Beta-blocker's Effect on Levels of Lactate (The BeLLa Study)

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Introduction

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Sepsis

- Sepsis is a **serious**, **life-threatening** condition due to a dysregulated immune response to infection

		2015	2016	2017
Total No. of Deaths		**19,862**	**20,017**	**20,905**
% of Total Deaths				
1.	**Cancer** [ICD10 : C00-C97]	29.7	29.6	29.1
2.	**Pneumonia** [ICD10 : J12-J18]	19.4	19.3	20.1
3.	**Ischaemic heart diseases** [ICD10 : I20-I25]	16.7	17.0	18.5
4.	**Cerebrovascular diseases (including stroke)** [ICD10 : I60-I69]	6.8	6.6	6.3
5.	**External causes of morbidity and mortality** [ICD10 : V01-Y89]	4.5	4.4	4.0
6.	**Hypertensive diseases (including hypertensive heart disease)** [ICD10 : I10-I15]	3.9	4.0	3.4
7.	**Nephritis, nephrotic sydrome & nephrosis** [ICD10 : N00-N07, N17-N19, N25-N27]	2.3	1.9	2.4
8.	**Urinary tract infection** [ICD10 :N39.0]	2.2	2.3	1.9
9.	**Other heart diseases** [ICD10 : I00-I09, I26-I51]	2.2	1.9	1.9
10.	**Diabetes mellitus** [ICD10 : E10-E14]	1.3	1.7	1.5
10.	**Chronic obstructive lung diseases** [ICD10 : J40-J44]	1.8	1.6	1.5

Figures from the Ministry of Health, Singapore, 2018

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Lactate in Sepsis

- A triage tool to assess severity of sepsis
- Septic shock
  - Lactate >2 mmol/L without hypovolaemia
  - Vasopressor requirement to maintain MAP >65 mmHg
- Used as resuscitative endpoint[2]
  - Lower median 6-hour lactate level and higher lactate clearance associated with better outcomes
- Guides siting of care and intensification of treatment

[1]*Shankar-Hari et al. 2016*
[2]*Ngyuen et al. 2004; Ryoo et al. 2018*

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Lactate in Sepsis

- Incumbent hypothesis: Poor tissue perfusion leads to tissue hypoxia and subsequent **anaerobic metabolism** in end organs[1]

- Multiple studies have challenged this theory
  - *Boekstegers et al. 1994*
  - *Sair et al. 2001*
  - *Levey et al. 2005*
  - *Marik et al. 2014*

[1]*Huckabee et al. 1961; Weil at al. 1970*

Lactate in Sepsis

- Incumbent hypothesis: Poor tissue perfusion leads to tissue hypoxia and subsequent anaerobic metabolism in end organs

- Alternative hypothesis: Stimulation of the **beta-2 adrenergic pathway** → higher levels of pyruvate → conversion to lactate[1]

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[1] *Revelly et al. 2005*

Lactate in Sepsis

- Incumbent hypothesis: Poor tissue perfusion leads to tissue hypoxia and subsequent anaerobic metabolism in end organs

- Alternative hypothesis: Stimulation of the beta-2 adrenergic pathway leads to higher levels of pyruvate and its subsequent conversion to lactate

- Blockade of the beta-2 adrenergic pathway → lower levels of lactate → **undertriage** of patients

Previous Literature

Long-Term β-Blocker Therapy Decreases Blood Lactate Concentration in Severely Septic Patients.

Contenti et al. *Crit Care Med* 2015; 43:2616–2622

Results
Serum lactate levels significantly **lower** in patients previously treated with beta-blockers. (3.9 +/- 2.3 mmol/L vs 5.6 +/- 3.6 mmol/L)

Previous Literature

Long-Term β-Blocker Therapy Decreases Blood Lactate Concentration in Severely Septic Patients.

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Limitations

- **Retrospective** single centre cohort study of 265 emergency department (ED) patients

- **Chart review** of archived data of patients hospitalized through ED using final coded diagnosis

Previous Literature

Long-Term β-Blocker Therapy Decreases Blood Lactate Concentration in Severely Septic Patients.

Contenti et al. *Crit Care Med* 2015; 43:2616–2622

Limitations

- Recruitment limited to patients with **severe sepsis or septic shock**

- Beta-blocker group had relatively high number of patients with **urinary tract infection**

- No information on the **use** of beta-agonist or **compliance** to beta-blockers

Hypothesis

- Beta-blockers will decrease lactate levels in septic patients by a **clinically important difference of 1.5 mmol/L or more**

  - *E.g. Patient A with lactate of 1.5 mmol/L vs Patient B with lactate of 3.0 mmol/L*

  - *E.g. Patient A with lactate of 3.0 mmol/L vs Patient B with lactate of 4.5 mmol/L*

Aims and Objectives

Primary objective:

- To evaluate the **difference in mean lactate levels** among septic ED patients on chronic beta-blocker therapy compared to those without

Secondary objectives:

- To evaluate
  1. Proportion of ICU admission
  2. Proportion of inpatient mortality in patients on chronic beta-blocker therapy compared to those without

Study Design

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Study Design

Prospective observational study

- ✓ Emergency Medicine Department at National University Hospital
- ✓ March 2017 to August 2018 (18 months)
- ✓ 24-hour recruitment
- ✓ Written informed consent

Study Design

Sample Size Calculation

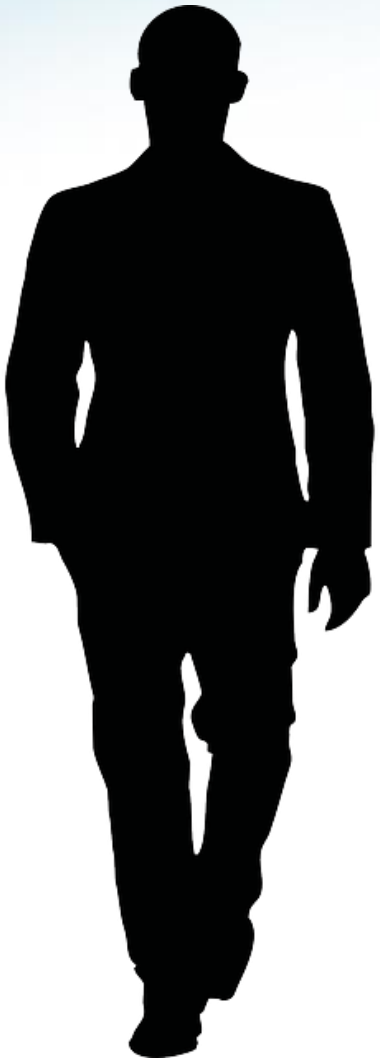
- Based on previous departmental data, prevalence of beta blocker use was estimated to be **20%**

- To look for a clinically significant difference of **1.5 mmol/L** in serum lactate measurement

- Alpha = **0.05**
- Power = **0.8**
- Standard deviation = **3.00**

- Sample size calculated as **228**

Inclusion Criteria



- ✓ 45 years of age and above **AND:**

- ✓ Temperature ≥ 37.8°C outpatient or at presentation OR localizing symptoms/signs of infection **AND**

- ✓ 1 or more components of the quick SOFA score
  - ❖ Altered mentation from baseline
  - ❖ RR ≥ 22 breaths/min
  - ❖ SBP ≤ 100mmHg

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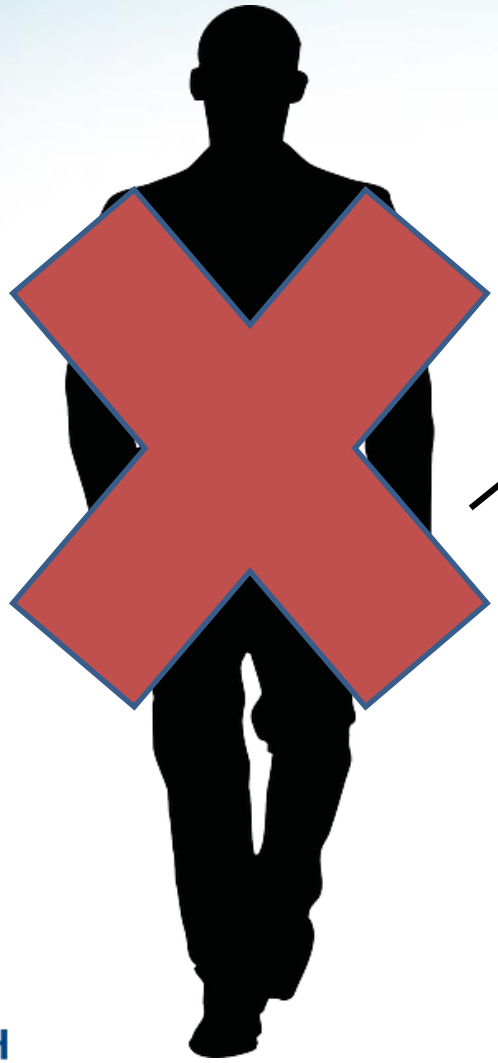
Exclusion Criteria



- × Chronic liver disease
- × Presence of scleral icterus
- × Refusal of consent
- × DNR patients
- × Patients on metformin
- × Patients who had received either long or short-acting beta-adrenergic agonist treatment prior to sampling

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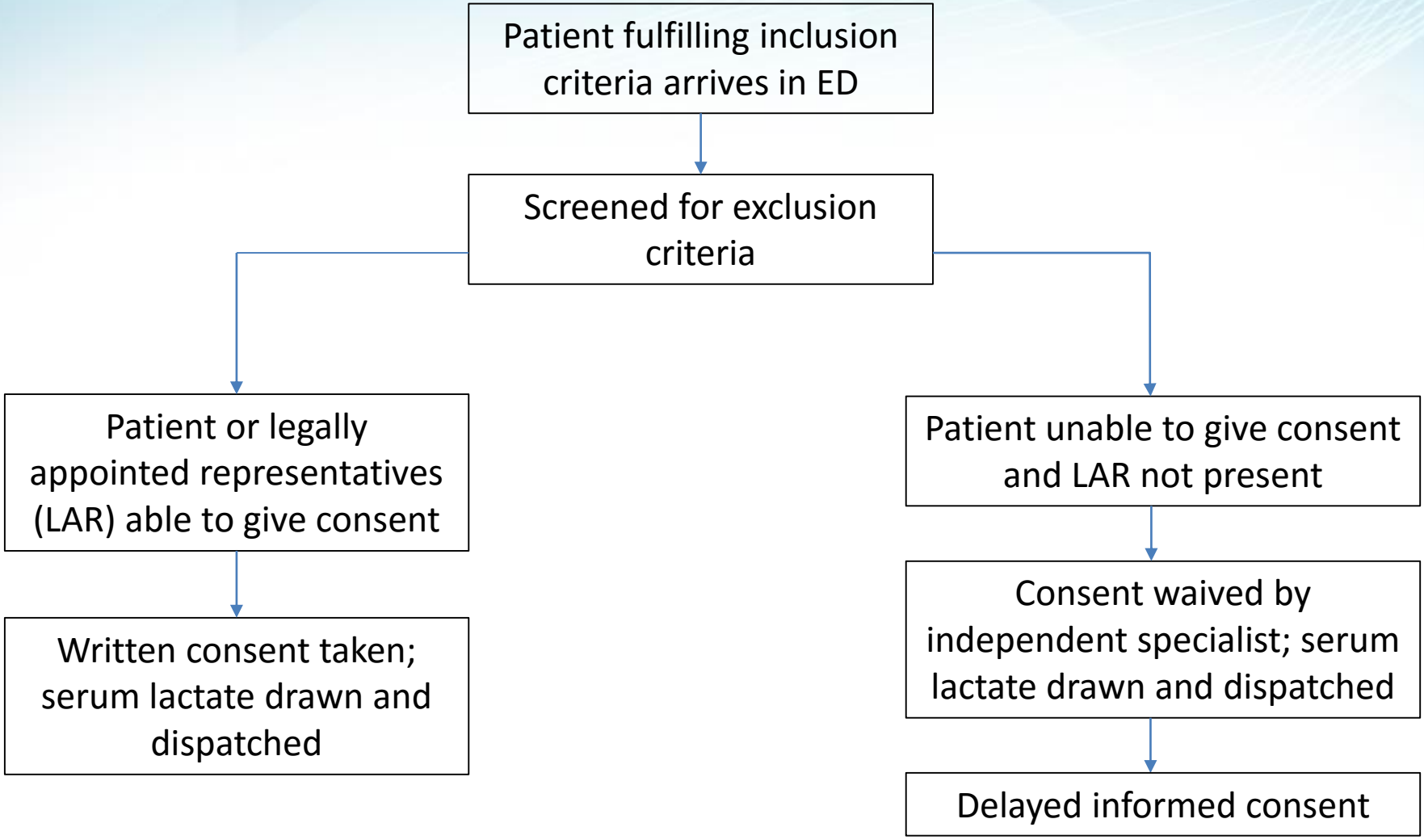
Study Protocol



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Results

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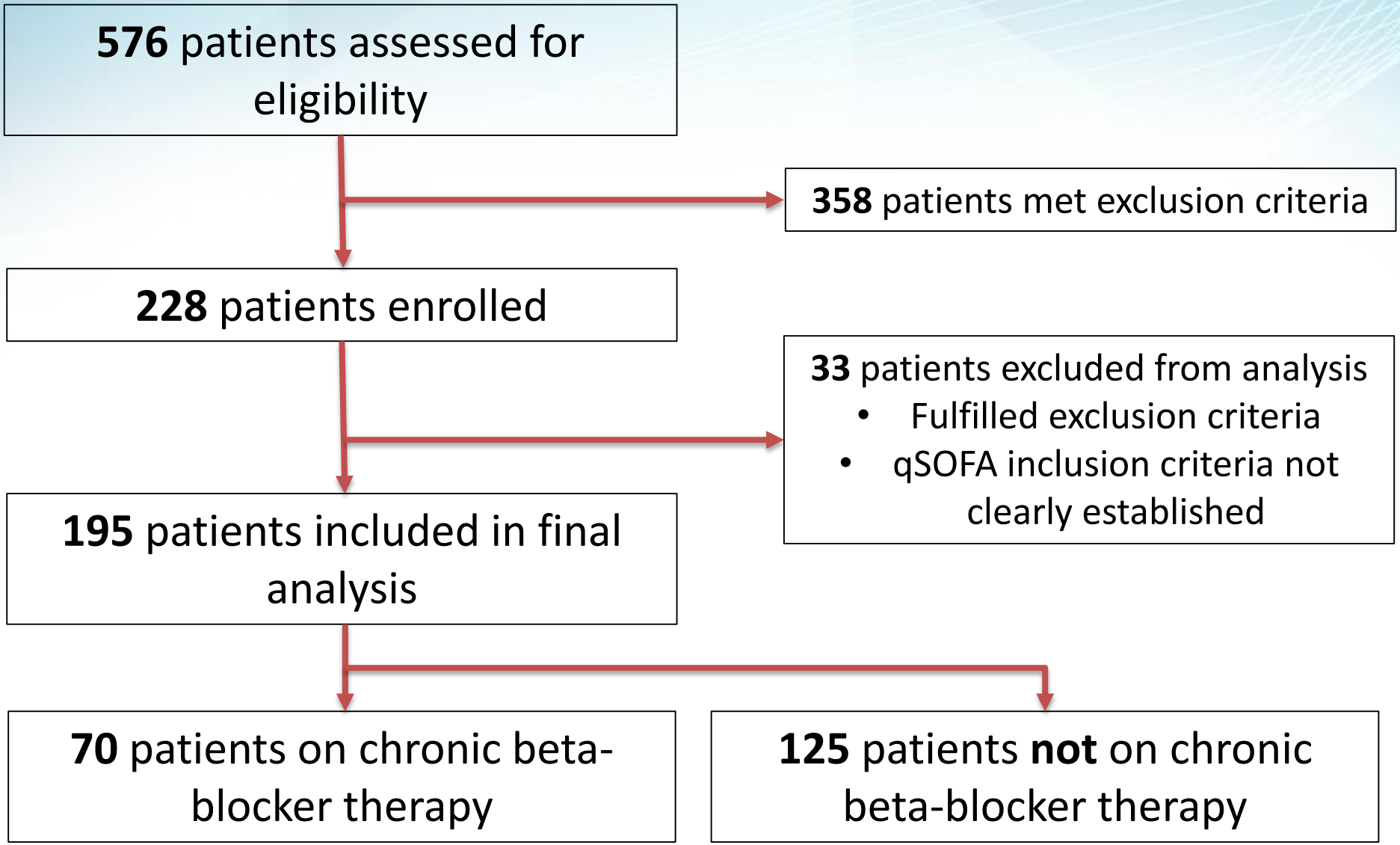
Study Recruitment



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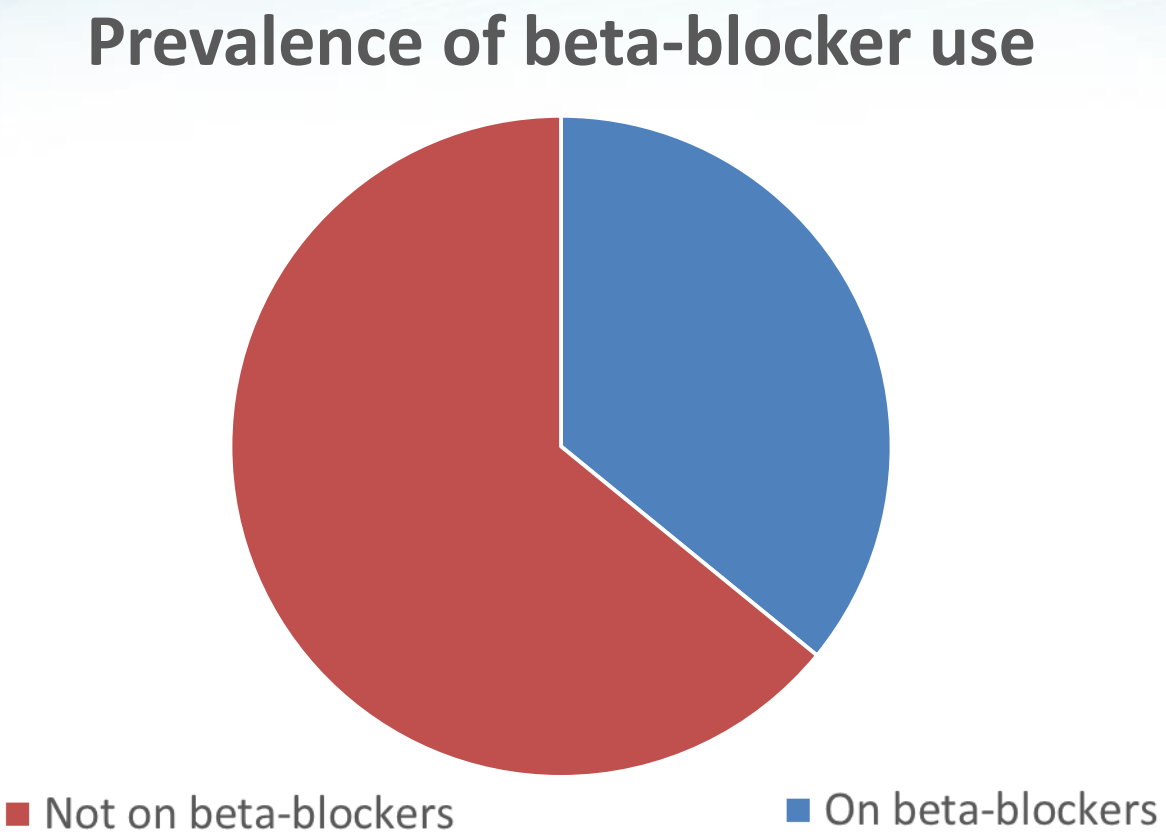
Study Recruitment



Overall, **36%** beta-blocker use within study population

Demographics

Variables	Beta-blockers (N = 70)	No beta-blockers (N = 125)	P value
Females, n (%)	33 (47.1)	55 (44.0)	0.672
Age (years), median (IQR)	77.5 (61.8 – 85.0)	70 (60.0 – 79.0)	0.038

Chi-squared test for gender; Mann-Whitney *U* test for age.

Baseline Characteristics – Vital Signs

Variables	Beta-blockers (N = 70)	No beta-blockers (N = 125)	P value*
Systolic blood pressure (mmHg)	135.0 (119.8 – 159.3)	131.0 (112.5 – 148.5)	0.201
Diastolic blood pressure (mmHg)	68.5 (61.0 – 80.0)	69.0 (62.0 – 82.0)	0.446
Mean arterial pressure (mmHg)	94.8 (80.3 – 103.3)	91.0 (80.5 – 102.0)	0.649
Heart rate (beats per minute)	91.5 (80.8 – 104.0)	108.0 (92.0 – 118.5)	<0.001
Glasgow Coma Scale	15 (14 – 15)	15 (15 – 15)	0.270
qSOFA	1 (1 – 2)	1 (1 – 1)	0.196

All variables expressed in median (IQR). *Mann-Whitney *U* test

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Baseline Characteristics – Comorbidities

Variables	Beta-blockers (N = 70)	No beta-blockers (N = 125)	P value*
Hypertension	57 (81.4)	80 (64.0)	0.011
Diabetes mellitus	31 (44.3)	26 (20.8)	0.001
Dyslipidaemia	50 (71.4)	54 (43.2)	<0.001
Ischaemic heart disease	35 (50.0)	17 (13.6)	<0.001
Renal impairment	35 (50.0)	26 (20.8)	<0.001
Malignancy	8 (11.4)	38 (30.4)	0.003

All variables expressed in n (%). *Chi-squared test

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Baseline Characteristics – Infection Type

Variables	Beta-blockers (N = 70)	No beta-blockers (N = 125)	P value*
Respiratory	37 (52.9)	67 (53.6)	0.941
Genitourinary	8 (11.4)	20 (16.0)	
Skin and soft tissue	9 (12.9)	11 (8.8)	
Gastrointestinal	3 (4.3)	6 (4.8)	
Hepatobiliary	4 (5.7)	5 (4.0)	
Undifferentiated	2 (2.9)	4 (3.2)	
Others	7 (10.0)	12 (9.6)	

All variables expressed in n (%). *Fisher's exact test

Baseline Characteristics – Infection Severity

Variables	Beta-blockers (N = 70)	No beta-blockers (N = 125)	P value*
SOFA	3 (2 – 5)	2 (1 – 3)	<0.001
MEDS	8 (5 – 9.25)	8 (6 – 9)	0.768
PIRO	12 (10 – 14)	12 (9 – 13)	0.594
Modified PIRO	12 (10 – 14)	11 (9 – 13)	0.069

All variables expressed in median (IQR). *Mann-Whitney *U* test

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Results – Primary Outcome

Variable	Beta-blockers (N = 70)	No beta-blockers (N = 125)	P value*
Serum venous lactate, mean (SD)	1.45 (1.17)	1.57 (1.45)	0.540

*Student's *t* test

Sensitivity analyses

No significant difference in mean lactate between groups after excluding the following:

- Patients who were non-compliant to beta-blocker therapy
- Patients who had missing information regarding timing and date of last dose of beta-blockers

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Results – Analysis by Sepsis Severity

	Beta-blockers		No beta-blockers		P value*
	Number of patients, n (%)	Serum venous lactate, mean (SD)	Number of patients, n (%)	Serum venous lactate, mean (SD)	
SOFA (% of cohort)					
0 to 6 (95.9)	66 (94.3)	1.68 (1.54)	121 (96.8)	1.77 (1.71)	0.478
7 to 9 (4.1)	4 (5.7)	2.22 (1.30)	4 (3.2)	2.21 (1.73)	0.995

*Student's *t* test

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Results – Analysis by Sepsis Severity

	Beta-blockers		No beta-blockers		P value*
	Number of patients, n (%)	Serum venous lactate, mean (SD)	Number of patients, n (%)	Serum venous lactate, mean (SD)	
MEDS (% of cohort)					
0 to 4 (12.3)	8 (11.4)	1.69 (1.49)	16 (12.8)	1.69 (1.40)	0.978
5 to 7 (27.2)	18 (25.7)	1.75 (1.67)	35 (28.0)	1.95 (1.74)	0.490
8 to 12 (54.3)	40 (57.1)	1.70 (1.53)	66 (52.8)	1.77 (1.76)	0.680
13 to 18 (6.2)	4 (5.7)	1.60 (1.10)	8 (6.4)	1.40 (1.67)	0.645

*Student's *t* test

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Results – Analysis by Sepsis Severity

	Beta-blockers		No beta-blockers		P value*
	Number of patients, n (%)	Serum venous lactate, mean (SD)	Number of patients, n (%)	Serum venous lactate, mean (SD)	
PIRO (% of cohort)					
0 to 9 (23.1)	12 (17.1)	1.71 (1.41)	33 (26.4)	1.58 (1.53)	0.579
10 to 14 (65.1)	53 (75.7)	1.65 (1.52)	74 (59.2)	1.74 (1.59)	0.504
15 to 19 (11.8)	5 (6.7)	2.40 (1.88)	18 (14.4)	2.46 (2.27)	0.951

Results – Secondary Outcomes

Variables	Beta-blockers (N = 70)	No beta-blockers (N = 125)	P value*
ICU admission	13 (18.6)	12 (9.6)	0.072
28-day all cause mortality	3 (4.3)	15 (12.0)	0.074

All values expressed in n (%). *Chi-squared test

Conclusion

Conclusion

- Chronic use of beta blockers **does not** significantly change levels of serum lactate in septic patients

- **No significant differences** in rates of ICU admission or 28-day mortality

Thank You

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