Thrombose et COVID-19

Marc Carrier

Université d’Ottawa

Divulgation des conflits d'intérêts possibles du conférencier

Type d'affiliation	Noms
Je suis membre d'un comité consultatif ou d'un comité similaire pour une organisation commerciale.	Bayer, BMS, Servier, Leo Pharma, BMS, Pfizer, Sanofi
J'ai été rétribué par une organisation commerciale (notamment au moyen de cadeaux).	
J'ai reçu une subvention ou des honoraires d'une organisation commerciale.	
Je participe (ou j'ai participé au cours des deux dernières années) à un essai clinique.	Leo Pharma, BMS, Pfizer

Objectifs

- Discuter de l’incidence de la thromboembolie veineuse (TEV) et artérielle chez les patients hospitalisés avec COVID-19.

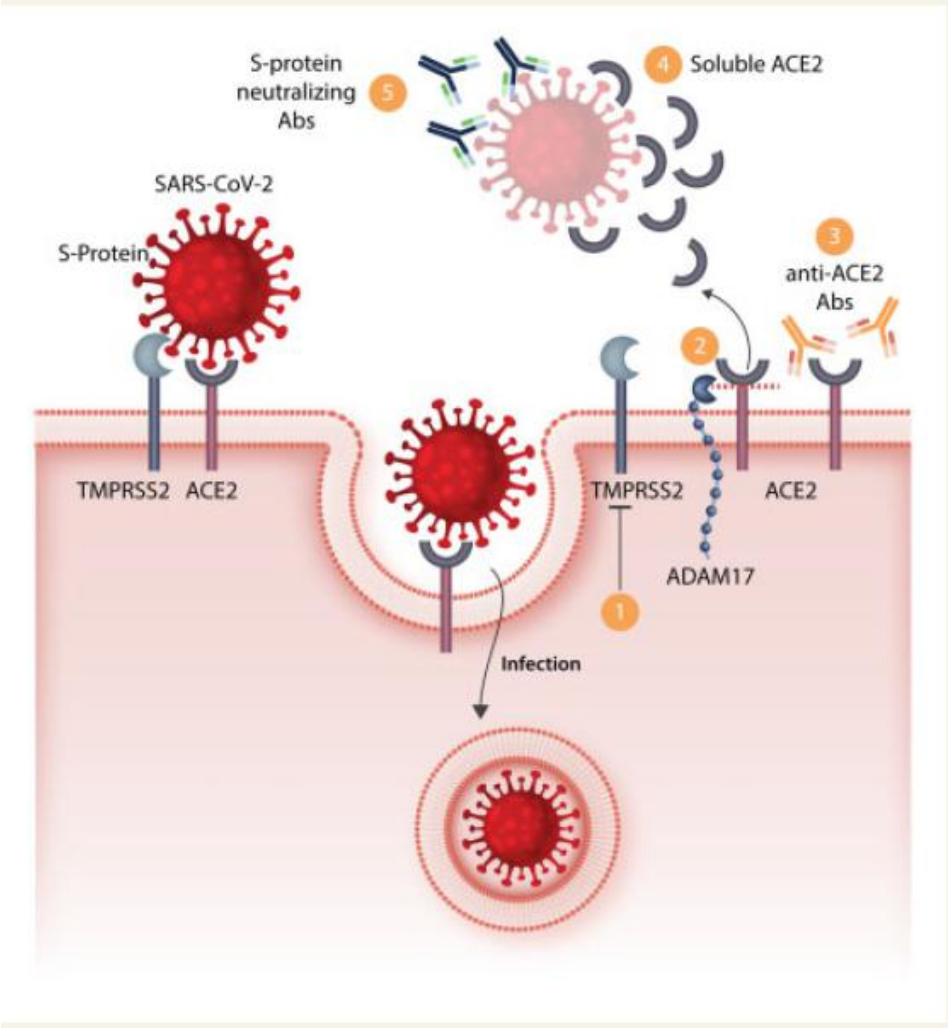
- Revoir les données probantes sur la prévention et la prise en charge de la thrombose chez les patients avec COVID-19.

- Réviser les lignes directrices (ACCP, ISTH, etc.).

TEV et COVID-19

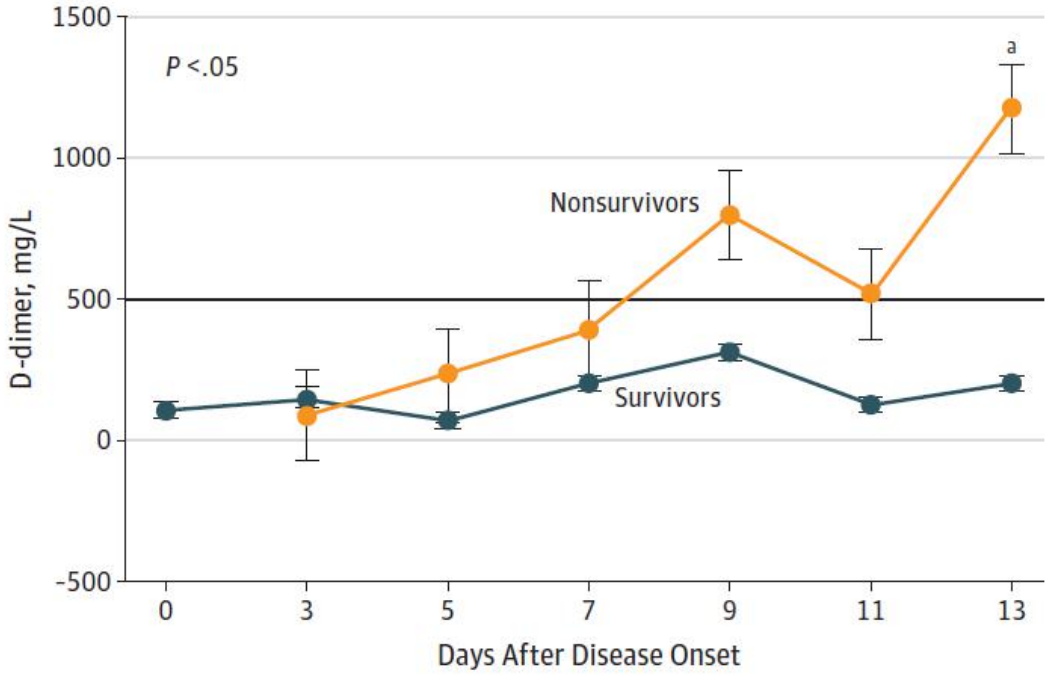
Pathophysiologie de l'infection SARS-CoV-2

- SARS-CoV-2 pénètre la cellule hôte via une interaction entre la protéine de surface du virus et le récepteur le l'enzyme de conversion the l'angiotensine (ACE2)
  - Épithélium pulmonaire, endothélium, cerveau, cœur, reins.
- ACE2 dégrade l'angiotensine II
  - Accumulation de l'angiotensine II peut contribuer à l'hypercoagulabilité

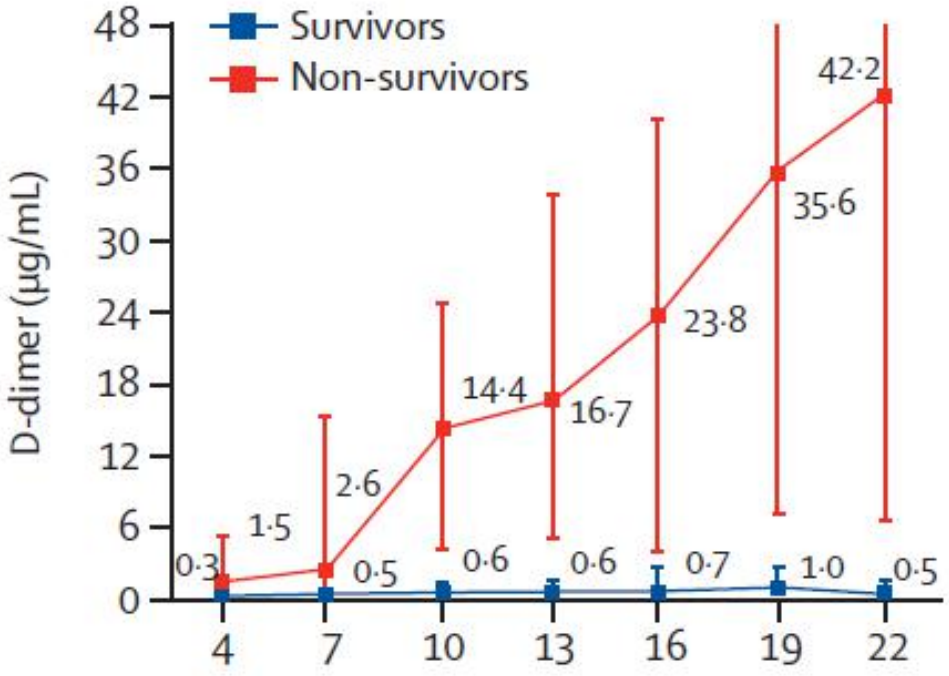


Guzik TJ *et al*, Cardiovascular Research (2020) 116, 1666–1687

Coagulopathie et COVID-19: données initiales de Chine



Wang D *et al*, JAMA 2020



Zhou F *et al*, Lancet 2020

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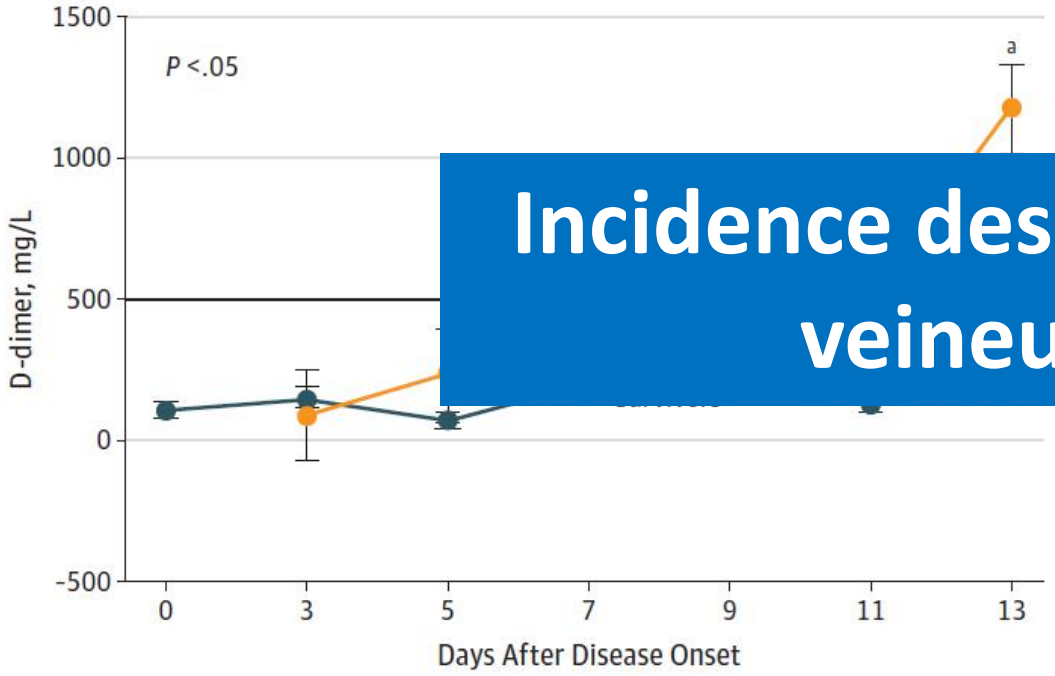
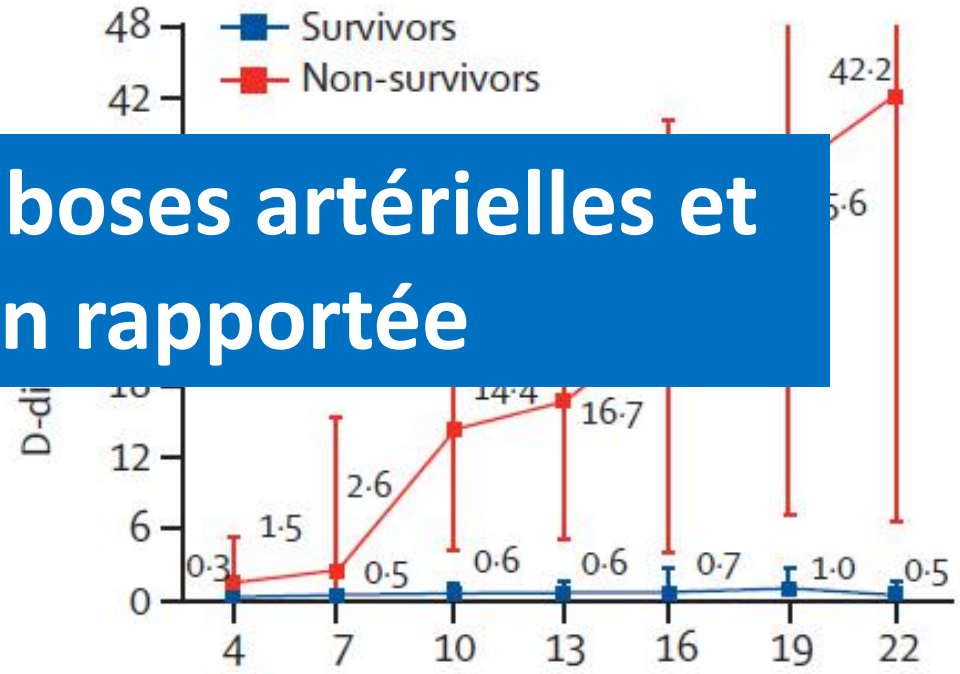


Incidence des thromboses artérielles et veineuses non rapportée



Wang D *et al*, JAMA 2020

Zhou F *et al*, Lancet 2020

Coagulopathie et COVID-19

Paramètres	COVID-19	Ccorrélation clinique
Plaquettes	20-30% des patients ont une légère thrombocytopénie (100-150)	Pas d'association claire avec la mortalité
Lymphocytes	Lymphopénie modérée ou sévère (75-83% avec compte lymphocytes de < 1.5)	Lymphopénie sévère (< 0.5) and et une augmentation de la lactate déhydrogénase sont souvent associés aux soins critiques
Temps de prothrombine	Légère prolongation (15-16 sec)	Pronostic (possiblement associé avec la mortalité)
D-Dimère	Souvent très élevé (4-6x ULN)	Pronostic (possiblement associé avec la mortalité)
Fibrinogène	Souvent élevé à la fin de la maladie	Réduction possible lors de l'hospitalisation ((10 à 14 jours) après l'admission

Bhatraju PK, et al. *NEJM*. 2020;0(0):null. doi:10.1056/NEJMoa2004500
Guan W, et al. *NEJM*. 2020;0(0):null. doi:10.1056/NEJMoa2002032
Tang Y-W, et al. *J Cli Microbiol*. April 2020. doi:10.1128/JCM.00512-20
Fan BE, et al. *Amer J Hematol*. n/a(n/a). doi:10.1002/ajh.25774

Coagulopathie et COVID-19: données initiales d'Europe

Thrombosis Research 191 (2020) 148–150

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis

F.A. Klok[a,*], M.J.H.A. Kruip[b], N.J.M. van der Meer[c,d], M.S. Arbous[e], D. Gommers[f], K.M. Kant[g], F.H.J. Kaptein[a], J. van Paassen[e], M.A.M. Stals[a], M.V. Huisman[a,1], H. Endeman[f,1]

Intensive Care Med
https://doi.org/10.1007/s00134-020-06062-x

ORIGINAL

High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study

Julie Helms[1,2], Charles Tacquard[3], François Severac[4], Ian Leonard-Lorant[5], Mickaël Ohana[5], Xavier Delabranche[3], Hamid Merdji[1,6], Raphaël Clere-Jehl[1,2], Malika Schenck[7], Florence Fagot Gandet[7], Samira Fafi-Kremer[2,8], Vincent Castelain[7], Francis Schneider[7], Lélia Grunebaum[9], Eduardo Anglés-Cano[10], Laurent Sattler[9], Paul-Michel Mertes[3], Ferhat Meziani[1,6*] and CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis)

BRIEF REPORT

High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients

Jean-François Llitjos[1] | Maxime Leclerc[2] | Camille Chochois[2] | Jean-Michel Monsallier[3] | Michel Ramakers[2] | Malika Auvray[2] | Karim Merouani[3]

Thrombosis Research 191 (2020) 9–14

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Full Length Article

Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy

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Incidence des TEV chez les patients aux soins intensifs de 17 à70%

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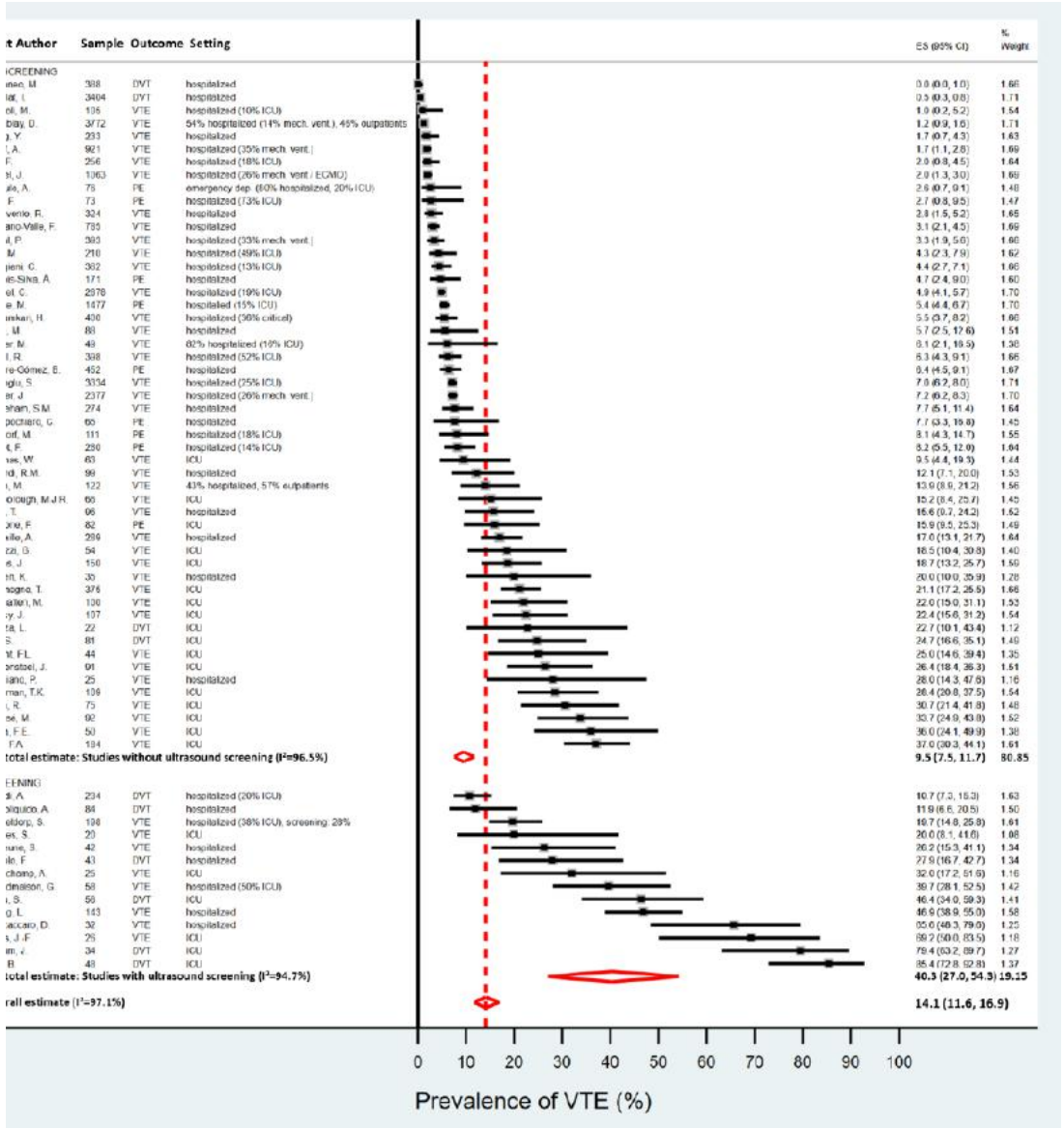
COVID-19: incidence des TEV



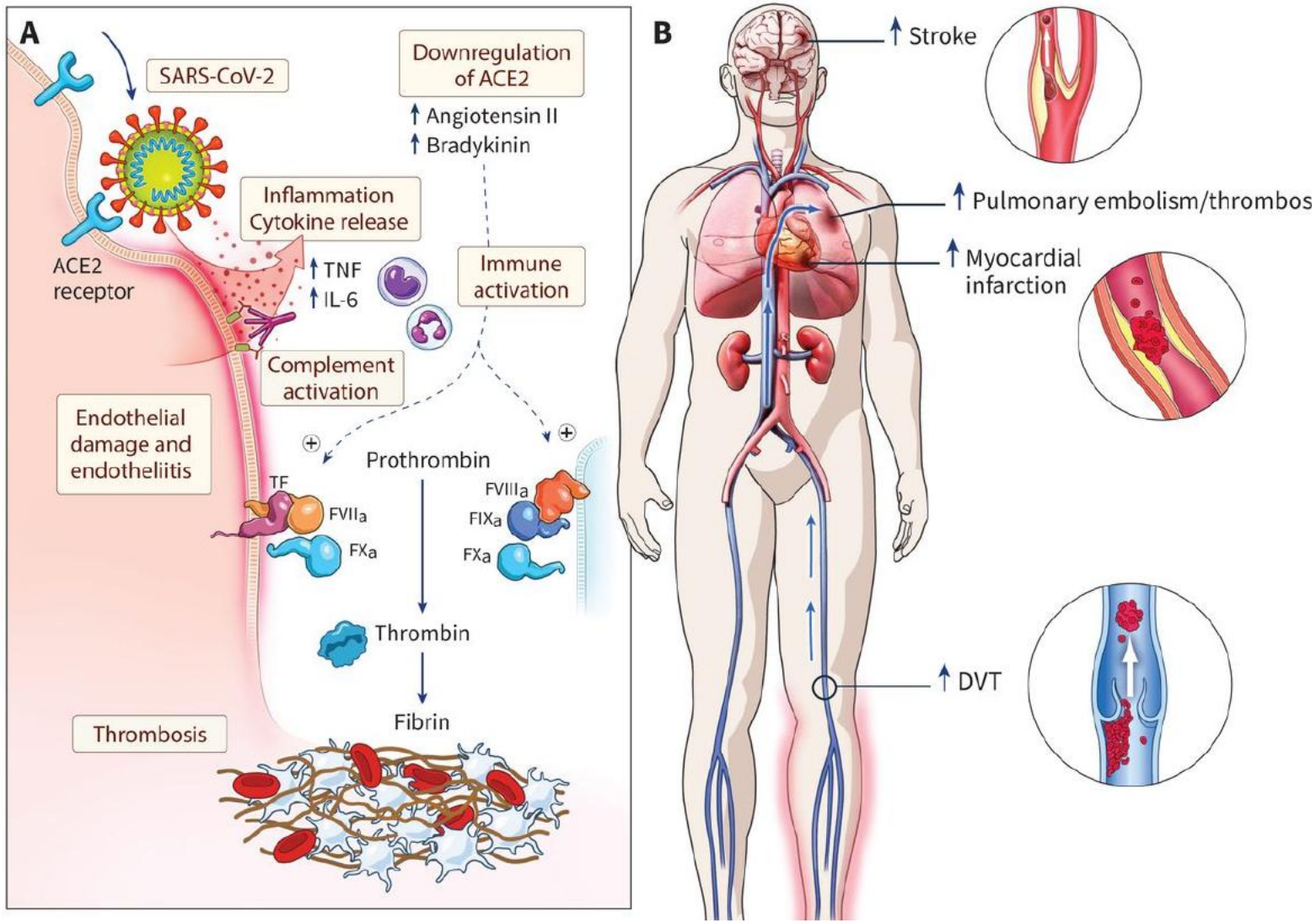
➢**9.5% (95%CI 7.5-12)**

➢**40% (95%CI 27-54)**

Nopp S *et al*, RPTH 2020

Pathophysiologie des thromboses et COVID

- Inflammation
- Dommage endothélial
  - Entrée du virus
  - Poumons, cœur, reins, intestins
- Activation immunitaire
  - Tempête de cytokines



COdoy LC *et al*, CMAJ 2020 October 5;192:E1156-61. doi: 10.1503/cmaj.201240;

Autres bénéfices des HBPMs et HNF?

Diminution de l’entrée du virus

Diminution de la formation des NETs

Inhibition de l’héparanase

Clinical Guidelines

American Society of Hematology 2020 guidelines on the use of anticoagulant in patients with COVID-19

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia

Adam Cuker,[1] Gowthami M. Arepally,[2] Beng H. Chong,[3] Douglas B. Cines,[1] Andreas Greinacher,[4] Yves Gruel,[5] Lori A. Linkins,[6] Stephen B. Rodner,[7] Sixten Selleng,[8] Theodore E. Warkentin,[6,9] Ashleigh Wex,[10] Reem A. Mustafa,[11,12] Rebecca L. Morgan,[11] and Nancy Santesso[11]

[1]Department of Medicine, Department of Pathology, and Department of Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [2]Department of Medicine, Duke University Medical Center, Durham, NC; [3]Department of Haematology, University of New South Wales, Sydney, NSW, Australia; [4]Institute of Immunology and Transfusion Medicine, University of Greifswald, Greifswald, Germany; [5]Department of Haematology-Haemostasis, Trousseau Hospital, Tours, France; [6]Department of Medicine, McMaster University, Hamilton, ON, Canada; [7]Pryor Cashman LLP, New York, NY; [8]Department of Anaesthesiology, University of Greifswald, Greifswald, Germany; [9]Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada; [10]Washington Prime Group Inc., Columbus, OH; [11]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada; and [12]Department of Medicine, University of Missouri-Kansas City, Kansas City, MO

Background Heparin-induced thrombocytopenia (HIT) is an adverse drug reaction mediated by platelet-activating antibodies that target complexes of platelet factor 4 and heparin. Patients are at markedly increased risk of thromboembolism.

Objective These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in their decisions about diagnosis and management of HIT.

Methods ASH formed a multidisciplinary guideline panel balanced to minimize potential bias from conflicts of interest. The McMaster University GRADE Centre supported the guideline development process, including updating or performing systematic evidence reviews. The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess evidence and make recommendations, which were subject to public comment.

Results The panel agreed on 32 recommendations. The recommendations address screening of asymptomatic patients for HIT, diagnosis and initial management of patients with suspected HIT, treatment of acute HIT, and special situations in patients with acute HIT or a history of HIT, including cardiovascular surgery, percutaneous cardiovascular intervention, renal replacement therapy, and venous thromboembolism prophylaxis.

Conclusions Strong recommendations include use of the 4Ts score rather than a gestalt approach for estimating the pretest probability of HIT and avoidance of HIT laboratory testing and empiric treatment of HIT in patients with a low probability 4Ts score. Conditional recommendations include the choice among non-heparin anticoagulants (argatroban, bivalirudin, danaparoid, fondaparinux, direct oral anticoagulants) for treatment of acute HIT.

Summary of recommendations

These guidelines are based on updated and original systematic reviews of evidence conducted under the direction of the McMaster University Grading of Recommendations Assessment, Development and Evaluation (GRADE) Centre with international collaborators. The panel followed best practice for guideline development recommended by the Institute of Medicine and the Guidelines International Network.[1-4] The panel used the GRADE approach[5-11] to assess the certainty in the evidence and formulate recommendations.

Heparin-induced thrombocytopenia (HIT) is a prothrombotic adverse drug reaction, mediated in most cases by immunoglobulin G antibodies that target complexes of platelet factor 4 (PF4) and heparin.[12] Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are the most widely used

Submitted 9 August 2018; accepted 14 September 2018. DOI 10.1182/bloodadvances.2018024489.

Resources for implementing these guidelines, including apps, patient decision aids, and teaching slide sets, may be accessed at the ASH web page hematology.org/vte.

The full-text version of this article contains a data supplement.

Est-ce que les AODs, HBPMs, HNF, fondaparinux, argatroban, ou bivalirudin à des doses prophylactiques, intermédiaires ou thérapeutiques devraient être utilisés chez les patients COVID-19 hospitalisés?

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;

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with prophylactic-intensity	Risk difference with anticoagulation at intermediate- or therapeutic-intensity
ALL-CAUSE MORTALITY follow up: 14 days	2626 (1 study)	⨁◯◯◯ VERY LOW	HR 0.86 (0.73 to 1.02)	148 per 1,000	19 fewer per 1,000 (38 fewer to 3 more)
PE follow up: range 4 days to 28 days	82 (1 study)	⨁◯◯◯ VERY LOW	OR 0.09 (0.02 to 0.57)	16 per 1,000	15 fewer per 1,000 (16 fewer to 7 fewer)
PROXIMAL LOWER EXTREMITY DVT follow up: 28 days	41 (1 study)	⨁◯◯◯ VERY LOW	OR 0.35 (0.06 to 2.02)	20 per 1,000	13 fewer per 1,000 (18 fewer to 19 more)
VTE follow up: range 6 days to 28 days	0 (1 study)	-	-	Baseline risk (2 studies, range 2.0% to 3.1%).	
MAJOR BLEEDING follow up: 14 days	0 (2 studies)	⨁◯◯◯ VERY LOW	-	Pooled baseline risk of 1.7% (5 studies). Studies with follow up between 4 days and 12 days lowest OR 1.42 and highest adjusted HR 3.89. This translates into 7 more per 1000 to 46 more major bleedings per 1000 patients.	

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Recommandations de ASH

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

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

Remarks:

- **Individualized assessment important**
- **No validated risk assessment models for in patients with COVID-19**
- **No direct high-quality evidence comparing different anticoagulants**

Études en cours

- Doses prophylactiques, intermédiaires ou thérapeutiques?
  - Trois études canadiennes en cours
    - Doses prophylactiques vs thérapeutiques chez les patients COVID hospitalisés
      - ATTACC
      - RAPID-COVID
    - Doses prophylactiques vs thérapeutiques chez les patients COVID aux soins intensifs
      - HALO-COVID

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VTE (DVT or PE) follow up: range 18 days to 28 days	118 (2 studies)	⊕◯◯◯ VERY LOW	OR 0.87 (0.45 to 1.67)	130 per 1,000	15 fewer per 1,000 (67 fewer to 70 more)
MAJOR BLEEDING follow up: mean 16 days	141 (1 study)	⊕◯◯◯ VERY LOW	OR 3.84 (1.44 to 10.21)	84 per 1,000	176 more per 1,000 (33 more to 400 more)

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				Risk with prophylactic intensity	Risk difference with anticoagulation at intermediate or therapeutic-intensity
MORTALITY follow up: range 14 days to 22 days	141 (1 study)	⨁◯◯◯ VERY LOW	OR 0.73 (0.33 to 1.76)	236 per 1,000	52 fewer per 1,000 (143 fewer to 116 more)
PE follow up: range 14 days to 20 days	82 (1 study)	⨁◯◯◯ VERY LOW	OR 0.09 (0.02 to 0.57)	98 per 1,000	88 fewer per 1,000 (96 fewer to 40 fewer)
PROXIMAL LOWER EXTREMITY DVT follow up: range 14 days to 20 days	41 (1 study)	⨁◯◯◯ VERY LOW	OR 0.35 (0.06 to 2.02)	106 per 1,000	66 fewer per 1,000 (99 fewer to 87 more)
VTE (DVT or PE) follow up: range 18 days to 28 days	118 (2 studies)	⨁◯◯◯ VERY LOW	OR 0.87 (0.45 to 1.67)	130 per 1,000	15 fewer per 1,000 (67 fewer to 70 more)
MAJOR BLEEDING follow up: mean 16 days	**141 (1 study)**	**⨁◯◯◯ VERY LOW**	**OR 3.84 (1.44 to 10.21)**	**84 per 1,000**	**176 more per 1,000 (33 more to 400 more)**

Recommandations de ASH

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

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

Remarks:

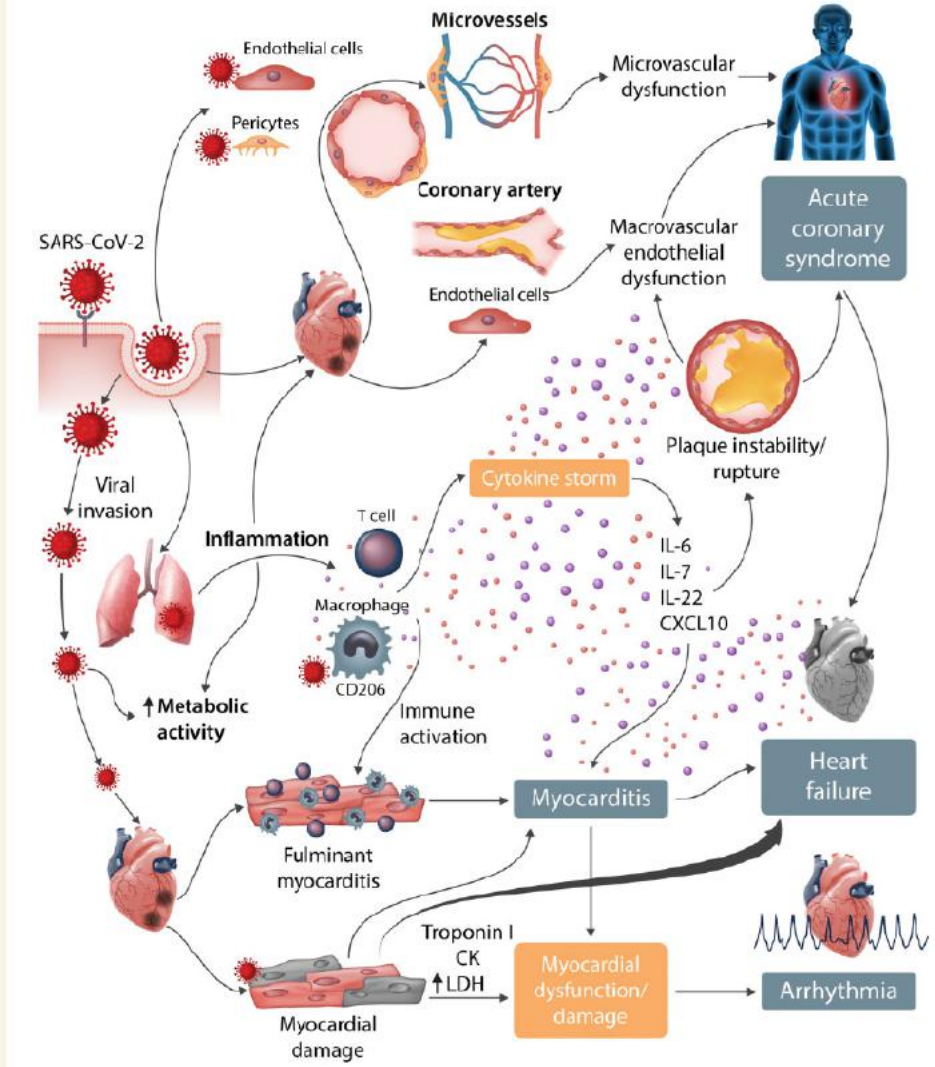
- **Individualized assessment important**
- **No validated risk assessment models for in patients with COVID-19**
- **No direct high-quality evidence comparing different anticoagulants**

Thromboses artérielles et COVID-19

Infarctus du myocarde et COVID-19

- 7 à 17% des patients avec COVID
- Généralement du type 2
  - Secondaire à une augmentation de la demande
- Les bénéfices de la revascularisation cardiaque sont limités
- Dommages au myocarde sont généralement causés par:
  - “tempête de cytokines”
    - Augmentation de IL6, ferritine, LDH et D-dimère
  - Dysfonction du myocarde directement causée par le COVID
  - Cardiomyopathie (Takotsubo) ou myocardite

Pathophysiologie des problèmes cardiovasculaires et COVID



Guzik TJ *et al*, Cardiovascular Research (2020) 116, 1666–1687

COVID-19 et accidents vasculaires cérébraux (AVC)

- Données récentes démontrant une augmentation du risque d'AVC chez les patients avec COVID-19

- Risque plus élevé comparativement à d'autres syndromes viraux
  - 7.6 plus élevé que l'influenza
  - 1.6% vs. 0.2%

- Incidence de l'AVC est rapportée entre 1 et 3% chez les patients atteints de COVID-19
  - AVC ischémiques: 0.4 à 2.7
  - AVC hémorragiques: 0.3 à 0.9%

Merkle AE et al. JAMA Neurol 2020 (published on-line July 2nd 2020); Ellul MA, Lancet Neurol 2020;19:767-83; Yaghi S et al. Stroke 2020:51:2002-11.

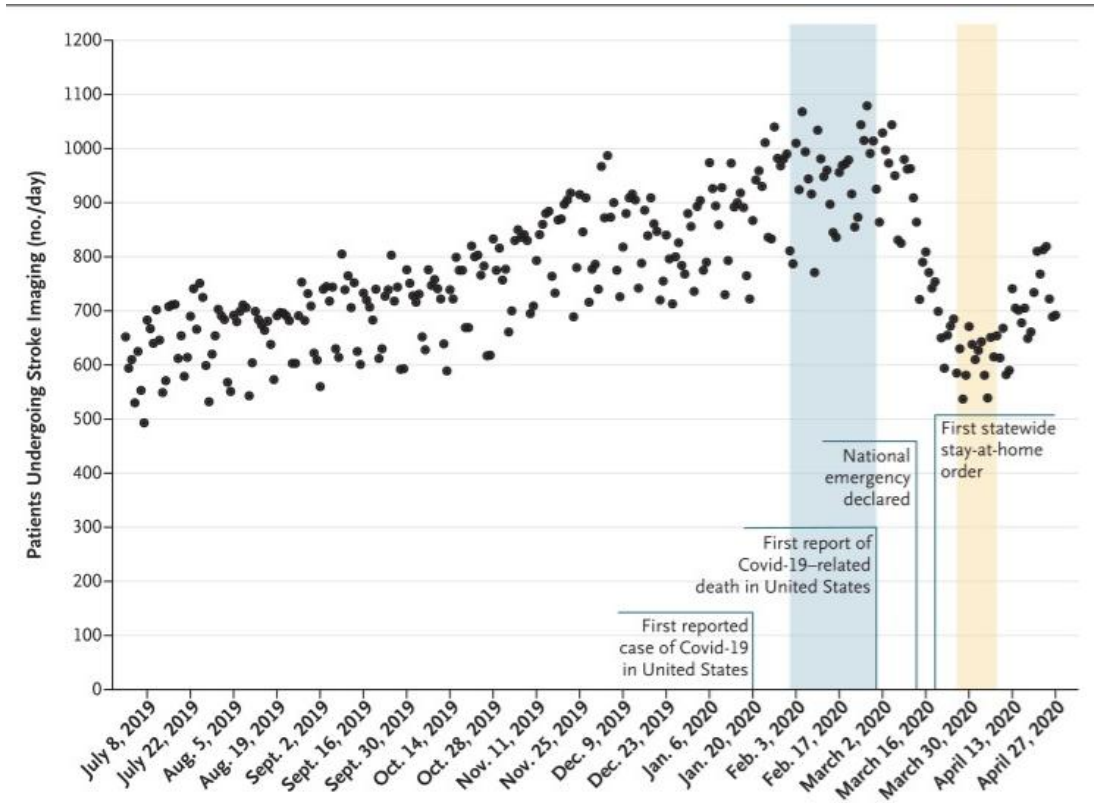
Pathophysiologie - COVID-19 et AVC

- Hypercoagulabilité causée par:
  - Inflammation systémique
  - “tempête de cytokines”
  - Réponse immunitaire post-infection
  - Vasculopathie ou endothéliopathie virale
- Thrombose angiopathique
  - Particules virales ont été isolées dans l’endothélium de différents organes, dont le cerveau

Ellul MA, Lancet Neurol 2020;19:767-83; Varga Z et al. Lancet 2020;395:1417-1418; Paniz-Mondolfi A et al. J Med Viral 2020;92-699-702

COVID-19 et AVC

- Plusieurs régions ont rapporté une augmentation du nombre d'AVC des larges vaisseaux (généralement cryptogéniques)
- Diminution d'AVC mineurs
  - Possiblement relié à la quarantaine ou à l'isolement social
  - Diminution de l'utilisation d'imagerie diagnostique pour le diagnostique d'AVC
    - Diminution de 39%



Kansagra AP et al. N Engl J Med 2020:383:400-01.

AVC chez les jeunes atteints de COVID

- Taux d'AVC 7X plus élevé chez les jeunes (moins de 50 ans) comparativement à l'année dernière (la plupart des cas chez les patients atteints de COVID).

- Moyenne d'âge chez les patients avec AVC et COVID est 59 ans comparativement de 74 ans chez les patients non-COVID.

- Généralement, les jeunes patients avec AVC et COVID n'ont pas d'autres facteurs de risque de maladies vasculaires

Belani P et al. AJNR Am J Neuroradiol 2020; e-pub Jun 25; Escallard S et al. Stroke 2020;51:2540-43; Fifi JT, Mocco J et al. Lancet Neurol 2020:14:713-714

AVC chez les jeunes atteints de COVID

Table 1. Clinical Characteristics of Five Young Patients Presenting with Large-Vessel Stroke.*

Variable	Patient 1	Patient 2	Patient 3	Patient 4
Age — yr	33	37	39	44
Sex	Female	Male	Male	Male
Medical history and risk factors for stroke†	None	None	Hyperlipidemia, hypertension	Undiagnosed diabetes
Medications	None	None	None	None
NIHSS score‡				
On admission	19	13	16	23
At 24 hr	17	11	4	19
At last follow-up	13 (on day 14)	5 (on day 10)	NA; intubated and sedated, with multiorgan failure	19 (on day 12)
Outcome status	Discharged to rehabilitation facility	Discharged home	Intensive care unit	Stroke unit
Time to presentation — hr	28	16	8	2
Signs and symptoms of stroke	Hemiplegia on left side, facial droop, gaze preference, homonymous hemianopia, dysarthria, sensory deficit	Reduced level of consciousness, dysphasia, hemiplegia on right side, dysarthria, sensory deficit	Reduced level of consciousness, gaze preference to the right, left homonymous hemianopia, hemiplegia on left side, ataxia	Reduced level of consciousnes global dysphasia, hemiplegi right side, gaze preference
Vascular territory	Right internal carotid artery	Left middle cerebral artery	Right posterior cerebral artery	Left middle cerebral artery
Imaging for diagnosis	CT, CTA, CTP, MRI	CT, CTA, MRI	CT, CTA, CTP, MRI	CT, CTA, MRI
Treatment for stroke	Apixaban (5 mg twice daily)	Clot retrieval, apixaban (5 mg twice daily)	Clot retrieval, aspirin (81 mg daily)	Intravenous t-PA, clot retrieval hemicraniectomy, aspirin (8 mg daily)
Covid-19 symptoms	Cough, headache, chills	No symptoms; recently exposed to family member with PCR-positive Covid-19	None	Lethargy
White-cell count — per mm^3	7800	9900	5500	9000
Platelet count — per mm^3	427,000	299,000	135,000	372,000
Prothrombin time — sec	13.3	13.4	14.4	12.8
Activated partial-thromboplastin time — sec	25.0	42.7	27.7	26.9

Oxley TJ et al. N Engl J Med 2020:382:e60.

Recommandations

- L’ajout d’antiplaquettaires pour une prévention primaire n’est pas recommandée
  - Dose nécessaire?
  - Interactions médicamenteuses possibles

- Un essai évaluant l’utilisation de l’aspirine, du clopidogrel et du rivaroxaban (2.5 mg BID) (et atorvastatin et omeprazole) a débuté en Angleterre.