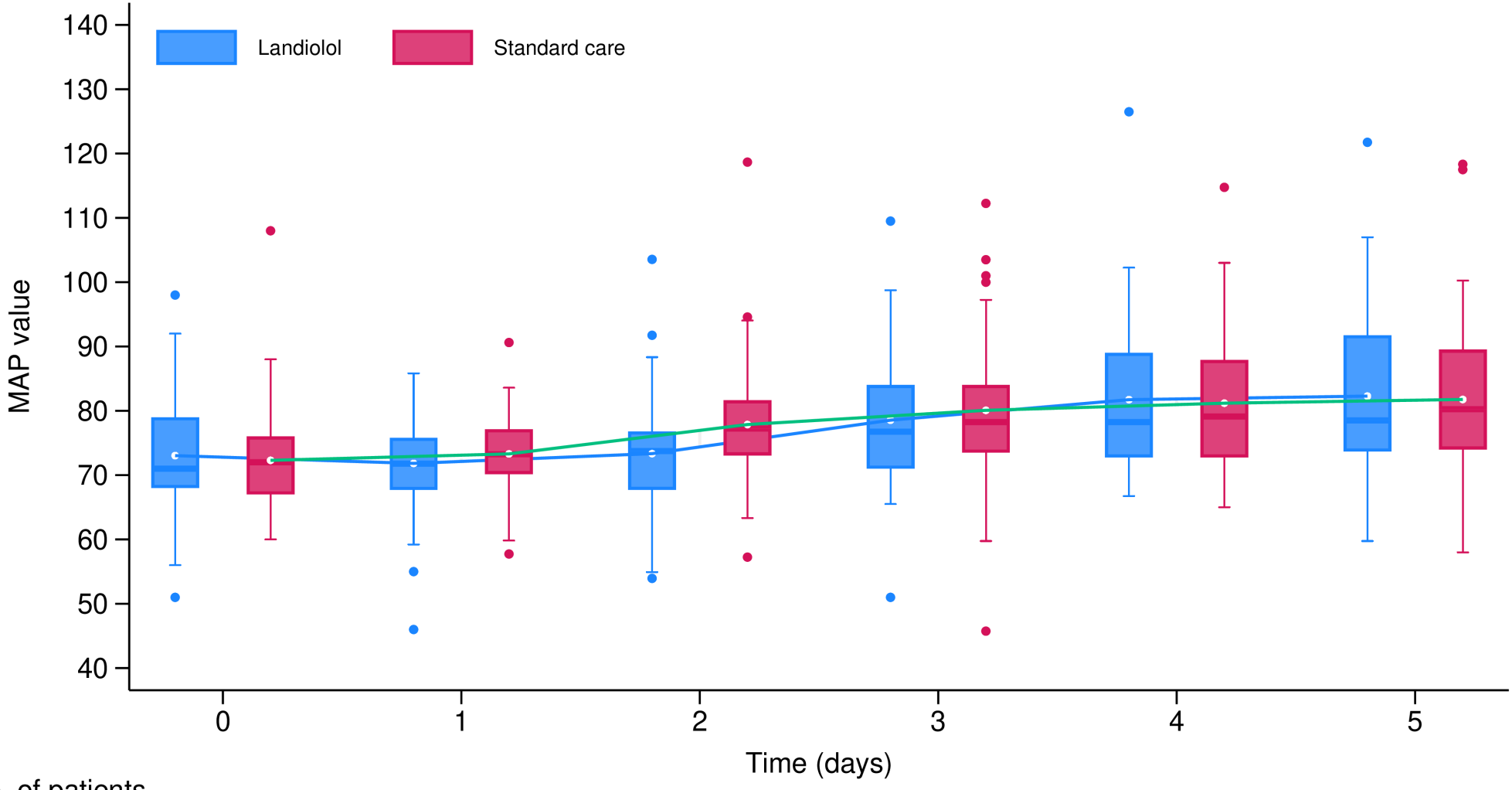
ǂ Only one patient was recruited who had COVID-19 into the study.

‡ In the study there were 9 (7.1%) withdrawals, all on the Landiolol arm (all patients withdrew from treatment but remained in follow-up). Of these, 8 patients were withdrawn by the clinician and 1 patient was withdrawn by the personal legal representative.

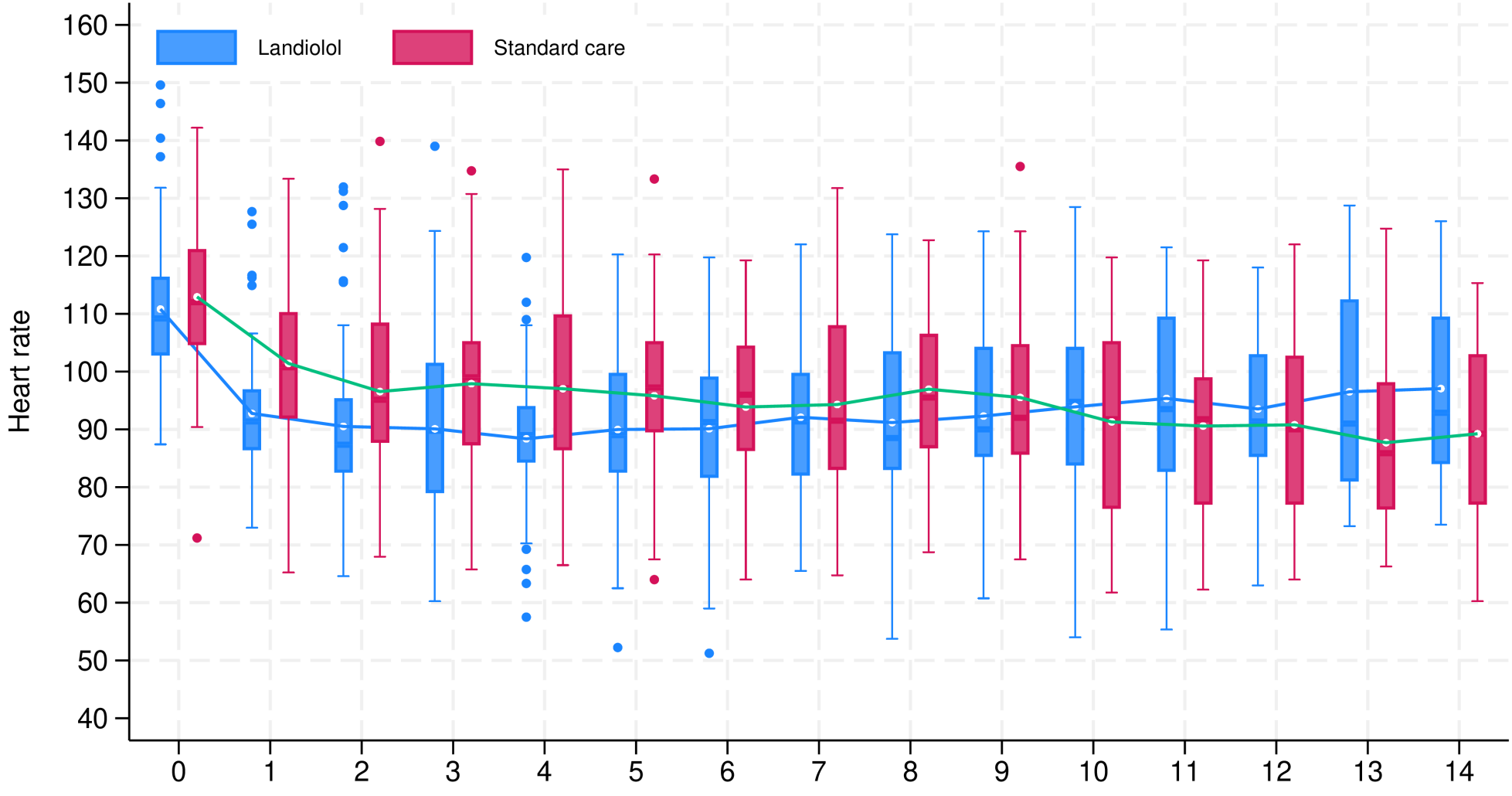


No. of Patients

Landiolol	58	57	48	41	38	34	32	28	23	22	22	19	17	13	15
Standard care	59	61	50	45	45	34	37	32	27	23	25	26	21	19	17



No. of patients						
Landiolol	63	63	57	51	45	42
Standard care	63	63	61	58	53	50



No. of patients															
Landiolol	63	63	57	51	45	41	40	34	29	29	27	27	24	22	22
Standard care	63	63	61	57	52	49	45	40	37	36	31	30	27	24	23