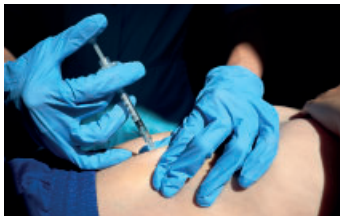
research

Mortality in patients with ACS receiving high flow oxygen p 353



Prophylactic anticoagulation and mortality for inpatients with covid-19 p 354

Diagnostic accuracy of SARS-CoV-2 lateral flow immunoassays p356

ORIGINAL RESEARCH Pragmatic, cluster randomised, crossover trial

High flow oxygen and risk of mortality in patients with a suspected acute coronary syndrome

Stewart RAH, Jones P, Dicker B, et al

Cite this as: *BMJ* 2021;372:n355

Find this at: http://dx.doi.org/10.1136/bmj.n355

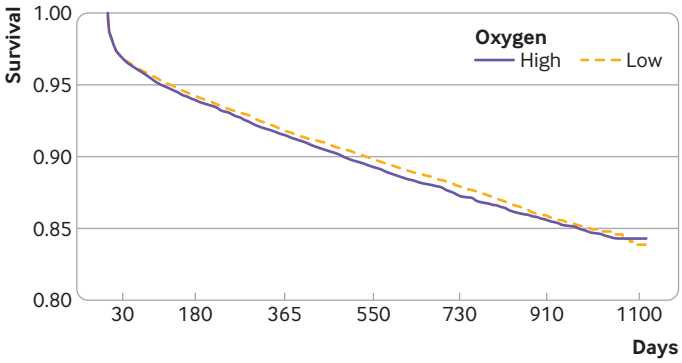
Study question What is the association between high flow supplementary oxygen and 30 day mortality in patients presenting with a suspected acute coronary syndrome?

Methods A pragmatic, cluster randomised, crossover trial evaluated two oxygen protocols used as part of routine care in patients presenting with a suspected acute coronary syndrome to ambulances and hospitals throughout New Zealand. The high oxygen protocol recommended oxygen at 6-8 L/min by face mask for ischaemic symptoms or electrocardiographic changes, irrespective of the oxygen saturation level. The low oxygen protocol recommended oxygen only if the oxygen saturation was less than 90%, with a target saturation of less than 95%. 30 day mortality was determined from adminstrative data for the two protocols in 40 872 patients over two years: 20 304 patients were managed using the high oxygen protocol and 20 568 were managed using the low oxygen protocol. Results were also evaluated for patients with a final diagnosis of ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (non-STEMI).

Study answer and limitations For patients with suspected acute coronary syndrome, 30 day mortality for the high and low oxygen groups was 3.0% (n=613) and 3.1% (n=642), respectively (odds ratio 0.97, 95% confidence interval 0.86 to 1.08). For patients with STEMI, 30 day mortality for the high and low oxygen groups was 8.8% (n=178) and 10.6% (n=225), respectively (0.81, 0.66 to 1.00), and for patients with non-STEMI was 3.6% (n=187) and 3.5% (n=176), respectively (1.05, 0.85 to 1.29). The study could not exclude the possibility of a small mortality benefit from supplementary oxygen in selected circumstances, such as for patients with STEMI and hypoxaemia.

What this study adds In most patients with a suspected acute coronary syndrome and ischaemic symptoms, supplementary high flow oxygen was found to be neither beneficial nor harmful.

Funding, competing interests, and data sharing This study was supported by the National Heart Foundation of New Zealand and Health Research Council of New Zealand (fellowships to RAHS and MT). No competing interests. Requests for study data can be made to the corresponding author (rstewart@adhb.govt.nz).



No at risk

High	19 698	19 076	18 577	13 951	10 084	6368	574
Low	19 929	19 374	18 880	15 378	9700	4766	463

Kaplan-Meier plot showing all cause mortality for patients with suspected acute coronary syndrome managed on high and low oxygen protocols

Prophylactic anticoagulation for inpatients with covid-19

ORIGINAL RESEARCH Cohort study

Early initiation of prophylactic anticoagulation for prevention of covid-19 mortality in patients admitted to hospital in the US

Rentsch CT, Beckman JA, Tomlinson L, et al

Cite this as: *BMJ* 2021;372:n311
Find this at: http://dx.doi.org/10.1136/bmj.n311

Study question Is early initiation of prophylactic anticoagulation compared with no anticoagulation associated with decreased risk of death in patients admitted to hospital with covid-19?

Methods This study estimated the effect of prophylactic anticoagulation compared with no anticoagulation in patients admitted to hospital in the United States Department of Veterans Affairs between 1 March and 31 July 2020 with laboratory confirmed covid-19 and without contraindication to prophylactic anticoagulation. The risk of death within 30 days of hospital admission was compared between those who did and those who did not receive prophylactic anticoagulation within 24 hours of hospital admission, accounting for a large number of personal and clinical characteristics.

Study answer and limitations 3627 of 4297 (84.4%) patients admitted to hospital with covid-19 received prophylactic anticoagulation within 24 hours of admission. 622 deaths occurred within 30 days of hospital admission; 513 among those who received prophylactic anticoagulation. The cumulative incidence of mortality at 30 days was 14.3% among those who received prophylactic anticoagulation and 18.7% among those who did not, resulting in a 27% decreased risk for 30 day mortality (hazard ratio 0.73, 95% confidence interval 0.66 to 0.81). Similar associations were found for inpatient mortality and initiation of therapeutic anticoagulation. Receipt of prophylactic anticoagulation was not associated with increased risk of bleeding that required transfusion (hazard ratio 0.87, 0.71 to 1.05). Owing to the observational nature of the study, a degree of uncertainty persists that can only be addressed through randomised trials.

What this study adds Early initiation of prophylactic anticoagulation compared with no anticoagulation among patients admitted to hospital with covid-19 was associated with a decreased risk of 30 day mortality and no increased risk of serious bleeding events.

COMMENTARY Risk-benefit balance may depend on illness severity

Most people with covid-19 have mild disease, but after 5-10 days an important minority develop pneumonia and require hospital admission to treat hypoxia. This group is in a marked prothrombotic state and has high rates of hospital associated venous thromboembolism.[1]

Early in the pandemic, deep vein thromboses and high rates of occlusive changes on computed tomography pulmonary angiograms were seen in at least 70% of patients with severe covid-19. Although these were initially thought to be pulmonary emboli, many patients had only isolated segmental and subsegmental changes, probably caused by the in situ thrombosis (termed immunothrombosis) that occurs in all forms of acute respiratory distress syndrome,[2 3] although more commonly with covid-19.[4 5]

Randomised controlled trials show that drug based thromboprophylaxis with low molecular weight heparin (LMWH) reduces the risk of hospital associated venous thromboembolism by about 50% in medical and critically ill inpatients.[6]

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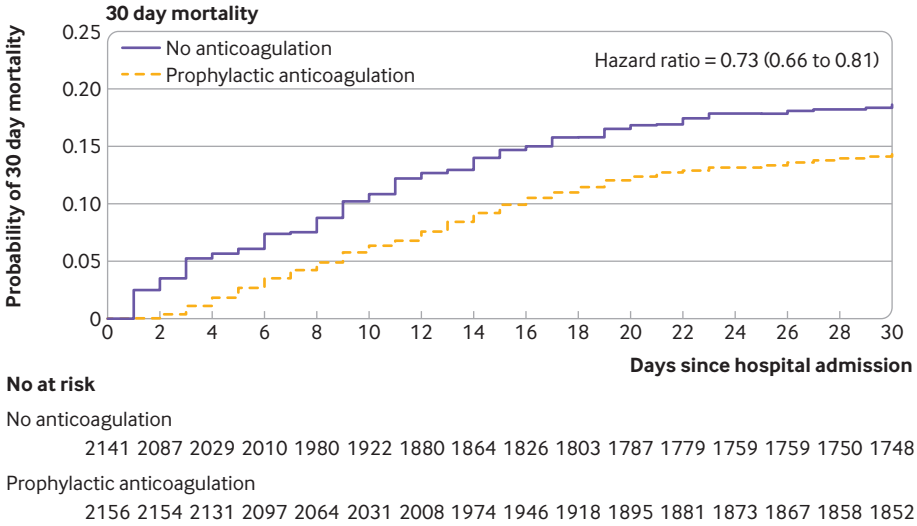
Risk factors that qualify patients for thromboprophylaxis are reduced mobility; acute infective illness, such as pneumonia; and admission for critical care. Thus, adults admitted to hospital with covid-19 pneumonia should automatically receive thromboprophylaxis.

Good data to guide thromboprophylaxis with LMWH in patients admitted with covid-19 is urgently needed, however,



Inverse probability treatment weighted Kaplan-Meier plots. Numbers at risk were calculated by multiplying weights by constant factor k, where k was the ratio of observed sample size to number in the pseudopopulation after inverse probability treatment weighting; in this study, k=4297/8576

Funding, competing interests, and data sharing
This work was supported by the National Institute on Alcohol Abuse and Alcoholism and Department of Veterans Affairs (VA) Health Services Research & Development and Office of Research and Development. No competing interests or relationships outside the submitted work are reported. Owing to VA regulations and ethics agreements, the analytic datasets used for this study are not permitted to leave the VA firewall without a data use agreement. For more information visit https://www.virec.research.va.gov or contact VIReC@va.gov.

and the retrospective study by Rentsch and colleagues in this issue confirms that thromboprophylaxis is associated with improved mortality in these patients.[12]

At the same time, an interim analysis of combined data from three separate randomised controlled trials—the anticoagulation arm of the platform trial REMAP-CAP, ATTACC, and ACTIV4a—recently reported the impact of different doses of anticoagulation on outcomes. The trials used similar protocols, run in parallel. According to details provided by press release and on Twitter, the trio compared prophylactic heparin at therapeutic doses (either LMWH or unfractionated heparin) with local standard care in patients admitted to hospital with severe or moderate covid-19. In all three trials, heparin was given for 14 days or until hospital discharge (or after stopping supplemental oxygen in ATTACC), whichever was sooner.[13] The primary outcome was a combination of mortality and the number of days free from organ support in critical care at day 21.

In December, the joint data safety monitoring board paused the trials for participants with severe covid-19 because those receiving therapeutic doses of heparin showed increased mortality relative to controls and greater requirement for oxygen support (odds ratio for survival or decreased need for organ support 0.76 (95% confidence interval 0.6 to 0.97). Risk of major bleeding was also increased, from 1.8% in controls receiving standard care to 3.7% in those receiving anticoagulation.

Further research should consider whether benefit from therapeutic dose heparin is confined to patients with moderate covid-19

In contrast, on 21 January, the arms recruiting patients with moderate disease were also paused, but this time owing to an apparent superiority of anticoagulation at therapeutic doses. The results were analysed according to whether D dimer levels were low or high at presentation, but results were similar, suggesting that baseline D dimer tests are of no value in assessing thrombotic risk in patients admitted to hospital with covid-19 pneumonia. Those participants with moderate disease receiving prophylactic anticoagulation at therapeutic doses were significantly more likely than controls to achieve the primary outcome of survival or reduced requirement for organ support (low D dimer levels: median odds ratio 1.57 (95% confidence interval 1.14 to 2.19); high D dimer levels 1.53 (1.09 to 2.17)).

Among patients who were moderately ill at baseline, major bleeding was seen in 0.9% of controls receiving standard care and 1.6% of those receiving anticoagulation at therapeutic doses.

If the findings are confirmed, further research should consider whether benefit from therapeutic dose LMWH or unfractionated heparin is confined to patients with moderate covid-19; whether the apparent benefit of heparins could be related to their anti-inflammatory and antiviral effects, not just to their anticoagulant effect[14]; whether heparin influences rates of immunothrombosis; and finally, the relative effects of standard versus intermediate thromboprophylaxis in severe covid-19, and intermediate versus therapeutic thromboprophylaxis in moderate covid-19.

The risk of hospital associated venous thromboembolism for medical inpatients is greatest in the first 90 days post-discharge,[9] and many units are using unlicensed extended thromboprophylaxis with LMWH or direct acting oral anticoagulants for patients discharged after covid-19.[8 9] Recent retrospective data showing low rates of hospital associated venous thromboembolism post-discharge are reassuring,[15-17] but randomised trials formally evaluating the need for extended thromboprophylaxis are now required.

Cite this as: *BMJ* 2021;372:n487
Find the full version with references at http://dx.doi.org/10.1136/bmj.n487

SARS-CoV-2 lateral flow assays for possible use in national covid-19 seroprevalence surveys (React 2)

Moshe M, Daunt A, Flower B, et al

Cite this as: *BMJ* 2021;372:n423
Find this at: http://dx.doi.org/10.1136/bmj.n423

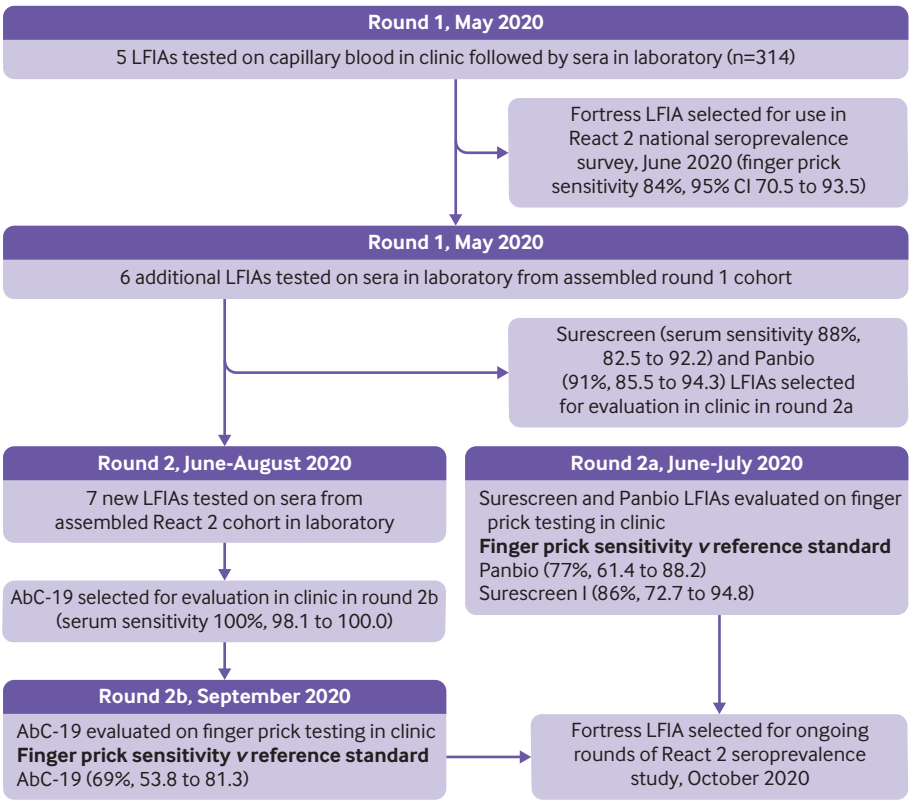
Study question How well do newly developed lateral flow immunoassays (LFIAs) perform in detecting previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and is the performance suitable for use in large scale seroprevalence studies such as the React 2 (real time assessment of community transmission 2) programme in the United Kingdom?

Methods Laboratory sensitivity and specificity analyses were performed for seven LFIAs on a minimum of 200 serum samples from participants with confirmed SARS-CoV-2 infection and 500 prepandemic serum samples. Three LFIAs with laboratory sensitivity superior to the finger prick sensitivity of the LFIA currently used in React 2 were further evaluated through finger prick testing on participants with confirmed previous SARS-CoV-2 infection. Two LFIAs (Surescreen, Panbio) were evaluated in clinics in June-July 2020, and a third LFIA (AbC-19) in September 2020. A spike protein enzyme linked immunoassay and a hybrid double antigen binding assay were used as laboratory reference standards to detect SARS-CoV-2 antibodies.

Study answer and limitations The sensitivity and specificity of seven new LFIAs that were analysed using sera varied from 69% to 100%, and from 98.6% to 100%, respectively (compared with the two reference standards). Sensitivity on finger prick testing was 77% (95% confidence interval 61.4% to 88.2%) for Panbio, 86% (72.7% to 94.8%) for Surescreen, and 69% (53.8% to 81.3%) for AbC-19 compared with the reference standards. Sensitivity for sera from matched clinical samples performed on AbC-19 was significantly higher with serum than with finger prick testing at 92% (80.0% to 97.7%, P=0.01). Because the incidence of new SARS-CoV-2 infections was low when new LFIAs became available for evaluation (June-July and September 2020), most serum samples were from participants infected during the first wave of the pandemic (March-April 2020).

What this study adds One new LFIA was identified with clinical performance suitable for potential inclusion in seroprevalence studies. However, none of the LFIAs tested had clearly superior performance to the LFIA currently used in React 2 seroprevalence surveys, and none showed sufficient sensitivity and specificity to be considered for routine clinical use.

Funding, competing interests, and data sharing
Supported by the Department of Health and Social Care, the National Institute for Health Research Biomedical Research Centre of Imperial College NHS Trust, and Francis Crick Institute. PC, MM, and RT hold intellectual property rights on the hybrid double antigen binding assay. Full details on bmj.com. Data available on request.



Timeline and selection process for lateral flow immunoassay (LFIA) evaluation. React 2=real time assessment of community transmission 2