Cardiac Implications due to COVID-19 Infections

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OUTLINE

- Incidence and Mortality
- Pathogenesis/ Mechanism
- Therapeutic Implication
- The New Paradigm of Microangiopathy / Thrombosis
INTRODUCTION

Cardiovascular Disease (CVD) Manifestation:

Pre-existing (underlying) CVD

De-novo (no underlying) CVD

National Health Commission of China (NHC)

Cardiovascular Disease (CVD) symptoms:

• Palpitations
• Chest tightness

Breathless:
• Respiratory problem
• Cardiovascular disease

Pre Existing CVD Comorbidity

Hypertension
Coronary Heart Disease
Chronic Kidney Disease, or Diabetes

Severe symptoms of COVID-19:
• 58% had Hypertension,
• 25% had Heart Disease
• 44% had Arrhythmia

Mortality data by NHC
35% history of hypertension
17% had a history of coronary heart disease

Underlying CVD ➔ Aggravate Pneumonia
Symptoms Severity

De Novo– No Underlying CVD

- Myocardial Injury associated with the Covid-19 occurred in 5 of the first 41 patients COVID-19 in Wuhan
  - ↑ in high-sensitivity cardiac troponin I (hs-cTnI) levels

- Another report of 138 in Wuhan, 36 patients with severe symptoms were treated in the ICU
  - ↑ (CK)-MB level and hs-cTnI level

- First autopsy of a 53-year-old woman with chronic renal failure in Jinyintan Hospital showed acute MI (data not published; personal communication with a pathologist from the Chinese Academy of Science)

- **Washington:** 1/3 critically ill COVID-19 develop Cardiomyopathy

## Predictor In Hospital Death

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk Factor Present</th>
<th>Risk Factor Absent</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;65 yr of age</td>
<td>147/1474 (10.0)</td>
<td>368/7436 (4.9)</td>
<td>1.93 (1.60–2.41)</td>
</tr>
<tr>
<td>Female sex</td>
<td>179/3571 (5.0)</td>
<td>336/5339 (6.3)</td>
<td>0.79 (0.65–0.95)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>103/1010 (10.2)</td>
<td>412/7900 (5.2)</td>
<td>2.70 (2.08–3.51)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>29/189 (15.3)</td>
<td>486/8721 (5.6)</td>
<td>2.48 (1.62–3.79)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>35/304 (11.5)</td>
<td>480/8606 (5.6)</td>
<td>1.95 (1.33–2.86)</td>
</tr>
<tr>
<td>COPD</td>
<td>32/225 (14.2)</td>
<td>483/8685 (5.6)</td>
<td>2.96 (2.00–4.40)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>46/491 (9.4)</td>
<td>469/8419 (5.6)</td>
<td>1.79 (1.29–2.47)</td>
</tr>
<tr>
<td>Receiving ACE inhibitor</td>
<td>16/770 (2.1)</td>
<td>499/8140 (6.1)</td>
<td>0.33 (0.20–0.54)</td>
</tr>
<tr>
<td>Receiving ARB</td>
<td>38/556 (6.8)</td>
<td>477/8354 (5.7)</td>
<td>1.23 (0.87–1.74)</td>
</tr>
<tr>
<td>Receiving statin</td>
<td>36/860 (4.2)</td>
<td>479/8050 (6.0)</td>
<td>0.35 (0.24–0.52)</td>
</tr>
</tbody>
</table>

Mortality and Cardiac Marker

Cardiac Implication of COVID-19

Cardiac Implication of COVID-19

- Direct vascular infection
- Systemic proinflammatory stimulation (cytokine storm)
- Hypercoagulability
- \(\uparrow\) Sympathetic stimulation
- Acute respiratory distress syndrome and superimposed infection

- \(\uparrow\) Vascular cellular inflammation
- Plaque rupture
- \(\uparrow\) Myocardial oxygen demand
- Hypoxia

\(\downarrow\) Myocardial oxygen supply

\(\uparrow\) MYOCARDIAL INFARCTION RISK
Cardiac Implication of COVID-19

Cardiac Implication of COVID-19

Viral infections

- Acute respiratory distress syndrome and superimposed infection
- Sympathetic stimulation
- Myocarditis myocyte necrosis
- Proinflammatory cytokines
- Direct myocardial infection

- Hypoxia
- Myocardial oxygen demand

- Myocardial oxygen supply

↑ HEART FAILURE RISK
Cardiac Implication of COVID-19

Heart Failure / Cardiomyopathy

Myocarditis
Proinflammatory effects
↑ Sympathetic stimulation

Heart Failure / Cardiomyopathy

↑ ARRHYTHMIAS RISK
The Link Between Covid-19 and Cardiac Involvement
Case of Acute Myopericarditis

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woman</td>
<td>53 y.o</td>
<td>Positive for Covid-19</td>
</tr>
</tbody>
</table>

**March, 2020**

- **Chief complain:** Severe fatigue for 2 days
- **Past medical history:** Fever and dry cough for 1 week before

Blood Pressure : 90/50 mmHg
Heart Rate : 100 b/m
Oxygen saturation: 98%
Temp : 36.6 celcius

**Case of Acute Myopericarditis**

**CHEST RADIOGRAPHY FINDING**

The patient did not show any respiratory involvement during the clinical course.

**ECHOCARDIOGRAPHY**

- Normal Dimension
- LVH
- Global Hypokinetic with LVEF 40%
- Mild PE

Case of Acute Myopericarditis

URGENT CORONARY ANGIOGRAPHY

Normal Coronary Angiographic findings.
Case of Acute Myopericarditis

CARDIAC MAGNETIC RESONANCE

- Diffuse Biventricular Hypokinetetic with LVEF 35%
- Myocardial Edema
  \[\text{Acute Myocarditis}\]
- Mild PE \[\text{Pericarditis}\]

Drug Related Heart Damage

Many antiviral drugs can cause cardiac insufficiency, arrhythmia, or other cardiovascular disorders.
Prone to Devastating Arrhythmia

Drug Interaction and Risk of Arrhythmia

Table 15 Arrhythmological considerations of novel experimental pharmacological therapies in COVID-19 infection

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>AV CONDUCTION</th>
<th>QRS INTERVAL</th>
<th>QTc INTERVAL</th>
<th>TDP RISK</th>
<th>AAD DRUGS INTERACTIONS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHLOROQUINE</strong></td>
<td></td>
<td>Mild †</td>
<td>Mild †</td>
<td>Moderate †</td>
<td>Very-low risk of TdP (72 cases of VF/VT/TdP/LQTS in FAERS registry)</td>
<td>SEVERE† Amiodarone, Flecainide, Mexiletine, Sotalol, Defi etilide MODERATE‡ Disopyramide, Propafenone, Quinidine, Digoxin MILD§ Metoprolol, Nebivolol, Propranolol, Timolol, V ersapamil</td>
<td>- Very low risk of cardiotoxicity during chronic therapy is reported(^{10,10}) - In a study in SLE it was negatively associated with AVB (P = 0.01) as was its longer use (6.1 ± 6.9 vs. 1.0 ± 2.5 years, P = 0.016)(^{10,12}) - Proarrhythmia occurs mostly with overdosage or in chronic therapy (&gt; years)(^{3,8}) - Proemetic effect is common - Risk of retinopathy, myopathy/neuropathy during chronic therapy is reported</td>
</tr>
<tr>
<td><strong>HYDROXY-</strong></td>
<td>Mild †</td>
<td>Mild †</td>
<td>Mild †</td>
<td>Moderate †</td>
<td>Very-low risk of TdP (222 cases of VF/VT/TdP/LQTS in FAERS registry)</td>
<td>See Chloroquine</td>
<td>- Very low risk of cardiotoxicity during chronic therapy is reported(^{10,10}) - Proarrhythmia occurs mostly with overdosage or in chronic therapy (&gt; years)(^{3,8}) - Less cardiotoxicity reported than with Chloroquine(^{2,9}) - In a study of pregnant women with Ro/La antibodies, AVBs were more frequent in those not using hydroxychloroquine(^{2,9})</td>
</tr>
<tr>
<td><strong>CHLOROQUINE</strong></td>
<td></td>
<td>(222) (^{1,2,9})</td>
<td>(222) (^{1,2,9})</td>
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<td>(222) (^{1,2,9})</td>
<td>(222) (^{1,2,9})</td>
</tr>
<tr>
<td><strong>AZITHROMYCINE</strong></td>
<td>Mild †</td>
<td>Mild †</td>
<td>Mild †</td>
<td>Moderate-Severe †</td>
<td>Low risk of TdP Cumulative incidence SCD = 64.6/1 million(^{1,2,9}) ROR for TdP = 4.76 compared to other</td>
<td>SEVERE† Amiodarone, Disopyramide, Defi etilide, Flecainide, Propafenone, Sotalol MODERATE§</td>
<td>In a study during treatment days 1 to 5, patients receiving azithromycin had significantly increased risk of serious arrhythmia (HR = 1.77, 95% CI, 1.20-2.62) compared with patients receiving amoxicillin(^{1,14})</td>
</tr>
</tbody>
</table>

ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic The European Society of Cardiology 2020.
<table>
<thead>
<tr>
<th>HR</th>
<th>AV CONDUCTION</th>
<th>QRS INTERVAL</th>
<th>QTc INTERVAL</th>
<th>TDP RISK</th>
<th>AAD DRUGS INTERACTIONS*4</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOPINAVIR/RITONAVIR</td>
<td>NR</td>
<td>Moderate†</td>
<td>Mild ‡</td>
<td>Moderate ‡</td>
<td>Low risk of TdP (27 cases of Vf/VT/TP/LQTS in FAERS registry)</td>
<td>SEVERE* Amiodarone, Dronedarone, Disopyramide, Doxetilide, Flecaïnide, Sotalol</td>
</tr>
<tr>
<td>TOCILIZUMAB</td>
<td>No ECG changes described*36</td>
<td>Unknown</td>
<td>Mild †</td>
<td>Unknown</td>
<td>MILD* Amiodarone, Quindine</td>
<td></td>
</tr>
<tr>
<td>FINGOLIMOD/SIPONIMOD</td>
<td>Moderate-Severe †</td>
<td>Mild-moderate †</td>
<td>Unknown</td>
<td>Mild †</td>
<td>Unknown</td>
<td>MODERATE* Beta-blockers, Ca2+ blockers, Iabasénone, Amiodarone, Flecaïnide, Propafenone</td>
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<td></td>
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<td>* In a study of 3591 patients, 31 patients (0.8%) developed bradycardia (&lt;45 bpm), 62 patients (1.6%) had second-degree Mobitz I and/or 2:1 AV blocks*199,</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>* In study of 5573 patients new-onset first-degree AVB was experienced by 122 (2.4%) in-home and 74 (0.5%) in-clinic patients, and Wenckebach (Mobitz type I) second-degree AVB by four (0.07%) and nine (0.1%) patients, with no cases of third-degree AVB*199,</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>* In study of 66 patients with MS fingolimod lead to an increase of vagal activation which persisted even after 14 months of treatment*137,</td>
</tr>
<tr>
<td>REMDESIVIR</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
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<tr>
<td>INTERFERON ALFACON-1</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>RIBAVIRIN</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>METILPREDNISOLONE</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
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<td>Unknown</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>* High dose intravenous prednisolone might cause acute sinus bradycardia<em>20 or in MS patients sinus tachycardia, bradycardia and rarely AF and VT</em>304,</td>
</tr>
</tbody>
</table>

ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic The European Society of Cardiology 2020.
The Importance of QTc

Obtain Baseline ECG

A: if not on any QT prolonging agents, K / Mg within normal limits, and most recent ECG is within 30 days, a new ECG may not be necessary.
B: Ideally, discontinue QT prolonging agents.

Normal Baseline QT
- QTc < 470 ms
- QTc < 500 ms in wide QRS patient
  - Administer Hydroxychloroquine
  - Obtain ECG 2 hours after 2nd dose (of 400 mg)

Marginal Baseline QT
- QTc 470 – 500 ms
- QTc 500 – 550 ms in wide QRS patient
  - Caution Required

Abnormal Baseline QT
- QTc > 500 ms
- QTc > 550 ms in wide QRS patient
  - Do not start Hydroxychloroquine
  - Discuss risk/benefit pre-initiation

Notes:
- High risk patients for development of Torsade de Pointes, who should be considered for continuous telemetry monitoring include those with LV dysfunction (LV EF <40%)
- Wide QRS defined as > 120 ms
- Must discontinue drug for any evidence of Torsade de Pointes

Version 1.1 (March 22, 2020)
How to Manage The Deadly Combination?

The New Paradigm of Microangiopathy / Thrombosis
Clinical Manifestation of Microangiopathy Thrombosis

Covid-19 Blue Toes

Lacey Livodoid Rash

Potential Therapeutic Strategy
Mount Sinai COVID-19 Anticoagulation Algorithm

Version 1.1 (April 9, 2020)

Admitted patients with moderate or severe COVID-19

**High Risk**
- ↑ O₂ requirement
- ↑ D-dimers
- ↑ creatinine
- ↑ CRP

**Yes**
- Apixaban 2.5-5mg PO BID
  - or
  - Enoxaparin SC 40mg QD

**No**
- **Yes**
- **No**
  - **Yes**
    - Enoxaparin SC 1mg/kg BID
  - **No**
    - **Yes**
      - Apixaban 5mg PO BID (or heparin drip per PE protocol)
    - **No**
      - **Yes**
        - Apixaban 5mg BID
        - or Adjusted Dose Enoxaparin
      - **No**

**Admitted to an ICU?**

**Yes**
- Heparin drip per PE protocol (goal PTT 70 - 110) or Enoxaparin SC 1mg/kg BID.
  - Consider IPA protocol.

**No**
- **Yes**
  - **No**

**CrCl >50**
- **Yes**
  - **No**

**On RRT†**

**Inclusion:** All admitted patients with moderate or severe COVID-19

**Exclusion:** High risk of bleeding as judged by treating physician

**Obtain at baseline and daily:**
- CBC, PT/PTT, D-dimer

**Hold anticoagulation if:**
- Platelet count <50,000; INR>1.5
- Evidence of current or recent bleeding

**If patients take AC at home:**
- May switch to therapeutic enoxaparin or heparin (as per algorithm) for the duration of hospitalization, unless contraindicated

**Rivaroxaban may be used in place of Apixaban at any indication**

**Discharged COVID-19 patient on therapeutic anticoagulation while hospitalized**

**Consider Prophylactic AC for 2 weeks post discharge (Apixaban 5mg PO BID for 2 wks)**

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**#High Risk:** No precise metrics exist. Consider exam (eg O₂ sat<90%, RR >24), ↑O₂ requirement (eg, ≥4L NC), labs (eg, ↑d-dimers, C-reactive protein)

**↑RRT – Renal Replacement Therapy**

**↑ If ≥80 years of age or weight ≤60 kg, reduce apixaban to 2.5 mg BID**

**If CrCl <30: enoxaparin 0.5mg/kg BID with anti-Xa level after 3rd dose**

**Efficacy and dose not established; prophylactic or treatment doses acceptable**
Covid-19 has a broad cardiac implications that can lead to devastating outcome especially with pre-existing CVD

Covid-19 has several pathological mechanism that might result in ACS, Myocarditis, HF / Cardiomyopathy and Arrhythmia

Drug to drug interaction and Covid-19 pathology could cause malignant arrhythmia and should be warrant

Microangiopathic thrombosis should be recognized as a new therapeutic strategy
THANK YOU
The ACE-2 Pathway

Controversies of ACE-I/ARB in Preexisting CVD Treatment

Controversies of ACE-I/ARB in Prexisting CVD Treatment

ACEI/ARB Strategy

Hypertension Hospitalized With COVID-19

User of ACEI/ARB before COVID-19

You May Continue or Give ACEI/ARB in COVID-19 patient

Naive

ACEI/ARB Strategy

Any patient taking an ACE-1 inhibitor or an ARB

For current benefits, e.g. severe or uncontrolled hypertension or heart failure

1. Benefits outweigh risk of coronavirus infection
   - Continue

2. Standard risk of coronavirus infection
   - Continue
   - Stop

3. High risk of coronavirus infection: household contacts, healthcare workers
   - Consider stopping

For long-term benefits, e.g. well-controlled mild hypertension

- Continue
- Resume

No COVID-19

Positive for COVID-19

Recovered from COVID-19

CEBM – University of Oxford, EK, 2020
AFC Position Statement on ACE-I and ARBs use related to COVID-19 outbreak

Scientists have shown that COVID-19 glycoprotein binds to the cell membrane protein angiotensin-converting enzyme 2 (ACE-2) to enter human cells. The structure of the ACE-2 receptor protein is on the surfaces of the respiratory cells. To COVID-19, ACE-2 is a receptor, an entranceway, in the airways and alveolus, as well as in blood vessel linings. Hypothetically, treatment with ACE-I or ARBs could possibly amplify the effects of COVID-19 and that patients on these antihypertensives may fare worse. Some medical professionals have become concerned and patients have possibly stopped taking ACE-I or ARBs medication.

However, there is no clinical evidence or trial in human to show that we should discontinue ACE inhibitors or ARBs as stopping these drugs could precipitate acute events and worsened cardiac failure. There is currently no guideline that stated otherwise. The AFC (ASEAN Federation of Cardiology) would like to emphasize that this speculation of the unsafety of ACE-I or ARBs pertinent to COVID-19 is not evidence-based.

The American Heart Association, American College of Cardiology, European Society of Cardiology, European Society of Hypertension, and International Society of Hypertension have all issued similar recent statements urging continuation of the renin-angiotensin-aldosterone system antagonists in patients, despite theoretical concerns that their use might worsen outcomes in the event of infection with COVID-19.

Anwar Santoso, M.D., Ph.D., F.A.S.C.C
President of AFC

Ng Wei Kit, M.D., F.A.S.C.C
Secretary General of AFC
<table>
<thead>
<tr>
<th>Features</th>
<th>Common findings in vasculitides</th>
<th>Severe CoViD-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious Triggers</td>
<td>Many known viral triggers: Hepatitis</td>
<td>SARS-CoV-2</td>
</tr>
<tr>
<td>Lung</td>
<td>B/C, Varicella, HIV, Epstein-Barr Virus, Cytomegalovirus, SARS-CoV-1</td>
<td>Organizing pneumonia, modest peri-vascular inflammation.</td>
</tr>
<tr>
<td>Reported organ involvement</td>
<td>CV, neuro, GI, renal, skeletal muscle</td>
<td>Cardiomyopathy, renal, gastrointestinal Anosmia, Delirium</td>
</tr>
<tr>
<td>Thrombotic events</td>
<td>Arterial / venous involvement. (Varies by specific disease).</td>
<td>Massive d-dimer elevations that correlates with death. DVT, pulmonary embolism, catheter thrombosis</td>
</tr>
<tr>
<td>Systemic inflammation</td>
<td>Mildly elevated inflammatory cytokines. (IL-6 generally &lt; 100)</td>
<td>Mildly elevated inflammatory cytokines (IL-6 generally &lt; 100)</td>
</tr>
<tr>
<td></td>
<td>Low albumin.</td>
<td>Low albumin, PCT</td>
</tr>
</tbody>
</table>

Abbreviations: HIV – Human immunodeficiency virus; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; PCT – procalcitonin; ECMO – extra-corporeal membrane oxygenation; DVT – deep venous thrombosis
Mount Sinai COVID-19 Anticoagulation Algorithm

Definition of high risk for progression to ICU
- There is insufficient evidence to precisely define “high-risk” or provide specific cut-off values for individual factors
- Clinicians should consider a combination of exam findings (e.g., labored breathing, RR >24, decreased O₂ sat<90%), increased O₂ requirement (eg, ≥4L NC), and lab biomarkers (eg, elevated CRP, elevated creatinine, rising d-dimer >1.0).

Rationale for early anticoagulation
- Pathophysiology of COVID-19 associated respiratory disease is consistent with pulmonary vascular thromboemboli with increased dead space ventilation
- Autopsy studies have demonstrated venous thromboembolism in deceased coronavirus patients¹
- Early anticoagulation is necessary to prevent propagation of microthrombi at disease presentation
- Anticoagulation may be associated with decreased mortality²

Rationale for choice of anticoagulant
- Heparins bind tightly to COVID-19 spike proteins³,⁴
- Heparins also downregulate IL-6 and directly dampen immune activation⁵
- DOACs do not appear to have these anti-inflammatory properties
- Rivaroxaban can be used in place of Apixaban in this algorithm

References
## Incidence of Thrombosis in COVID-19

| Venous and arterial thromboembolic events in hospitalized COVID-19 patients. |
|---|---|---|---|
| **Thromboembolic events** | **Intensive care unit** | **General ward** | **Total** |
| | **n** | % of closed cases (n = 48) | % of imaging tests performed* | **n** | % of closed cases (n = 314) | % of imaging tests performed* | **n** | % of closed cases (n = 362) | % of imaging tests performed |
| At least one thromboembolic event | 8 | 16.7% (95%CI 8.7%–29.6%) | – | 20 | 6.4% (95%CI 4.2%–9.6%) | – | 28 | 7.7% (95%CI 5.4%–11.0%) | – |
| VTE | 4 | 8.3% | 22% | 12 | 3.8% | 46% | 16 | 4.4% | 36% |
| PE (± DVT) | 2 | 4.2% | 25% | 8 | 2.5% | 36% | 10 | 2.8% | 33% |
| Isolated pDVT | 1 | 2.1% | 7% | 3 | 1.0% | 44% | 4 | 1.1% | 21% |
| Isolated dDVT | 0 | – | – | 1 | 0.3% | 13% | 1 | 0.3% | 13% |
| Catheter-related DVT | 1 | 2.1% | 50% | 0 | – | – | 1 | 0.3% | 50% |
| Ischemic stroke | 3 | 6.3% | – | 6 | 1.9% | – | 9 | 2.5% | – |
| ACS/MI | 1 | 2.1% | 3% | 1 | 1.0% | – | 4 | 1.1% | – |

ACS, acute coronary syndrome; DVT, deep vein thrombosis; MI, myocardial infarction; pDVT, proximal deep vein thrombosis; dDVT, distal DVT; PE, pulmonary embolism; VTE, venous thromboembolism.