

STRESS-L Investigator Meeting 2021

10:00 – 11:30



Funded by NIHR

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NHS University Hospitals Birmingham NHS Foundation Trust

WARWICK CLINICAL TRIALS UNIT

‘Virtual’ Housekeeping!

- State name, role & your hospital site in the chat function
- Using the chat function/raise hand
- Mute microphone when others presenting
- Recording meeting

Agenda

10:00 – 10:10	**Welcome and Introductions** Prof Tony Whitehouse
10:10 – 10:20	**Background to STRESS-L and why Septic Shock matters?** Prof Tony Whitehouse
10:20 – 10:25	**Patient Public Involvement (PPI) - Real life experience of sepsis** Lee Bettles, PPI rep on TMG
10:25 – 10:40	**Trial recruitment status, changes since COVID and support for sites** Prof Tony Whitehouse Emma Skilton, Trial Manager
10:40 – 10:45	**New sites set up process** Belinder Ghuman, Trial Coordinator
10:45 – 11:00	**Experiences of recruiting sites** Royal Liverpool Hospital Derriford Hospital
11:00 – 11:20	**Q&A Feedback sessions** Prof Tony Whitehouse, Emma Skilton & Belinder Ghuman
11:20 – 11:30	**Round up and thank you** Prof Tony Whitehouse

BACKGROUND TO STRESS-L AND WHY SEPTIC SHOCK MATTERS

Prof Tony Whitehouse

STRESS-L

Funded by NIHR

STudy into the REversal of Septic Shock with Landiolol

Prof Tony Whitehouse
Consultant Critical Care and Anaesthesia, QEHB
University of Birmingham

Background

Research

Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock

A Randomized Clinical Trial

Andrea Morelli, MD; Christian Ertmer, MD; Martin Westphal, MD; Sebastian Rehberg, MD; Tim Kampmeier, MD; Sandra Ligges, PhD; Alessandra Orecchioni, MD; Annalia D'Egidio, MD; Fiorella D'Ippoliti, MD; Cristina Raffone, MD; Mario Venditti, MD; Fabio Guarracino, MD; Massimo Girardis, MD; Luigi Tritapepe, MD; Paolo Pietropaoli, MD; Alexander Mebazaa, MD; Mervyn Singer, MD, FRCP

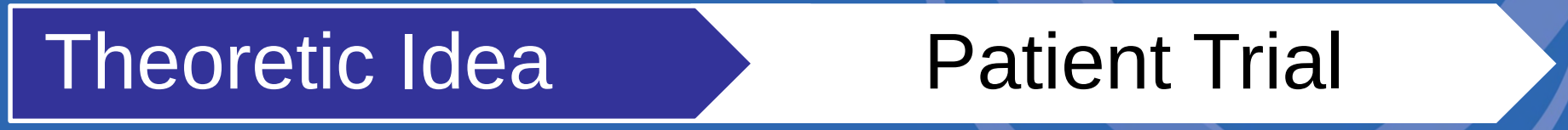
Morelli A et al
JAMA. 2013 Oct 23;310(16):1683-91. doi:10.1001/jama.2013.278477.
PMID: 24108526

Beta Blockers in Sepsis

Usual Treatment Development



Morelli

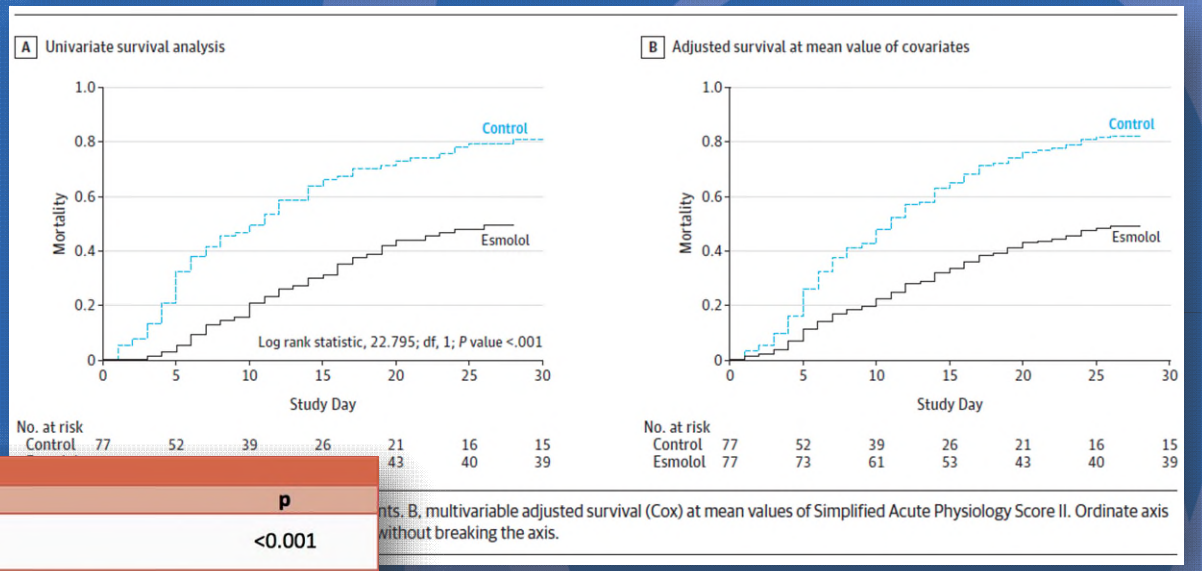


Research

Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock
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nts. B, multivariable adjusted survival (Cox) at mean values of Simplified Acute Physiology Score II. Ordinate axis without breaking the axis.

Primary Outcome			
Measure	**Esmolol**	**Contol**	**p**
Target HR 80-94 Median AUC (IQR)	-28/min (-37 to -21)	-6min (-14 to 0)	<0.001
AUC = Area under curve; IQR = Interquartile range; p = probability			

Secondary Outcomes				
Measure	**Esmolol**	**Contol**	**Adjusted hazard ratio (95% C.I.)**	**p**
Noradrenaline requirements Median AUC	-0.11ug/kg/min	-0.01ug/kg/min		0.003
Fluid requirements Median AUC	3975ml/d	4425ml/d		<0.001
Stroke volume index Median AUC	4ml/m/2	1ml/m/2		0.02
28 day mortality	49.1%	80.5%	0.39 (0.26-0.59)	<0.001
C.I = Confidence Interval				

Outcome	No. (%) Esmolol (n = 77)	Control (n = 77)	*P* Value
Mortality			
28 d	38 (49.4)	62 (80.5)	<.001
ICU	44 (57.1)	68 (88.3)	<.001
Hospital	52 (67.5)	70 (90.9)	<.001
Length of ICU stay, d			
Median (IQR)	19 (11-27)	14 (7-25)	.03
Survivors', median (IQR)	17 (9-28)	21 (11-34)	.70
Cause of death, No./total, (%)			
Multiple organ failure	15/52 (28.8)	26/70 (37.1)	.71
Refractory hypotension	32/52 (61.6)	44/70 (62.9)	
Unknown cause	5/52 (9.6%)		

Abbreviations: ICU, intensive care unit; IQR, interquartile range.



Research

Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock
A Randomized Clinical Trial

Andrea Morelli, MD; Christian Ertmer, MD; Martin Westphal, MD; Sebastian Rehberg, MD; Tim Kampmeier, MD; Sandra Ligges, PhD; Alessandra Orecchioni, MD; Annalia D'Egidio, MD; Fiorella D'Ippoliti, MD; Cristina Raffone, MD; Mario Venditti, MD; Fabio Guarracino, MD; Massimo Girardis, MD; Luigi Tritapepe, MD; Paolo Pietropaoli, MD; Alexander Mebazaa, MD; Mervyn Singer, MD, FRCP

- Criticisms / Comments
  - Very Sick Population
    - Median dose of noradrenaline approaching 0.4ug/kg/min at enrolment
    - High prevalence of multi-resistant organisms cultured
  - High use of levosimendan 49.4% in esmolol group
  - 28 day mortality of 80% in the control group
  - A non-standard method of calculating SAPS II scores

What was the mechanism for these findings?

Heart Rate Control or Immune Modulation?

Heart rate control or Immune modulation?

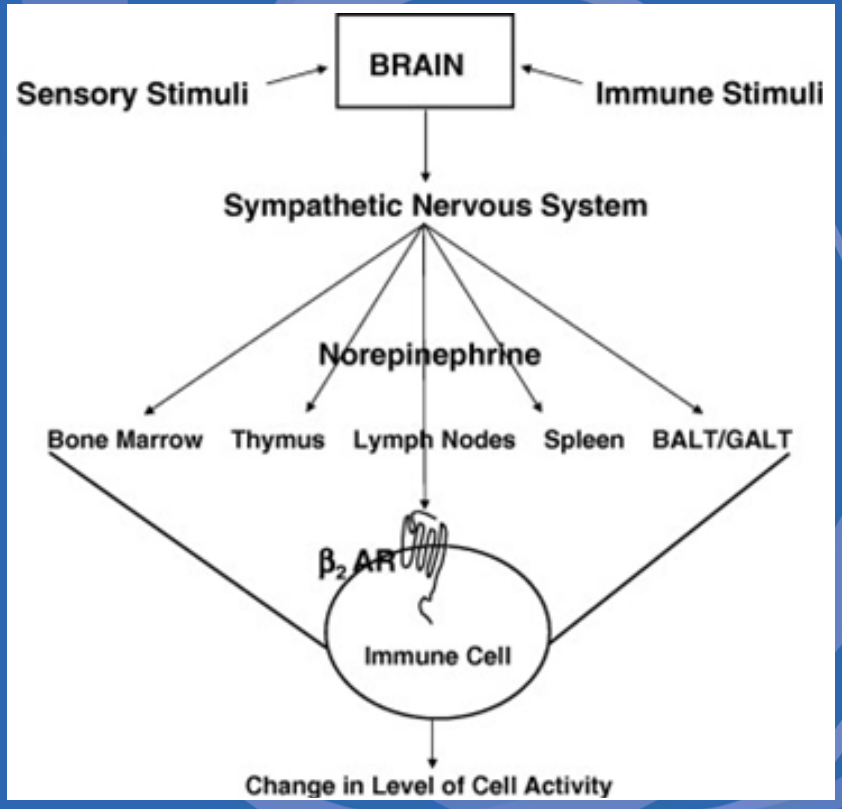
- 'The Stressed Heart'
  - Beta-blockers are established treatment
  - Excessive sympathetic activation also leads inflammation, oxidative stress, and abnormal calcium handling
    - left ventricular dilatation, apical ballooning, myocardial stunning, apoptosis, and necrosis.
    - Takotsubo cardiomyopathy
  - ?Excess mortality from Ischaemic Heart Disease



Heart rate control or Immune modulation?

- Spleen, thymus and bone marrow are innervated by the sympathetic system
- Majority of lymphoid tissue express beta-adrenergic receptors on their surface

- Survival benefits associated with heart rate reduction induced by beta-blockade
  - Mice, rats and pigs




Hepatology
ORIGINAL ARTICLE
Gut 2015;64:1111–1119. doi:10.1136/gutjnl-2013-306502
Non-selective β-blockers are associated with improved survival in patients with ascites listed for liver transplantation
Joanna A Leithead,[1,2] Neil Rajoriya,[1] Nadeem Tehami,[1] James Hodg
Bridget K Gunson,[1,2] Dhiraj Tripathi,[1] James W Ferguson[1]
Propranolol ameliorates and epinephrine ex
and chronic viral myocarditis
Ju-Feng Wang,[1,*] Achim Meissner,[2,*] Sohail Malek,[1] Yu C
Jielin Zhang,[3] Victor Chu,[1] Thomas G. Hampton,[1] Clyd
Walter H. Abelmann,[1] Ivo Amende,[1] and James P
RESEARCH ARTICLE
American Journal of Hematology
Beta-blockers improve survival outcomes
multiple myeloma: a retrospective evaluation
nts with
Yi L. Hwa,[1] Qian Shi,[2] Shaji K. Kumar,[1] Martha Q. Lacy,[1] Morie A. Gertz,[1] Prashant Kapoor,[1] Francis K. Buadi,[1]
Nelson Leung,[1,3] David Dingli,[1] Ronald S. Go,[1] Suzanne R. Hayman,[1] Wilson I. Gonsalves,[1] Stephen Russell,[1]
hn A. Lust,[1] Yi Lin,[1] S. Vincent Rajkumar,[1] and Angela Dispenzieri[1,*]
Beta-Blocker Exposure is Associated With Improved Survival After Severe Traumatic Brain Injury
Bryan A. Cotton, MD, Kimberly B. Snodgrass, PharmD, Sloan B. Fleming, PharmD, Robert O. Carpenter, MD,
The Journal of TRAUMA® Injury, Infection, and Critical Care
J Trauma. 2007;62:26–35.
Beta-Blocker Use Is Associated with Improved Outcomes in Adult Burn Patients
Saman Arbabi, MD,
Stewart C. Wang, M
The Journal of TRAUMA® Injury, Infection, and Critical Care
J Trauma. 2004;56:265–271.
Beta-Blocker Use is Associated With Improved Outcomes in Adult Trauma Patients
Saman Arbabi, MD, MPH, Eric M. Campion, MD, Mark R. Hemmila, MD, Melissa Barker, RN,
Mary Dimo, PharmD, Karla S. Ahrns, RN, Andreas D. Niederbichler, MD, Kyros Ipaktchi, MD,
and Wendy L. Wahl, MD
The Journal of TRAUMA® Injury, Infection, and Critical Care
J Trauma. 2007;62:56–62.

The New England
Journal of Medicine

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VOLUME 345 OCTOBER 25, 2001 NUMBER 17

REVERSAL OF CATABOLISM BY BETA-BLOCKADE AFTER SEVERE BURNS

DAVID N. HERNDON, M.D., DAVID W. HART, M.D., STEVEN E. WOLF, M.D., DAVID L. CHINKES, PH.D., AND ROBERT R. WOLFE, PH.D.

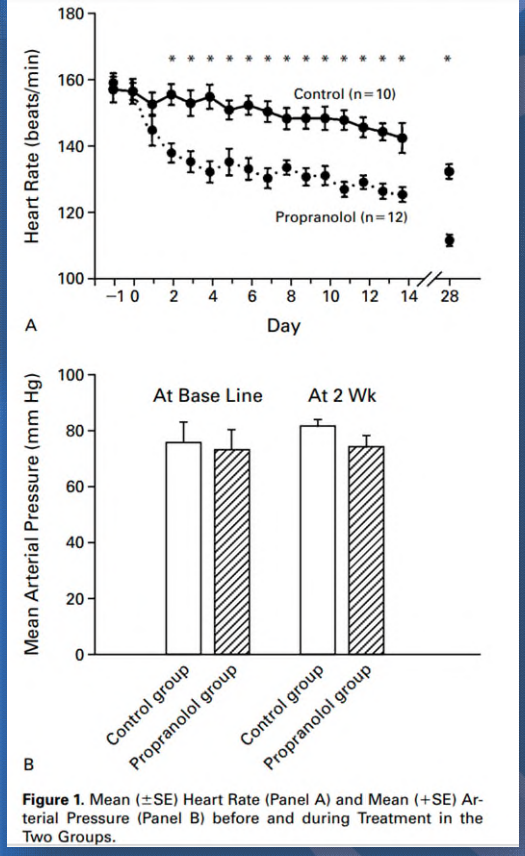


Figure 1. Mean (±SE) Heart Rate (Panel A) and Mean (+SE) Arterial Pressure (Panel B) before and during Treatment in the Two Groups.

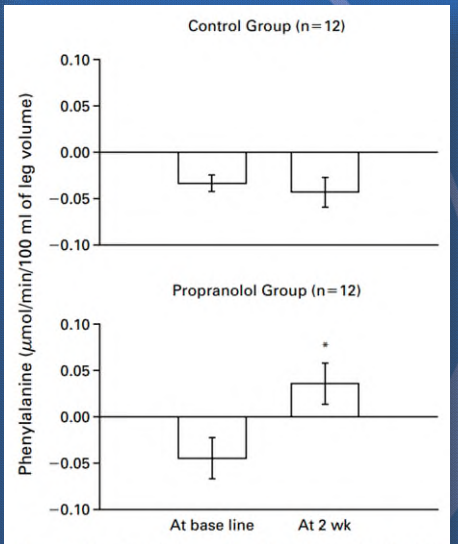
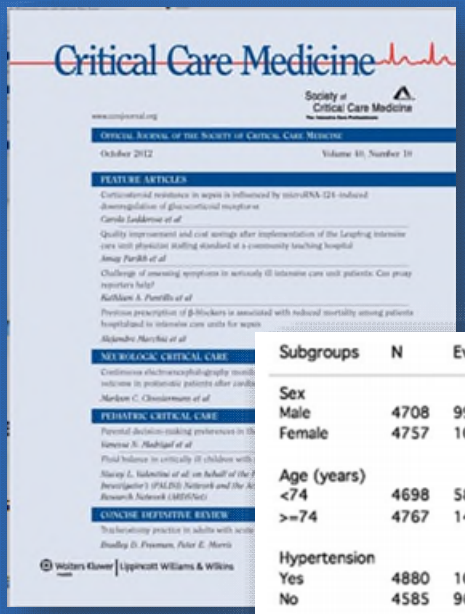


Figure 2. Mean (±SE) Change from Base Line in the Net Balance of Muscle-Protein Synthesis and Breakdown during Two Weeks of Treatment.

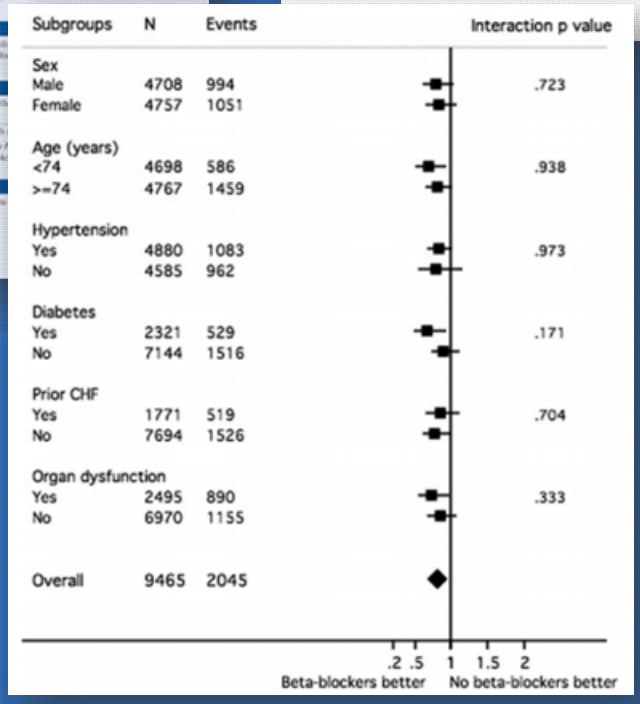
Values were obtained with use of a five-hour kinetic study that used isotopically labeled phenylalanine. The asterisk indicates a significant difference between the two groups (P=0.001 by t-test) and a significant difference between the base-line value and the value at two weeks (P=0.002 by paired t-test).

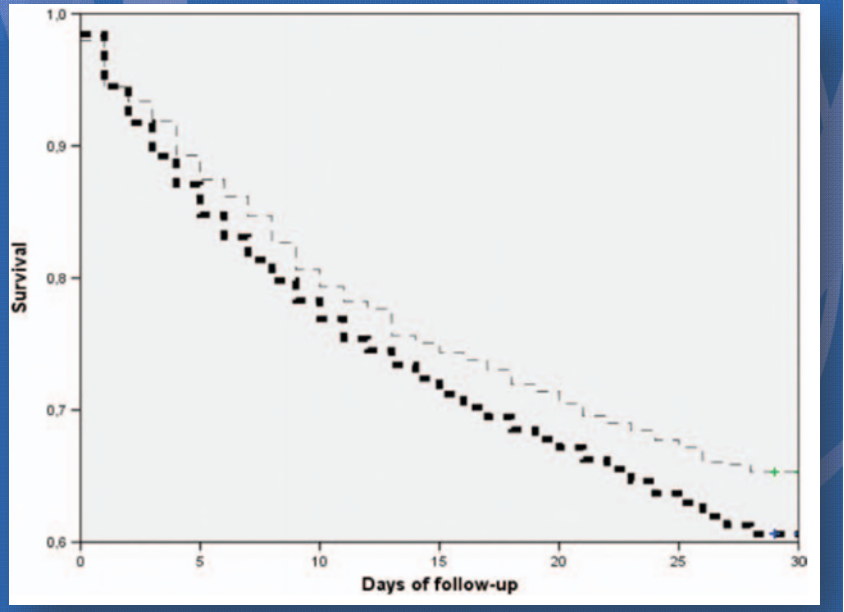


Previous prescription of β-blockers is associated with reduced mortality among patients hospitalized in intensive care units for sepsis*

Alejandro Macchia, MD; Marilena Romero, PhD; Pablo Dino Comignani, MD; Javier Mariani, MD; Antonio D'Ettorre, PhD; Nadia Prini, MD; Mariano Santopinto, MD; Gianni Tognoni, MD

Crit Care Med 2012 Vol. 40, No. 10





BJA

British Journal of Anaesthesia, 0 (0): 1–10 (2017)

doi: 10.1093/bja/aex231
Clinical Investigation

CLINICAL INVESTIGATION

Continuing chronic beta-blockade in the acute phase of severe sepsis and septic shock is associated with decreased mortality rates up to 90 days

C. Fuchs[1,*,†], S. Wauschkuhn[1,†], C. Scheer[1], M. Vollmer[2], K. Meissner[1], S.-O. Kuhn[1], K. Hahnenkamp[1], A. Morelli[3], M. Gründling[1] and S. Rehberg[1]

[1]Department of Anaesthesiology, University Hospital of Greifswald, Ferdinand-Sauerbruch-Strasse, 17475 Greifswald, Germany, [2]Institute of Bioinformatics, University Hospital of Greifswald, Greifswald, Germany and [3]Department of Cardiovascular, Respiratory, Nephrological, Anesthesiological and Geriatric Sciences, University of Rome, La Sapienza, Rome, Italy

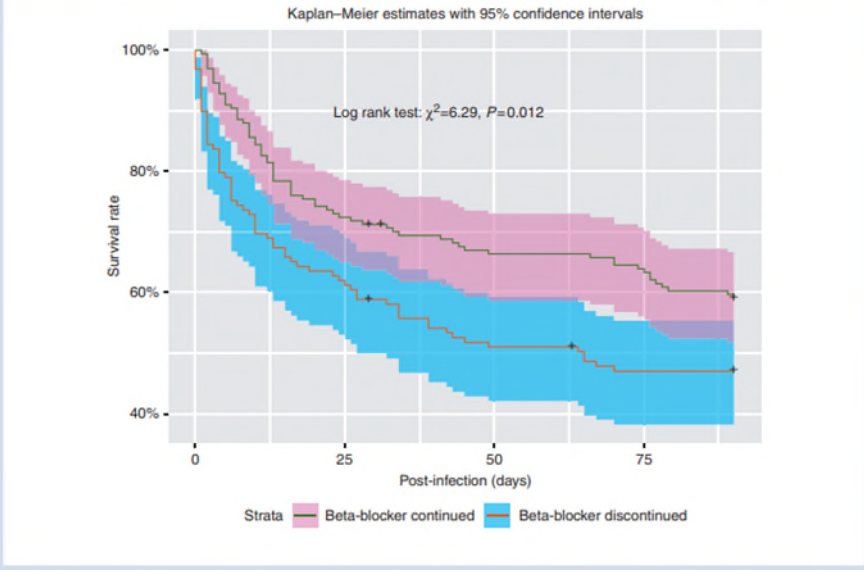


Fig 2 Kaplan-Meier estimates of the survival functions. Survival functions of the first 90 days after sepsis onset are given for patients with continued (red) and discontinued (blue) beta-blocker therapy with 95% confidence bounds. The survival information till 90 days is right censored (indicated by plus sign).

296 patients with severe sepsis or septic shock and pre-existing, chronic oral beta-blocker therapy
Decreased:

- Hospital (P=0.03)
- 28-day (P=0.04)
- 90-day mortality (40.7% vs 52.7%; P=0.046) in contrast to beta-blocker cessation

RESEARCH Open Access
Christensen et al. Critical Care 2011, 15:R87
http://ccforum.com/content/15/2/R87
CRITICAL CARE

Preadmission beta-blocker use and 30-day mortality among patients in intensive care: a cohort study

Steffen Christensen[1,2*], Martin Berg Johansen[1], Else Tønnesen[2], Anders Larsson[3], Lars Pedersen[1], Stanley Lemeshow[4] and Henrik Toft Sørensen[1]

Table 1 Characteristics of ICU patients, Aarhus University Hospital, 1999 to 2005

	Overall		Propensity-score-matched cohorts	
	No current use of beta-blockers N (%)	Current use of beta-blockers N (%)	No current use of beta-blockers N (%)	Current use of beta-blockers N (%)
Overall	6,531 (80.8%)	1,556 (19.2%)	1,556 (0%)	1,556 (100%)
Age group				
46 to 59	2,100 (32.2%)	344 (22.1%)	307 (19.7%)	344 (22.1%)
60 to 75	2,880 (44.1%)	740 (47.6%)	790 (50.7%)	740 (47.6%)
75+	1,551 (23.7%)	472 (30.3%)	459 (29.5%)	472 (30.3%)
Gender				
Female	2,796 (42.8%)	598 (38.4%)	623 (40.0%)	598 (38.4%)
Male	3,735 (57.1%)	958 (61.6%)	933 (60.0%)	958 (61.6%)

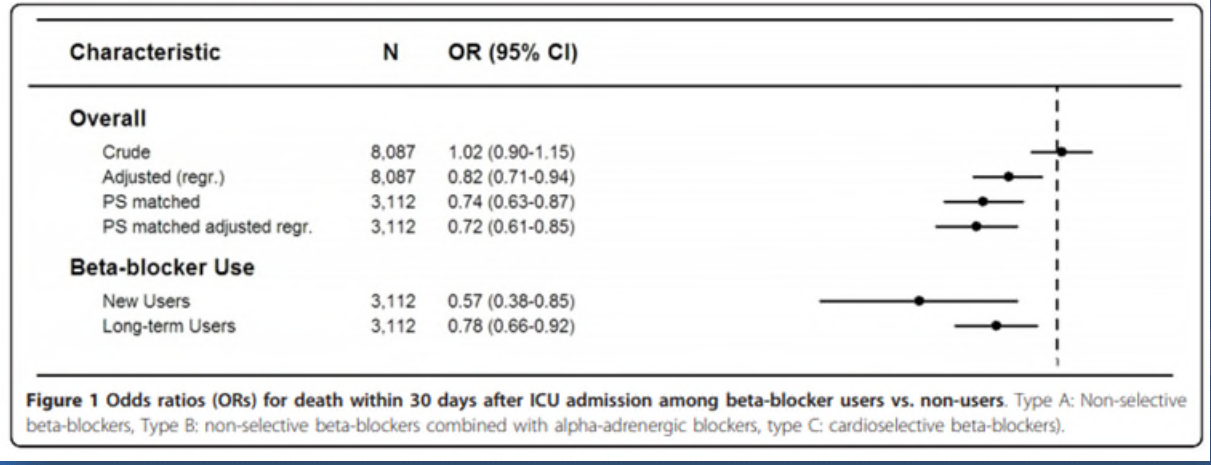


Figure 1 Odds ratios (ORs) for death within 30 days after ICU admission among beta-blocker users vs. non-users. Type A: Non-selective beta-blockers, Type B: non-selective beta-blockers combined with alpha-adrenergic blockers, type C: cardioselective beta-blockers).

STRESS-L Trial
Are Beta-Blockers Effective in Septic Shock?

- NIHR EME funded £1.6 million
  - QEHB as Sponsor
  - Multi-Centre, UK-wide
- Randomised trial
  - Can't blind because HR not affected in untreated group
- Open to 35 centres initially
  - Now able to open to 51
- TOTAL: 340 Patients

STRESS-L Trial
Are Beta-Blockers Effective in Septic Shock?

- All ICU Patients to be screened
  - SEPSIS 3 + adequate fluid resuscitation + vasopressor support >24 hours + Tachycardia>95 bpm
  - Receiving 0.1 mcg/kg/min Noradrenaline
  - Randomised to receive Standard Care or Standard Care + Landiolol to achieve HR 85-95 bpm
- Exclusions
  - Pre-existing beta-blockers
  - Severe cardiac dysfunction (NYHA grade 3 or more)
  - Untreated second or third degree heart block
  - Standard contraindications to beta blockers such as asthma and severe Raynaud's disease
  - 'Chronic' Infections or patients likely to have recurrent infection e.g. Acute Pancreatitis

STRESS-L Trial
Are Beta-Blockers Effective in Septic Shock?

- Randomisation to Standard Care or Standard Care + Landiolol
  - Landiolol provided gratis by manufacturers
  - Landiolol dose to be titrated until HR<95

- Protocolised but Pragmatic BP and HR management
  - Trial taking place in highly monitored environment with staff who are skilled in the daily use of CV active drugs

- Daily collection of SOFA score for 14 days or until ICU discharge
  - SOFA score is a set of 6 parameters each daily collected in ICU as part of routine care
  - Central Lab Blood on Pre, D1, 2, 4 and 6

STRESS-L Trial
Are Beta-Blockers Effective in Septic Shock?

- Primary Outcome
  - Change in SOFA score over ICU admission or 14 days

STRESS-L Trial
Are Beta-Blockers Effective in Septic Shock?

- Secondary outcomes
  - Mortality / Length of Stay (ICU / Hospital)
  - Δ CV Support (SOFA / SAPS)
  - Changes in:
    - inflammatory cytokines (IL-6, IL-10)
    - markers of myocyte damage (B-type Natriuretic Peptide (BNP), troponin)
    - Catecholamines, cortisol and lipid metabolites
  - A sub-group of patients
    - Phagocytic and oxidative burst activity
    - Immature neutrophils CD16

Operations

Warwick CTU

QEHB R&D

Data Monitoring Group

Chair: David Harrison, ICNARC

Prof Paul Dark, Manchester

Prof Rupert Pearce, Barts and London

STRESS-L

Trial Steeri

Chair: Prof Tim Walsh, Edinburgh

Prof Charles Hinds, Barts and London

Prof Claire Hulme, Leeds

Karen Keates, Lay Member

Management Group

Prof Janet Lord

Prof Mervyn Singer

Dr T Whitehouse

Thank you



Intensive Care Med (2013) 39:165–228
DOI 10.1007/s00134-012-2769-8

GUIDELINES

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012

R. P. Dellinger
Mitchell M. Levy
Andrew Rhodes
Djillali Annane
Herwig Gerlach
Steven M. Opal
Jonathan E. Sevransky
Charles L. Sprung
Ivor S. Douglas
Roman Jaeschke
Tiffany M. Osborn
Mark E. Nunnally
Sean R. Townsend
Konrad Reinhart
Ruth M. Kleinpell
Derek C. Angus
Clifford S. Deutschman
Flavia R. Machado
Gordon D. Rubenfeld
Steven Webb
Richard J. Beale
Jean-Louis Vincent
Rui Moreno
The Surviving Sepsis Campaign Guidelines Committee
including The Pediatric Subgroup*

I. Inotropic therapy

1. A trial of dobutamine infusion up to 20 micrograms/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP (grade 1C).
2. Not using a strategy to increase cardiac index to predetermined supranormal levels (grade 1B).

Lee Bettles

PPI representative
STRESS-L



Background



The fear of Sepsis



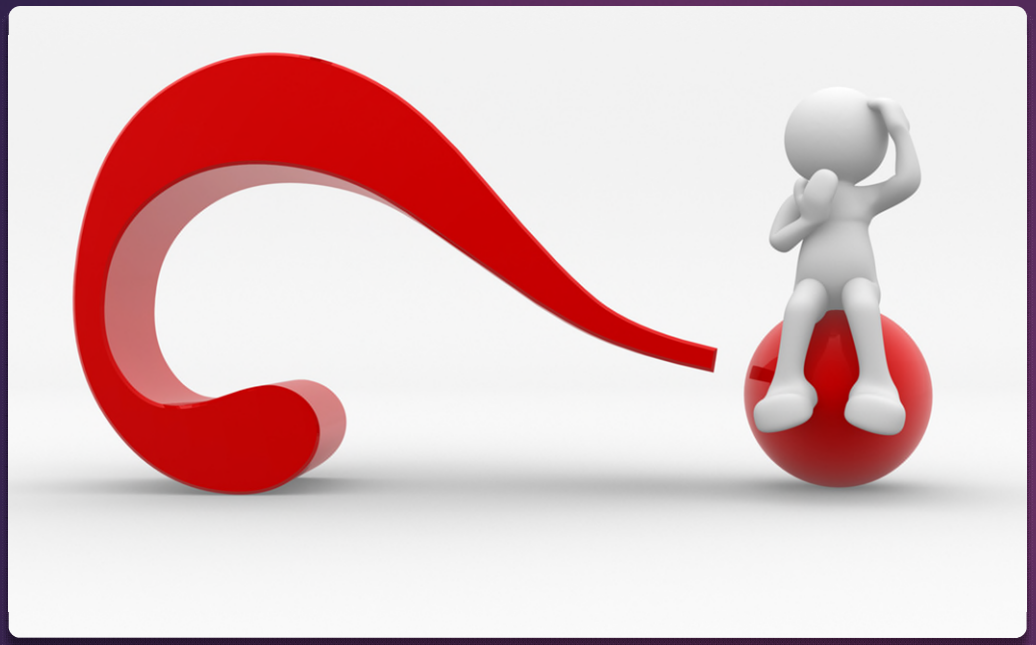
The ‘blessing’ of Sepsis



Life is a decision



PPI work



Thank you!

Any questions?

TRIAL RECRUITMENT STATUS, CHANGES SINCE COVID AND SUPPORT FOR SITES

Emma Skilton

Coordination: Warwick CTU



Emma Skilton
Trial Manager



Belinder Ghuman
Trial Coordinator



Prof Ranjit Lall
Warwick Lead

☎ 07385029213

✉ stress-l@warwick.ac.uk

www.warwick.ac.uk/stressl

www.stress-l.org

@StressLTrial



Jo Grumett
QA manager

Anower Hussain
Statistician



Scott Regan
Senior Project Manager

Will Bozic
Data Entry
Clerk

STRESS-L

Trial recruitment status

- Most recent patient recruited: *31 May 2021*
- Total number of patients recruited: **119**
- Continued support from NIHR EME
- Current recruitment extension: Feb 2022
- Costed extension to be submitted August 2021



Trial site status

- Sites restarted and open: **15**
- Sites restarted since COVID but currently paused to screening: **9**
- Sites pending restart since COVID: **12**

STRESS-L Recruitment sites



- Queen Elizabeth Hospital Bir...
- Birmingham Heartlands Hos...
- Royal Victoria Hospital
- St Mary's Hospital
- Charing Cross Hospital
- Hammersmith Hospital
- University College Hospital
- Nottingham University Hospi...
- St Thomas' Hospital
- Musgrove Park Hospital
- King's Mill Hospital
- Sunderland Royal Hospital
- Bristol Royal Infirmary
- Royal Devon and Exeter NHS...
- Dorset County Hospital
- Royal Cornwall Hospital
- Derriford Hospital
- Queen Alexandra Hospital
- The Royal Liverpool Universi...
- King's College Hospital
- Russells Hall Hospital
- Royal Free Hospital
- University Hospital Coventry ...
- Craigavon Area Hospital
- Leeds General Infirmary
- York Hospital
- Rotherham General Hospital
- Addenbrooke's Hospital
- Royal Sussex County Hospital
- Northampton General Hospital
- Aberdeen Royal Infirmary
- Glasgow QEH
- Hull Royal Infirmary
- St George's Hospital
- Royal Glamorgan Hospital
- Royal Blackburn Hospital
- Newcastle RVI
- Wolverhampton New Cross ...
- Walsall Manor Hospital
- Leicester Royal Infirmary
- Royal Bolton Hospital
- Royal Oldham Hospital

Updated info since COVID

- COVID patients eligible but do not take bloods
- Verbal consent can be sought from patient or Personal Legal Representative. An **impartial witness** must countersign the consent form. Process fully documented in medical notes **including how the impartial witness was selected.**
- Blood sampling will continue beyond End of Noradrenaline visit.
- IMP temperature excursion procedure

Co-enrolment

- Key to facilitating research and creating a collaborative environment

- Current approved co-enrolling trials:

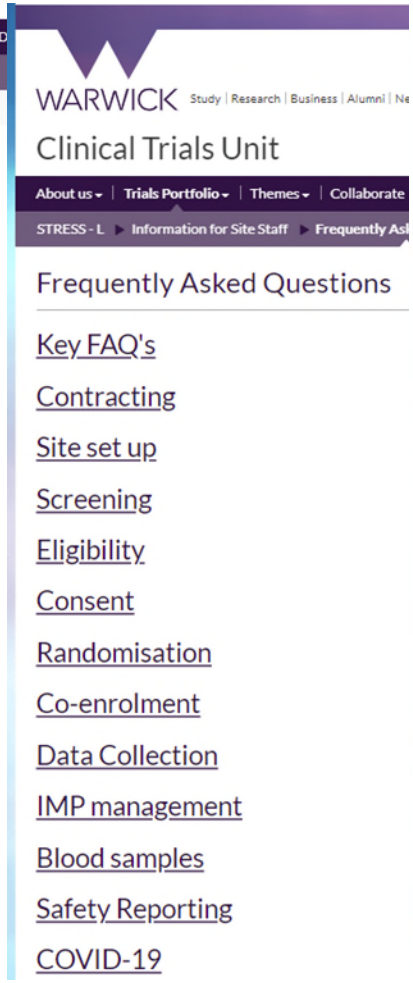
- PIM COVID (COVID trial)
- RECOVERY-RS (COVID trial)
- REMAP CAP (COVID trial)
- A-STOP
- ADAPT-Sepsis
- BLING III
- CRYOSTAT-2
- EFFORT
- EuroPN
- FLO-ELA
- GenOMICC
- Infections
- Oral Health VAP
- PHIND
- PQIP
- REST
- STARRT-AKI
- TAME
- TARDIS
- UKLVR
- VACIRiSS
- IMPACT 2
- UK-ROX
- PHIND
- ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging (COVID trial)



Trial resources

Clinical Trials Unit





STRESS-L

STRESS-L Trial Participant Completion Checklist

No.	Task	Guidance	Done
1	**Screen patient**	• ICU patients with septic shock diagnosis as per Sepsis-3 criteria, received vasopressors for 24 hours and noradrenaline should be screened.	☐
2	**Complete eligibility form and noting**	• Update patient's medical notes to document the patient is eligible for the trial. The documentation of the eligibility must include the current heart rate and noadrenaline dose at the time of the assessment, time of noradrenaline start and time lactate criteria achieved. • Paper CRF eligibility form must be signed by appropriately delegated medically qualified physician.	☐
3	**Obtain consent**	• If patient lacks capacity, obtain consent from Personal Legal Representative (PerLR). Research nurse can obtain consent from PerLR if local NHS Trust policy permits. • If PerLR not available, obtain consent from Professional Legal Representative (ProLR).	☐
4	**Randomise patient**	• Dial **024676 932 036** to randomise patient via automated 24/7 IVR system. • Complete paper CRF randomisation form. Appropriately delegated member of staff must sign form.	☐
5	**Obtain Day 0 blood samples**	• All blood samples must be taken for both arms (interventional & standard care). Blood samples **should not** be taken for suspected or confirmed positive COVID-19 patients. • Interventional arm: take prior to start of Landiolol administration • Please refer to lab manual for further guidance.	☐
6	**Complete baseline ECG**	• Complete for both arms (interventional & standard care) • Take prior to start of Landiolol administration.	☐
7	**Commence Landiolol infusion**	• If randomised to landiolol arm **only.** • Refer to IMP management manual and Landiolol Dosing chart laminates for further guidance.	☐
8	**Baseline data collection**	• Following critical data must be entered within 24 hours post randomisation: - > Noradrenaline start date and time ☐ - > Other vasopressor start date and time ☐ - > Heart Rate Day 0 Hour 0 ☐ - > Noadrenaline Dose Day 0 Hour 0 ☐	
9	**Submit paper CRFs**	• Paper eligibility and randomisation forms must ideally be submitted to WCTU within 24 hours post randomisation. ☐ • Temporary Inotrope and Beta Blocker Dosage CRFs to be completed and returned on paper at Day 14 until database is updated. ☐ • Please refer to Data Transfer Working Instructions for further guidance.	
10	**Daily data collection**	• Completed up until Day 14 as long as the patient remains on ICU. • Please refer to CRF instructions for further guidance.	☐
11	**Blood sample collection**	• Day 0: x1 PaxGene RNA, x1 PaxGene DNA, x3 Green Lithium Heparin tubes ☐ • Day 1: x1 PaxGene RNA, x3 Green Lithium Heparin tubes. ☐ • Days 2, 4 and 6: x3 Green Lithium Heparin tubes. ☐ • EONT: x1 PaxGene RNA, x3 Green Lithium Heparin tubes. ☐ • Please refer to lab manual for further guidance.	
12	**Submit blood sample storage log**	• Submit paper blood sample storage log at Day 14 to WCTU.	☐
13	**Complete follow up data**	• Submit Day 28 and Day 90 survival data follow up.	☐
14	**Complete End of Trial PI sign off form**	• Submit once instructed to by WCTU at the end of the trial.	☐

STRESS-L

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INCLUSION CRITERIA

- **18+** — Adults aged 18 years or above
- Being treated on an ICU (includes HDU patients)
- Clearly defined septic shock episode according to Sepsis 3
- Receiving vasopressor support to maintain target blood pressure for ≥24 hours
- Heart rate ≥95bpm at randomisation
- Treated with noradrenaline at rate of ≥0.1 mcg/kg/min at randomisation

If vasopressor stops and restarts, when does 24 hour vasopressor window clock begin?

Includes ANY type of vasopressor; not just noradrenaline

- Stops and restarts **LESS than 12 hours** → 24 hour window begins at start of INITIAL vasopressor treatment
- Stops and restarts **AFTER 72 hours** → 24 hour window begins at start of SECOND vasopressor treatment
- Stops and restarts **AFTER 12 hours but before 72 hours** → Contact trial team to confirm eligibility

How long should a patient receive noradrenaline for?

A patient does not need to receive noradrenaline for duration of 24 hour window but treatment at a rate of ≥0.1 mcg/kg/min must be established to treat septic shock at the time of randomisation

Eligible

- Previous or on-going beta blocker use for pre-existing condition
- Treated with beta agonists e.g. Dobutamine
- Atrial Fibrillation (AF) Treat with Landiolol or potassium, magnesium or amiodarone (NOT another beta blocker)

NOT Eligible

- Received vasopressor support for more than 72 hours to treat sepsis OR any other medical condition e.g. head injury
- Clearly defined septic shock episode cannot be identified
- Tachycardia is NOT sepsis driven

NEW

STRESS-L

A quick guide to consent

Does the patient have capacity to provide informed consent?

YES

Approach patient with information sheet to discuss trial

Are there concerns of viral transmission due to COVID-19?

YES

Ask impartial witness to be present **for discussion** to obtain verbal consent and to **sign the consent form alongside the investigator obtaining consent.** Patient does not sign the consent form but is provided with a signed copy. Full process is documented in medical records.

NO

Obtain written informed consent from patient and document in medical records.

NO

Is a **Personal Legal Representative (PerLR)** available to consult for consent?

YES

Contact personal legal representative (PerLR) via telephone due to COVID-19

Ask impartial witness to be present **for discussion** to obtain verbal consent and to **sign the consent form alongside the investigator obtaining consent.** Post signed copy to the PerLR. They do not have to return a signed copy. Full process is documented in medical records.

NO

Identify **Professional Legal Representative (ProfLR)** and obtain written informed consent and document in medical records.

REMEMBER

Consent is an ongoing process and if patient regains capacity or PerLR available after enrolment, they should be approached for consent.

Personal Legal Representative:

Relative, partner or close friend who is engaged in caring for participant (not professionally or for payment) and is willing to be consulted.

Professional Legal Representative:

Registered medically qualified physician, independent to the trial and is willing to be consulted. Approached if PerLR is not available.

Impartial witness:

Independent of the study and cannot be unfairly influenced by people involved with the study. E.g. non-research bedside nurse/clinician.

Trial resources

Landiolol dosage chart laminates

STRESS-L: STudy into the REversal of Septic Shock with Landiolol (Beta Blockade)

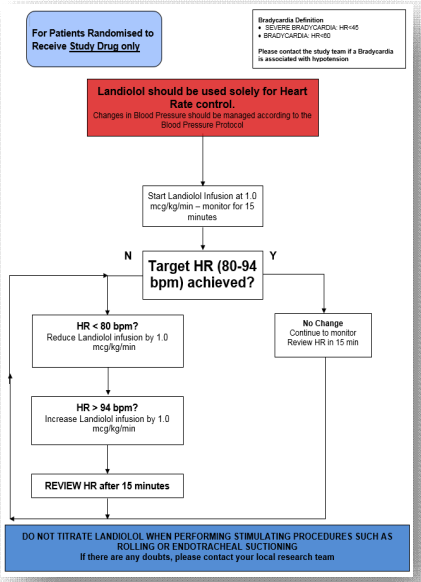
Conversion table for continuous intravenous infusion: micrograms/kg/min to ml/h (Landiolol Hydroc
mg/ml strength):

Body weight (kg)	1 mcg/kg/min	2 mcg/kg/min	3 mcg/kg/min	4 mcg/kg/min	5 mcg/kg/min	6 mcg/kg/min	7 mcg/kg/min	8 mcg/kg/min	mcg/
40	0.4	0.8	1.2	1.6	2.0	2.4	2.8	3.2	
45	0.5	0.9	1.4	1.8	2.3	2.7	3.2	3.6	
50	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	
55	0.6	1.1	1.7	2.2	2.8	3.3	3.9	4.4	
60	0.6	1.2	1.8	2.4	3.0	3.6	4.2	4.8	
65	0.7	1.3	2.0	2.6	3.3	3.9	4.6	5.2	
70	0.7	1.4	2.1	2.8	3.5	4.2	4.9	5.6	
75	0.8	1.5	2.3	3.0	3.8	4.5	5.3	6.0	
80	0.8	1.6	2.4	3.2	4.0	4.8	5.6	6.4	
85	0.9	1.7	2.6	3.4	4.3	5.1	6.0	6.8	
90	0.9	1.8	2.7	3.6	4.5	5.4	6.3	7.2	
95	1.0	1.9	2.9	3.8	4.8	5.7	6.7	7.6	
100	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	

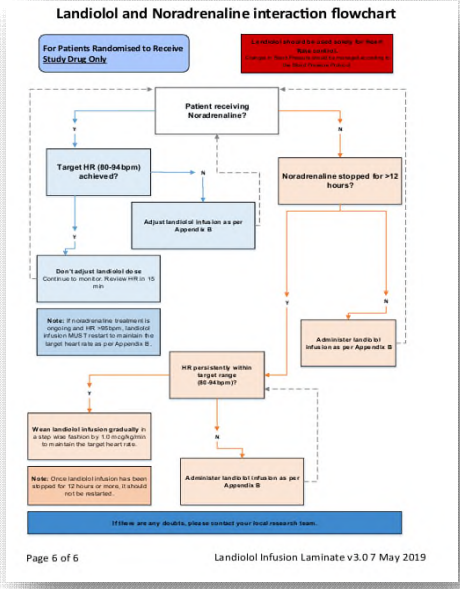
CI Certificate of Appreciation



Landiolol infusion flowchart



Landiolol and Noradrenaline interaction flowchart



ADD HOSPITAL LOGO

STRESS-L

STudy into the REversal of Septic Shock with Landiolol (Beta Blockade)

This hospital is taking part in research into Sepsis

The STRESS-L Trial is running in this unit...

What is the purpose of this trial?

The STRESS-L Trial wants to see if giving a beta-blocker (Landiolol) improves recovery and survival from septic shock.

ICU Staff and Relative posters

Whilst your relative/friend the STRESS-L Trial...

If your relative/friend is unable we may ask if you think they w with detailed information expl you to think about what you kn

If you decided that your friend/ affect the standard of care they

Further information and co

If, at any time, you would like f research team:
Tel: XXX
Email: XXX
Website: www.stress-l.org

Funded by NIHR

STRESS-L

STRESS-L: STudy into the REversal of Septic Shock with Landiolol (Beta Blockade)

STRESS-L is an open-label, multicentre randomised controlled trial comparing the use of Landiolol (beta blockade) infusion with standard care versus standard care alone in septic shock patients.

The trial aims to investigate if Landiolol improves mean organ failure scores during ICU admission.

We are looking to recruit 340 patients into the trial, and need your help to do it!

www.warwick.ac.uk/stress-l stress-l@warwick.ac.uk

Are you treating an adult with Septic Shock on ICU?
YES
Have they been receiving continuous vasopressor infusion for less than 72 hours?
YES
Have they received adequate fluid resuscitation?
YES
Are they on a noradrenaline dose ≥0.1 mcg/kg/min?
YES
Your patient could be eligible for the STRESS-L Trial.
Please call the local research team:
ADD TEL NO.

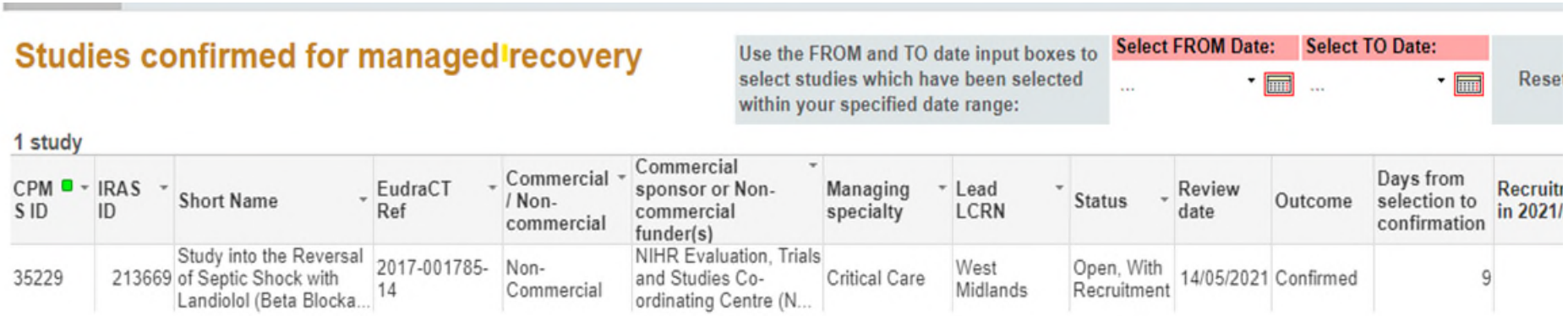
Eligibility card laminates



Landiolol & Noradrenaline flowchart

Support for sites

- *Managed Recovery Process status confirmed* – urgent and CRN support available



Studies confirmed for managed recovery

Use the FROM and TO date input boxes to select studies which have been selected within your specified date range:

Select FROM Date: ... Select TO Date: ... Rese

1 study

CPM S ID	IRAS ID	Short Name	EudraCT Ref	Commercial / Non-commercial	Commercial sponsor or Non-commercial funder(s)	Managing specialty	Lead LCRN	Status	Review date	Outcome	Days from selection to confirmation	Recruit in 2021/
35229	213669	Study into the Reversal of Septic Shock with Landiolol (Beta Blocka...	2017-001785-14	Non-Commercial	NIHR Evaluation, Trials and Studies Co-ordinating Centre (N...	Critical Care	West Midlands	Open, With Recruitment	14/05/2021	Confirmed	9	

Support for sites

- Bi-monthly CRN meetings with PI's
- 1:1 telephone/email support
  07385 029 213 stress-l@Warwick.ac.uk
- Monthly site teleconference check ins
  Next: Tuesday 13 July 15:00 – 15:30
- Associate PI scheme

NEW SITES SET UP PROCESS

Belinder Ghuman

New sites set up process

Key requirements

- ICU/HDU facilities
- Admit septic shock & tachycardic patients
- Do not routinely use beta blockers to treat septic shock
- IMP fridge storage facilities & calibrated thermometer on ICU & pharmacy
- Minimal weekend work to process blood samples.
- ICU experience & confident with routine data collection from ICU medical records.

STRESS-L



STRESS-L

CAN MY SITE TAKE PART IN STRESS-L?

A trial investigating the reversal of septic shock using beta blockade (Landiolol)

A mechanistic study with outcomes that matter to sepsis patients

Capacity	Achievable recruitment target (1 patient every 3 months). Sites can open to recruitment while monitoring capacity levels due to COVID-19.	✓
IMP administration	Bedside ICU nurses and clinicians can be locally trained on the IMP infusion protocol and are not required to have GCP training or to be listed on the delegation log.	✓
IMP storage and supplies	A fridge is required in pharmacy and on ICU to store the IMP. A general ICU fridge can be used only if the IMP is stored on a dedicated labelled shelf for IMP stock only. Sponsor is responsible for re-ordering IMP stock to reduce the burden on site staff.	✓
Data Collection	Minimal follow up data collection of survival status at Day 28 and 90 is required. Extensive data collection is only required during the first 48 hours post randomisation. All data should be available from routine medical notes.	✓
GCP training	Medically qualified physicians responsible for overseeing the clinical care of trial patients, assessing eligibility and signing IMP prescriptions are not required to have GCP training.	✓
Blood Sampling	Blood samples not required when patient stops Landiolol and noradrenaline (on average by day 3). Some weekend work will be required to process blood samples however, this will be minimal due to low patient recruitment target.	✓
Training	Full training slide sets and site file trial documentation are available on the trial website.	✓
COVID-19	Patients with COVID-19 are eligible for the trial but blood samples should **not** be taken for these patients.	✓
Co-enrolement	See the trial website for further details of all studies co-enrolling with STRESS-L (including COVID-19 trials).	✓

New sites set up process

Funding

- £800 pharmacy set up, maintenance and close down fee issued upon greenlight
- £500 per patient recruitment and follow up fee
- £7.53 per participant – drug accountability per patient
- £12.54 per participant – drug dispensing per patient

https://warwick.ac.uk/fac/sci/med/research/ctu/trials/stressl/health/sitesetup/

EXPERIENCES OF RECRUITING SITES

Royal Liverpool

Derriford

Our STRESS-L journey

Prof Dr med Ingeborg Welters

Critical Care Research Team

Royal Liverpool University Hospital

Phone: 0151 706 2410

Email: ITUresearchteam@rlbuht.nhs.uk

NHS
Liverpool University Hospitals
NHS Foundation Trust

STRESS-L





Study preparation:

- Good research infrastructure
  - 5 critical care research nurses (part-time)
  - 2-4 clinical research fellows (part-time)
  - Consultant coinvestigators
- Screening and recruitment 7 days/week
- Discussion of trial at Directorate level
- Presentation of STRESS-L trial at doctors' induction
- Teaching of bedside nursing staff
- Good relationship between research and bedside staff
- Early approach of relatives for consent

Recruitment:

- January 2019: STRESS-L opened
  - 216 patients screened
  - 6 patients recruited
    - 3 patients treated with landiolol
    - 3 patients received standard care
- June 2019: First patient recruited

- 3 Interventional patients
  - August 2019
  - January 2020
  - May 2021
- Duration of Landiolol treatment
  - 1st patient: 5 days
  - 2nd patient: 14 days
  - 3rd patient: 6 days

Breakdown of excluded patients:

- HR < 95 bpm
  - Nearly 50%
- Noradrenaline <0.1mcg/kg/min
  - About 10%
- Withdrawal of care or dying:
  - <10%
- Declined consent
  - <5%
- (Previous B-Blocker treatment)
  - About 10%
- Other:
  - About 15%

Impact of COVID-19

- Screening & Recruitment paused for all non-COVID studies
  - 17.3.2020 - 11.9.2020
  - Since 11.9.2021: COVID patients included in screening
- September 2020 – February 2021:
  - 2nd and 3rd COVID surge:
    - Only 13 patients screened
  - Majority of COVID patients not eligible:
    - No septic shock (no lactate >2.0, noradrenaline requirement too low)
- Since March 2021: 33 patients screened
- May 2021: 2 patients recruited

Experience with landiolol treatment:



What worked well:

- Randomisation early in the day
- Training of bedside nurses
- Ongoing staff support at bedside
  - Titration of landiolol
  - Evening phone calls after handover
- Visible landiolol effect
  - Within 30-45 mins
  - Good heart rate reduction
- Little variation in landiolol dose
- No difficulties in weaning of landiolol

What was challenging:

- Maintaining engagement amongst nursing and medical staff
- Lack of confidence to use unknown drug
  - Reluctance to titrate landiolol according to protocol
  - Protocol deviations especially out of hours
- Implementation of tight alarm limits
- Provision of study drug supply out of hours

A challenging patient:

- Young patient
- Complex history of haematological malignancy for over 10 years
- History of high baseline heart rate requiring treatment
- Complex drug requirements for underlying disease
- Treatment with B-blocker until 3 weeks before admission
- Admitted with neutropenic sepsis
  - ?line
  - ?pneumonia
- Randomised to landiolol

A challenging patient:



- Ca. 30 hours after starting treatment with landiolol:
  - Heart rate target never achieved despite maximum landiolol dose
  - Increasing noradenaline requirements
  - Initiation of vasopressin
- Concerns that landiolol contributes to noradrenaline/vasopressin requirements
- Discussion to stop or reduce trial drug between PI and attending consultant
- Decision to continue overnight

A challenging patient:

- Next morning:
  - Heart rate target still not achieved despite maximum dose of landiolol
  - New spikes of temperature
- Clinical impression that landiolol contributes to haemodynamic instability
- Attending consultant wishes to stop landiolol
- Discussion with CI
  - Decision lies with clinical team
  - Patient safety comes first
- Landiolol stopped late morning

A challenging patient:

- Within hours after stopping landiolol:
  - Successful weaning of vasopressin
  - Reduction of noradrenaline
- Clinical impression of new episode of sepsis/flare up of infection
- Successful haemodynamic stabilisation within hours

A challenging patient:

- Decision to restart landiolol mid-afternoon
  - Proactively supported by attending consultant
  - Reluctance to increase dose in line with protocol because if previous haemodynamic instability
  - Full protocol compliance achieved within <18h
- Successful control of heart rate achieved
  - Mid-range dose of landiolol
- No haemodynamic impact of landiolol
- Smooth weaning of landiolol
- Reported as protocol deviation

Learning points:

- Maximum landiolol dose without heart rate control
  - Think about new episode of sepsis
- Discussion with CI extremely useful
- Patient safety comes first
- Restarting landiolol was safe and successful
- Close discussion with attending consultant
- Bedside support & teaching of nursing essential
- Reassurance of bedside nurses
- Out of hours support
- Discussion with Warwick CTU how to report SAE/protocol deviation

Summary

STRESS-L

- Interventional drug trial
- Opportunity to learn about and use a novel drug
- Smooth consent process
- Effective HR reduction with landiolol achievable
- Protocolised drug administration
- Training and support of bedside nurses essential
- Close communication between research and clinical teams

STRESS-L



Q&A feedback sessions

Prof Tony Whitehouse

Emma Skilton

Belinder Ghuman

FAQs

Common eligibility queries

Eligible	Not eligible
Previous or on-going beta blocker use for pre-existing condition	Received vasopressor support for more than 72 hours to treat sepsis OR any other medical condition e.g. head injury
Treated with beta agonists	Clearly defined septic shock episode cannot be identified
Atrial Fibrillation (AF) – treat with potassium, magnesium or amiodarone (NOT another beta blocker)	Tachycardia is not sepsis driven

Remember:

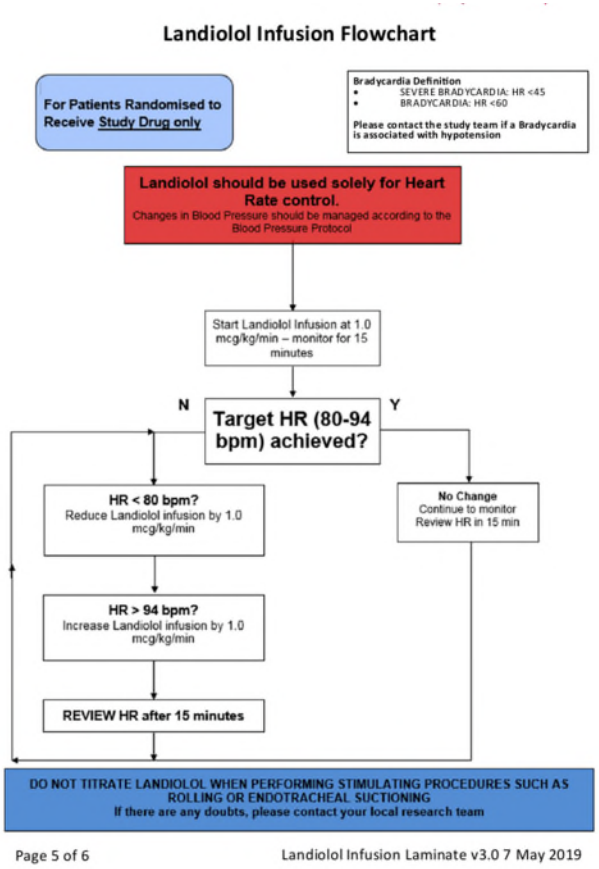
Patients should not be recruited if a **withdrawal of care** decision is in place or imminent.

If a participant has a DNAR in place because they are frail and unable to physically withstand the process of resuscitation but is otherwise being treated to prolong life, they might be eligible.

FAQs

Landiolol experience

- Very sick patient population
- 19 vials used per patient on average
- 5 patients received max dose of 40 mcg/kg/min
- Mean max dose 18mcg/kg/min

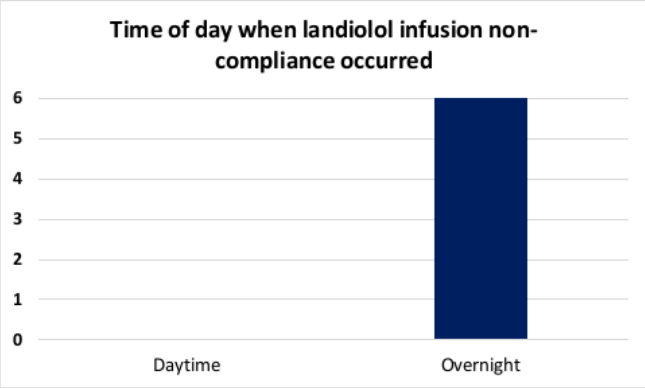


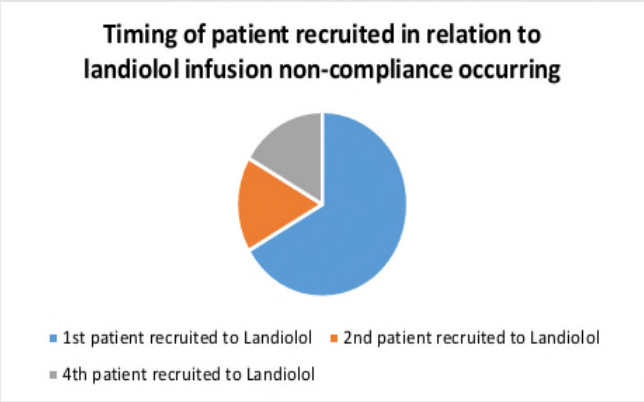
FAQs

Site experience using Landiolol

- Positive experience overall
- PI encourage to maintain equipoise
- Easy drug to titrate and similar to other ICU drugs
- Initial dead space in the drug line (20-30mins) before effects of drug are seen
- Engage with pharmacy to ensure adequate supply. Have plan for over the weekend/out of hours

Landiolol infusion protocol compliance





Suggested preventative actions

- Conduct 1:1 handovers between research nurses and ICU staff
- Ideally, research nurse stay until overnight ICU staff arrive to conduct handover
- Ring overnight staff once handover complete
- Send monthly group emails and newsletters to ICU staff
- Reminder of trial in medical handover checklist and nursing safety briefs
- Set alarms on monitors to alert ICU staff when patients heart rate is below 80 bpm
- Advert and information for STRESS-L on staff intranet page
- Display posters in ICU staff areas

STRESS-L LANDIOLOL INFUSION PROTOCOL GUIDANCE

STudy into the REversal of Septic Shock with Landiolol (Beta Blockade)

LANDIOLOL MUST ONLY BE ADMINISTERED TO STRESS-L PATIENTS

Start trial landiolol treatment at a rate of **1.0 mcg/kg/min** and monitor every **15 minutes** to maintain within the target HR range of **80 – 94 bpm**

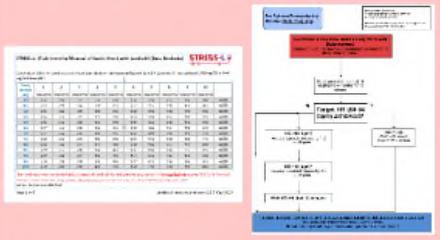
Contact your local research team for further information:
☎ _____

Heart rate = <80 bpm?	Heart rate = 80 – 94 bpm?	Heart rate = >94 bpm?
Reduce landiolol infusion by 1.0 mcg/kg/min	No change. Continue to monitor and review HR in 15 mins	Increase landiolol infusion by 1.0 mcg/kg/min

KEY GUIDANCE

- **Do not** exceed max dose – **40 mcg/kg/min**
- **Heart rate <80 bpm = reduce landiolol infusion**
- Be aware of the units. Patients will be administered landiolol in 1.0 **mcg/kg/min** increments
- Patients should only be prescribed landiolol for a maximum of **14 days**
- Once Noradrenaline has stopped for >12 hours and heart rate remains in the target heart range, landiolol should be weaned
- Once Noradrenaline has stopped for >12 hours and landiolol has stopped for >12 hours, landiolol treatment **must not recommence**
- In emergencies landiolol infusion should be adjusted immediately as appropriate in lieu of 15 minute heart rate review

See our infusion protocol and dosing chart handouts for further guidance:



www.warwick.ac.uk/stressl stress-l@warwick.ac.uk

QUESTIONS?

