Blood thinners and COVID: The findings guiding patient care

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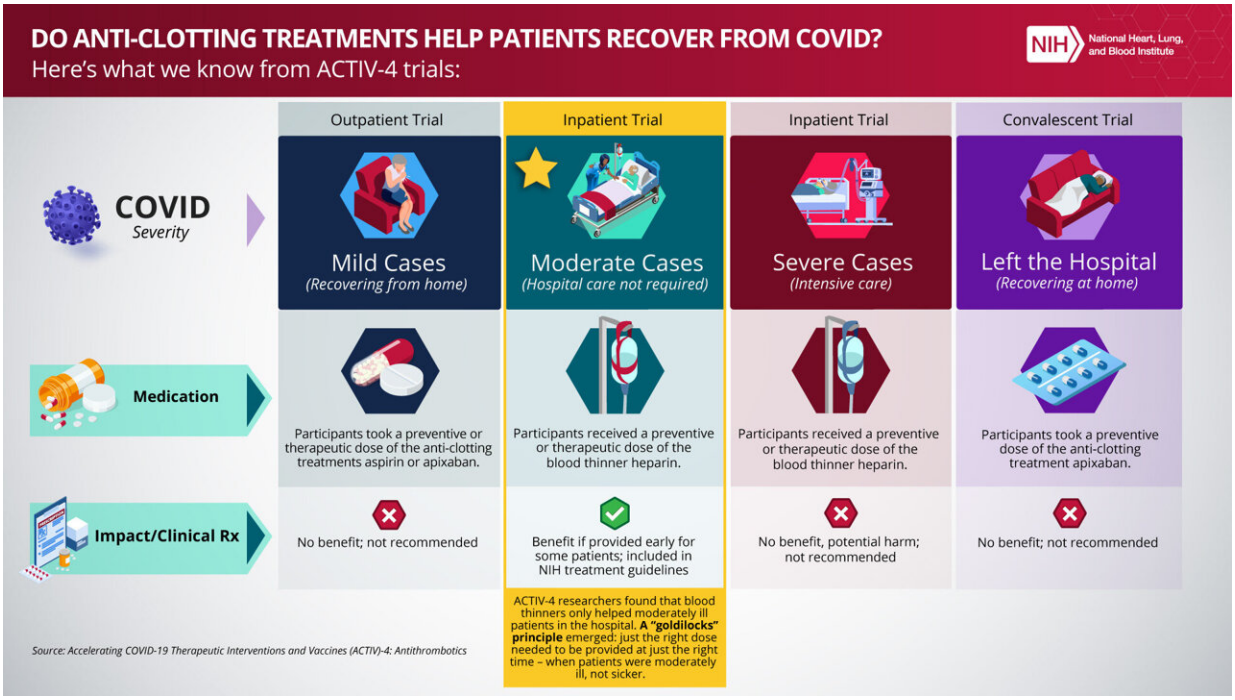

Here's what we know from ACTIV-4 trials:. Credit: NHLBI

When SARS-CoV-2, the virus that causes COVID-19, first emerged in late 2019, researchers quickly assembled to understand its effects and figure out how to stop its spread. Soon, late-night phone calls and global collaborations morphed into international alliances, including the NIH-supported Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV), a public-private partnership that started in April

2020.

Since its launch, ACTIV has used evolving evidence, data from clinical trials, and research teamwork to fast-track testing, vaccines, and treatment. ACTIV-4: Antithrombotics, one of ACTIV's several master protocols, is part of this effort. The goal of this suite of adaptive trials has been to evaluate how blood thinners and anti-clotting medications can minimize risks for severe complications from COVID.

Doctors and researchers noted that many patients who died from COVID when the pandemic first started had developed blood clots throughout their bodies, including in tiny blood vessels. This unusual clotting, one of many life-threatening effects of the disease, could create multiple health complications, including organ damage, heart attacks, strokes, and pulmonary embolisms.

"Since the pandemic started, we have been studying what treatments, in what amounts, and at what point of infection can help patients," said Andrei Kindzelski, M.D, Ph.D., a program officer in the Translational Blood Sciences and Resources branch of NHLBI's Division of Blood Diseases and Resources. "The adaptive nature of ACTIV-4 trials has allowed us to assess the effectiveness of different medications in specific patient populations within a very short time, while enabling these findings to influence clinical practice."

Here is what researchers have learned so far:

Blood thinners don't help people with mild illness recovering at home

"At the beginning of the pandemic, there were many reports of patients who came to the emergency room with blood clots," Kindzelski said.

"The next question was, what can we recommend to minimize these risks and help keep people out of the hospital?"

Physicians were eager to see if anti-clotting medications, like aspirin and apixaban, could offset risks for these types of complications and others. As a result, researchers created an ACTIV-4 outpatient trial to assess how anti-clotting treatments could help people recovering from mild cases of COVID at home.

In September 2020, more than 500 adults, ages 40-80, enrolled in the trial. The study included three treatment groups: one took aspirin twice a day for 45 days; the other two took a higher or lower dose of apixaban for the same duration. A fourth group served as a control by taking a placebo.

About one person on average from each group, including the control, experienced a major complication. However, blood clotting was rare and participants across all four groups experienced similar outcomes. As a result, researchers ended the trial earlier than planned, in June 2021.

"The trial enabled us to inform physicians that there was no need to prescribe anti-clotting medications for patients newly diagnosed with COVID who did not require hospitalization at that time," said Jean M. Connors, M.D., a study co-chair for this trial. She explained the risk of complications was low and forgoing treatment would also avoid risks for bleeding.

Today, nearly three years after the study started, researchers have been able to offer additional insights about why blood clotting was uncommon among many people with mild illness.

First, as COVID tests became available, more people reported their results and outcomes. Like this outpatient trial, they showed that most

young adults, barring no underlying risks, could recover okay at home. Vaccines had also become available and proved highly effective at curbing risks for severe outcomes. Additionally, the pandemic had reached a point where barriers to receiving medical care were finally easing for people who were not severely ill.

Because ACTIV's design allowed an early end to trials that were no longer prudent, researchers quickly shifted to studying treatments that might help patients who needed them most.

Strong doses of blood thinners help patients receiving hospital care for moderate illness

With the ACTIV-4 inpatient study, researchers focused on helping patients receiving hospital care for moderate and severe illness. They evaluated how smaller or preventive doses of the blood thinner heparin—already used as part of standard care—compared to stronger, therapeutic doses. They quickly found the stronger doses improved outcomes for patients with moderate illness.

However, a "goldilocks" principle applied: Patients needed to receive this stronger dose at just the right time—when they were moderately ill, not sicker. Otherwise, if their illness progressed and they required intensive care, a therapeutic dose could exacerbate risks for bleeding and prolong the need for critical care.

"What we found was very interesting," said Judith S. Hochman, M.D., a principal investigator of the study, cardiologist, and senior associate dean for clinical sciences at the New York University Grossman School of Medicine. "We thought that the highest-risk patients would benefit the most, but they didn't."

These findings were supported by thousands of patients who participated in the ACTIV4 inpatient trial and other international trials, including the Randomized, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) and Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC).

Researchers found that 4% of the adults who received heparin had better outcomes than those who received the preventative dose. They were less likely to receive intensive care and more likely to be discharged from the hospital within 21 days.

Following these findings, the NIH clinical care guidelines were immediately updated to recommend physicians provide a full dose of heparin to hospitalized patients with moderate illness. As ACTIV and other adaptive platform trials progressed, Hochman and researchers also found that other variables, including BMI, could inform treatment decisions.

For example, adults with moderate illness who were affected by obesity (their BMI was at least 30) and who received a strong dose of heparin, had a greater chance of experiencing worse outcomes, such as needing intensive care.

"This is the exact opposite of what we hypothesized," Hochman said. "This is one of the reasons it's very important to do randomized clinical trials."

Blood thinners don't curb risks for clotting among patients who've left the hospital

In addition to looking at how blood thinners could offset risks for clotting among patients in the hospital, researchers studied if blood

thinners could help patients after they left the hospital.

In February 2021, the ACTIV-4 convalescent trial launched and ultimately enrolled more than 1,200 patients to test if a lower dose of apixaban could decrease the risk for blood clotting or death within the first 30 days after patients left the hospital.

About 2% of people in the treatment group and 2% in the control group developed blood clots or died.

"We found that the risk of clots or death after discharge from the hospital was lower than initially estimated," said Thomas L. Ortel, M.D., Ph.D., study chair for the ACTIV-4 convalescent trial. To find a benefit with apixaban, researchers would need to enroll many more patients than originally planned. Considering this, along with the low incidence of complications and a steady decline in COVID hospitalizations, researchers ended the trial early in June 2022.

"Physicians can now see, similar to the outpatient study, that anti-clotting treatments should not be given routinely to patients for an extended period after they leave the hospital," Ortel said.

Here are questions researchers are still studying:

Will repurposed drugs strengthen recovery among adults who received hospital care?

Through the ACTIV-4 inpatient trial, researchers studied if adding P2y12 inhibitors, a targeted anti-clotting treatment, to heparin improved outcomes for patients. They also studied if crizanlizumab, a treatment used to improve blood flow for sickle cell disease, and SGLT-2 inhibitors, common diabetes drugs, could offset risks for major

cardiovascular events.

The P2Y12 inhibitors and crizanlizumab did not improve 21-day outcomes, and the SGLT-2 inhibitor trial ended enrollment early in March 2023.

However, the ACTIV-4 inpatient researchers are following patients for up to a year after they enrolled in the study to see if P2Y12 inhibitors and other treatments, like heparin and the SGLT-2 inhibitors, may make a difference in long-term recovery.

Can altering the body's response to infection strengthen recovery?

The ACTIV-4 host tissue trial provided another layer to the inpatient study by evaluating how new or repurposed treatments could help hospitalized patients by altering the body's response to infection.

Researchers recently studied if an infusion with one of two investigational drugs, TXA127 or TRV027, aimed at blocking the early stages of the body's response to the virus, could reduce risks for severe inflammation and clotting in the lungs and other organs. Contrary to promising findings in the lab, the drugs did not improve outcomes for patients.

Through this trial, researchers are also studying if fostamatinib, a treatment for a rare bleeding disorder called chronic immune thrombocytopenia, can alleviate illness for patients with severe COVID.

Based on prior studies, researchers suspect that if fostamatinib can intervene during early stages of infection, it may be able to head off some of the inflammatory events that can follow: extreme clotting,

progressive illness, needing advanced breathing support, and critical care.

While enrollment in the remaining ACTIV-4 trials for hospitalized patients has ended, the analyses are ongoing.

"Already," Kindzelski said, "the outcomes of the ACTIV-4 trials have provided much needed and timely clinical guidance to minimize COVID-associated thrombotic events."

More information:

- For more information about ACTIV, visit https://www.nih.gov/research-training/medical-research-initiatives/activ/COVID-19-therapeutics-prioritized-testing-clinical-trials.
- To access current COVID treatment guidelines, visit https://www.COVID19treatmentguidelines.nih.gov.
- To learn about NIH-supported COVID research, visit https://COVID19.nih.gov.

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