COVID-19 and the cardiovascular system

COVID-19 primarily causes lung injury, but the disease also affects the cardiovascular system in a number of ways. First, in many countries, cardiovascular care pathways have been disrupted by the pandemic. Second, individuals with cardiovascular disease are at increased risk of hospitalization with, and death from COVID-19. Last, COVID-19 causes a range of immediate cardiovascular complications, principally thrombo-embolic events (both venous and arterial), myocardial injury, and cardiac arrhythmias. Whether COVID-19 leads to specific long-term cardiovascular sequelae remains unclear.

Generalized hyper-inflammation and multi-organ damage are the hallmark of severe COVID-19, promoted by immune cell activation and release of pro-inflammatory cytokines [such as interleukin (IL)-1, IL-6, and tumour necrosis factor-alpha], as well as D-dimers, ferritin, and C-reactive protein. The ensuing coagulopathy, Neutrophil-Extracellular-Traps (NET)osis, and platelet activation, lead to widespread vascular inflammation and dysfunction across multiple beds. Moreover, SARS-CoV-2 can directly infect endothelial cells through the ACE2 receptor, causing vascular damage and apoptosis. Indeed, localized immunothrombosis and microangiopathy are a ubiquitous finding in pulmonary COVID-19 autopsies and underlie the typical pattern of diffuse alveolar damage and hypoxia, but also the cardiac, cerebral, renal, and hepatic damage seen in severe presentations.

The power of large simple trials

At the beginning of the COVID-19 pandemic, mortality was high (25–30% among hospitalized patients in the UK) and there were no proven treatments. Several therapies were adopted based on non-randomized studies or small trials. It was unlikely that any one therapy would provide large benefits, but moderate reductions in important outcomes, such as mortality, would be worthwhile. To detect such effects, and reliably assess possible harms, large-scale randomization was needed.

Inspired by the International Study of Infarct Survival (ISIS) trials—which assessed the effects of nine different treatments on mortality in acute myocardial infarction, and together randomized over 130 000 patients in the 1980s in a series of factorial trials—RECOVERY aimed to assess the effects of several potential treatments on all-cause mortality among hospitalized COVID-19 patients. Akin to the ISIS studies, trial procedures were simple so that randomization could be integrated into routine care, with minimal additional work for front-line staff. It took 9 days from final protocol to first patient recruited, with over 11 000 participants enrolled in the first 100 days. The trial now spans all acute hospital centres in the UK and has expanded internationally.

RECOVERY trial design

RECOVERY used a combination of parallel-arm, factorial, and sequential randomizations to assess several potential therapeutic areas: (i) antiviral (hydroxychloroquine, lopinavir-ritonavir, convalescent plasma, and monoclonal anti-SARS-CoV-2 antibodies), (ii) immunomodulatory (dexamethasone, tocilizumab, azithromycin, colchicine, and baricitinib), and (iii) antithrombotic (aspirin). Participants received either the allocated study treatment plus standard-of-care or the standard-of-care alone (in an open-label design).

Patients of any age hospitalized with proven or suspected COVID-19 are potentially eligible. The primary outcome is 28-day all-cause mortality; secondary outcomes are successful discharge, and use of invasive ventilation or death (among patients not on invasive ventilation at randomization). Follow-up data on cardiac arrhythmias were collected from May 2020 onwards and on thrombo-embolic and bleeding events from November 2020. Other interventions and assessments are underway in an embedded phase-II part of the study, among children, and across international sites.

RECOVERY key findings

By June 2021, RECOVERY has recruited over 40 000 participants (about 10% of all hospitalized patients in the UK)—Table 1. The mean age is ~65 years, and about a third are women. Diabetes, cardiac disease, and chronic lung disease are present in about a quarter, and between 3% and 8% have severe kidney disease.

In June 2020, RECOVERY showed that dexamethasone (a cheap, widely available corticosteroid) reduced mortality by 15%, with...
## Table 1  Summary of selected baseline characteristics and outcomes of completed treatment comparisons in the RECOVERY trial

| Comparison: n participants including the control arm (date enrolment closed) | Selected baseline characteristics | Primary and secondary outcomes: proportion in active vs. control (rate or risk ratio, 95% confidence interval) | Selected subsidiary and exploratory outcomes: proportion in active vs. control (rate or risk ratio, 95% confidence interval) |
|---|---|---|---|
| | Age (years) | Invasive ventilation (%) | Diabetes (%) | Chronic lung disease (%) | Heart disease (%) | Severe renal impairment (%) | Mortality at 28 days | Discharged alive within 28 days | Invasive ventilation or deathb | Use of renal replacement therapyc | Cardiac arrhythmias | Thromboembolic events | Bleeding events |
| Hydroxychloroquine: 4716a (5 June 2020) | 65.4 | 17 | 27 | 22 | 26 | 8 | 2.7% vs. 2.5% (1.09, 0.97–1.23) | 60% vs. 63% (0.90, 0.83–0.98) | 31% vs. 27% (1.14, 1.03–1.27) | 7.9% vs. 7.9% (1.00, 0.81–1.23) | 8.2% vs. 6.3% | NA | NA |
| Dexamethasone: 6425a (8 June 2020) | 66.1 | 16 | 24 | 21 | 27 | 8 | 2.3% vs. 2.6% (0.83, 0.75–0.93) | 67% vs. 64% (1.10, 1.03–1.17) | 26% vs. 28% (0.93, 0.85–1.01) | 4.4% vs. 7.5% (0.61, 0.48–0.76) | 5.3% vs. 6.3% | NA | NA |
| Lopinavir-ritonavir: 5040a (29 June 2020) | 66.2 | 4 | 28 | 24 | 26 | 8 | 2.3% vs. 2.2% (1.03, 0.91–1.17) | 69% vs. 70% (0.98, 0.91–1.05) | 29% vs. 27% (1.09, 0.99–1.20) | 4.2% vs. 4.2% (0.99, 0.75–1.32) | 4.1% vs. 4.6% | NA | NA |
| Azithromycin: 7763a (27 November 2020) | 65.3 | 6 | 28 | 25 | 27 | 6 | 2.2% vs. 2.2% (0.97, 0.87–1.07) | 69% vs. 68% (1.04, 0.98–1.10) | 25% vs. 26% (0.95, 0.87–1.03) | 4.1% vs. 4.4% (0.94, 0.75–1.18) | 4.4% vs. 4.8% | NA | NA |
| Convalescent plasma: 11558 (15 January 2021) | 63.5 | 5 | 27 | 24 | 23 | 6 | 2.4% vs. 2.4% (1.00, 0.93–1.07) | 66% vs. 66% (0.99, 0.94–1.03) | 29% vs. 29% (0.99, 0.93–1.05) | 4.4% vs. 4.3% (1.04, 0.87–1.23) | 3.9% vs. 4.4% | NA | NA |
| Tocilizumab: 4116 (24 January 2021) | 63.6 | 14 | 29 | 23 | 23 | 6 | 3.1% vs. 3.5% (0.85, 0.76–0.94) | 57% vs. 50% (1.22, 1.12–1.33) | 35% vs. 42% (0.84, 0.77–0.92) | 6.0% vs. 8.3% (0.72, 0.58–0.90) | 5.6% vs. 6.6% | NA | NA |
| Colchicine: 11340 (4 March 2021) | 63.4 | 5 | 26 | 22 | 21 | 3 | 2.1% vs. 2.1% (1.01, 0.93–1.03) | 70% vs. 70% (0.98, 0.94–1.03) | 25% vs. 25% (1.02, 0.96–1.09) | 3.8% vs. 3.6% (1.07, 0.88–1.29) | 4.2% vs. 4.2% | 5.7% vs. 5.9% | 1.1% vs. 1.1% |
| Aspirin: 14892 (21 March 2021) | 59.2 | 5 | 22 | 19 | 11 | 3 | 1.7% vs. 1.7% (0.96, 0.89–1.04) | 75% vs. 74% (1.06, 1.02–1.10) | 21% vs. 22% (0.96, 0.90–1.03) | 3.7% vs. 3.7% (1.00, 0.85–1.18) | 3.1% vs. 3.5% | 4.6% vs. 1.6% | 1.0% (1.55, 0.76–1.23) |

Rate ratio for the outcomes of 28 days of mortality, hospital discharge, and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes.

aAllocation 1:2 for treatment vs. control arms.

bExcluding those receiving invasive ventilation at randomization.

cExcluding those on dialysis or haemofiltration at randomization.
significant heterogeneity by baseline respiratory status: mortality was reduced by about a third in those on invasive ventilation and a fifth in patients requiring oxygen, with no detectable benefit among those not receiving oxygen at randomization. Dexamethasone also improved time to discharge, cessation of invasive ventilation, and receipt of renal replacement therapy in February 2021, the study showed that tocilizumab (an IL-6 receptor antagonist) further reduced mortality by about 15% in patients with hypoxia and elevated blood C-reactive protein levels. Modulation of vascular inflammation may have contributed to these beneficial effects, given that both corticosteroids and tocilizumab have recognized anti-inflammatory properties at the vascular level. These results confirm that immune activation is a major driver of respiratory failure, multi-organ damage, and mortality in COVID-19, which can be targeted synergistically. While RECOVERY did not employ enrichment strategies based on biomarkers of vascular inflammation or dysfunction, it is conceivable that the benefits seen might have been higher in patients in such conditions. Linkage with detailed datasets such as the International Severe Acute Respiratory and emerging Infections Consortium Coronavirus Clinical Characterisation Consortium (ISARIC4C), or collection of imaging data through collaboration with projects such as the Oxford Risk Factors And Non Invasive Imaging Study (ORFAN) may help to understand the mechanisms by which immunomodulatory therapies are effective in COVID-19 and further clarify in whom they work best.

RECOVERY also showed that a number of treatments (hydroxychloroquine, lopinavir-ritonavir, azithromycin, convalescent plasma, and colchicine) are not effective in hospitalized COVID-19 patients—avoiding unnecessary patient exposure and allowing healthcare systems to focus resources on useful interventions. In some cases, RECOVERY also represented the largest randomized safety assessment to date. This is particularly relevant for hydroxychloroquine and azithromycin, which have indications besides COVID-19 and have particular concerns about arrhythmia risk. Arrhythmic events were nominally higher with hydroxychloroquine vs usual care (8.2% vs. 6.3%), but similar with azithromycin (4.4% vs. 4.8%). The RECOVERY results (together with other trials) also suggest that hydroxychloroquine increases mortality in COVID-19 patients.

More recently, RECOVERY showed that aspirin (150 mg daily for 10 days or until discharge) did not reduce mortality, but increased successful discharge within 28 days (74.6% vs. 73.5%). Patients allocated aspirin had a 12% proportional reduction in thrombotic events (4.6% vs. 5.3%, including arterial and venous events) and a 55% proportional increase in major bleeding (1.6% vs. 1.0%). Antiplatelet therapy has been proposed as a potential therapy in COVID-19 due to several mechanisms, namely tackling alveolar microthrombosis. However, the effects of aspirin in RECOVERY—consistent with cardiovascular prevention trials—suggest that antiplatelet therapy does not have a significant role in reducing lung injury in hospitalized COVID-19 patients. This might be because any protective effect of aspirin on lung injury requires earlier administration; however, RECOVERY found no evidence of heterogeneity according to disease duration or severity. Alternatively, non-platelet pathways may be dominant, and therefore aspirin could not provide any significant benefit over either prophylactic or higher-dose background anticoagulation (received by 60% and 34% of participants in RECOVERY, respectively). Finally, microthrombosis may represent a consequence rather than a cause of alveolar damage, and may not be a modifiable therapeutic target; thus, any beneficial effects of aspirin in COVID-19 are determined, as in other populations, by the absolute risks of thrombo-embolic events and major bleeds.

Additional long-term analyses are ongoing, which will draw from the breadth of routinely-collected healthcare data available in the UK. While blood or imaging biomarkers of cardiovascular damage were not collected, any potential long-term benefits on clinical events such as heart failure, myocardial infarction, arrhythmias, or stroke can be captured through linkage to routine data on hospitalizations, primary care records, medications, and death certificates.

Lessons for the future

RECOVERY has demonstrated the importance of large randomized trials in the reliable assessment of treatment effects—and that this can be achieved rapidly using simple study design and procedures. Although the study has produced important results spanning both COVID-19 and cardiovascular disease, perhaps its most lasting contribution to the field might be the rediscovery of the simple, cardiovascular trial.

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Conflict of interest: I am employed by the Nuffield Department of Population Health (NDPH), University of Oxford. I have an Honorary contract with Oxford University Hospitals NHS Foundation Trust. I receive no honoraria or personal payments from industry in compliance with the NDPH policy for maintaining scientific independence. I am a co-applicant on research grants from The Medicines Company/Novartis and Novo Nordisk to the University of Oxford.

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