COVID-PACT

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European Society of Cardiology Congress 2022

David D. Berg, MD, MPH

On behalf of the COVID-PACT Investigators

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Disclosures

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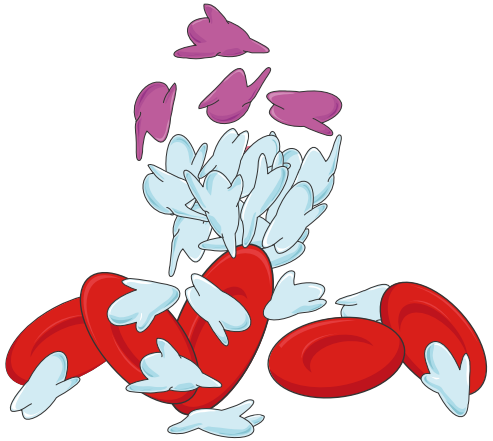
COVID-PACT was sponsored by the TIMI Study Group.

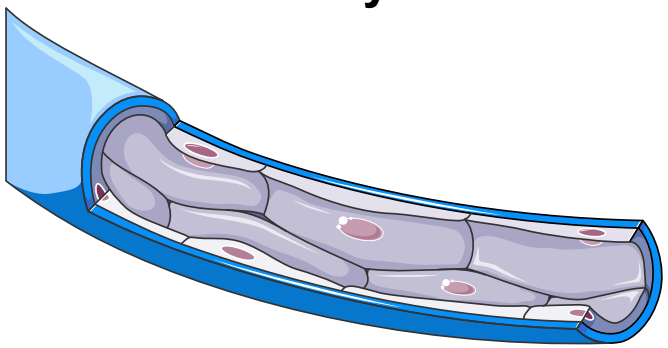
Background

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

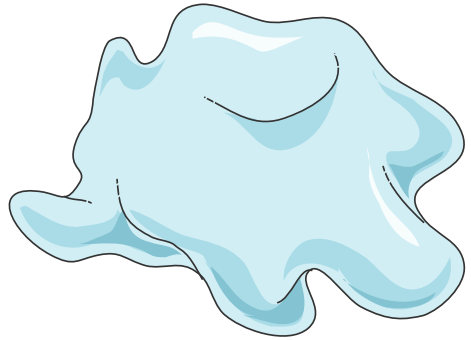
Activation of Coagulation Cascade



Systemic Endothelial Dysfunction



Hyper-reactive Platelet Response



Clin Infec Dis. 2021; 73(12):2294-2297.

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Background

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- 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) NEJM 2021;385(9):777-789.
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 <u>Superiority</u>**	**Stopped for <u>Futility</u>**
Other Findings		
Thrombosis	↓ (No formal hypothesis testing)	↓
Bleeding	↑	↑

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

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Objective

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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.

Trial Design

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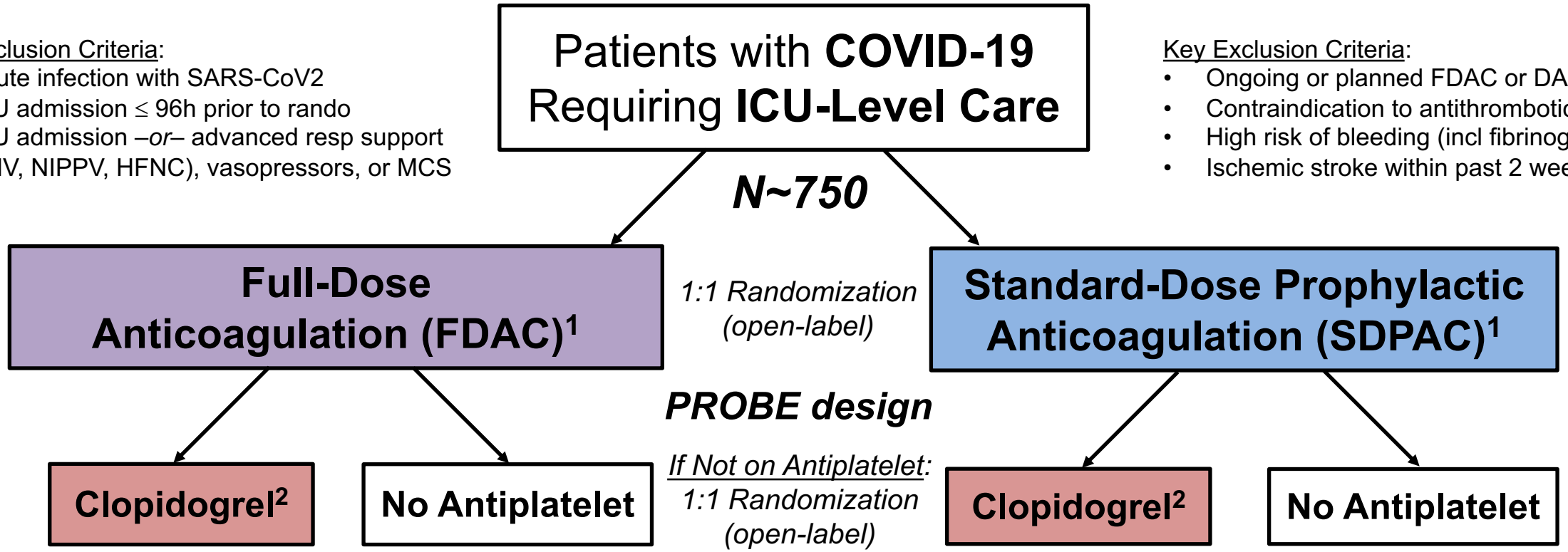
Key Inclusion Criteria:
- Acute infection with SARS-CoV2
- ICU admission ≤ 96h prior to rando
- ICU admission –*or*– advanced resp support (IMV, NIPPV, HFNC), vasopressors, or MCS

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



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

Followed through **hospital discharge** or **Day 28** post-randomization

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[1] *Acceptable initial AC regimens included UFH or LMWH*
[2] *300 mg loading dose on day of rando, then 75 mg daily*

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Endpoints

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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

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Endpoints

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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

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TIMI Study Group / CCCTN Coordinating Center

Marc Sabatine (Chair)	David Morrow (PI)	Erin Bohula (Investigator)	David Berg (Investigator)
Mathew Lopes (Fellow)	M. Polly Fish (Operations)	Vivian Baird-Zars (Operations)	Sabina Murphy (Statistics)
Julia Kuder (Statistics)	Jeong-Gun Park (Statistics)	Steve Wiviott (CEC)	Michelle O'Donoghue (Safety)

Steering Committee

Marc Sabatine	David Morrow	Erin Bohula	David Berg
Jean Connors	Edy Kim	Jason Katz	Sean van Diepen

Independent Data Monitoring Committee

James de Lemos (Chair)	Howard Cooper	Jeffrey Weitz	KyungAh Im (Statistics)

Clinical Events Committee

Eric Awtry	Clifford Berger	Kevin Croce	Akshay Desai
Eli Gelfand	Carolyn Ho	David Leeman	Ashvin Pande
Fredrick Ruberg	Garrick Stewart		

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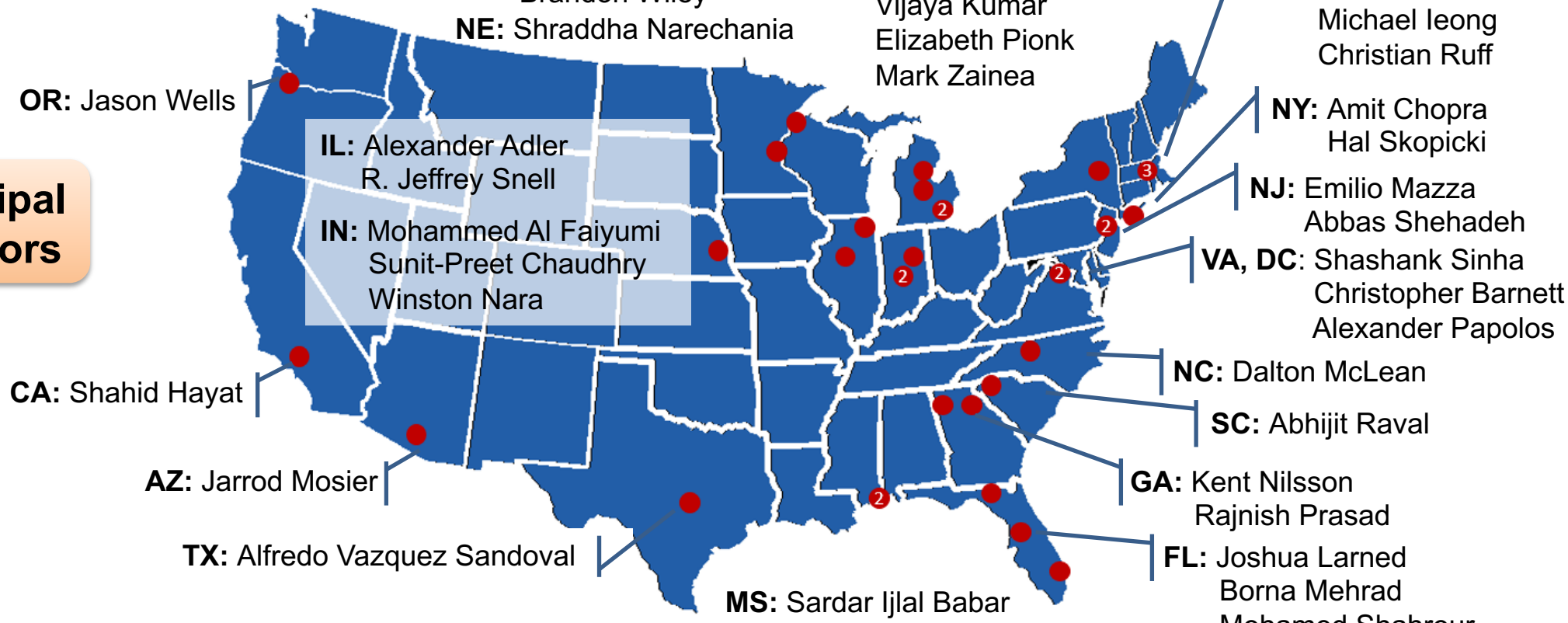
Enrollment

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

Site Principal Investigators



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

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Baseline Characteristics

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

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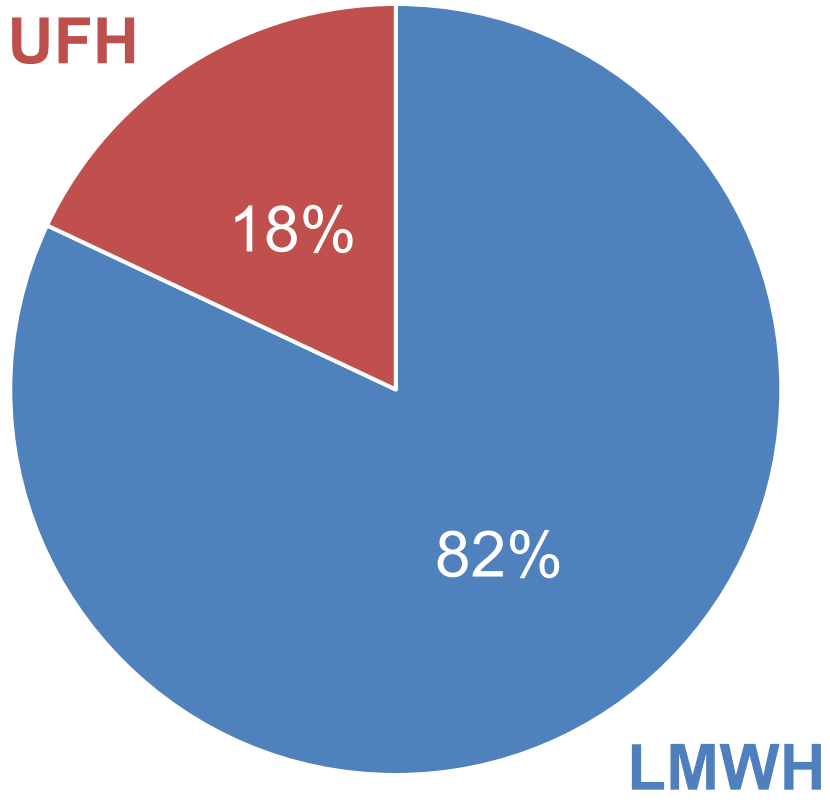
Median Time from Admission to Randomization: 2.1 days (1.5, 3.4 days)

Study Therapy

Initial Anticoagulant Selection



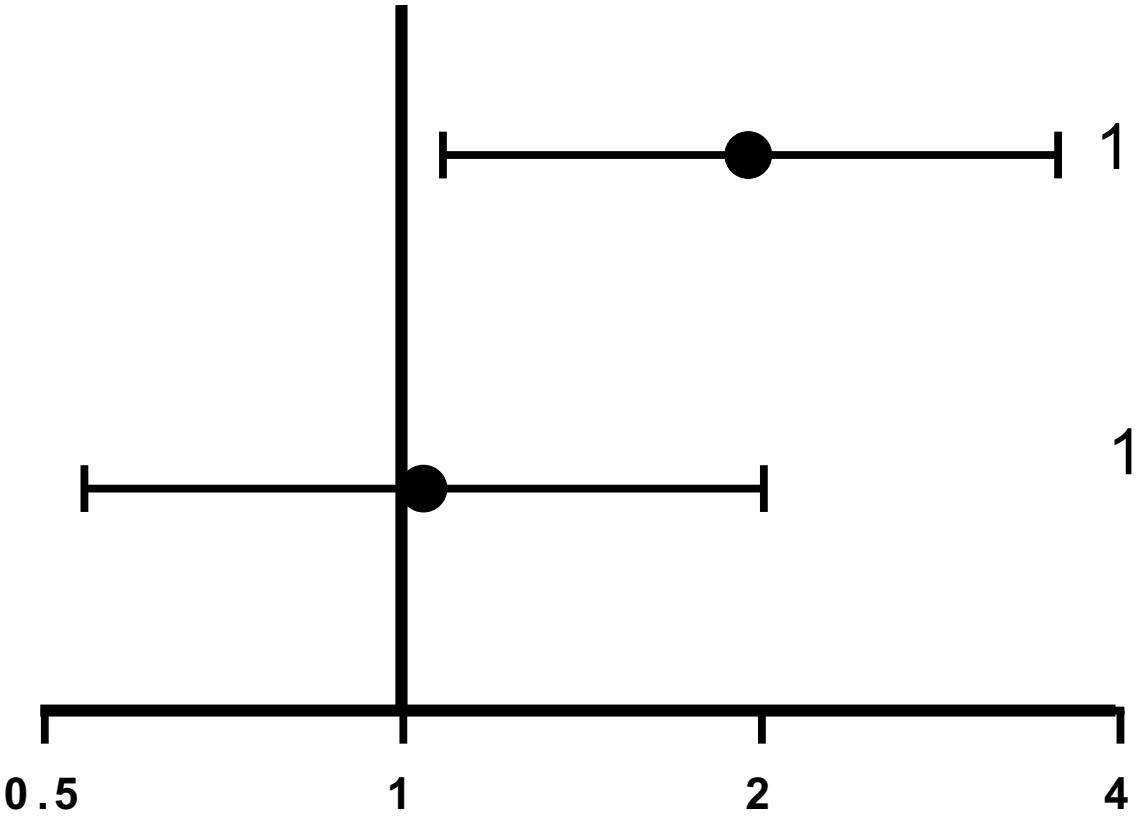
Anticoagulation Randomization

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

Antiplatelet Randomization

- Premature cessation of clopidogrel = 31%

Primary Endpoint (Win Ratio)



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

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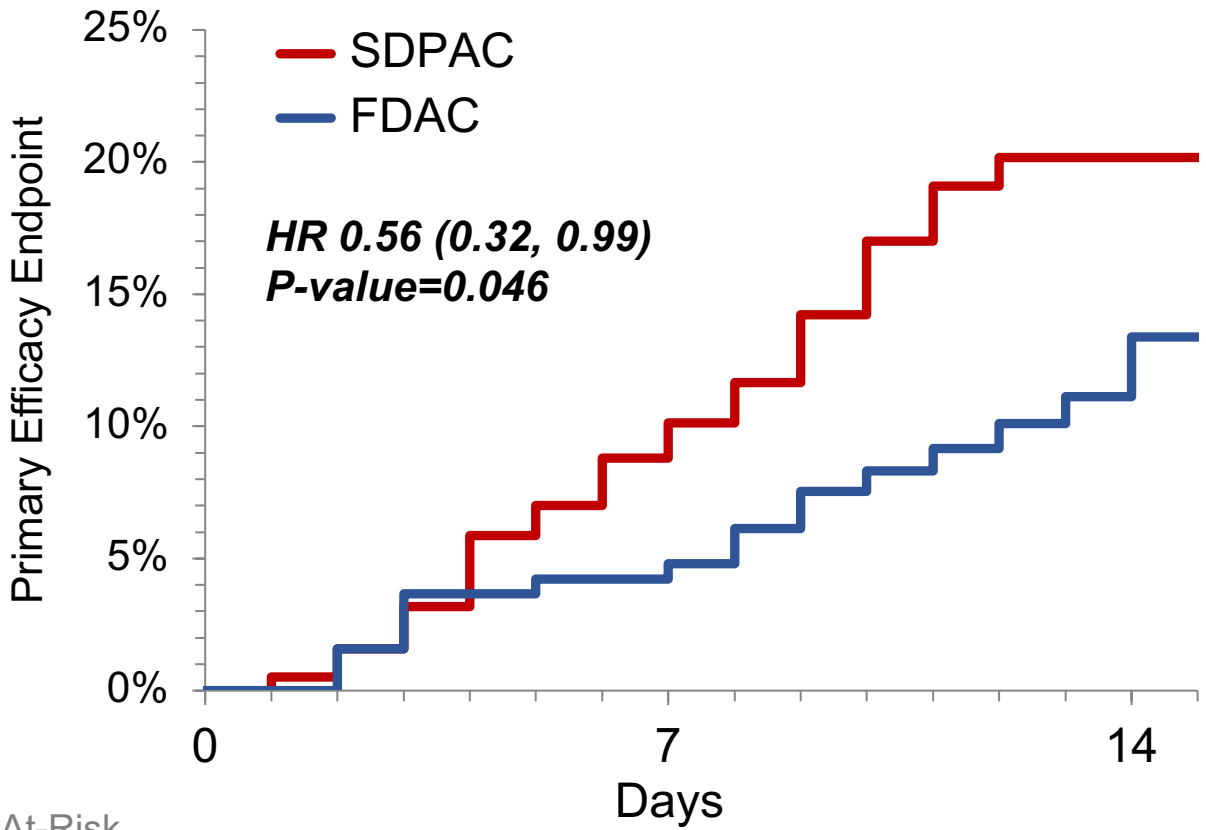
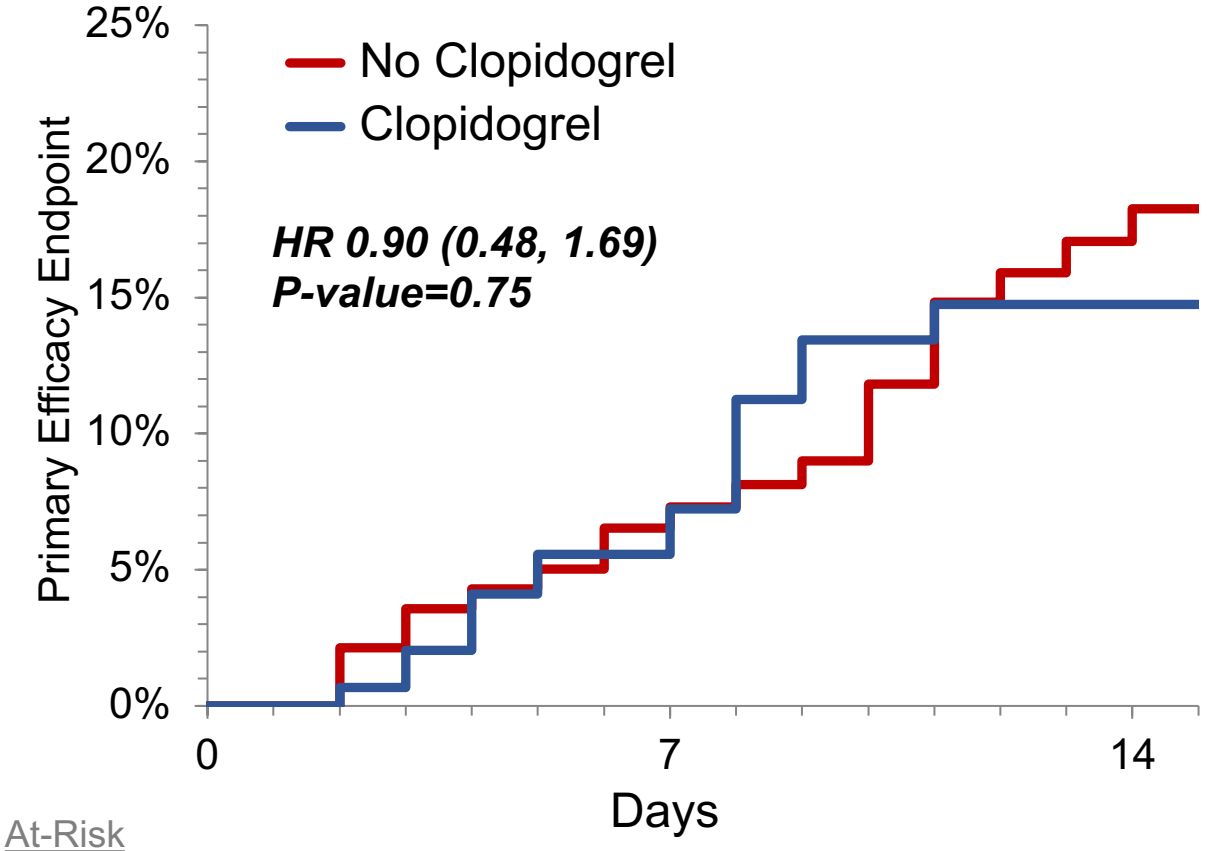
Primary Endpoint (Time to Event)

FDAC vs. SDPAC



At-Risk			
FDAC	191	158	69
SDPAC	191	129	54

Clopidogrel vs No AP



At-Risk			
Clopi	150	111	44
No Clopi	140	115	59

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Other Efficacy Endpoints

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Anticoagulation Randomization

	FDAC (N=191)	SDPAC (N=191)	HR (95% CI)
Primary efficacy[1]	19 (9.9)	29 (15.2)	0.56 (0.32, 0.99)
Key secondary efficacy[2]	14 (7.3)	23 (12.0)	0.55 (0.28, 1.08)
Venous thrombotic events (VTE)[3]	18	28	0.55 (0.31, 0.99)
Pulmonary embolism	6	7	0.78 (0.26, 2.34)
Clinically-evident DVT	9	16	0.51 (0.23, 1.16)
Clinically-silent DVT	5	6	0.59 (0.20, 1.77)
Arterial thrombotic events (ATE)[4]	1	2	0.49 (0.04, 5.73)

[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

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Primary Endpoint
Anticoagulation Randomization

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	On-Treatment	Intention-to-Treat
Stratified Win Ratio		
Primary endpoint	1.95 (1.08-3.55)	1.64 (0.95-2.82)
Key secondary endpoint	1.79 (0.92-3.47)	1.65 (0.88-3.07)
Time to Event		
Primary endpoint	0.56 (0.32-0.99)	0.72 (0.43-1.19)
Key secondary endpoint	0.55 (0.28-1.08)	0.66 (0.36-1.20)

Safety Endpoints (Anticoagulation)

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Anticoagulation Randomization

	FDAC (N=191)	SDPAC (N=191)	HR (95% CI)	P-value
Primary safety	4 (2.1)	1 (0.5)	3.86 (0.44, 34.28)	0.19
Fatal bleeding	0	0	-	-
Life-threatening bleeding	4	1	-	-
Secondary safety	15 (7.9)	1 (0.5)	12.30 (1.64, 92.08)	0.002
GUSTO severe bleeding	4	1	-	-
GUSTO moderate bleeding	11	0	-	-
All-cause mortality	36 (18.8)	32 (16.8)	0.91 (0.56, 1.48)	0.70

Safety Endpoints (Antiplatelet)

	Antiplatelet Randomization			
	Clopi (N=150)	No Clopi (N=140)	HR (95% CI)	P-value
Primary safety	2 (1.3)	2 (1.4)	1.00 (0.14, 7.18)	1.00
Fatal bleeding	0	0	-	-
Life-threatening bleeding	2	2	-	-
Secondary safety	6 (4.0)	9 (6.4)	0.87 (0.30, 2.55)	0.83
GUSTO severe bleeding	2	2	-	-
GUSTO moderate bleeding	4	7	-	-

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

Implications

- 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

Circulation

CIRCULATION. 2022; [PUBLISHED ONLINE AHEAD OF PRINT]. DOI: 10.1161/CIRCULATIONAHA.122.061533

ANTICOAGULATION AND ANTIPLATELET THERAPY FOR PREVENTION OF VENOUS AND ARTERIAL THROMBOTIC EVENTS IN CRITICALLY ILL PATIENTS WITH COVID-19: COVID-PACT

ERIN A. BOHULA, MD, DPHIL*; DAVID D. BERG, MD, MPH*; MATHEW S. LOPES, MD; JEAN M. CONNORS, MD; IJLAL BABAR, MD; CHRISTOPHER F. BARNETT, MD; SUNIT-PREET CHAUDHRY, MD; AMIT CHOPRA, MD; WILSON GINETE, MD; MICHAEL H. IEONG, MD; JASON N. KATZ, MD, MHS; EDY Y. KIM, MD, PHD; JULIA F. KUDER, MS; EMILIO MAZZA, MD, PHD; DALTON MCLEAN, MD; JARROD M. MOSIER, MD; ARI MOSKOWITZ, MD; SABINA A. MURPHY, MPH; MICHELLE L. O'DONOGHUE, MD, MPH; JEONG-GUN PARK, PHD; RAJNISH PRASAD, MD; CHRISTIAN T. RUFF, MD; MOHAMAD N. SHAHROUR, MD; SHASHANK S. SINHA, MD; STEPHEN D. WIVIOTT, MD; SEAN VAN DIEPEN, MD, MSC; MARK ZAINEA, MD; VIVIAN BAIRD-ZARS, MPH; MARC S. SABATINE, MD, MPH; DAVID A. MORROW, MD, MPH

*CONTRIBUTED EQUALLY

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