COVID-PACT

European Society of Cardiology Congress 2022

David D. Berg, MD, MPH
On behalf of the COVID-PACT Investigators
Disclosures

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COVID-PACT was sponsored by the TIMI Study Group.
Background

- Infection with SARS-CoV2 carries ↑ risk of thrombosis
- Risk is higher in patients requiring critical care
- Mechanisms are likely multiple

Thromboprophylaxis is standard in critically ill patients without COVID-19 to reduce the risk of VTE.

Multiple randomized trials have assessed benefit of anticoagulant and antiplatelet prophylaxis strategies in patients with COVID-19 with varied primary results.

- Differing study populations, regimens, designs, endpoints.
## Anticoagulation and Organ Failure

### Multiplatform Trial (Non-Critically Ill)
- *NEJM* 2021;385(9):790-802.

### Multiplatform Trial (Critically Ill)

### Intervention
- Therapeutic-Dose AC vs. Usual Care (Low or Intermediate Dose)

### Primary EP
- Number of days alive without organ support in 21 days

### PEP Result
- Stopped for **Superiority**
- Stopped for **Futility**

### Other Findings
- **Thrombosis**: (No formal hypothesis testing)
- **Bleeding**: 

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*Optimal thromboprophylaxis strategy in critically ill patients with COVID-19 remains uncertain*
Objective

To evaluate the efficacy and safety of:

(1) full-dose anticoagulation (FDAC) for prophylaxis vs standard dose prophylactic anticoagulation (SDPAC), and
(2) antiplatelet therapy (clopidogrel) vs no antiplatelet therapy for the prevention of venous and arterial thrombotic events in critically ill patients with COVID-19.
Patients with COVID-19 Requiring ICU-Level Care

N~750

1:1 Randomization (open-label)

**Full-Dose Anticoagulation (FDAC)**
- Clopidogrel
- No Antiplatelet

**Standard-Dose Prophylactic Anticoagulation (SDPAC)**
- Clopidogrel
- No Antiplatelet

**PROBE design**

If Not on Antiplatelet:
1:1 Randomization (open-label)

All patients undergo bilateral LE venous US between Day 10-14 post-randomization

Followed through hospital discharge or Day 28 post-randomization

Key Inclusion Criteria:
- Acute infection with SARS-CoV2
- ICU admission ≤ 96h prior to rando
- ICU admission –or– advanced resp support (IMV, NIPPV, HFNC), vaspressors, or MCS

Key Exclusion Criteria:
- Ongoing or planned FDAC or DAPT
- Contraindication to antithrombotic Rx
- High risk of bleeding (incl fibrinogen <200)
- Ischemic stroke within past 2 weeks

Acceptable initial AC regimens included UFH or LMWH

300 mg loading dose on day of rando, then 75 mg daily
# Endpoints

### Primary Efficacy EP
Hierarchical composite of:

1. Death due to venous or arterial thrombosis
2. Pulmonary embolism
3. Clinically evident DVT
4. Type 1 MI
5. Ischemic stroke
6. SEE or ALI
7. Clinically silent DVT

### Primary Safety EP
Composite of fatal or life-threatening bleeding

### Secondary Safety EP

**GUSTO moderate or severe bleeding**

- **Severe**: Fatal, intracranial, or causing hemodynamic compromise
- **Moderate**: Requiring transfusion without hemodynamic compromise
Endpoints

Key Secondary EP
Hierarchical composite of:
1. Death due to venous or arterial thrombosis
2. Pulmonary embolism
3. Clinically evident DVT
4. Type 1 MI
5. Ischemic stroke
6. SEE or ALI

Primary Safety EP
Composite of fatal or life-threatening bleeding

Secondary Safety EP
GUSTO moderate or severe bleeding
- Severe: Fatal, intracranial, or causing hemodynamic compromise
- Moderate: Requiring transfusion without hemodynamic compromise
Analytic Plan

• Each factorial intervention analyzed using:
  - Unmatched pair win ratio (hierarchical by element)
  - Time-to-first event analysis (non-hierarchical)

• Primary efficacy and safety analyses prespecified to be on-treatment comparisons (events occurring during randomized treatment or within 72h of last dose)
  - Designed to ascertain effect of therapy prior to crossover
  - Supported by secondary intention-to-treat analyses
## Trial Organization

### TIMI Study Group / CCCTN Coordinating Center

<table>
<thead>
<tr>
<th>Position</th>
<th>Name</th>
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<tbody>
<tr>
<td>Chair</td>
<td>Marc Sabatine</td>
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<tr>
<td>Fellow</td>
<td>Mathew Lopes</td>
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<td>Statistics</td>
<td>Julia Kuder</td>
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<tr>
<td>Investigator</td>
<td>Erin Bohula</td>
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<tr>
<td>(PI)</td>
<td>David Morrow</td>
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<tr>
<td>Operations</td>
<td>M. Polly Fish</td>
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<td>(Statistics)</td>
<td>Jeong-Gun Park</td>
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<tr>
<td>(Statistics)</td>
<td>Steve Wiviott</td>
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<tr>
<td>Investigator</td>
<td>Vivian Baird-Zars</td>
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<tr>
<td>(Operations)</td>
<td>Sabina Murphy</td>
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<tr>
<td>(Operations)</td>
<td>Michelle O’Donoghue</td>
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### Steering Committee

<table>
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<tbody>
<tr>
<td>Marc Sabatine</td>
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<tr>
<td>David Morrow</td>
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<td>Jean Connors</td>
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<td>Edy Kim</td>
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<td>Erin Bohula</td>
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<tr>
<td>Jason Katz</td>
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<tr>
<td>David Berg</td>
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<td>Sean van Diepen</td>
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### Independent Data Monitoring Committee

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<thead>
<tr>
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<tbody>
<tr>
<td>James de Lemos</td>
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<tr>
<td>Howard Cooper</td>
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<tr>
<td>Jeffrey Weitz</td>
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<td>KyungAh Im</td>
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### Clinical Events Committee

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Eric Awtry</td>
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<tr>
<td>Clifford Berger</td>
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<tr>
<td>Kevin Croce</td>
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<tr>
<td>Akshay Desai</td>
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<td>Eli Gelfand</td>
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<td>Carolyn Ho</td>
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<td>David Leeman</td>
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<td>Ashvin Pande</td>
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<td>Fredrick Ruberg</td>
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<td>Garrick Stewart</td>
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Enrollment

Enrollment: August 2020 – March 2022 (early closure)  Enrolling Sites: 34

Site Principal Investigators

MA: Katherine Berg
Ari Moskowitz
Michael Ieong
Christian Ruff

NJ: Emilio Mazza
Abbas Shehadeh

TX: Alfredo Vazquez Sandoval

AZ: Jarrod Mosier

CA: Shahid Hayat

IL: Alexander Adler
R. Jeffrey Snell

IN: Mohammed Al Faiyumi
Sunit-Preet Chaudhry
Winston Nara

MI: Chintalapudi Kumar
Vijaya Kumar
Elizabeth Pionk
Mark Zainea

MN: Wilson Ginete
Retu Saxena
Brandon Wiley

NE: Shraddha Narechania

NY: Amit Chopra
Hal Skopicki

VA, DC: Shashank Sinha
Christopher Barnett
Alexander Papulos

NC: Dalton McLean

SC: Abhijit Raval

GA: Kent Nilsson
Rajnish Prasad

FL: Joshua Larned
Borna Mehrad
Mohamed Shahrour

Total Patients Randomized in Anticoagulation Randomization: 390 (382 on-treatment)
Total Patients Randomized in Antiplatelet Randomization: 292 (290 on-treatment)
# Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>On-Treatment Cohort (n=382)</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>61 (51, 69)</td>
</tr>
<tr>
<td>Female</td>
<td>41%</td>
</tr>
<tr>
<td>BMI ≥ 30 kg/m²</td>
<td>68%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>59%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>32%</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>20%</td>
</tr>
<tr>
<td>ASCVD</td>
<td>14%</td>
</tr>
<tr>
<td>CKD</td>
<td>11%</td>
</tr>
<tr>
<td>SOFA Score</td>
<td>4 (4, 5)</td>
</tr>
<tr>
<td>Resp Support (at rando)</td>
<td></td>
</tr>
<tr>
<td>NIPPV or HFNC</td>
<td>84%</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>15%</td>
</tr>
<tr>
<td>D-dimer &gt;2x ULN</td>
<td>43%</td>
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</tbody>
</table>

Median Time from Admission to Randomization: 2.1 days (1.5, 3.4 days)
Study Therapy

Initial Anticoagulant Selection

- UFH: 18%
- LMWH: 82%

Anticoagulation Randomization
- Crossover
  - 34% in SDPAC vs. 17% in FDAC (p=0.0002)

Antiplatelet Randomization
- Premature cessation of clopidogrel = 31%
Primary Endpoint (Win Ratio)

FDAC vs. SDPAC

Clopidogrel vs No AP

Primary EP: (1) Death due to VTE/ATE, (2) PE, (3) clinically-evident DVT, (4) type 1 MI, (5) ischemic stroke, (6) SEE or ALI, (7) clinically-silent DVT

Win Ratio

1.95 (1.08-3.55)  
p=0.028

1.04 (0.54-2.01)  
p=0.90

Stratified Win Ratio (95% CI)

Favors SDPAC or No AP  Favors FDAC or Clopidogrel
Primary Endpoint (Time to Event)

FDAC vs. SDPAC

- SDPAC
- FDAC

HR 0.56 (0.32, 0.99)
P-value=0.046

At-Risk
FDAC 191
SDPAC 191

Days
0 7 14

Clopidogrel vs No AP

- No Clopidogrel
- Clopidogrel

HR 0.90 (0.48, 1.69)
P-value=0.75

At-Risk
Clopi 150
No Clopi 140

Days
0 7 14

At-Risk
FDAC 158
SDPAC 129

At-Risk
Clopi 111
No Clopi 115

Days
0 7 14

At-Risk
FDAC 69
SDPAC 54

At-Risk
Clopi 44
No Clopi 59
<table>
<thead>
<tr>
<th>Anticoagulation Randomization</th>
<th>FDAC (N=191)</th>
<th>SDPAC (N=191)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy(^1)</td>
<td>19 (9.9)</td>
<td>29 (15.2)</td>
<td>0.56 (0.32, 0.99)</td>
</tr>
<tr>
<td>Key secondary efficacy(^2)</td>
<td>14 (7.3)</td>
<td>23 (12.0)</td>
<td>0.55 (0.28, 1.08)</td>
</tr>
<tr>
<td>Venous thrombotic events (VTE)(^3)</td>
<td>18</td>
<td>28</td>
<td>0.55 (0.31, 0.99)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>6</td>
<td>7</td>
<td>0.78 (0.26, 2.34)</td>
</tr>
<tr>
<td>Clinically-evident DVT</td>
<td>9</td>
<td>16</td>
<td>0.51 (0.23, 1.16)</td>
</tr>
<tr>
<td>Clinically-silent DVT</td>
<td>5</td>
<td>6</td>
<td>0.59 (0.20, 1.77)</td>
</tr>
<tr>
<td>Arterial thrombotic events (ATE)(^4)</td>
<td>1</td>
<td>2</td>
<td>0.49 (0.04, 5.73)</td>
</tr>
</tbody>
</table>

\(^1\) Death due to VTE/ATE, PE, clinically-evident DVT, type 1 MI, ischemic stroke, SEE or ALI, or clinically-silent DVT
\(^2\) Death due to VTE/ATE, PE, clinically-evident DVT, type 1 MI, ischemic stroke, or SEE or ALI
\(^3\) PE or any DVT (clinically-evident or clinically-silent)
\(^4\) Type 1 MI, ischemic stroke, or SEE or ALI
## Primary Endpoint

**Anticoagulation Randomization**

<table>
<thead>
<tr>
<th></th>
<th>On-Treatment</th>
<th>Intention-to-Treat</th>
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<tbody>
<tr>
<td><strong>Stratified Win Ratio</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>1.95 (1.08-3.55)</td>
<td>1.64 (0.95-2.82)</td>
</tr>
<tr>
<td>Key secondary endpoint</td>
<td>1.79 (0.92-3.47)</td>
<td>1.65 (0.88-3.07)</td>
</tr>
<tr>
<td><strong>Time to Event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>0.56 (0.32-0.99)</td>
<td>0.72 (0.43-1.19)</td>
</tr>
<tr>
<td>Key secondary endpoint</td>
<td>0.55 (0.28-1.08)</td>
<td>0.66 (0.36-1.20)</td>
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</table>
# Safety Endpoints (Anticoagulation)

<table>
<thead>
<tr>
<th></th>
<th>FDAC (N=191)</th>
<th>SDPAC (N=191)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
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<tr>
<td><strong>Primary safety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Secondary safety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GUSTO severe bleeding</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GUSTO moderate bleeding</td>
<td>11</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>36 (18.8)</td>
<td>32 (16.8)</td>
<td>0.91 (0.56, 1.48)</td>
<td>0.70</td>
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### Safety Endpoints (Antiplatelet)

#### Antiplatelet Randomization

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Clopi (N=150)</th>
<th>No Clopi (N=140)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
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<td>4</td>
<td>7</td>
<td>-</td>
<td>-</td>
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Limitations

• Open-label design (though blinded EP adjudication)
• Recruitment stopped early due to waning COVID-19 rates
• Thrombotic event rate lower than expected based on initial epidemiology (however, sample size estimate conservative)
• Primary analyses prespecified to be on-treatment to mitigate impact of crossovers
  ➢ Crossover rate from SDPAC→FDAC high (similar to other trials)
  ➢ On-Rx and intention-to-treat provide boundaries for effect estimate
Conclusions

• In a trial specifically designed to assess thrombotic events in critically ill patients with COVID-19, a strategy of full-dose AC vs. standard-dose prophylactic AC:
  ➢ Reduced thrombotic complications
  ➢ Increased bleeding driven primarily by transfusions in hemodynamically stable patients

• The addition of clopidogrel did not reduce thrombotic complications or increase bleeding in this population
• Findings from COVID-PACT are relevant as consensus treatment guidelines for COVID-19 are revisited

  ➢ Current guidelines suggest using SDPAC over FDAC in critically ill patients with COVID-19 (including those managed with HFNC and NIPPV)

  ➢ Weighing thrombotic and bleeding risk, FDAC should be considered to prevent thrombotic complications in selected critically ill patients with COVID-19
ANTICOAGULATION AND ANTIPLATELET THERAPY FOR PREVENTION OF VENOUS AND ARTERIAL THROMBOTIC EVENTS IN CRITICALLY ILL PATIENTS WITH COVID-19: COVID-PACT

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*CONTRIBUTED EQUALLY

HTTPS://WWW.AHAJOURNALS.ORG/DOI/10.1161/CIRCULATIONAHA.122.061533
Thank You

www.timi.org