ASH Guidelines on Use of Anticoagulation in Patients with COVID-19

October 8, 2020

* This session is being recorded *
Disclosures

- Frederikus A Klok reports research grants from Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, MSD and Actelion, the Dutch Heart foundation, the Netherlands Organisation for Health Research and Development and the Dutch Thrombosis association, all outside this work.

- Dr. Siegal reports payments from BMS-Pfizer, Leo Pharma, and Portola for consulting, all concluding in April 2020. She also reports ongoing research funding from Novartis and is an unpaid member of board of directors for Thrombosis Canada.

- Dr. Nieuwlaat and Dr. Cuker have no conflicts to disclose.
Housekeeping

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• Please submit questions as they arise. You do not have to wait for the end of a session to pose a question.

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ASH Guidelines on Use of Anticoagulation in Patients with COVID-19

Robby Nieuwlaat, PhD, MSc

McMaster University
Methods

Overall
• GRADE methodology for guideline recommendation development
• Cochrane methodology for systematic reviews

Initial Phase
• PICO question generation and prioritization
• Selection of critical outcomes
• Systematic review for baseline risk estimates
• Systematic review for effect of different anticoagulation intensities

Living Phase
• Monthly updated searches for baseline risk estimates and prognostic factors
• Monthly updated searches for effect of different anticoagulation strategies
• Revisiting guideline recommendations if new evidence meets pre-specified criteria
Recommendation

Evidence synthesis

P | I | C | O

Outcome Critical
Outcome Critical
Outcome Important
Outcome Not important

Summary of findings & estimate of effect for each outcome

Grade overall quality of evidence across outcomes based on lowest quality of critical outcomes

Randomization raises initial quality
RCTs: high
Observational: low

1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade down
Grade up

1. Large effect
2. Dose response
3. Opposing bias & confounders

Grade recommendations (Evidence to Recommendation)
• For or against (direction) ↓↑
• Strong or conditional/weak (strength)

By considering balance of consequences (evidence to recommendations):
- Quality of evidence
- Balance benefits/harms
- Values and preferences
- Feasibility, equity and acceptability
- Resource use (if applicable)

EID framework GRADEpro

Formulate Recommendations (↓↑ | ⊕…)
“The panel recommends that ….should...”
“The panel suggests that ….should...”
“The panel suggests to not ...”
“The panel recommends to not...”

Transparency, clear, actionable Research?

Guideline

By considering balance of consequences (evidence to recommendations):
- Quality of evidence
- Balance benefits/harms
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EID framework GRADEpro

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Transparency, clear, actionable Research?
PICO Question Generation & Prioritization

- Brainstorming: inclusive list of potential PICO questions to address
- Importance rating: selecting the PICO questions with the most critical importance

Critically ill COVID-19

- Prophylactic intensity
  - Intermediate intensity
  - Therapeutic intensity

Acutely ill COVID-19

- Prophylactic intensity
  - Intermediate intensity
  - Therapeutic intensity
Outcome Selection

• Brainstorming: inclusive list of potential outcomes to address
• Importance rating: selecting the most critical outcomes for key stakeholders
  ➢ Using Health Outcome Descriptors (marker states) - https://ms.gradepro.org/

Critical Outcomes

• All-cause mortality
• Pulmonary embolism
• Deep venous thrombosis
• Major bleeding
• Multi-organ failure
• Ischemic stroke
• Intracranial hemorrhage/hemorrhagic stroke
• Invasive mechanical ventilation
• Limb amputation
• ICU admission
• ST-elevation myocardial infarction
Evidence for Effect of the Intervention

Baseline Risk  
5 per 1,000

Relative Effect  
RR = 0.40

Absolute Effect  
3 per 1,000 fewer
# GRADE Certainty of Evidence

**Table: GRADE’s approach to rating quality of evidence (aka confidence in effect estimates)**

For each outcome based on a systematic review and across outcomes (lowest quality across the outcomes critical for decision making)

<table>
<thead>
<tr>
<th>Study design</th>
<th>Initial confidence in an estimate of effect</th>
<th>Reasons for considering lowering or raising confidence</th>
<th>Confidence in an estimate of effect across those considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trials</td>
<td>High confidence</td>
<td>Lower if: Risk of Bias, Inconsistency, Indirectness, Imprecision, publication bias</td>
<td>High</td>
</tr>
<tr>
<td>Observational studies</td>
<td>Low confidence</td>
<td>Higher if: Large effect, Dose response, All plausible confounding &amp; bias, would reduce a demonstrated effect or would suggest a spurious effect if no effect was observed</td>
<td>Moderate</td>
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<td></td>
<td></td>
<td></td>
<td>Low</td>
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</table>

*upgrading criteria are usually applicable to observational studies only.
Baseline Risk – Systematic Review

- Incidence rate of selected outcomes:
  - In the two populations of interest
  - Among patients receiving prophylactic intensity anticoagulation

- Required:
  - Not high risk of bias (according to simplified QUIPS)
  - Reporting duration of follow-up

- Initial search date: 23-JUL-2020
- Screened: 14,816 citations
- Included: 51 Studies

- Analysis:
  - Pooled estimates using generalized linear mixed model
  - Descriptive, if only one study identified, or when pooling was considered in appropriate
Effect of Anticoagulation – Systematic Review

- Comparison of two or more anticoagulation intensities for prevention of VTE:
  - In the two populations of interest
  - Primarily addressing Prophylactic vs. Intermediate/Therapeutic intensity
- Required:
  - Pre-defined definitions for Prophylactic, Intermediate, Therapeutic intensity
  - Risk of bias assessed with ROBINS-I
- Initial search date: 20-AUG-2020
- Screened: 3,118 citations
- Included: 12 Studies
- Analysis:
  - Descriptive analysis of adjusted relative effect estimates
  - Pooling unadjusted relative effect estimates in meta-analysis
Evidence for Other Domains

• The panel considered additional Evidence-to-Decision domains to generate the recommendations:
  – Resource use
  – Cost-effectiveness
  – Health equity
  – Acceptability
  – Feasibility

• Evidence for these domains was also sought in the two reviews

• COVID-19 specific evidence not yet identified – the panel mainly relied on evidence from the ASH guidelines for the management of hospitalized medically ill patients, and their expertise
Living Phase – Systematic Reviews

Overall
• Monthly search updates
• Using explicit criteria for updating analyses and publication with new important information

Baseline risk
• Add evidence on prognostic factors
• Search strategy & eligibility criteria may become narrower as quantity and quality of evidence increases
• Use of machine learning to make regular screening manageable

Effect of anticoagulation intensity
• Search strategy & eligibility criteria may focus on RCTs as they become available
• Update analyses with new important data (explicit criteria)
Living Phase – Recommendations

• Continue to work closely with panel and systematic review team
• Reconsider recommendations when important new evidence is identified
• Using explicit criteria for reconsidering recommendations
  – Changes in the evidence of effects (certainty, direction, magnitude)
  – Changes in the evidence for other Evidence-to-Decision domains (cost-effectiveness, equity, others)
• Publish updated recommendations and supporting documents

Timely advice for decision-makers
Living Recommendations Process

Fig. 2. The main steps of the living guideline process, focused on the unit of update, that is, the living recommendation.
Main Challenges

Evidence

• Large number of citations
• Incomplete reporting
• Risk of bias
• Imprecision
• Evolving field in Living phase

Recommendation formulation process

• Very low certainty evidence
• Not relying on non-COVID-19 evidence
• Criteria to reconsider recommendations with important new evidence in Living phase
• Provide timely and stable guidance
Acknowledgements

Guideline Panel

Pantep Angchaisuksiri, MD (Ramathibodi Hospital, Mahidol University, Bangkok, Thailand)
Clifton Blair (Union, New Jersey) / Patient Representative
Adam Cuker, MD, MS (University of Pennsylvania) / Clinical Co-chair
Kathryn E. Dane, PharmD (Johns Hopkins Hospital)
Jennifer Davila, MD (Children's Hospital at Montefiore)
Maria DeSancho, MD, MSc (Weill Cornell Medicine)
David L. Diuguid, MD (Columbia University)
Daniel Griffin, MD, PhD (Columbia University and ProHealth Care, New Hyde Park, NY)
Susan R. Kahn, MD, MSc (McGill University)
Frederikus A. Klok, MD, PhD (Leiden University Medical Center Einthoven Laboratory)
Alfred Ian Lee, MD, PhD (Yale School of Medicine)
Reem Mustafa, MBBS, PhD, MPH (University of Kansas) / Methodology Co-chair
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Ashok Pai, MD (Kaiser Permanente, Oakland Medical Center)
Menaka Pai, MD, MSc (McMaster University) / Ex Officio, Guideline Oversight Subcommittee
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Kristen M. Sanfilippo, MD, MPH (Washington University in St. Louis)
Holger Schünemann, MD, PhD (McMaster University) / Methodology Co-chair
Deborah Siegal, MD, MSc (McMaster University)
Mike Skara (Cottage Grove, Indiana) / Patient Representative
Kamshad Touri (Ontario, Canada) / Patient Representative
Eric K. Tseng, MD, MSc (St. Michael's Hospital, Toronto) / Writer
Acknowledgements

Methods Team
Reem Mustafa, Robby Nieuwlaat, Holger Schünemann, Elie Akl, Kendall Alexander, Romina Brignardello-Petersen, Adam Cuker, Karin Dearness, Rob Kunkle, Ignacio Neumann, Eddrika Russell, Karla Solo, Adrienne Stevens, Wojtek Wiercioch

Systematic Review Team
Reyad Al Jabiri, Yazan Al Jabiri, Kendall Alexander, Antonio Bognanni, Imad Bouakl, Mary Boulos, Emma Cain, Matthew Chan, Rana Charide, Andrea Darzi, Samer Karam, Philipp Kolb, Claudia Li, Luis Enrique Colunga Lozano, Razan Mansour, Gian Paolo Morgano, Rami Morsi, Atefeh Noori, Thomas Piggott, Yuan Qiu, Yetiani Roldan, Finn Schünemann, Giovanna Schünemann, Holger Schünemann, Matthew Ventresca, Wojtek Wiercioch, Robby Nieuwlaat, Karla Solo
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Erik Klok, MD, PhD

Leiden University Medical Center
## Case Presentations

<table>
<thead>
<tr>
<th>Patient T</th>
<th>Patient K</th>
</tr>
</thead>
<tbody>
<tr>
<td>♂, Chinese, 73 years</td>
<td>♂, Caucasian, 52 years</td>
</tr>
<tr>
<td>BMI 34 kg/m², DM, hypertension</td>
<td>BMI 23 kg/m², Asthma</td>
</tr>
<tr>
<td>COVID-19 day 10</td>
<td>COVID-19 day 6</td>
</tr>
<tr>
<td>High fever, dyspneic at rest</td>
<td>Anosmia, shortness of breath with exercise</td>
</tr>
<tr>
<td>HR 123/min, RR 42/min, Sat 83% at 15L O2</td>
<td>HR 95/min, RR 20/min, sat 90% at room air</td>
</tr>
</tbody>
</table>
• What would be the optimal anticoagulant strategy in these 2 patients?
COVID-19 coagulopathy: initial reports (China)

Wang D et al, JAMA 2020  
Zhou F et al, Lancet 2020
COVID-19 coagulopathy: initial reports (China)

➢ Occurrence of VTE not mentioned

Wang D et al, JAMA 2020
Zhou F et al, Lancet 2020
COVID-19 coagulopathy: initial reports (Europe)
COVID-19 coagulopathy: initial reports (Europe)

- Incidence of VTE on ICU 17-70%
COVID-19 coagulopathy: autopsy studies

Wichmann D et al, Ann Int Med 2020
COVID-19: incidence of VTE

- 9.5% (95%CI 7.5-12)
- 40% (95%CI 27-54)

Nopp S et al, RPTH 2020
Pathophysiology of increased VTE risk

Price LC et al, Eur Respir J 2020
Beneficial non-anticoagulant mechanisms?

- Reduces viral entry to host cells
- Reduces NET formation
- Inhibits heparanase
Intensive anticoagulant therapy beneficial?

- High incidence of VTE
- Beneficial non-anticoagulant mechanisms (?)

- Immunothrombosis
- Overdiagnosis of VTE (?)
ASH Guidelines on Use of Anticoagulation in Patients with COVID-19

Deborah Siegal, MD, MSc

University of Ottawa
Recommendations for anticoagulant dose intensity in patients with COVID-19 who do not have suspected or confirmed venous thromboembolism

- Critically ill patients
- Acutely ill patients
How patients and clinicians should use these recommendations

<table>
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<tr>
<th></th>
<th><strong>STRONG Recommendation</strong></th>
<th><strong>CONDITIONAL Recommendation</strong></th>
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<tr>
<td><strong>For patients</strong></td>
<td>Most individuals would want the intervention.</td>
<td>A majority would want the intervention, but many would not.</td>
</tr>
<tr>
<td><strong>For clinicians</strong></td>
<td>Most individuals should receive the intervention.</td>
<td>Different choices will be appropriate for different patients, depending on their values and preferences. Use shared decision making.</td>
</tr>
</tbody>
</table>
What these guidelines are about

Anticoagulants carry **benefits** (reducing venous thromboembolism) and **risks** (life-threatening bleeding).

Recognizing and **mitigating risk for harm** from anticoagulants requires evidence-based approach to management.

This guideline focuses on **anticoagulant dose intensity** for critically ill and acutely ill hospitalized patients with COVID-19 who do not have suspected or confirmed venous thromboembolism.
### Case 1: COVID-19 Related Critical Illness

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Question #1

Should DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate- or therapeutic-intensity vs. prophylactic-intensity be used for patients with COVID-19 related critical illness who do not have suspected or confirmed VTE?
Should DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate-intensity or therapeutic-intensity vs. prophylactic intensity be used for patients with COVID-19 related critical illness who do not have suspected or confirmed VTE?

<p>| POPULATION: | Patients with COVID-19 related <strong>critical illness</strong> who do not have suspected or confirmed VTE |
| INTERVENTION: | DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate-intensity or therapeutic-intensity |
| COMPARISON: | Prophylactic-intensity |
| MAIN OUTCOMES: | Mortality; Pulmonary embolism; Proximal lower extremity DVT; Venous thromboembolism; Major bleeding; Multiple Organ Failure; Ischemic stroke; Intracranial hemorrhage; Invasive ventilation; Limb amputation; ICU hospitalization; ST-elevation myocardial infarction; |</p>
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<td>236 per 1,000</td>
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<td>88 fewer per 1,000 (96 fewer to 40 fewer)</td>
<td></td>
</tr>
<tr>
<td><strong>PROXIMAL LOWER EXTREMITY DVT</strong></td>
<td></td>
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<tr>
<td>follow up: range 14 days to 20 days</td>
<td>41 (1 study)</td>
<td>🎧◯◯◯◯ VERY LOW</td>
<td>OR 0.35 (0.06 to 2.02)</td>
<td>106 per 1,000</td>
<td>66 fewer per 1,000 (99 fewer to 87 more)</td>
<td></td>
</tr>
<tr>
<td><strong>VTE (DVT or PE)</strong></td>
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<tr>
<td>follow up: range 18 days to 28 days</td>
<td>118 (2 studies)</td>
<td>🎧◯◯◯◯ VERY LOW</td>
<td>OR 0.87 (0.45 to 1.67)</td>
<td>130 per 1,000</td>
<td>15 fewer per 1,000 (67 fewer to 70 more)</td>
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<tr>
<td><strong>MAJOR BLEEDING</strong></td>
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<tr>
<td>follow up: mean 16 days</td>
<td>141 (1 study)</td>
<td>🎧◯◯◯◯ VERY LOW</td>
<td>OR 3.84 (1.44 to 10.21)</td>
<td>84 per 1,000</td>
<td>176 more per 1,000 (33 more to 400 more)</td>
<td></td>
</tr>
</tbody>
</table>
The ASH guideline panel suggests using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation in patients with COVID-19 related critical illness who do not have suspected or confirmed VTE. The panel agreed that there was less uncertainty regarding the influence on undesirable effects (bleeding) compared with desirable effects (mortality and VTE). This was driven by extensive indirect evidence of dose-dependent effects of anticoagulation on bleeding.
Case 2: COVID-19 related acute illness

<table>
<thead>
<tr>
<th>Patient K</th>
</tr>
</thead>
<tbody>
<tr>
<td>♂, Caucasian, 52 years</td>
</tr>
<tr>
<td>BMI 23 kg/m², Asthma</td>
</tr>
<tr>
<td>COVID-19 day 6</td>
</tr>
<tr>
<td>Anosmia, shortness of breath with exercise</td>
</tr>
<tr>
<td>HR 95/min, RR 20/min, sat 90% at room air</td>
</tr>
</tbody>
</table>
Question #2

Should DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate-intensity or therapeutic-intensity vs. prophylactic-intensity be used for patients with COVID-19 related acute illness who do not have suspected or confirmed VTE?
Should DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate-intensity or therapeutic-intensity vs. prophylactic-intensity be used for patients with COVID-19 related acute illness who do not have suspected or confirmed VTE?

**POPULATION:**
Patients with COVID-19 related *acute illness* who do not have suspected or confirmed VTE

**INTERVENTION:**
DOACs, LMWH, UFH, fondaparinux, argatroban, or bivalirudin at intermediate-intensity or therapeutic-intensity

**COMPARISON:**
Prophylactic-intensity

**MAIN OUTCOMES:**
All-cause mortality; Pulmonary embolism; Proximal lower extremity DVT; Venous thromboembolism; Major bleeding; Multiple organ failure; Ischemic stroke; Intracranial hemorrhage; Invasive ventilation; Limb amputation; ICU hospitalization; ST-elevation myocardial infarction;
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Nº of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects (95% CI)</th>
<th>Risk with prophylactic-intensity</th>
<th>Risk difference with anticoagulation at intermediate- or therapeutic-intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALL-CAUSE MORTALITY</strong></td>
<td>2626 (1 study)</td>
<td>⬤⬤⬤⬤ VERY LOW</td>
<td>HR 0.86 (0.73 to 1.02)</td>
<td>148 per 1,000</td>
<td>19 fewer per 1,000 (38 fewer to 3 more)</td>
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<tr>
<td>follow up: 14 days</td>
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<tr>
<td><strong>PE</strong></td>
<td>82 (1 study)</td>
<td>⬤⬤⬤⬤ VERY LOW</td>
<td>OR 0.09 (0.02 to 0.57)</td>
<td>16 per 1,000</td>
<td>15 fewer per 1,000 (16 fewer to 7 fewer)</td>
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<tr>
<td>follow up: range 4 days to 28 days</td>
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<td><strong>PROXIMAL LOWER EXTREMITY DVT</strong></td>
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<tr>
<td><strong>VTE</strong></td>
<td>0 (1 study)</td>
<td>-</td>
<td>-</td>
<td>0/19 (0%) on therapeutic (other indications) vs. 39/179 (22%) on proph/intermediate (1 study).</td>
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<tr>
<td><strong>MAJOR BLEEDING</strong></td>
<td>0 (2 studies)</td>
<td>⬤⬤⬤⬤ VERY LOW</td>
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<td>Baseline (2 studies, range 2.0% to 3.1%); 0/19 (0%) on therapeutic (other indications) vs. 39/179 (22%) on proph/intermediate (1 study).</td>
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<td>Pooled baseline risk of 1.7% (5 studies); Follow-up 4 to 12 days: lowest OR 1.42 and highest adjusted HR 3.89 (7 more to 46 more major bleeds per 1000 patients)</td>
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<tr>
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</table>
Recommendation

The ASH guideline panel suggests using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation in patients with COVID-19 related acute illness who do not have suspected or confirmed VTE.

The panel agreed that there was less uncertainty regarding the influence on undesirable effects (bleeding) compared with desirable effects (mortality and VTE). This was driven by extensive indirect evidence of dose-dependent effects of anticoagulation on bleeding.

Conditional recommendation based on very low certainty in the evidence about effects:

- Individualized assessment
- No validated risk assessment models for in patients with COVID-19
- No direct high-quality evidence comparing different anticoagulants
### Very low certainty of evidence

#### Baseline risk studies
- Lack of definitions and/or descriptions of outcome measurement
- Incomplete/missing follow-up
- Incidence rates not reported (i.e. events per unit of follow-up)

#### Effect of anticoagulation studies
- Confounding with use of higher intensities in selected patients
- Lack of details regarding reported anticoagulant intensities
Thank you for joining today’s webinar!

• Visit [www.hematology.org/COVIDguidelines](http://www.hematology.org/COVIDguidelines) for access to:
  – Recommendations for anticoagulation in critically and acutely ill patients
  – Public comment open until October 16th
  – Links to full evidence profiles and evidence to decision tables

• Visit [www.hematology.org/covid-19](http://www.hematology.org/covid-19) for access to:
  – FAQs about COVID-19 and clinical hematology topics
  – Data summaries from the ASH RC COVID-19 registry for hematology
  – Resources for clinicians, researchers, and trainees

• Visit [www.ashondemand.org](http://www.ashondemand.org) to view this webinar recording on ASH On Demand.

• If you have questions or feedback, please contact [quality@hematology.org](mailto:quality@hematology.org)
Question & Answer Panel

• Use the Q&A box to send in questions to the presenters.