CRASH-19

Aspirin, losartan & simvastatin in hospitalised COVID-19 patients: a multinational randomised open-label factorial trial

TRIAL OVERVIEW

CRASH-19: AIM

- To assess the effectiveness and safety of supportive care interventions for patients hospitalised with suspected or confirmed acute COVID-19 infection with a focus on heart and lung protection

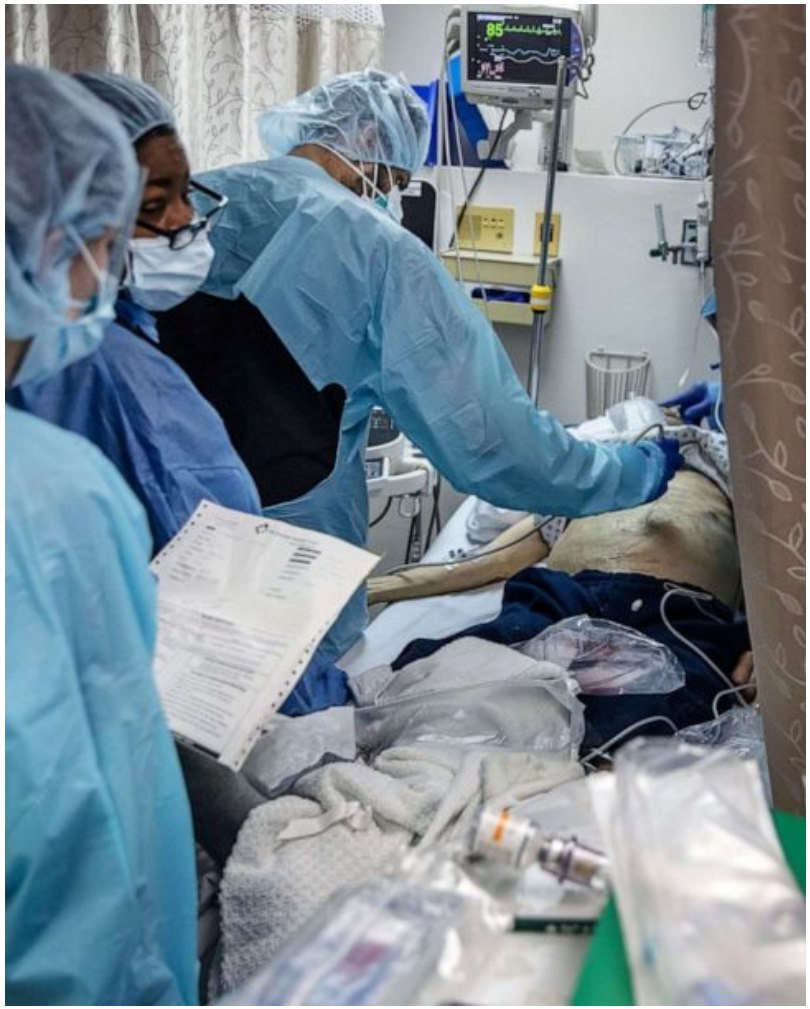
- To evaluate the effects of aspirin, losartan, and simvastatin in patients with suspected or confirmed acute COVID-19 infection compared with standard care

BACKGROUND

- SARS-CoV-2 viral (COVID-19) infection is a global public health emergency and has been classified as a pandemic by the World Health Organisation

- The outbreak is spreading rapidly and with over 4 million cases and 280,000 deaths globally as of 10th May 2020

- Effective treatments are needed urgently to reduce mortality and morbidity



BACKGROUND

- Most people with COVID-19 infection suffer only mild symptoms
- About 20% of people with COVID-19 infection will be hospitalised with more severe symptoms
- Severe symptoms may be associated with the following:
  - pneumonia which can lead to acute respiratory distress syndrome (ARDS). Respiratory failure from ARDS is the leading cause of mortality from COVID-19
  - increased myocardial injury (evidenced by elevated high-sensitivity troponin I) including myocarditis, acute myocardial infarction and exacerbation of heart failure. Patients with myocardial injury had a significantly higher in-hospital mortality rate*
  - procoagulant effects of inflammation leading to increased risk of vascular occlusive events

* Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. Published online March 25, 2020. doi:10.1001/jamacardio.2020.0950

RATIONALE FOR LOSARTAN USE IN COVID-19

- SARS-CoV-2 uses the ACE2 receptor for entry into target cells
- SARS-CoV-2 binding to ACE2 may reduce ACE2 activity, skewing the ACE/ACE2 balance to a state of heightened ACE2 activity leading to pulmonary vasoconstriction and inflammatory and oxidative organ damage, which increases the risk for acute lung injury
- Renin angiotensin system modulation by using angiotensin receptor blockers (ARBs) such as losartan may help mitigate some of the adverse effects of ACE2
- Increased levels of ACE2 may act as a competitive interceptor of SARS-CoV-2 and slow virus entry into the cells and protect from lung injury
- A retrospective study from Wuhan showed that COVID-19 patients >65 years taking ARBs were at a lower risk of developing severe lung damage than age-matched patients controls. No adverse effects were noted but concluded that more data are needed*
- By blocking the ACE2 receptor, losartan might reduce cardiovascular strain from excessive vasoconstriction in patients with COVID-19 infection

*https://www.medrxiv.org/content/10.1101/2020.03.20.20039586v1

RATIONALE FOR LOSARTAN 100mg

- Studies on optimal dose of losartan - 100 mg daily for blood pressure reduction
- Although usual starting dose for losartan is 50mg for chronic conditions e.g. hypertension, as eligible patients will already be overwhelmed by COVID-19, there is no time for titration as intervention is aimed at preventing further damage to heart and lungs
- Losartan has side effects including hyperkalaemia and hypotension
- We expect that as part of normal medical care, blood pressure and serum potassium levels will be periodically measured
- If any contraindication to losartan is present at baseline, do not randomise or if any develop after randomisation (e.g. hypotension or hyperkalaemia or hypotension) the dose can be reduced or stopped
- Treatment can be restarted when these problems are resolved

RATIONALE FOR ASPIRIN USE IN COVID-19

- Early evidence suggests that COVID-19 may predispose patients to arterial and venous thrombotic events
- Aspirin is an antiplatelet agent that reduces serious vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death)
- Aspirin may also have a role in preventing ARDS.
- Aspirin has been shown to reduced risk of ICU mortality in ARDS*

* Boyle et al. Critical Care (2015) 19:109 DOI 10.1186/s13054-015-0846-4

RATIONALE FOR ASPIRIN USE IN COVID-19

- Dose of aspirin investigated for treatment of ARDS ranged from 75 -300 mg/day
- Recommended cardioprotective dose of aspirin range between 75–160 mg/day* - largest trial (ISIS-2) used 160 mg/day
- Aspirin may increase the risk of bleeding, in light of the evidence that COVID-19 infection is highly prothrombotic we believe that the benefits of aspirin treatment should outweigh the risks
- Duration of use in the CRASH-19 trial is short – no longer than 28 days
- However, we cannot be sure of this which is why we are evaluating the effects of aspirin in this randomised trial

* Antithrombotic Trialists' Collaboration 2002. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 324: 71-86

RATIONALE FOR STATIN USE IN COVID-19

- RCTs show that statins reduce the risk of MI and stroke even among individuals with normal or low cholesterol
- Millions of people world-wide take statins and the evidence from RCTs show that benefits greatly exceed the risks
- Statins have other biological effects and may reduce the risk of ARDS - the most common cause of death in COVID-19 patients.
- The HARP-2 trial randomly allocated 540 ARDS patients to receive simvastatin (80mg) or placebo once daily for up to 28 days. There were fewer deaths in statin treated patients (22% versus 27%) although this could have been due to chance (RR=0.8, 95%CI 0.6 to 1.1)
- Secondary analyses of the HARP-2 trial data show that statins were effective in hyper-inflammatory ARDS, with significantly greater 28-day survival (p = 0.008) in simvastatin (68%) treated compared with placebo (55%) treated patients*

* Lancet Respir Med. 2018 September ; 6(9): 691–698. doi:10.1016/S2213-2600(18)30177-2

RATIONALE FOR STATIN USE IN COVID-19

- There is evidence that COVID-19 patients are likely to have this hyperinflammatory phenotype
- The drug (simvastatin) and dose (80mg daily) selection was used in the HARP-2 trial
- HARP-2 showed hepatic aminotransferase levels were higher in simvastatin treated patients (difference was not statistically significant) and the number of patients with serious adverse events or non-pulmonary organ failure was similar in treated and untreated patients
- There is sufficient evidence that assessing statin in a randomised trial is justified

Rationale for the CRASH-19 trial

- Epidemiological models show that the number of patients that will need mechanical ventilation for COVID-19 induced ARDS could greatly exceed supply.
- Optimising the effectiveness of supportive care is therefore of utmost importance and is the objective of this trial.
- Cardiac complications, in particular myocardial infarction and heart failure are common in viral pneumonia and the high troponin levels in COVID-19 non-survivors strongly suggest that cardiac events are an important cause of death.
- Acute respiratory distress syndrome (ARDS) is a clinical syndrome often seen in patients with viral pneumonia and is particularly common in severe COVID-19 infection.
- **Treatments that confer heart or lung protection have the potential to benefit COVID-19 patients**

CRASH-19: Design

Design:

- Multinational randomised open-label factorial trial
- 10, 000 patients
- Patients randomly allocated to one of eight arms

Inclusion criteria:

✓ Adults who are ≥40 years old

✓ With suspected or confirmed acute COVID-19 infection (fever and at least one symptom of respiratory disease)

✓ Requiring hospitalisation

Exclusion criteria:

× Patients already receiving, or with a definite indication or contraindication for any of the trial treatments

× Pregnant women

× Patients already on mechanical ventilation via an endotracheal tube

× Patients who are severely frail (completely dependent and approaching end of life who typically could not recover even from a mild illness) or terminally ill

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CRASH-19: RANDOMISATION

- Block randomisation will be used
- Randomisation will be to one of the following treatment arms:

- Arm 1: Aspirin 150 mg
- Arm 2: Losartan 100 mg
- Arm 3: Simvastatin 80 mg
- Arm 4: Aspirin 150 mg and Losartan 100 mg
- Arm 5: Aspirin 150 mg and Simvastatin 80 mg
- Arm 6: Losartan 100 mg and Simvastatin 80 mg
- Arm 7: Aspirin 150 mg, Losartan 100 mg and Simvastatin 80 mg
- Arm 8: Standard care control (no additional treatment)

Treatment is given once daily for up discharge death or 28 days after randomisation

CRASH-19: OUTCOMES

Primary Outcome:

- In-hospital death (cause of death will be recorded).

Secondary Outcomes:

- myocardial infarction
- cardiac failure
- severe cardiac arrythmia
- myocarditis
- respiratory failure including ARDS
- viral pneumonitis
- acute renal failure
- sepsis
- stroke
- gastrointestinal bleeding
- receipt of non-invasive ventilation or mechanical ventilation (by ET tube)
- serious adverse drug reactions
- ability to self-care at hospital discharge
- time to hospital discharge

TRIAL OVERVIEW

ASSESS ELIGIBILITY

Eligible if: Adult ≥ 40 years old, admitted to hospital with confirmed or suspected acute COVID-19 infection and doesn't fulfill exclusion criteria

COMPLETE INFORMED CONSENT PROCESS

COLLECT BASELINE DATA

RANDOMISE AND OBTAIN TREATMENT ALLOCATION

PRESCRIBE AND ADMINISTER TRIAL TREATMENT(S)

Trial treatment(s) to be administered once daily until the end of follow-up (or if the responsible clinician decides to cease treatment)

COLLECT OUTCOME DATA AT FOLLOW-UP: death, discharge or Day 28 (whichever is sooner)

CONSENT OVERIVEW

- Consent can be signed electronically and .pdf printed outside of infected zone
- Option of consent from patient if fully competent
- If not, relative if competent and available
- If no relative, a clinician not involved in the conduct of the trial

MINIMISING RISK OF COVID-19 TRANSMISSION

- Patients will be recruited and followed-up by clinicians working directly with patients with or suspected to have COVID-19
- All trial documents usually contained in the Investigator's Site File will be made available electronically on a tablet and mobile internet will provided
- Consent and all data will be collected and stored electronically on a secure google drive which named staff will access – paper copies can be printed off outside of the infected area as needed
- The tablet will remain within the infected area and will be cleaned with alcohol wipes between use
- Paper data forms can be used if needed for data collection outside of the infected area

ENTRY DATA FORM

ENTRY FORM

CRASH-19

PLEASE COMPLETE 1-30 BEFORE RANDOMISING THE PATIENT

ABOUT YOUR HOSPITAL *(please ensure all information below is contained in the medical records)*

1. Country		2. Hospital name, ID	

ABOUT THE PATIENT (circle one answer where options are given)

3. Date of admission to hospital	day	month	year	4. Sex	MALE	FEMALE
5. Age *(approximate if unknown)*	years			6. Current smoker?	YES	NO

7. COVID-19 status	SUSPECTED		CONFIRMED		NOT SUSPECTED *(do not randomise)*		
8. Difficulty breathing	YES	NO	9. Signs of hypoxia?			YES	NO
10. Breathing assisted by	NONE	OXYGEN ONLY	CPAP	BIPAP	MECHANICAL VENTILATION *(do not randomise)*		
11. Chronic respiratory disease	YES	NO	17. Liver disease			YES	NO
12. Cardiovascular disease	YES	NO	18. Cancer			YES	NO
13. Immunocompromised	YES	NO	19. Neurological disease			YES	NO
14. Body mass index >40 *(estimated)*	YES	NO	20. Current active infection			YES	NO
15. Diabetes mellitus	YES	NO	21. Other major disease			YES	NO
16. Renal failure	YES	NO	a. If Yes, describe				
22. Terminally ill / approaching end of life		YES	NO	*If YES, do not randomise*			
23. Any clinical indication for or contraindication to aspirin, losartan or statins				YES	NO	*If YES, do not randomise*	
24. Consent type	PATIENT	PERSONAL REPRESENTATIVE			PROFESSIONAL REPRESENTATIVE		
25. Blood Pressure (mmHg)	a. Systolic	b. Diastolic	26. Temperature (°C)				
27. Heart Rate (beats per minute)		28. Respiratory Rate (breaths per minute)					
29. Chest X ray / Chest CT results	NOT AVAILABLE	NORMAL	PNEUMONIA	OTHER			

30. Eligible? *(age ≥ 40, confirmed/suspected acute COVID-19, not pregnant, no contraindication to trial drugs, not on mechanical ventilation and not terminally ill / approaching end of life)*	YES	NO	*If YES, go online and upload baseline data to randomise*					
31. Insert RANDOMISATION number						*Record from randomisation screen. Write number in medical records. Prescribe and give intervention(s) immediately after randomisation.*		
32. Intervention(s) to be given *(for site use only)*	ASPIRIN	LOSARTAN	SIMVASTATIN	ASPIRIN + LOSARTAN	ASPIRIN + SIMVASTATIN	LOSARTAN + SIMVASTATIN	ASPIRIN + LOSARTAN + SIMVASTATIN	STANDARD CARE ONLY
33. Date of randomisation	day	month	year	34. Time of randomisation (24-hour clock)		hours	minutes	
35. Name of person randomising	first/last name			36. Signature				

SITE ADMIN - NON TRIAL DATA - USED ONLY FOR IDENTIFYING PATIENT FOR HOSPITAL FOLLOW UP ONLY

37. PATIENT DETAILS	a) Patient name	first/last name	c) Hospital ID number	
	b) Date of birth	day / month / year	d) Ward admitted to	

CRASH-19 – Entry form Version 1.0 [15 April 2020]

- Single sided entry form completed as soon as possible after admission
- Consider who will be responsible for this?
- Online randomisation
- All data to be entered directly online
- Tablet and internet connection will be provided
- Randomisation number MUST be recorded on patient medical records to allow for follow-up
- Trial drugs will be free to patients
- Ensure treatment is prescribed and given for hospital duration or up to 28 days
- Consider how drugs will be stored and administration recorded

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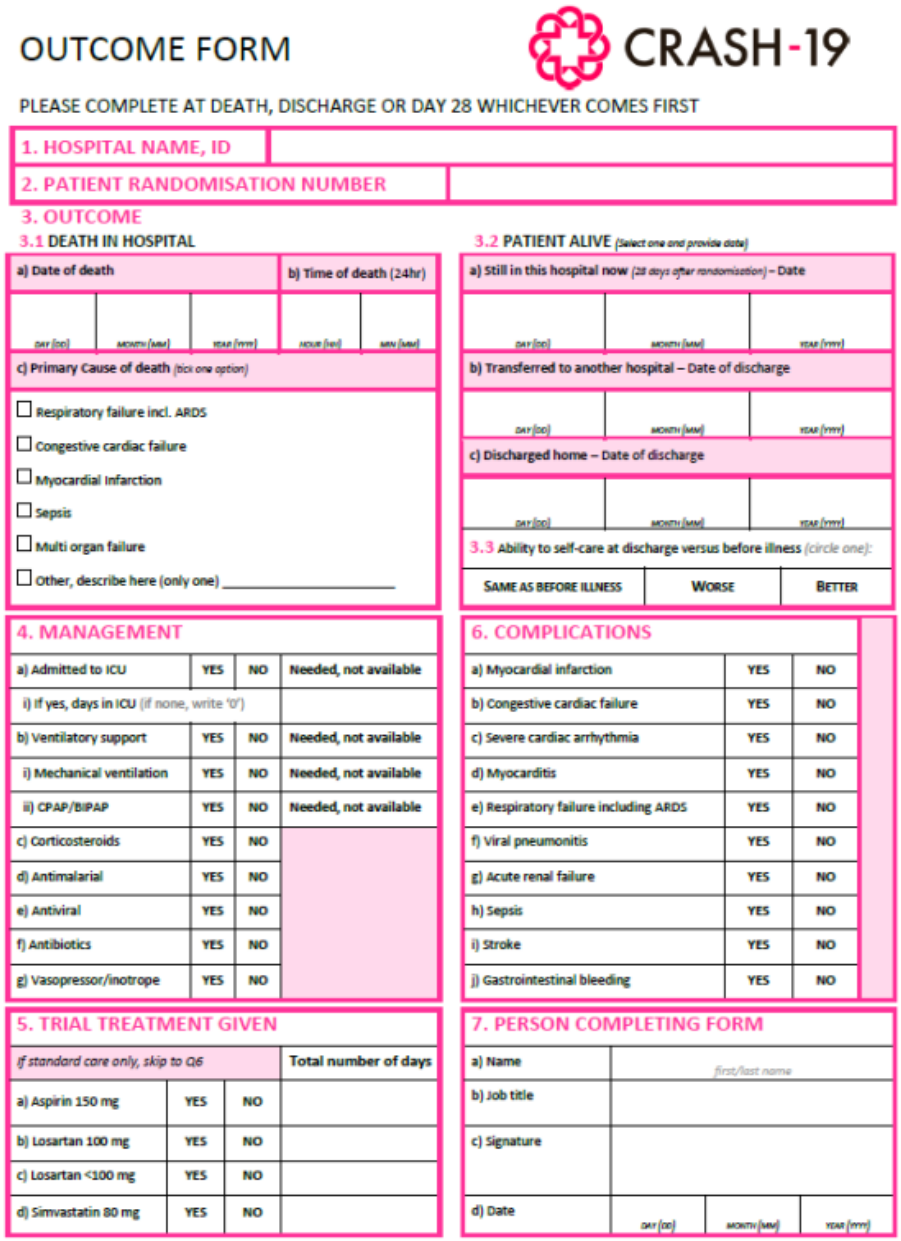
OUTCOME DATA FORM



OUTCOME FORM

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PLEASE COMPLETE AT DEATH, DISCHARGE OR DAY 28 WHICHEVER COMES FIRST

1. HOSPITAL NAME, ID

2. PATIENT RANDOMISATION NUMBER

3. OUTCOME

3.1 DEATH IN HOSPITAL

a) Date of death (DAY [DD] / MONTH [MM] / YEAR [YYYY])

b) Time of death (24hr) (HOUR [HH] / MIN [MM])

c) Primary Cause of death (tick one option)

- ☐ Respiratory failure incl. ARDS
- ☐ Congestive cardiac failure
- ☐ Myocardial infarction
- ☐ Sepsis
- ☐ Multi organ failure
- ☐ Other, describe here (only one) _____

3.2 PATIENT ALIVE (Select one and provide date)

a) Still in this hospital now (28 days after randomisation) – Date (DAY [DD] / MONTH [MM] / YEAR [YYYY])

b) Transferred to another hospital – Date of discharge (DAY [DD] / MONTH [MM] / YEAR [YYYY])

c) Discharged home – Date of discharge (DAY [DD] / MONTH [MM] / YEAR [YYYY])

3.3 Ability to self-care at discharge versus before illness (circle one):

SAME AS BEFORE ILLNESS	WORSE	BETTER

4. MANAGEMENT

a) Admitted to ICU	YES	NO	Needed, not available
i) If yes, days in ICU (if none, write '0')			
b) Ventilatory support	YES	NO	Needed, not available
i) Mechanical ventilation	YES	NO	Needed, not available
ii) CPAP/BIPAP	YES	NO	Needed, not available
c) Corticosteroids	YES	NO	
d) Antimalarial	YES	NO	
e) Antiviral	YES	NO	
f) Antibiotics	YES	NO	
g) Vasopressor/inotrope	YES	NO	

6. COMPLICATIONS

a) Myocardial infarction	YES	NO
b) Congestive cardiac failure	YES	NO
c) Severe cardiac arrhythmia	YES	NO
d) Myocarditis	YES	NO
e) Respiratory failure including ARDS	YES	NO
f) Viral pneumonitis	YES	NO
g) Acute renal failure	YES	NO
h) Sepsis	YES	NO
i) Stroke	YES	NO
j) Gastrointestinal bleeding	YES	NO

5. TRIAL TREATMENT GIVEN

If standard care only, skip to Q6			Total number of days
a) Aspirin 150 mg	YES	NO	
b) Losartan 100 mg	YES	NO	
c) Losartan <100 mg	YES	NO	
d) Simvastatin 80 mg	YES	NO	

7. PERSON COMPLETING FORM

a) Name	first/last name		
b) Job title			
c) Signature			
d) Date	DAY [DD]	MONTH [MM]	YEAR [YYYY]

CRASH-19 - Outcome Form Version 1.0 [15 April 2020]

- Single sided outcome form to be completed at death, discharge or Day 28 (whichever is sooner)
- Complete from medical records (so all information on the form has to be recorded there)
- All data to be entered directly online
- Consider how you will be able to follow-up patients as they move through the hospital
- There is no identifiable information on the data forms, how will you know which patient is which?
- Who will be responsible for follow-up?

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SAFETY

- If the clinician is concerned that any of the trial treatments are impacting the safety of the patient in anyway, the trial treatment should simply be stopped and the patient treated in line with local procedure (for hypotension from losartan see Protocol as dose variation is allowed)
- Serious adverse events believed to be related to a trial drug (which are not collected as an outcome) should be reported using the trial database within 24 hours of becoming aware of the event

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

CLINICAL TRIALS UNIT

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Clinical Trials Unit
London School of Hygiene & Tropical Medicine,
Keppel Street
London, WC1E 7HT, UK

Email: crash19@Lshtm.ac.uk
Phone: +44 (0)20 7299 4684

https://crash19.lshtm.ac.uk