NIH ACTIV: Rapidly Advancing Understanding, Prevention, and Treatment of COVID-19-Associated Coagulopathy (CAC)

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COVID-19 Has Severe Effects on the Lung, Heart, Vascular and Blood Coagulation Systems

What We Know About COVID-19-Associated Coagulopathy (CAC)

- **Blood clots in many** critically ill patients
- 71% of COVID-19 patients who died in China had **systemic coagulopathy**
- **Wide range** of affected patients
- Causing **pulmonary embolism, myocardial infarction, stroke, deep-vein thrombosis**
- Unclear if young people have > CAC rate
- **Increased levels of D-dimer*** strongly associated with increased mortality
- Microvascular thrombosis (arterial/venous)
- Compromised oxygenation and **multi-organ failure**

Currently no clear standard-of-care for anticoagulation in hospitalized COVID-19 patients

Urgent need for clinical evidence to guide practice

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*biomarker elevated in conditions associated with thrombosis*
Understanding, Preventing, and Treating COVID-19 Coagulopathy (CAC): A Collective Path Forward

**Identifying the Mechanism:**
What is/are the clotting trigger(s) from COVID-19 viral infection (e.g. endothelial dysfunction/injury, inflammatory response)?

**Understanding Disease Severity:** What is the role of thrombosis in lung dysfunction, organ failure?

**Generating Evidence to Guide Clinical Care:**
What is the best treatment of coagulopathy in COVID-19 patients at different stages of illness?
ACTIV Public-Private Partnership: An Integrative Strategy to Advance COVID-19 Therapeutics

**Working groups**

**Preclinical**
- Increase access to animal models
- Identify informative assays

**Therapeutics clinical**
- Prioritize and test potential therapeutic agents
- Develop master protocol for clinical trials

**Clinical trial capacity**
- Develop survey instruments
- Develop inventory of clinical trial networks
- Guide deployment of innovative solutions

**Vaccines**
- Accelerate evaluation of vaccine candidates
- Identify biomarkers to speed approval
- Provide evidence to address safety concerns

**ACTIV-4 : PROTECT-COVID 19**

**Federal Partners**
- NIH
- CDC
- FDA
- BARDA
- BARD

**Non-Profit Partners**
- Foundation for the National Institutes of Health
- Bill & Melinda Gates Foundation
- Fred Hutchinson Cancer Research Center
- RTI International

**Bio/Pharma Industry Partners**
- AbbVie
- Amgen
- AstraZeneca
- Bristol Myers Squibb
- Evotec
- GlaxoSmithKline
- Johnson & Johnson
- KSQ Therapeutics
- Eli Lilly and Company
- Merck & Co., Inc.
- Novartis
- Pfizer
- Roche
- Sanofi
- Takeda
- Vir Biotechnology

ACTIV PPP leverages trans-NIH clinical trial capacity for adaptive clinical trial designs with Master Protocols and conducts cross-disciplinary research with biorepositories for leading-edge natural history studies.

- Leverage networks’ expertise and efficiency
  - Enhance recruitment speed; facilitate specialized sub-studies

- Maximize knowledge: Sampling, Imaging, Analysis
  - Risk stratification; clinical phenotyping
  - Stroke and blood-brain barrier
    - Imaging capacities for blood-brain barrier impairment at selected site(s)
  - Interface between inflammation and coagulation
    - Innate immune response
    - Adaptive immune response
ACTIV-4 Master Protocol: Testing Anti-Thrombotic Strategies

Randomized Trial of Anti-Thrombotic Strategies in COVID-19 (PROTECT-COVID 19)

- First open-label trial to compare blood-clotting regimens in COVID-19 + patients
- Phase III clinical trial with focus on low and high doses of heparin
- Evolving as an adaptive platform clinical trial to study other anticoagulants, antiplatelet agents
- Studies will identify biomarkers to enable patient risk stratification

- 1,000 COVID-19 + patients, starting in NY & approximately 15 additional sites
- Includes hospitalized patients with a D-dimer >500 ng/ml
- Patients randomized to higher-dose versus lower-dose heparin in 1:1 ratio.

Antithrombotic: Prophylaxis and Treatment

COVID-19+ Progression

Prevention
Outpatient Asymptomatic
Outpatient Symptomatic
Emergency Department
Hospital Vent/CPAP-free
Hospital ICU
Convalescence
Recovered

NIH
National Heart, Lung, and Blood Institute
ACTIV Public-Private Partnership: A Rapid Response to Reduce COVID-19 Morbidity and Mortality

**ACTIV Public-Private Partnership**
*Accelerating COVID-19 Therapeutic Interventions & Vaccines*

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- Novartis
- Pfizer
- Roche
- Sanofi
- Takeda
- Vir Biotechnology