RIVAROXABAN TO REDUCE THE RISK OF MAJOR VENOUS AND ARTERIAL THROMBOTIC EVENTS, HOSPITALIZATION AND DEATH IN MEDICALLY ILL OUTPATIENTS WITH COVID-19: PRIMARY RESULTS OF THE PREVENT-HD RANDOMIZED CLINICAL TRIAL

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Disclosures

Research support from Bristol-Myers Squibb/Pfizer Alliance, Bayer, Janssen, Alexion, Amgen and Boston Scientific Corporation, and consulting fees from Bristol-Myers Squibb/Pfizer Alliance, Boston Scientific Corporation, Janssen, NAMSA, Prairie Education and Research Cooperative, Boston Clinical Research Institute, and Amgen
• Hospitalized COVID-19 patients were recommended to receive thromboprophylaxis as "acute, medically ill" patients per guidelines from ACC, ACCP, WHO, and the ISTH

• Rivaroxaban was approved in the United States for the prophylaxis of VTE in hospitalized acute, medically ill patients who are at risk for VTE and at low risk for bleeding

• D-dimer in COVID-19 was identified as a marker of a procoagulant state and a risk factor for VTE, clinical deterioration, and death

• Despite focus on hospitalized patients, the majority of patients with COVID-19 were treated as outpatients

• Outpatients with COVID-19 were suspected to be at risk for venous and arterial thrombotic events, especially in setting of risk factors

• Histopathological evidence suggested that at least part of the deterioration in lung function leading to hospitalization may have been due to in situ pulmonary artery thrombosis

Piazza G, Morrow D. JAMA. 2020;324:2548
HYPOTHESIS

• Early initiation of thromboprophylactic dosing of rivaroxaban in higher risk outpatients with COVID-19 may:
  • Lower the incidence of venous and arterial thrombotic events
  • Reduce in situ pulmonary thrombosis and reduce the worsening of pulmonary function that may lead to hospitalization
  • Reduce all-cause mortality

• We also hypothesized that the study could be performed in a limited number of integrated health networks in the US in a totally virtual manner (ie no in person visits or lab tests) with data available on 100% of participants via standard eCRFs and electronic medical records
STUDY DESIGN

Randomized, double-blind, placebo-controlled, event-driven study\(^1\)

**Symptomatic Patients with Positive COVID-19 Test for Infection (eg, PCR, antigen)**

- **Visit:** Screen (TC or IWI)
- **Visit:** Day 1 (TC or IWI)
- **Visit:** Day 3 (±1) (TC or IWI)
- **Visit:** Day 14 (±7) (TC or IWI)
- **Visit:** Day 35 (±6) (Last Dose, EOT) (TC or IWI)
- **Visit:** Day 49 (±7) (Follow-up, EOT) (TC or IWI)

**Stratification** by the time from COVID-19 positive test to randomization (1 to 5 days inclusive, 6 to 14 days inclusive)

- **Screening Visit** Day -14 to Day -1#
- **Randomization Visit (Baseline) Day 1**
- **Double-Blind Treatment Period**
  - Rivaroxaban 10 mg OD (+ standard of care)
  - Placebo OD (+ standard of care)

**Post Treatment Period**

EOS, End of study; EOT, end of treatment; IWI, Interactive Web Interface; OD, once daily; PCR, polymerase chain reaction; TC, telephone contact.

Inclusion Criteria

- Age ≥18 years
- COVID-19 positive laboratory test
- Symptoms attributable to COVID-19
- Initial treatment plan does not include hospitalization
- Presence of at least one additional risk factor:
  - Age > 60 years
  - Prior history of: VTE, Thrombophilia, CAD, PAD, CVD or ischemic stroke, cancer (other than basal cell carcinoma), diabetes requiring medication, heart failure
  - Body Mass Index ≥35 kg/m²
  - D-dimer > upper limit of normal for local laboratory
  - Patient known to health system

Exclusion Criteria

- Increased risk of bleeding
- Any illness causing increased risk of bleeding
- Known allergies, hypersensitivity, or intolerance to rivaroxaban or its excipients
- Positive COVID-19 antibody or serology test after 2-week period of acute COVID-19 infection
- Known diagnosis of triple positive (positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies) antiphospholipid syndrome
Primary Efficacy Endpoint  
Time to first occurrence of a composite endpoint of symptomatic venous thromboembolism (VTE), myocardial infarction (MI), ischemic stroke, acute limb ischemia, noncentral nervous system (non-CNS) systemic embolization, all-cause hospitalization, and all-cause mortality up to Day 35

Principal Safety Endpoint  
Time to first occurrence of International Society on Thrombosis and Hemostasis (ISTH) critical site and fatal bleeding on treatment (+ 2 days)

Key Assumptions and Statistical Design

Power = 90%, 2 sided-alpha = 0.05, for a 30% reduction (HR 0.70) assuming a placebo event rate of 10%

333 events required

Expected enrollment: ~4000

ITT analysis, primary

Modified ITT analysis (all participants taking at least 1 dose of study intervention): pre-specified sensitivity analysis

Safety Endpoints: On treatment + 2 days
REASONS FOR ENDING ENROLLMENT EARLY

• Lower than expected blinded pooled event incidence (3.2%) compared with what was planned (8.5%) (41 out of planned 333)

• Falling death rate (~2% to 0.2% nationwide), falling hospitalization rate nationwide
  • Increased use of highly effective vaccines
  • Increased use of highly effective monoclonal antibodies
  • Beginning use of highly effective oral antivirals with significant treatment interactions with rivaroxaban precluding concomitant use

• Waning of the number of COVID-19 cases after Delta and Omicron surges
  • Delta and Omicron appeared less severe in terms of complications

• Very low likelihood to be able to achieve the required number of events
STUDY FLOW

11,200 Potential patients contacted to discuss study

1298 Patients screened

14 Patients screen failed

1284 Patients randomized and included in ITT Analysis

641 Assigned to rivaroxaban

42 Did not receive rivaroxaban

599 Received rivaroxaban

50 Discontinued rivaroxaban prematurely

1197 Patients included in the Safety Analysis

640 Completed study participation
   1 Withdrew consent
   0 Were lost to follow up

643 Assigned to placebo

45 Did not receive placebo

598 Received placebo

66 Discontinued placebo prematurely

641 Completed study participation
   2 Withdrew consent
   0 Were lost to follow up
### Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographics and Baseline Characteristics</th>
<th>Rivaroxaban (n=641)</th>
<th>Placebo (n=643)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, SD)</td>
<td>56.3 (13.1)</td>
<td>55.7 (13.3)</td>
</tr>
<tr>
<td>Sex (female) %</td>
<td>62.2</td>
<td>59.7</td>
</tr>
<tr>
<td>Race (non-white) %</td>
<td>27.5</td>
<td>27.8</td>
</tr>
<tr>
<td>Ethnicity (Hispanic or Latino) %</td>
<td>14.8</td>
<td>15.1</td>
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<tr>
<td>BMI (Median, SD)</td>
<td>32.6 (7.9)</td>
<td>33.1 (8.1)</td>
</tr>
<tr>
<td>Smoking Status %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>5.5</td>
<td>4.2</td>
</tr>
<tr>
<td>Former</td>
<td>30.3</td>
<td>27.4</td>
</tr>
<tr>
<td>Never</td>
<td>64.3</td>
<td>68.4</td>
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<tr>
<td>Stratum (Days after + COVID-19 test) %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1-5</td>
<td>50.2</td>
<td>49.9</td>
</tr>
<tr>
<td>Day 6-14</td>
<td>49.8</td>
<td>50.1</td>
</tr>
<tr>
<td>COVID-19 Vaccinated %</td>
<td>2.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Monoclonal Ab %</td>
<td>1.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Baseline aspirin use %</td>
<td>17.2</td>
<td>17.7</td>
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</table>

### Risk Factors (%)

<table>
<thead>
<tr>
<th>Risk Factors (%)</th>
<th>Rivaroxaban (n=641)</th>
<th>Placebo (n=643)</th>
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</thead>
<tbody>
<tr>
<td>Age ≥60 years</td>
<td>49.5</td>
<td>51.5</td>
</tr>
<tr>
<td>BMI ≥35 kg/m²</td>
<td>40.4</td>
<td>42.5</td>
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<tr>
<td>History of diabetes requiring Rx</td>
<td>22.0</td>
<td>20.7</td>
</tr>
<tr>
<td>History of cancer</td>
<td>11.9</td>
<td>13.2</td>
</tr>
<tr>
<td>History of CAD</td>
<td>5.6</td>
<td>5.1</td>
</tr>
<tr>
<td>Prior history of VTE</td>
<td>5.0</td>
<td>4.8</td>
</tr>
<tr>
<td>History of thrombophilia</td>
<td>3.3</td>
<td>2.0</td>
</tr>
<tr>
<td>History of CVD or ischemic stroke</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>History of PAD</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>D-dimer &gt; ULN (within 2 weeks of COVID-19 test)</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Subjects with 1 risk factor</td>
<td>65.4</td>
<td>63.1</td>
</tr>
<tr>
<td>Subjects with 2 risk factors</td>
<td>26.2</td>
<td>29.5</td>
</tr>
<tr>
<td>Subjects with 3 or more risk factors</td>
<td>8.1</td>
<td>7.3</td>
</tr>
</tbody>
</table>
PRIMARY EFFICACY OUTCOME
ITT vs mITT ANALYSIS SETS

**ITT (n=1284)**
- Primary Composite: Rivaroxaban 3.4, Placebo 3.0
- VTE: Rivaroxaban 0.0, Placebo 0.5
- Ischemic Stroke: Rivaroxaban 0.3, Placebo 0.3
- All Cause Hospitalization: Rivaroxaban 21, Placebo 17
- Death: Rivaroxaban 0.3, Placebo 0.3

**mITT (n=1197)**
- Primary Composite: Rivaroxaban 2.7, Placebo 2.5
- VTE: Rivaroxaban 0.0, Placebo 0.3
- Ischemic Stroke: Rivaroxaban 0.0, Placebo 0.3
- All Cause Hospitalization: Rivaroxaban 11, Placebo 15
- Death: Rivaroxaban 1, Placebo 2

Note: mITT = randomized participants who took at least one dose of study intervention
PRIMARY EFFICACY OUTCOME
ITT vs mITT ANALYSIS SETS

**ITT**

**mITT**
ADDITONAL ANALYSES
ITT ANALYSIS SET

First Major Secondary Outcome

Symptomatic VTE and Arterial Thrombotic Events and All-cause Mortality

Rivaroxaban
Placebo

HR: 0.29
(0.06, 1.37)
P=0.095

Log Rank P=0.025

Post Hoc Exploratory Outcome:
Symptomatic VTE and Arterial Thrombotic Events
SAFETY OUTCOMES: BLEEDING
SAFETY ANALYSIS SET

% with Outcome Event

- **Rivaroxaban**
- **Placebo**

<table>
<thead>
<tr>
<th>Outcome Event</th>
<th>Rivaroxaban</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal and Critical Site Bleeding</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ISTH Major Bleeding</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Non-major Clinically Relevant Bleeding</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Trivial Bleeding</td>
<td>2.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*p=0.01*
<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Arms</th>
<th>Primary Efficacy</th>
<th>Primary Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREVENT-HD</td>
<td>1284</td>
<td>Rivaroxaban 10 mg 1x/d vs. placebo for <strong>35</strong> days</td>
<td>↔ symptomatic VTE, MI, ischemic stroke, acute limb ischemia, non-CNS embolization, all-cause hospitalization, and all-cause mortality up</td>
<td>↔ ISTH critical site and fatal bleeding on treatment</td>
</tr>
<tr>
<td>ACTIV-4B</td>
<td>657</td>
<td>Aspirin 81 mg 1x/d vs. apixaban 2.5 mg 2x/d vs. apixaban 5 2x/d vs. placebo for <strong>45</strong> days</td>
<td>↔ all-cause mortality, symptomatic venous or arterial thromboembolism, MI, stroke, or hospitalization for cardiovascular or pulmonary cause</td>
<td>↑ ISTH major and clinically relevant nonmajor bleeding (aspirin/apixaban vs. placebo)</td>
</tr>
<tr>
<td>GATES MRI</td>
<td>497</td>
<td>Rivaroxaban 10 mg 1x/d vs. placebo for <strong>21</strong> days</td>
<td>↔ progression to moderate-severe disease, per Gates MRI scale</td>
<td>↔ adverse event</td>
</tr>
<tr>
<td>OVID</td>
<td>472</td>
<td>Enoxaparin 40 mg 1x/d vs. no prophylaxis for <strong>14</strong> days</td>
<td>↔ any hospitalization and all-cause death</td>
<td>↔ ISTH major bleed</td>
</tr>
<tr>
<td>APOLLO</td>
<td>411</td>
<td>Apixaban 2.5 mg 2x/d vs. placebo for <strong>30</strong> days</td>
<td>↔ days alive and out of the hospital</td>
<td>-</td>
</tr>
<tr>
<td>ETHIC</td>
<td>243</td>
<td>Enoxaparin 40 mg 1x/d or 2x/d (≥100 kg) vs. no prophylaxis for <strong>21</strong> days</td>
<td>↔ all-cause hospitalization and all-cause mortality</td>
<td>-</td>
</tr>
<tr>
<td>Gonzalez-Ochoa</td>
<td>243</td>
<td>Sulodexide 1,000 LRU 1x/d vs. placebo for <strong>21</strong> days</td>
<td>↓ need for hospital care</td>
<td>-</td>
</tr>
</tbody>
</table>
CONCLUSIONS

• Rivaroxaban, prescribed for 35 days in non-hospitalized patients with symptomatic COVID-19 at-risk for thrombosis, was not found to reduce a composite endpoint of venous and arterial thrombotic events, hospitalization, and death

• There was a significant reduction in venous and arterial thrombotic events

• Bleeding overall was low and generally consistent with the known safety profile of rivaroxaban

• With the caveat that the trial was underpowered to provide a definitive conclusion, these data do not support routine antithrombotic prophylaxis in non-hospitalized patients with symptomatic COVID-19
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Independent Data Monitoring Committee: James Douketis, Joshua Beckman, Michael Szarek

RED CAP Cloud: David Sunderhaft, Jaya Rao

Academic Research Organization: Colorado Prevention Center

Contract Research Organization: ICON

Sponsor: Janssen R&D

The numerous coordinators, patients and families that made this all possible
BACK UP SLIDES
Two years of coronavirus deaths in the United States

Average number of daily reported coronavirus deaths in the U.S.

May 2020
100K total deaths

February 2021
500K total deaths

February 2022
937K total deaths

Thrombotic Events in PREVENT-HD

★ = VTE
★ = Ischemic Stroke

Notes: Seven-day rolling average number of reported COVID-19 deaths. Excludes deaths in U.S. territories and those not assigned to a specific geographic location.

PEW RESEARCH CENTER
PREVENT-HD RANDOMIZED 1284 PARTICIPANTS AT 14 INTEGRATED HEALTH NETWORKS IN THE US

- Kaiser – Northern CA
- Kaiser – Southern CA
- Emory
- Atlanta VA
- Grady/Morehouse University
- Franciscan Research Center
- Mayo Clinic
- Henry Ford
- Northwell Health
- Meritus Health
- Northshore
- Texas Health
- University of Arizona
- University of Colorado
- Vanderbilt
- Advent Health

* Source: Janssen COVID Operational Tool, 7-AUG-2020
THANK YOU