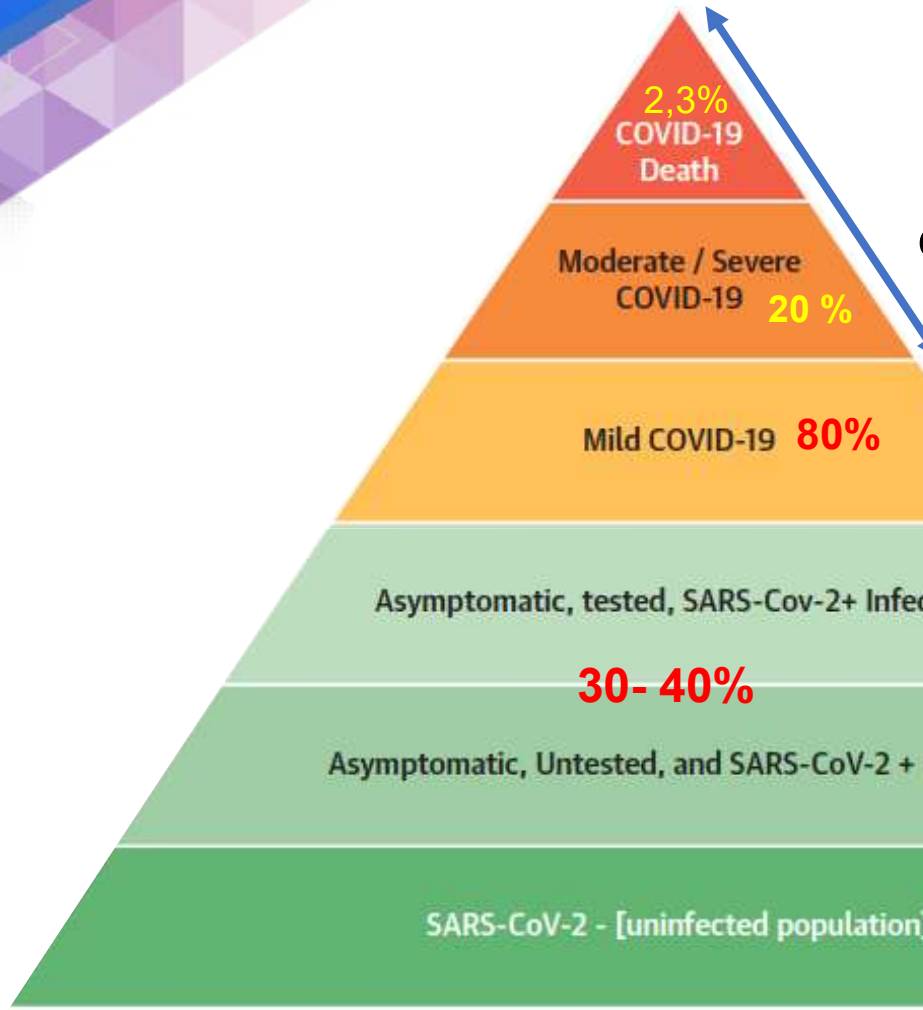
2021

Gestions des anticoagulants en réanimation au cours de l'infection sévère a SARS-COV-2

Pr Souheil Elatrous



SDRA
Coagulopathie et évènements thrombotiques

ORIGINAL RESEARCH

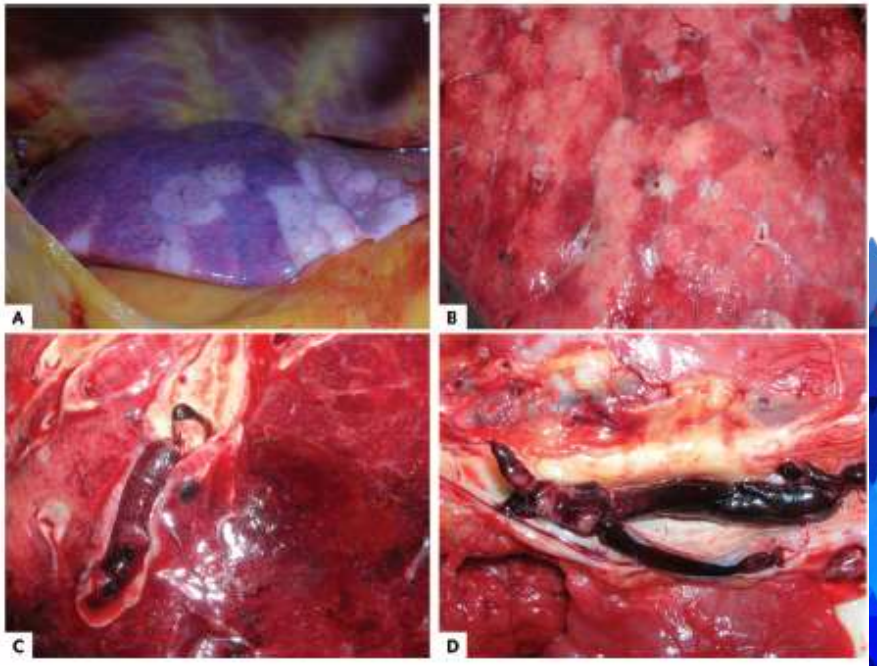
Annals of Internal Medicine

Autopsy Findings and Venous Thromboembolism in Patients With COVID-19

A Prospective Cohort Study

Wichmann et al Ann Intern Med. 2020;173:268-277

- Autopsie de 12 patients COVID -19 en Allemagne
- Autopsie révèle 7/12 TVP (58%) non suspectée avant le décès.
- Embolie pulmonaire cause directe de décès chez 4 patients.



COVID-19

Maladie thromboembolique

Anticoagulation

- Résultats des autopsies
- Anomalies des paramètres de coagulation
- Incidence élevée des complications thromboemboliques
- Hypoxémie > les lésions

[1] Epidémiologie

Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study

*Lionel Piroth, Jonathan Cottenet, Anne-Sophie Mariet, Philippe Bonniaud, Mathieu Blot, *Pascale Tubert-Bitter, *Catherine Quantin*

***Lancet Respir Med* 2021; 9: 251–59**

	COVID-19 (n=89 530)	2018–19 seasonal influenza (n=45 819)	p value
Acute respiratory failure	24 317 (27·2%)	7977 (17·4%)	<0·0001
Pulmonary embolism	3086 (3·4%)	412 (0·9%)	<0·0001
Venous thrombosis (including pulmonary embolism)	4367 (4·9%)	766 (1·7%)	<0·0001
Septic shock	2551 (2·8%)	918 (2·0%)	<0·0001
Myocardial infarction	558 (0·6%)	506 (1·1%)	<0·0001
Atrial fibrillation	11 129 (12·4%)	7222 (15·8%)	<0·0001
Stroke	1068 (1·2%)	569 (1·2%)	0·44
Haemorrhagic stroke	253 (0·3%)	93 (0·2%)	0·0061
Ischaemic stroke	714 (0·8%)	405 (0·9%)	0·097
Transient ischaemic attack	161 (0·2%)	92 (0·2%)	0·40
Acute kidney failure	5761 (6·4%)	2227 (4·9%)	<0·0001
Invasive mechanical ventilation	8684 (9·7%)	1833 (4·0%)	<0·0001
Admission to ICU	14 585 (16·3%)	4926 (10·8%)	<0·0001
Mean (SD) stay in ICU, days	15 (14)	8 (9)	<0·0001
Median (IQR) stay in ICU, days	10 (4–21)	5 (2–10)	<0·0001
Mechanical ventilation among ICU patients	10 430/14 585 (71·5%)	3004/4926 (61·0%)	<0·0001
In-hospital death	15 104 (16·9%)	2640 (5·8%)	<0·0001
Expected in-hospital death with influenza age-specific mortality	5355 (6·0%)	..	..
Standardised mortality ratio	2·82	..	..
In-hospital death among patients in ICU	3949/14 585 (27·1%)	885/4926 (18·0%)	<0·0001
Mean (SD) stay in ICU among non-deceased patients, days	15 (15)	8 (9)	<0·0001
Median (IQR) stay in ICU among non-deceased patients, days	10 (3–21)	5 (2–9)	<0·0001
In-hospital death among patients in ICU with mechanical ventilation	3312/10 430 (31·8%)	780/3004 (26·0%)	<0·0001
In-hospital death among non-ventilated patients in ICU	477/2773 (17·2%)	81/1496 (5·4%)	<0·0001

Data are n (%) or n/N (%) unless otherwise indicated. ICU=intensive care unit. Data are for patients who were hospitalised for COVID-19 between March 1 and April 30, 2020, and for patients who were hospitalised for seasonal influenza between Dec 1, 2018, and Feb 28, 2019.

***Table 2:* Main outcomes of patients hospitalised in France for COVID-19 or seasonal influenza**

Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study

*Lionel Piroth, Jonathan Cottenet, Anne-Sophie Mariet, Philippe Bonniaud, Mathieu Blot, *Pascale Tubert-Bitter, *Catherine Quantin*

***Lancet Respir Med* 2021; 9: 251–59**

	COVID-19 (n=89 530)	2018–19 seasonal influenza (n=45 819)	p value
Acute respiratory failure	24 317 (27·2%)	7977 (17·4%)	<0·0001
Pulmonary embolism	3086 (3·4%)	412 (0·9%)	<0·0001
Venous thrombosis (including pulmonary embolism)	4367 (4·9%)	766 (1·7%)	<0·0001
Mean (SD) stay in ICU among non-deceased patients, days	15 (15)	8 (9)	<0·0001
Median (IQR) stay in ICU among non-deceased patients, days	10 (3–21)	5 (2–9)	<0·0001
In-hospital death among patients in ICU with mechanical ventilation	3312/10 430 (31·8%)	780/3004 (26·0%)	<0·0001
In-hospital death among non-ventilated patients in ICU	477/2773 (17·2%)	81/1496 (5·4%)	<0·0001

Data are n (%) or n/N (%) unless otherwise indicated. ICU=intensive care unit. Data are for patients who were hospitalised for COVID-19 between March 1 and April 30, 2020, and for patients who were hospitalised for seasonal influenza between Dec 1, 2018, and Feb 28, 2019.

***Table 2:* Main outcomes of patients hospitalised in France for COVID-19 or seasonal influenza**

Incidence

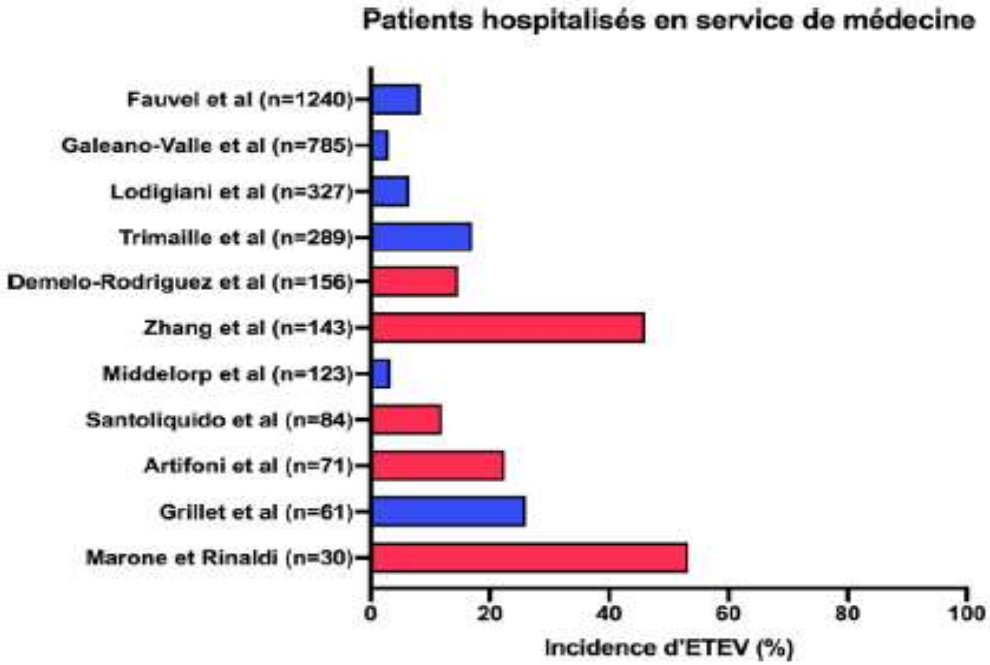
- **Varie de 4,8% à 85%**
- Liées **à plusieurs facteurs**
  - Lieux (réanimation – non réanimation)
  - Types d'événements (symptomatique ou non symptomatique).
  - Stratégie diagnostique (recherche systématique ou en cas de symptômes)
  - Degrés de thromboprophylaxie

Mise au point

COVID-19 et pathologie thromboembolique veineuse

COVID-19 and venous thromboembolism

A. Trimaille[a], G. Bonnet[b,*]



Annales de Cardiologie et d'Angéiologie 69 (2020) 370–375

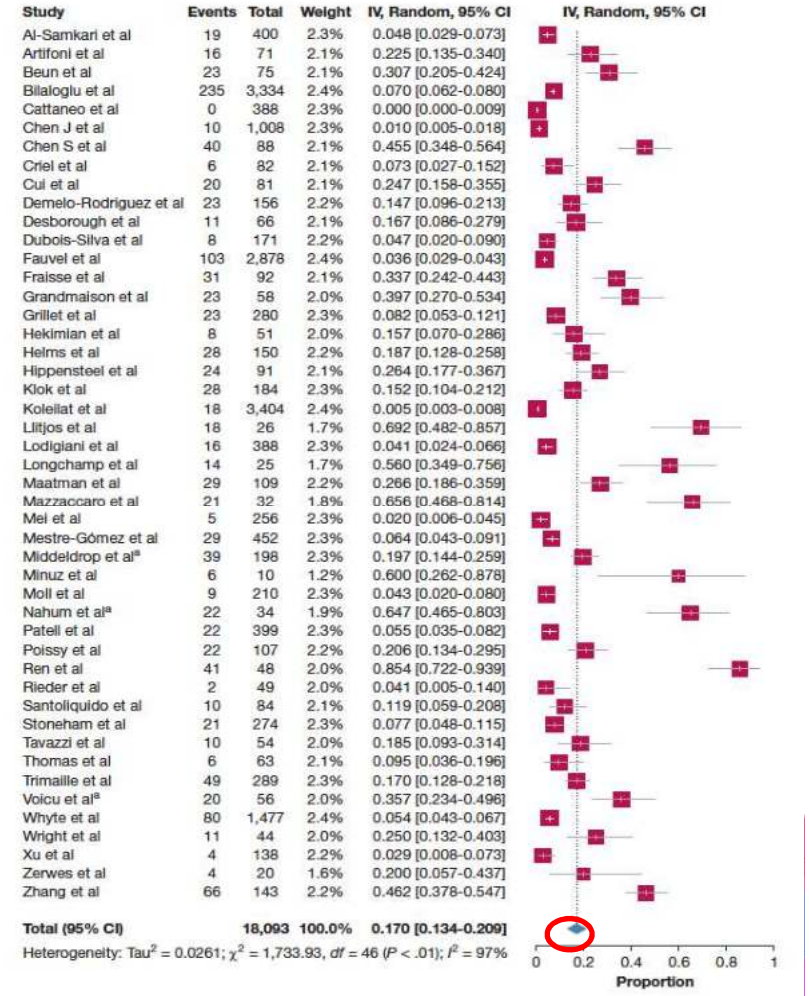
Incidence of VTE and Bleeding Among Hospitalized Patients With Coronavirus Disease 2019

A Systematic Review and Meta-analysis

David Jiménez, CHEST 2021; 159(3):1182-1196

- 36 études
- 11000 patients

Incidence 17% (12% TVP et 7,1 EP)



Study	Events	Total	Weight	IV, Random, 95% CI
Al-Samkari et al	19	400	2.3%	0.048 [0.029-0.073]
Artifoni et al	16	71	2.1%	0.225 [0.135-0.340]
Beun et al	23	75	2.1%	0.307 [0.205-0.424]
Bilaloglu et al	235	3,334	2.4%	0.070 [0.062-0.080]
Cattaneo et al	0	388	2.3%	0.000 [0.000-0.009]
Chen J et al	10	1,008	2.3%	0.010 [0.005-0.018]
Chen S et al	40	88	2.1%	0.455 [0.348-0.564]
Criel et al	6	82	2.1%	0.073 [0.027-0.152]
Cui et al	20	81	2.1%	0.247 [0.158-0.355]
Demelo-Rodriguez et al	23	156	2.2%	0.147 [0.096-0.213]
Desborough et al	11	66	2.1%	0.167 [0.086-0.279]
Dubois-Silva et al	8	171	2.2%	0.047 [0.020-0.090]
Fauvel et al	103	2,878	2.4%	0.036 [0.029-0.043]
Fraisse et al	31	92	2.1%	0.337 [0.242-0.443]
Grandmaison et al	23	58	2.0%	0.397 [0.270-0.534]
Grillet et al	23	280	2.3%	0.082 [0.053-0.121]
Hekimian et al	8	51	2.0%	0.157 [0.070-0.286]
Helms et al	28	150	2.2%	0.187 [0.128-0.258]
Hippensteel et al	24	91	2.1%	0.264 [0.177-0.367]
Klok et al	28	184	2.3%	0.152 [0.104-0.212]
Kolelilat et al	18	3,404	2.4%	0.005 [0.003-0.008]
Llitjos et al	18	26	1.7%	0.692 [0.482-0.857]
Lodigiani et al	16	388	2.3%	0.041 [0.024-0.066]
Longchamp et al	14	25	1.7%	0.560 [0.349-0.756]
Maatman et al	29	109	2.2%	0.266 [0.186-0.359]
Mazzaccaro et al	21	32	1.8%	0.656 [0.468-0.814]
Mei et al	5	256	2.3%	0.020 [0.006-0.045]
Mestre-Gómez et al	29	452	2.3%	0.064 [0.043-0.091]
Middeldrop et al[a]	39	198	2.3%	0.197 [0.144-0.259]
Minuz et al	6	10	1.2%	0.600 [0.262-0.878]
Moll et al	9	210	2.3%	0.043 [0.020-0.080]
Nahum et al[a]	22	34	1.9%	0.647 [0.465-0.803]
Patell et al	22	399	2.3%	0.055 [0.035-0.082]
Poissy et al	22	107	2.2%	0.206 [0.134-0.295]
Ren et al	41	48	2.0%	0.854 [0.722-0.939]
Rieder et al	2	49	2.0%	0.041 [0.005-0.140]
Santoliquido et al	10	84	2.1%	0.119 [0.059-0.208]
Stoneham et al	21	274	2.3%	0.077 [0.048-0.115]
Tavazzi et al	10	54	2.0%	0.185 [0.093-0.314]
Thomas et al	6	63	2.1%	0.095 [0.036-0.196]
Trimaille et al	49	289	2.3%	0.170 [0.128-0.218]
Voicu et al[a]	20	56	2.0%	0.357 [0.234-0.496]
Whyte et al	80	1,477	2.4%	0.054 [0.043-0.067]
Wright et al	11	44	2.0%	0.250 [0.132-0.403]
Xu et al	4	138	2.2%	0.029 [0.008-0.073]
Zerwes et al	4	20	1.6%	0.200 [0.057-0.437]
Zhang et al	66	143	2.2%	0.462 [0.378-0.547]
Total (95% CI)		**18,093**	**100.0%**	**0.170 [0.134-0.209]**

Heterogeneity: Tau^2 = 0.0261; χ^2 = 1,733.93, *df* = 46 (*P* < .01); I^2 = 97%

Figure 2 – *Forest plot showing the incidence of VTE among hospitalized patients with COVID-19. [a]Shortest assessment period. COVID-19 = navirus disease 2019; IV = Inverse-Variance.*

Intensive Care Med (2020) 46:1089–1098
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)

- 4 réanimations, 1 mois
- 150 patients ARDS Covid-19 comparés a une cohorte historique de patients Non COVID-19
- Tous sous anticoagulants (70% dose préventive et 30% dose curative)
- 64 / 150 évènements thrombotiques

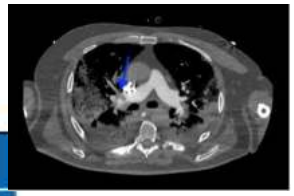


Table 3 Outcomes of COVID-19 ARDS and non-COVID-19 ARDS

	Population before matching ($n=383$)				Population after matching ($n=222$)			
	Non-COVID-19-ARDS ($n=233$)	COVID-19-ARDS ($n=150$)	OR [95% IC]	*p*-value	Non-COVID-19-ARDS ($n=145$)	COVID-19-ARDS ($n=77$)	OR [95% IC]	*p*-value
Thrombo-embolic complications—*n* (%)	14 (6)	27 (18)	3.4 [1.7–7.3]	<0.001	7 (4.8)	9 (11.7)	2.6 [1.1–6.1]	0.04
Pulmonary embolisms—*n* (%)	3 (1.3)	25 (16.7)	15.2 [4.5–80.4]	<0.001	3 (2.1)	9 (11.7)	6.2 [1.6–23.4]	0.01
Deep vein thrombosis—*n* (%)	3 (1.3)	3 (2)	1 [0.1–9.2]	1	2 (1.4)	0 (0)	–	–
Myocardial infarction—*n* (%)	6 (2.6)	0 (0)	0 [0–1.3]	0.09	2 (1.4)	0 (0)	–	–
Cerebral ischemic attack—*n* (%)	1 (0.4)	2 (1.3)	3.1 [0.2– 185.5]	0.68	0 (0.0)	0 (0)	–	–
Limb ischemia—*n* (%)	0 (0)	1 (0.7)	Inf [0.0–Inf]	0.78	0 (0.0)	0 (0)	–	–
Mesenteric ischemia—*n* (%)	3 (1.3)	1 (0.7)	0.5 [0.0–6.5]	0.98	2 (1.4)	1 (1.3)	0.96 [0.09–9.8]	0.97
Nb of RRT filter per dialyzed patient—median, IQR	1 [2–1]	3 [2–7]	–	<0.001	2.0 [1.0–2.5]	3.0 [2.0–6]	–	0.03
Nb of RRT filter per day of RRT—median, IQR	0.3 [0.3; 0.5]	0.7 [0.5; 1]	–	<0.001	0.3 [0.3; 0.4]	0.7 [0.5; 1]	–	<0.001
ECMO oxygenator thrombosis—*n* (%)	1/10 (10)	2/12 (16.7)	–	0.59	1/7 (14.3)	0/4 (0)	–	–
Hemorrhagic complications—*n* (%)	1 (1.8)	4 (2.7)	2.4 [0.27–28.5]	0.6	2 (1.4)	0 (0)	–	–

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy

Contents lists available at ScienceDirect

Thrombosis Research

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

Incidence of thrombotic complications in critically ill ICU patients with COVID-19

Klok FA et al Thrombosis research 2020;191: 145-147

Incidence cumulative 31% (95%CI 20-41%)
(25 EP, 1 TVP, 2 Thrombose sur KT et 2 AVC)

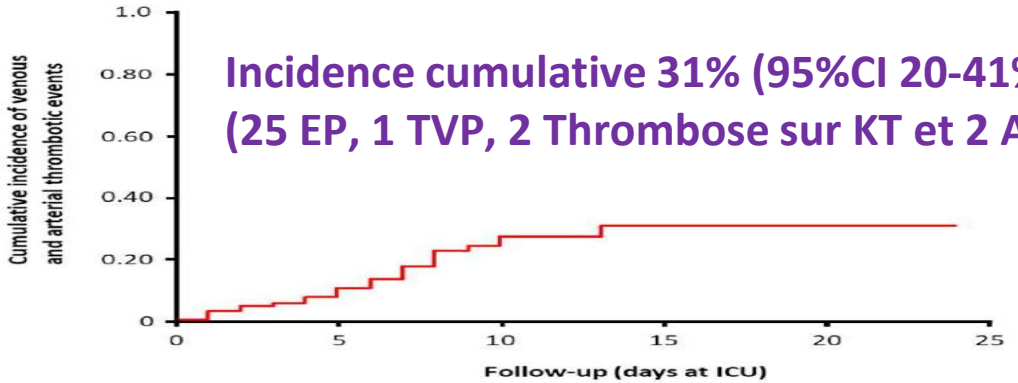


Fig. 1. Cumulative incidence of venous and arterial thrombotic complications during the course of intensive care unit admission of patients with proven COVID-19 pneumonia.

- 3 USI EN Pays bas
- 184 patients COVID 19
- Traitement anticoagulant standard
- Incidence composite de MTE et complications thrombotique artérielle

Prevalence of Thrombotic Complications in ICU-Treated Patients With Coronavirus Disease 2019 Detected With Systematic CT Scanning

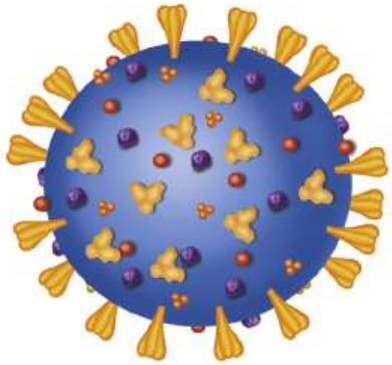
Mirsadraee S et al. CCM 2021; 49(5):804-815

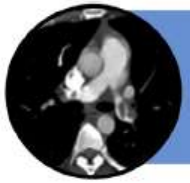
- Etude rétrospective; Mars 2020 – Juin 2020; Royaume-Uni
- Thromboprophylaxie chez tous les patients sauf un
- TDM systématique à l'admission
- 72 patients (35 ECMO)
- 54 complications thrombotiques chez 42 patients (58%)
  - 34 EP(47%),
  - 15 TVP(21%),
  - 5 (7%) thromboses artérielles systémiques
- Suspicion clinique 7%
- Biomarqueurs de la coagulation ou inflammation ne sont pas discriminant

Registry of Arterial and Venous Thromboembolic Complications in Patients With COVID-19

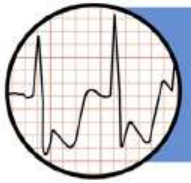
Piazza G J Am Coll Cardio 2021 72(2):403-404

CENTRAL ILLUSTRATION Cardiovascular Complications in Patients With Coronavirus Disease-2019 at 30 Days From Diagnosis

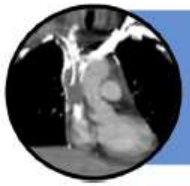




Major Arterial or Venous Thromboembolism
- ICU 35.3%
- Hospitalized non-ICU 2.6%



Major Adverse Cardiovascular Events
- ICU 45.9%
- Hospitalized non-ICU 6.1%



Symptomatic Venous Thromboembolism
- ICU 27%
- Hospitalized non-ICU 2.2%
- Despite 85%-90% thromboprophylaxis rate

Cathéter +++

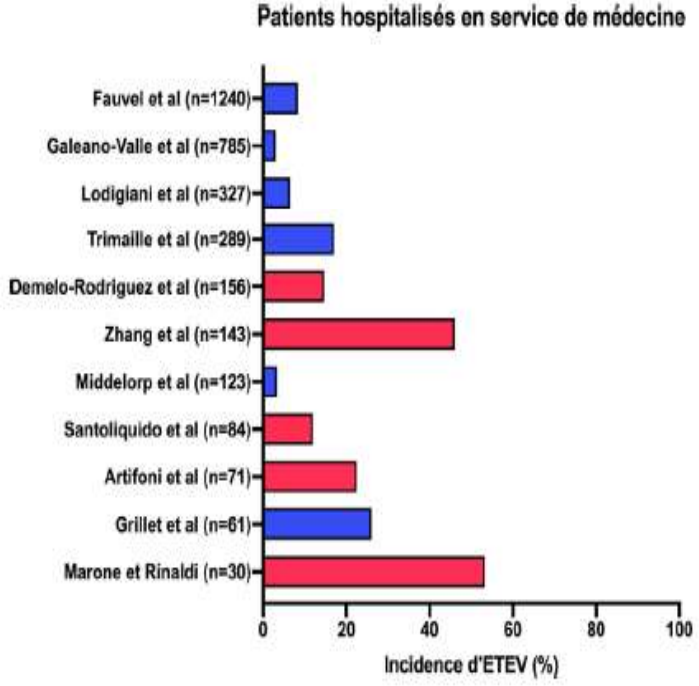
Mise au point

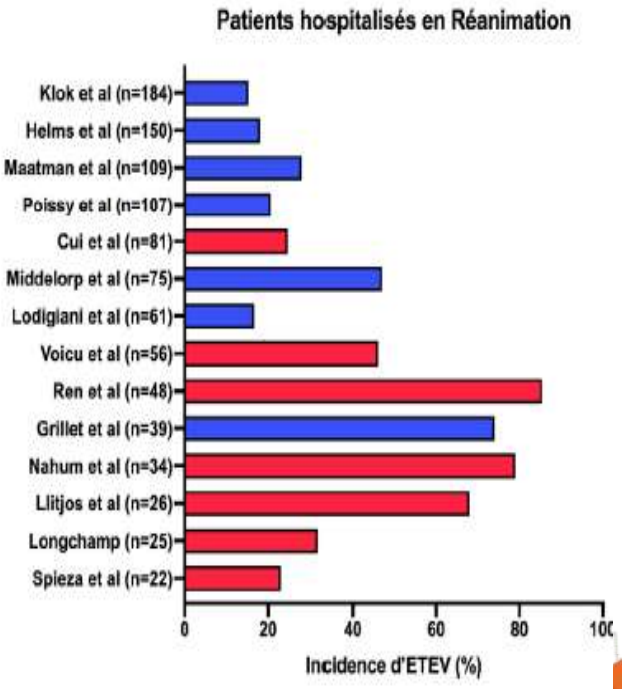
COVID-19 et pathologie thromboembolique veineuse

COVID-19 and venous thromboembolism

A. Trimaille [a], G. Bonnet [b,*]

Annales de Cardiologie et d'Angéiologie 69 (2020) 370–375





Particularités

- **Précoce**
  - Incidence EP 27% parmi 349 patients COVID-19 (20% diagnostic à l'admission)

    Mouhat B et al. Eur respir J 2020; 56(4)2001-11
  - Incidence cumulative 21%, 50% surviennent les premières 24h

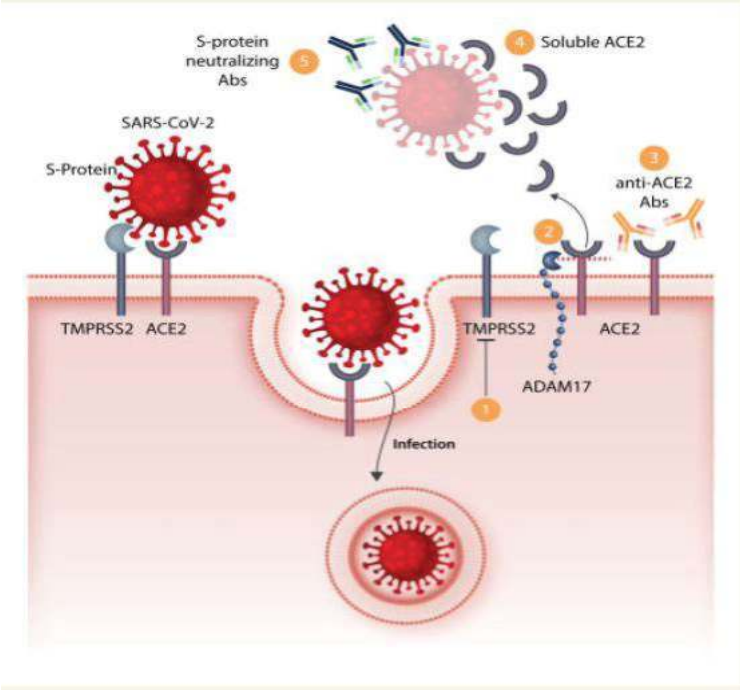
    Lodogiani C et al Thromb Res 2020;19:9-14
- **Associée à une sévérité plus importante** (VM et **Réanimation**) et à une lourde mortalité (HR: 1,82)

  Bilaloglu S et al. JAMA 2020; 324(8):799-801.

[2] Mécanismes physiopathologiques

SARS-COV 2

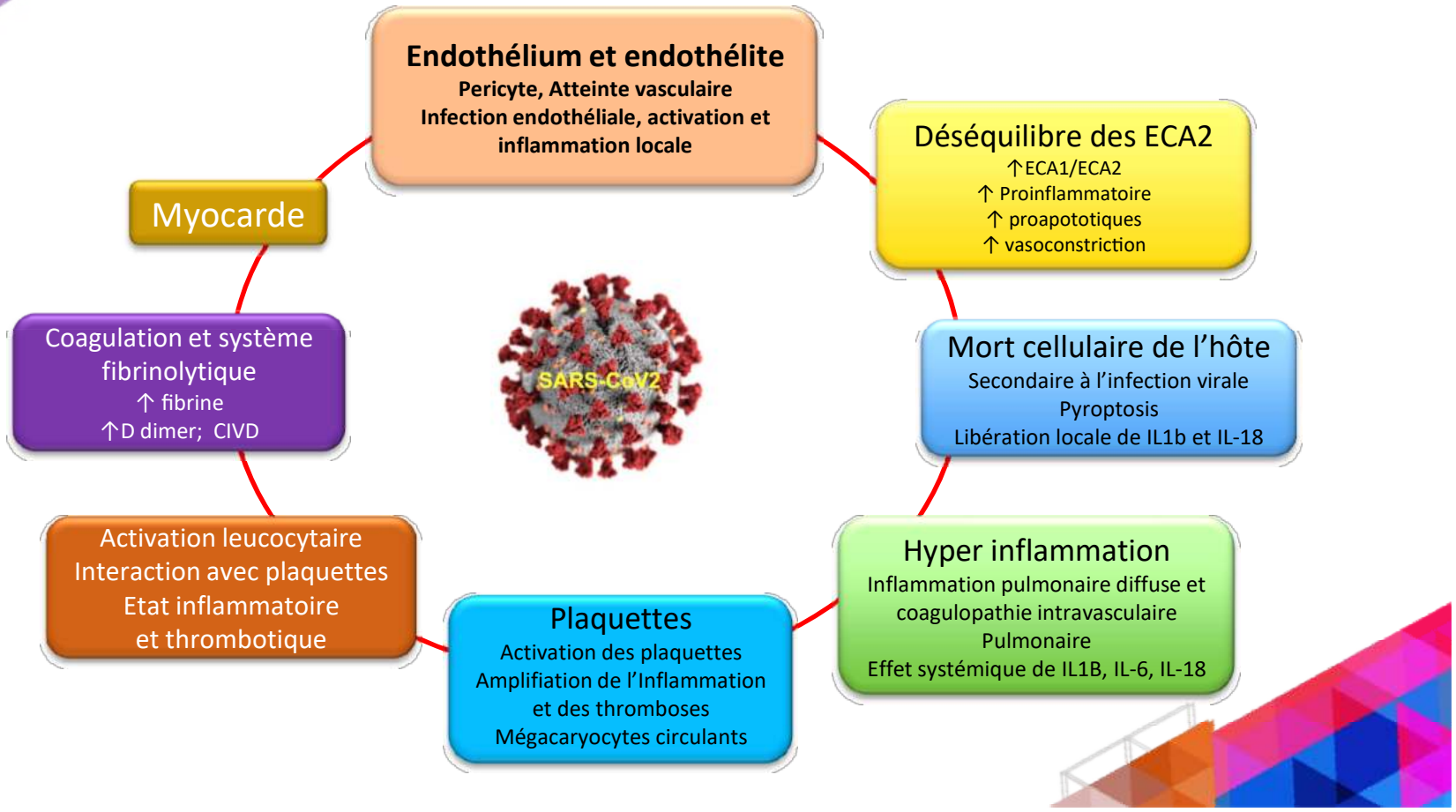
Interaction entre protéine S virale et le récepteur de l'enzyme de conversion de l'angiotensine 2



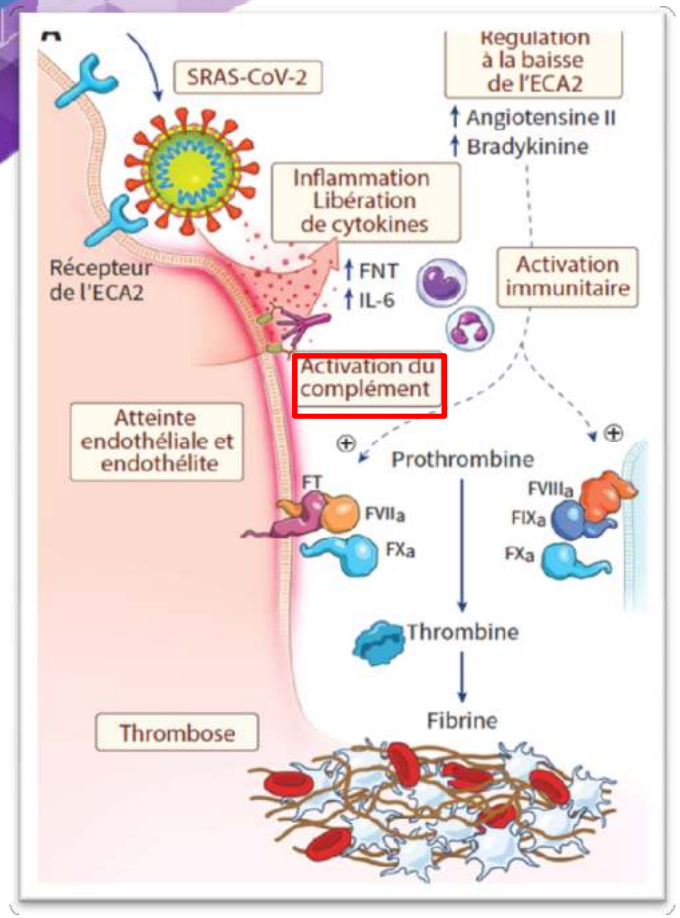
Cellule

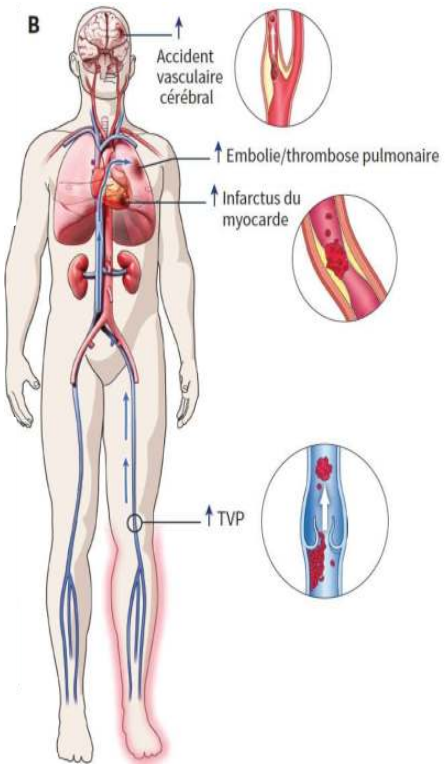
pneumocyte II, Cerveau, Cœur, les reins et endothélium

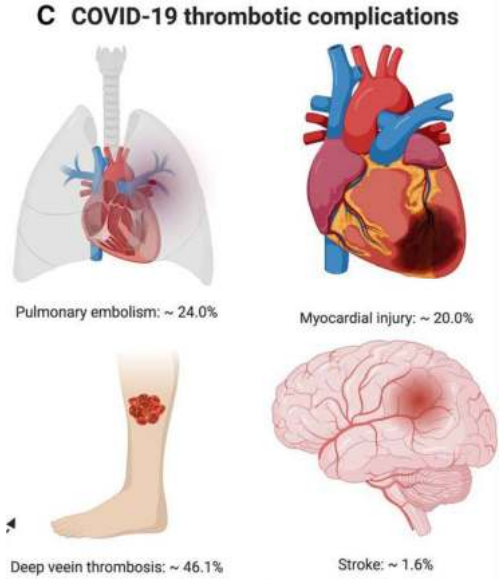
Effets sur le système cardiovasculaire et de coagulation

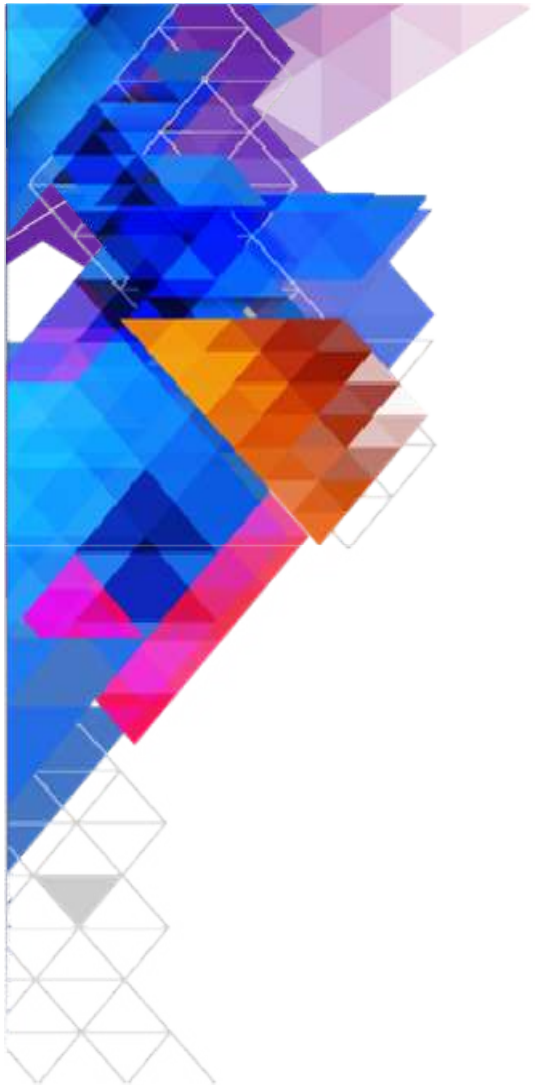


Mécanisme de la thrombose









[3] Diagnostic

Diagnostic

- **Embolie pulmonaire**
  - **Suspicion clinique :** mais symptômes et signes similaires (dyspnée et hypoxémie)
  - Score de Wells : sous estime la probabilité d'EP au cours du COVID-19 *Kirsch B et al Am J Med 2021;134(5): 688-690*
  - D-Dimer + probabilité clinique

Prevalence of Thrombotic Complications in ICU-Treated Patients With Coronavirus Disease 2019 Detected With Systematic CT Scanning

Mirsadraee S. et al CCM 2021;5: 804-815

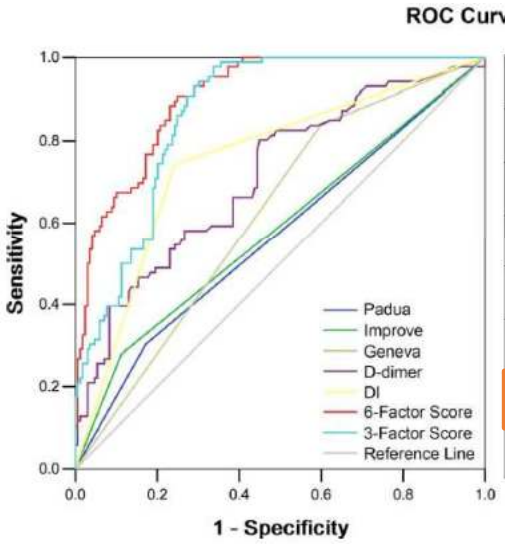
Laboratory Result	All Patients ($n = 72$), n (%)	No Thromboembolic Event ($n = 30$; 42%), n (%)	Thromboembolic Event ($n = 42$; 58%), n (%)	p[a]
D-dimer (ng/mL)				0.427
0–240 (normal value)	3 (4)	0	0	
241–2,000	18 (25)	9 (30)	9 (23)	
2,000–10,000	36 (50)	18 (60)	18 (46)	
> 10,000	15 (21)	3 (10)	12 (31)	

ORIGINAL ARTICLE

jth

Clinical characteristics and risk factors for symptomatic venous thromboembolism in hospitalized COVID-19 patients: A multicenter retrospective study

Li JY et al J Thromb Haemost. 2021;19:1038–1048.



Model	Cut-Off	Sensitivity	Specificity	AUC	95%CI	P value
Padua	1.5	0.302	0.828	0.565	0.489-0.641	0.088
Improve	1.5	0.279	0.888	0.583	0.507-0.660	0.030
Geneva	1.5	0.837	0.402	0.620	0.550-0.690	0.002
D-dimer	0.695	0.802	0.550	0.711	0.644-0.779	3.44×10^{-8}
DI	1.5	0.744	0.757	0.751	0.686-0.816	5.91×10^{-11}
3-Factor	0.171	0.930	0.710	0.865	0.822-0.907	1.67×10^{-21}
6-Factor	0.272	0.907	0.751	0.905	0.870-0.940	4.00×10^{-26}

FIGURE 4 Receiver operating characteristic (ROC) curve of models predicting symptomatic venous thromboembolism (VTE) in COVID-19 patients. Area under the ROC curve (AUC) was estimated in seven models; the Youden index was used to determine sensitivity and specificity; 255 COVID-19 patients (86 VTE cases and 169 non-VTE cases) with complete data were included in this analysis; DI: D-dimer increment; 6-factor model: age, cancer, interval from COVID-19 onset to admission, fibrinogen concentration, D-dimer level on admission, and D-dimer increment ≥1.5 fold; 3-factor experimental score (Wuhan score): fibrinogen, D-dimer on admission, and DI ≥1.5; Equation: Logit(P) = −3.954 + 0.304 × D-dimer + 2.775 × DI (No = 1, Yes = 2) − 0.385 × Fibrinogen

[4] Prise en charge thérapeutique

Prophylaxie

Héparine

- En plus de l'activité anticoagulante l'héparine a d'autres effets bénéfiques:
  - Suppression des taux de cytokine inflammatoires
  - Inhibition du complément
  - Suppression de la chimiotaxie et de la migration des neutrophiles
  - Prévenir l'atteinte endothéliale en bloquant l'histone et l'ADN cellulaire et en protégeant l'étanchéité de la jonction endothéliale
  - Effets antiviraux directes en induisant des changements de conformation de la protéine S du SARS-COV-2 → empêcherait d'envahir les cellules et de se fixer à l'ECA2.
- HBPM > Héparine

Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study

Rentsch CT. BMJ 2021;372:n311

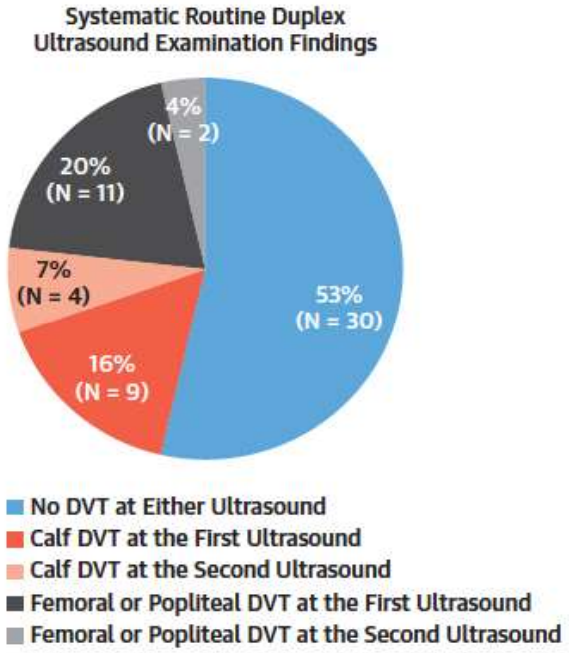
Table 3 | Absolute and relative risks associated with prophylactic anticoagulation in the first 24 hours of hospital admission with coronavirus disease 2019

			Unweighted	IPT weighted	
Outcomes	No of patients	No of events	Hazard ratio (95% CI)	Cumulative incidence (95% CI)	Hazard ratio (95% CI)
30 day mortality:					
Prophylactic anticoagulation	3627	513	0.85 (0.69 to 1.05)	14.3 (13.1 to 15.5)	0.73 (0.66 to 0.81)
No anticoagulation	670	109	Ref	18.7 (15.1 to 22.9)	Ref
Inpatient mortality:					
Prophylactic anticoagulation	3627	418	0.82 (0.66 to 1.03)	11.7 (10.7 to 12.8)	0.69 (0.61 to 0.77)
No anticoagulation	670	92	Ref	16.4 (13.0 to 20.5)	Ref
Initiating therapeutic anticoagulation:					
Prophylactic anticoagulation	3627	573	1.14 (0.91 to 1.42)	15.6 (14.4 to 16.8)	0.81 (0.73 to 0.90)
No anticoagulation	670	92	Ref	18.8 (15.2 to 23.1)	Ref

IPT=inverse probability of treatment.

High Prevalence of Deep Vein Thrombosis in Mechanically Ventilated COVID-19 Patients

Voicu S. et al J Am Coll Cardiol 2020; 18(9):2358-2363



26/56 (46%) TVP

Dose préventive :

Enoxaparine : 41 patients

HNF 8 patients

Dose curative

7 patients

- Dose préventive standard insuffisante en réanimation ?
- Résistance à l'héparine

- En réanimation 80 % on une résistance à l'HNF et 50% ont une activité anti X_a suboptimale avec les HBPM
- Le mécanisme n'est pas complétement élucidé mais il peut être attribué au taux élevé de facteur VIII et fibrinogène et le faible taux d'antithrombine.

White D et al. J Thromb Res. 2020; 50:287-291

Impact of High-Dose Prophylactic Anticoagulation in Critically Ill Patients With COVID-19 Pneumonia

CHEST

Tacquard C. CHEST 2021; 159(6):2417-2427

- Etude observationnelle, 8 réanimations françaises
- Suivi J1 à J14: Anticoagulation, thromboses, hémorragies
- 538 patients inclus

TABLE 2] Thrombotic Complications and Their Respective Cumulative Incidence Within the First Two Weeks of Hospitalization in the ICU

Type of Thrombosis	No. (%)	Cumulative Incidence[a]
All thrombosis	122 (100)	22.7 (19.2-26.3)[b]
Pulmonary embolism	64 (52)	12.0 (9.2-14.7)[b]
DVT	18 (15)	5.0 (2.7-7.3)[c]
Catheter thrombosis	14 (11)	3.9 (1.9-5.9)[c]
Stroke	4 (3)	1.1 (0.1-2.2)[c]
Other thrombosis	2 (2)	0.5 (0.0-1.3)[c]
Mesenteric infarction	1 (2)	0.2 (0.0-1.0)[c]
Myocardial infarction	1 (1)	0.2 (0.0-0.8)[c]
RRT filter clotting	13 (11)	22.8 (11.8-33.7)[c,d]
ECMO clotting	5 (4)	11.6 (1.9-21.3)[c,e]

Impact of High-Dose Prophylactic Anticoagulation in Critically Ill Patients With COVID-19 Pneumonia

CHEST

Tacquard C. CHEST 2021; 159(6):2417-2427

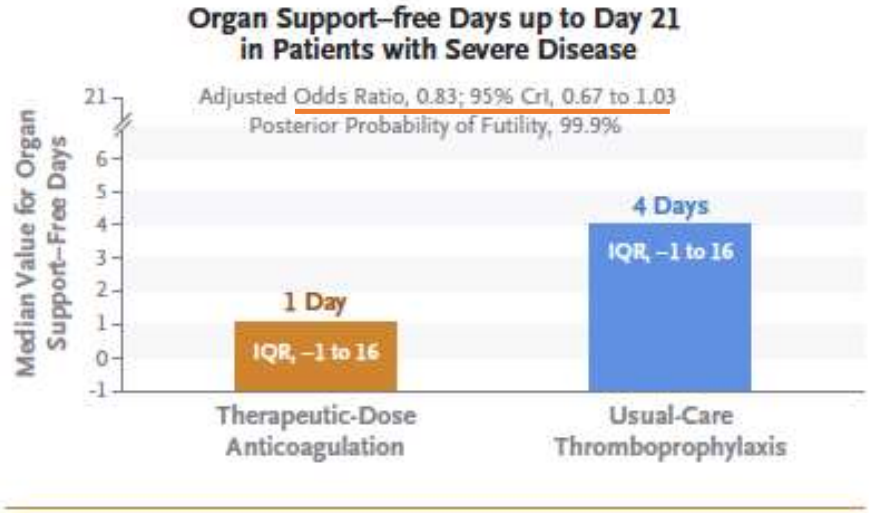
Anticoagulation à dose intermédiaire ou curative est associée à une réduction significative du risque de complication thromboembolique (hazard ratio, 0.81; 95% CI, 0.66-0.99) sans augmentation du risque de saignement (HR, 1.11; 95% CI, 0.70-1.75)

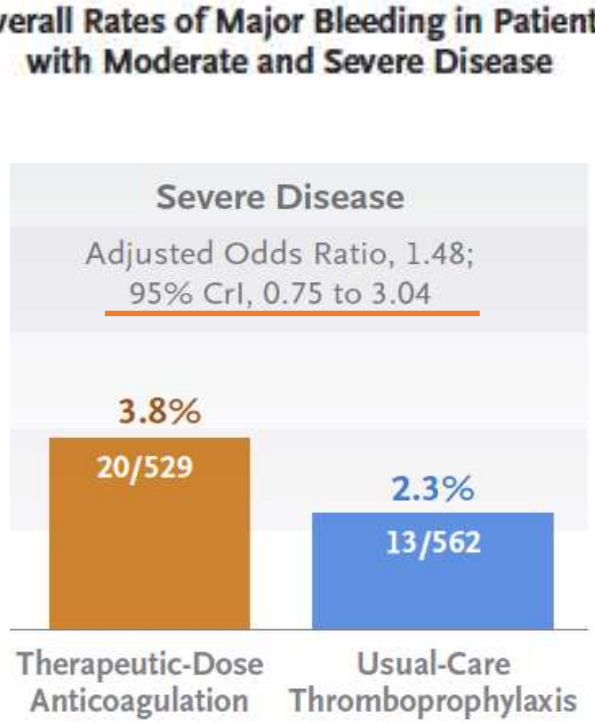
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 26, 2021 VOL. 385 NO. 9

Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*


Organ Support–free Days up to Day 21
in Patients with Severe Disease
Adjusted Odds Ratio, 0.83; 95% CrI, 0.67 to 1.03
Posterior Probability of Futility, 99.9%
Median Value for Organ Support–Free Days
21
6
5
4
3
2
1
0
-1
1 Day
IQR, −1 to 16
4 Days
IQR, −1 to 16
Therapeutic-Dose Anticoagulation
Usual-Care Thromboprophylaxis


Overall Rates of Major Bleeding in Patients
with Moderate and Severe Disease
Severe Disease
Adjusted Odds Ratio, 1.48;
95% CrI, 0.75 to 3.04
3.8%
20/529
2.3%
13/562
Therapeutic-Dose Anticoagulation
Usual-Care Thromboprophylaxis

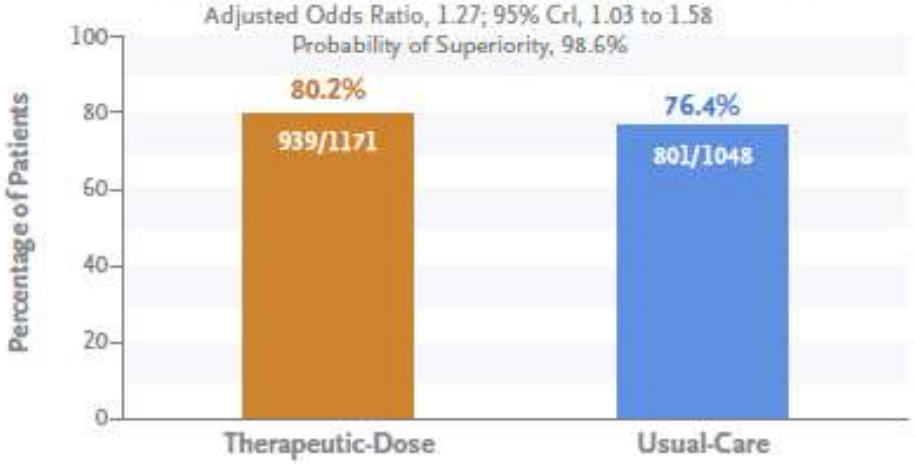
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

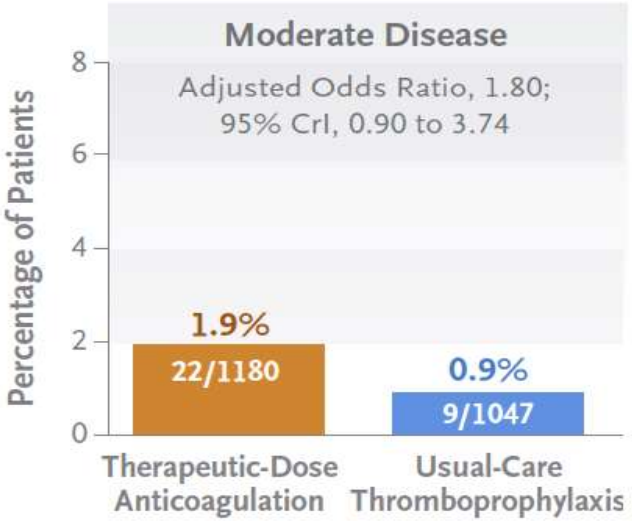
Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

The ATTACC, ACTIV-4a, and REMAP-CAP Investigators*

Percentage of Patients with Moderate Disease Who Survived until Hospital Discharge without Receiving Organ Support



Overall Rates of Major Bleeding in Patients with Moderate and Severe Disease

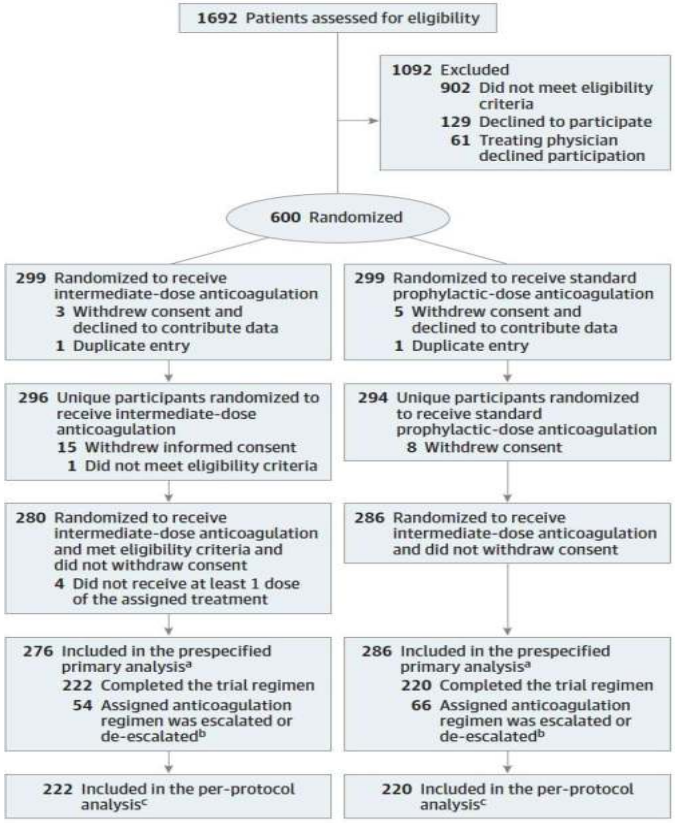


JAMA | Original Investigation

Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit
The INSPIRATION Randomized Clinical Trial

JAMA. 2021;325(16):1620-1630

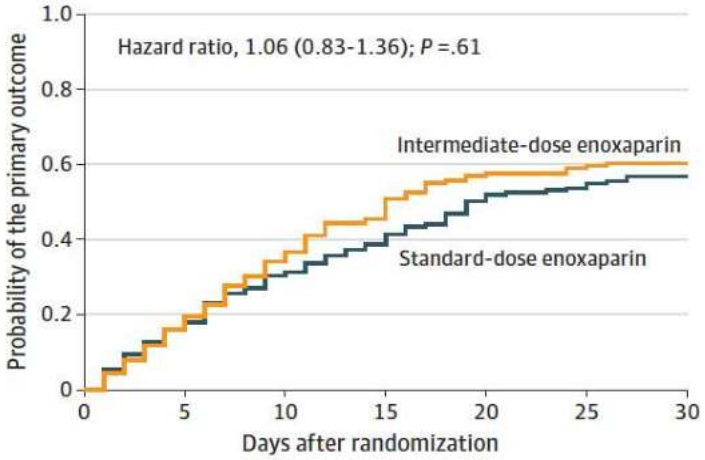
Enoxaparine 1 mg/kg



Enoxaparine 40 mg/j

Table 2. Primary, Secondary, and Exploratory Outcomes Within 30 Days of Enrollment in the Prespecified Primary Analysis in a Study of the Effect of Intermediate- vs Standard-Dose Prophylactic Anticoagulation Among Patients With COVID-19 Admitted to the Intensive Care Unit (ICU)

Outcome	No. (%)		Absolute difference (95% CI), %	Odds ratio (95% CI)	*P* value
	Intermediate dose (n = 276)	Standard dose (n = 286)			
Primary outcome					
Composite of adjudicated acute venous thromboembolism, arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all-cause mortality[a]	126 (45.7)	126 (44.1)	1.5 (−6.6 to 9.8)	1.06 (0.76 to 1.48)	.70
Secondary outcomes					
All-cause mortality	119 (43.1)	117 (40.9)	2.2 (−5.9 to 10.3)	1.09 (0.78 to 1.53)	.50
Adjudicated venous thromboembolism	9 (3.3)	10 (3.5)	−0.2 (−3.2 to 2.7)	0.93 (0.37 to 2.32)	.87
Ventilator-free days, median (IQR)[b]	30 (3 to 30)	30 (1 to 30)	0 (0 to 0)	NA	.50[c]



Outcome	No. (%)		Absolute difference (95% CI), %	Odds ratio (95% CI)	*P* value
	Intermediate dose (n = 276)	Standard dose (n = 286)			
Safety outcomes					
Major bleeding[e]	7 (2.5)	4 (1.4)	1.1 (−1.1 to 3.4)	1.83 (0.53 to 5.93)	.33
BARC classification					
Type 3a (hemoglobin drop of 3-5 g/dL or any transfusion)	3 (1.1)	4 (1.4)	−0.3 (−2.1 to 1.5)	0.78 (0.17 to 3.49)	.73
Type 3b (hemoglobin drop >5 g/dL)	1 (0.4)	0[f]	0.3 (−0.3 to 1.0)		.30
Type 3c (intracranial hemorrhage)	1 (0.4)	0[f]	0.3 (−0.3 to 1.0)		.30
Type 5 (fatal bleeding)	2 (0.7)	0[f]	0.7 (−0.2 to 1.7)		.14
Clinically relevant nonmajor bleeding (BARC type 2)[g]	12 (4.3)	5 (1.7)	2.5 (−0.2 to 5.4)	2.55 (0.92 to 7.04)	.07
Composite of major and non-major bleeding	17 (6.2)	9 (3.1)	3.0 (−0.4 to 6.4)	2.02 (0.89 to 4.61)	.08
Thrombocytopenia					
Mild (<100 $\times 10^3/\mu L$)[h]	50 (18.2)	57 (19.9)	−1.4 (−7.9 to 5.0)	0.89 (0.58 to 1.36)	.62
Moderate (<50 $\times 10^3/\mu L$)[h]	14 (5.1)	20 (7.0)	−0.8 (−4.6 to 2.8)	0.71 (0.35 to 1.44)	.61
Severe (<20 $\times 10^3/\mu L$)	6 (2.2)	0[f]	2.2 (0.4 to 3.8)		.01

ORIGINAL ARTICLE

Anticoagulation strategies and risk of bleeding events in critically ill COVID-19 patients

Gabara C et al Medicina Intensiva (in press)

Table 2 Characteristics of the patients depending on the anticoagulant dose received.

	Prophylactic dose (*n* = 78)	Intermediate dose (*n* = 94)	Therapeutic dose (*n* = 29)
Gender, male *n* (%)	56 (72%)	65 (69%)	21 (72%)
Age in years, mean (SD)	59.5 (13.6)	62.4 (12.5)	**68.1 (9.6)**[a,b]
Obesity, *n* (%)	3 (4%)	**19 (20%)**[c]	3 (10%)
Smoker, *n* (%)	7 (9%)	2 (2%)	2 (7%)
Comorbidities, *n* (%)	62 (80%)	76 (81%)	27 (93%)
Immunosuppression, *n* (%)	7 (9%)	10 (11%)	0 (0%)
Need of IMV, *n* (%)	39 (50%)	54 (57%)	19 (66%)
Need of vasoactive support, *n* (%)	40 (51%)	37 (39%)	14 (48%)
VTE, *n* (%)	14 (18%)	21 (22%)	6 (21%)
Bleeding, *n* (%)	4 (5%)	**14 (15%)**[d]	**9 (31%)**[a]
Major, *n* (%)	2 (3%)	8 (9%)	**6 (21%)**[c]
CNS	1 (25%)	1 (13%)	3 (50%)
Retroperitoneal	1 (25%)	2 (25%)	1 (17%)
Gastrointestinal	0 (0%)	5 (63%)	2 (33%)
Non-major, *n* (%)	2 (3%)	6 (6%)	3 (10%)
Mortality, *n* (%)	17 (22%)	17 (18%)	8 (28%)

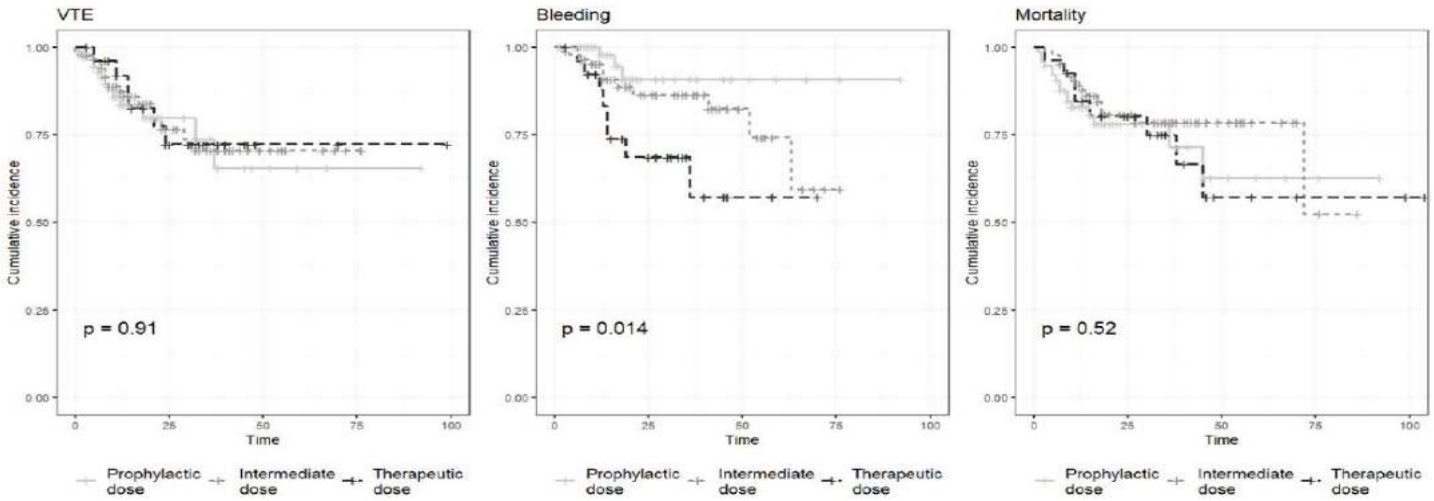


Table 3 Logistic multivariable regressions.

	Venous thromboembolism		Bleeding	
Clinical characteristics	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Age	1.03 (0.99–1.06)	0.11	1.03 (0.99–1.09)	0.17
Male Sex	0.38 (0.16–0.94)	**0.03**	0.43 (0.15–1.24)	0.12
Obesity	2.19 (0.72–6.65)	0.16	1.28 (0.32–5.03)	0.73
Comorbidities	0.77 (0.28–2.15)	0.62	1.31 (0.32–5.37)	0.7
Renal impairment	0.45 (0.05–3.95)	0.47	0.7 (0.07–6.82)	0.76
IVM	1.55 (0.75–3.24)	0.24	4.25 (1.47–12.29)	**0.008**
Anticoagulant dose				
Prophylactic vs intermediate doses	1.13 (0.51–2.51)	0.77	3.1 (0.94–10.45)	0.064
Prophylactic vs therapeutic doses	0.87 (0.29–2.68)	0.81	5.93 (1.55–22.72)	**0.009**

Abbreviations: IMV: invasive mechanical ventilation; CI: confidence interval; vs: versus.

ESC European Society of Cardiology
European Heart Journal - Cardiovascular Pharmacotherapy (2021) 0, 1–10
https://doi.org/10.1093/ehjcvp/pvab070
ORIGINAL ARTICLE
Thrombosis and antithrombotic therapy

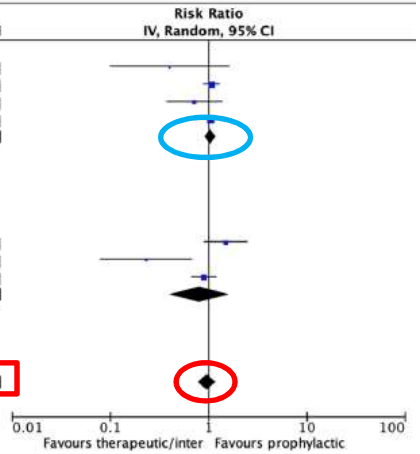
Safety and efficacy of different prophylactic anticoagulation dosing regimens in critically and non-critically ill patients with COVID-19: a systematic review and meta-analysis of randomized controlled trials

- 07 études : ERC
- 5154 patients suivi 33 jours
- Critère principal de jugement: mortalité et saignement
- Critères secondaires : MTV, Infarctus myocarde, AVC, thrombose artérielle systémique

Ortega-Paz et al European Heart Journal - Cardiovascular Pharmacotherapy (2021) 0, 1–10

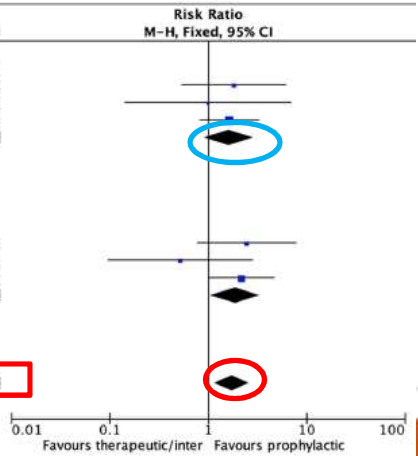
All-cause death

Study or Subgroup	Favours therapeutic/inter Events	Total	Prophylactic Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Critically ill						
HESACOVID	2	10	5	10	2.1%	0.40 [0.10, 1.60]
INSPIRATION	127	276	123	286	26.5%	1.07 [0.89, 1.29]
Perepu et al.	13	87	18	86	7.9%	0.71 [0.37, 1.37]
REMAP-CAP, ACTIV-4a, ATTACC Critically ill	199	534	200	564	28.2%	1.05 [0.90, 1.23]
Subtotal (95% CI)		**907**		**946**	**64.7%**	**1.03 [0.91, 1.18]**
Total events	341		346			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.23$, df = 3 (P = 0.36); $I^2 = 7\%$						
Test for overall effect: Z = 0.52 (P = 0.61)						
1.1.2 Non-critically ill						
ACTION COALITION	35	310	23	304	11.4%	1.49 [0.90, 2.46]
RAPID	4	228	18	237	3.4%	0.23 [0.08, 0.67]
REMAP-CAP, ACTIV-4a, ATTACC non-critically ill	86	1171	86	1048	20.5%	0.89 [0.67, 1.19]
Subtotal (95% CI)		**1709**		**1589**	**35.3%**	**0.80 [0.40, 1.61]**
Total events	125		127			
Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 10.01$, df = 2 (P = 0.007); $I^2 = 80\%$						
Test for overall effect: Z = 0.62 (P = 0.53)						
Total (95% CI)		**2616**		**2535**	**100.0%**	**0.96 [0.78, 1.18]**
Total events	466		473			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 13.75$, df = 6 (P = 0.03); $I^2 = 56\%$						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: $Chi^2 = 0.50$, df = 1 (P = 0.48), $I^2 = 0\%$						

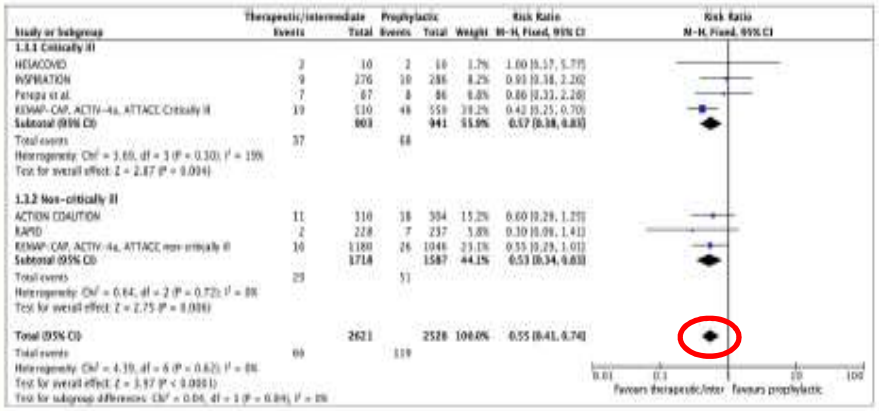


Major bleeding

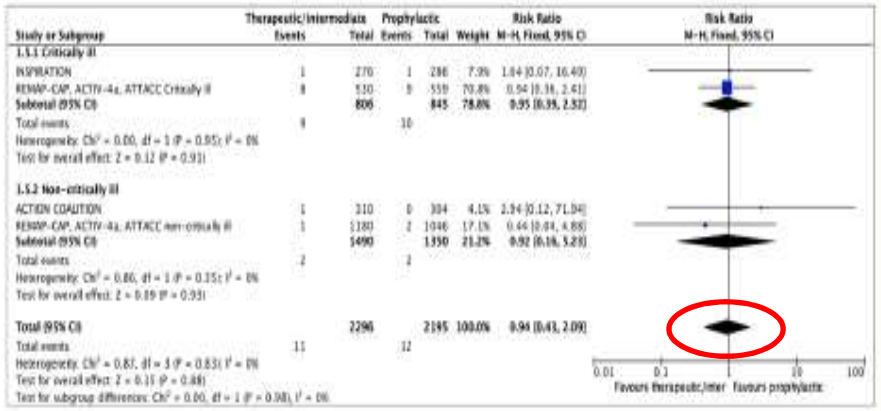
Study or Subgroup	Therapeutic/intermediate Events	Total	Prophylactic Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Critically ill						
HESACOVID	0	10	0	10		Not estimable
INSPIRATION	7	276	4	286	10.9%	1.81 [0.54, 6.13]
Perepu et al.	2	87	2	86	5.6%	0.99 [0.14, 6.86]
REMAP-CAP, ACTIV-4a, ATTACC Critically ill	20	529	13	562	35.0%	1.63 [0.82, 3.25]
Subtotal (95% CI)		**902**		**944**	**51.5%**	**1.60 [0.91, 2.84]**
Total events	29		19			
Heterogeneity: $Chi^2 = 0.28$, df = 2 (P = 0.87); $I^2 = 0\%$						
Test for overall effect: Z = 1.62 (P = 0.11)						
1.2.2 Non-critically ill						
ACTION COALITION	10	310	4	304	11.2%	2.45 [0.78, 7.73]
RAPID	2	228	4	237	10.9%	0.52 [0.10, 2.81]
REMAP-CAP, ACTIV-4a, ATTACC non-critically ill	22	1180	9	1047	26.5%	2.17 [1.00, 4.69]
Subtotal (95% CI)		**1718**		**1588**	**48.5%**	**1.86 [1.04, 3.33]**
Total events	34		17			
Heterogeneity: $Chi^2 = 2.57$, df = 2 (P = 0.28); $I^2 = 22\%$						
Test for overall effect: Z = 2.10 (P = 0.04)						
Total (95% CI)		**2620**		**2532**	**100.0%**	**1.73 [1.15, 2.60]**
Total events	63		36			
Heterogeneity: $Chi^2 = 2.99$, df = 5 (P = 0.70); $I^2 = 0\%$						
Test for overall effect: Z = 2.64 (P = 0.008)						
Test for subgroup differences: $Chi^2 = 0.13$, df = 1 (P = 0.72), $I^2 = 0\%$						



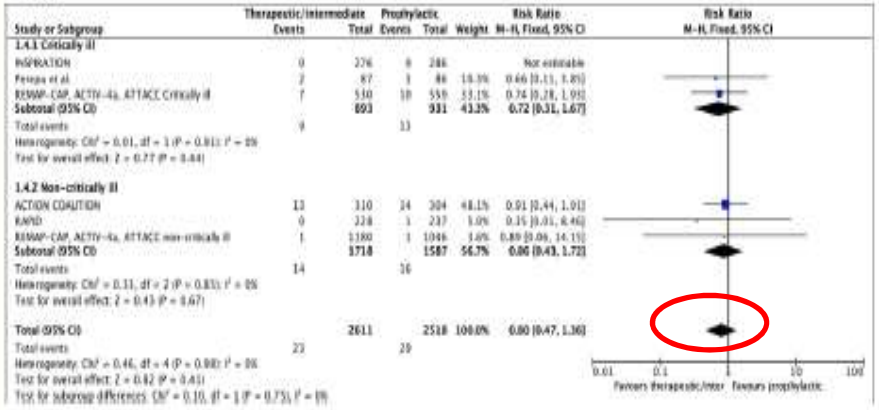
VTE



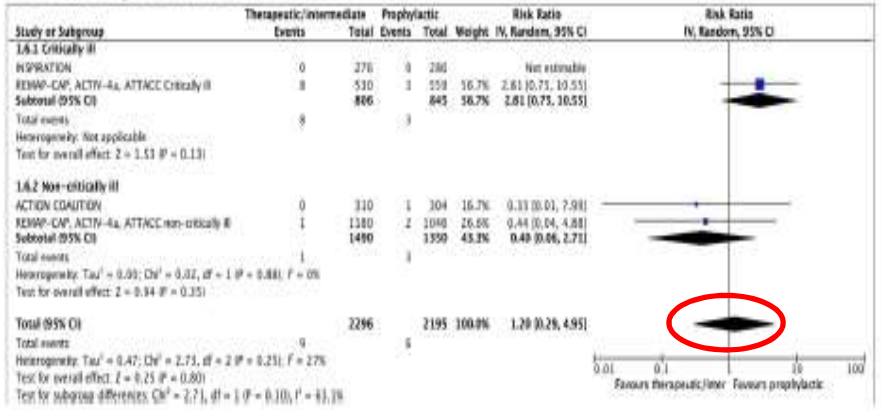
Stroke

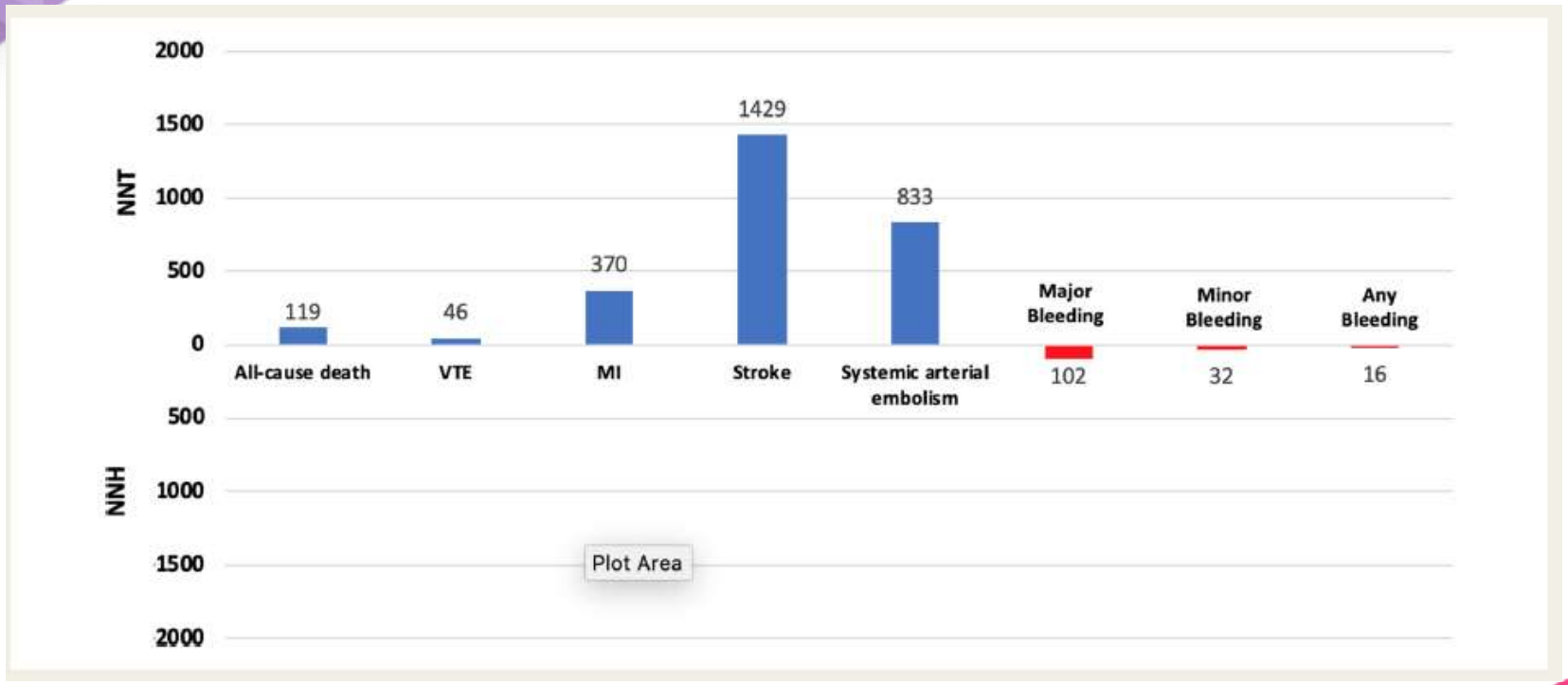


MI



Arterial systemic embolism




2000
1500
1000
500
0
500
1000
1500
2000
NNT
NNH
119
46
370
1429
833
102
32
16
All-cause death
VTE
MI
Stroke
Systemic arterial embolism
Major Bleeding
Minor Bleeding
Any Bleeding
Plot Area

PRÉVENTION DU RISQUE THROMBOEMBOLIQUE VEINEUX ET SURVEILLANCE DE L'HÉMOSTASE CHEZ LES PATIENTS HOSPITALISÉS POUR COVID-19 : PROPOSITIONS RÉACTUALISÉES (AVRIL 2021)

GROUPE D'INTÉRÊT EN HÉMOSTASE PÉRIOPERATOIRE (GIHP) ET GROUPE D'ÉTUDE SUR L'HÉMOSTASE ET LA THROMBOSE (GFHT)

Table 1. Anticoagulation prophylactique (dose, posologie) selon l'indice de masse corporelle et la clairance de la créatinine.

Clairance de la créatinine	IMC	Prophylaxie à dose standard	Prophylaxie à dose intermédiaire	Prophylaxie à dose thérapeutique
>30 ml/min	< 30	HBPM par ex. enoxaparine 4000 UI/24h*	HBPM par ex. enoxaparine 4000 UI/12h	HBPM par ex. enoxaparine 100 UI/kg/12h, sans dépasser 10 000 UI/12h
	> 30	HBPM par ex. enoxaparine 4000 UI/12h	HBPM par ex. enoxaparine 6000 UI/12h	
15-30 ml/min	< 30	HBPM par ex. enoxaparine 2000 UI/24h	HNF bolus puis 200 UI/kg/24h IVSE adapté à l'anti-Xa	HNF bolus puis 500 UI/kg/24h IVSE adapté à l'anti-Xa
	> 30	HBPM par ex. enoxaparine 2000 UI/12h		
<15 ml/min	< 30	HNF 5000 UI/12h en sous-cutané ou IVSE		
	> 30	HNF 5000 UI/8h en sous-cutané ou IVSE		
Cible d'activité anti-Xa		Aucune	HBPM : éviter le surdosage (< 1,5 UI/mL pour l'enoxaparine et la tinzaparine) HNF : activité détectable et < 0,5 UI/mL	HBPM : éviter le surdosage (< 1,5 UI/mL pour l'enoxaparine et la tinzaparine) HNF : 0,5-0,7 UI/mL

Faut-il étendre la durée après la sortie du patient ?

THROMBOSIS AND HEMOSTASIS

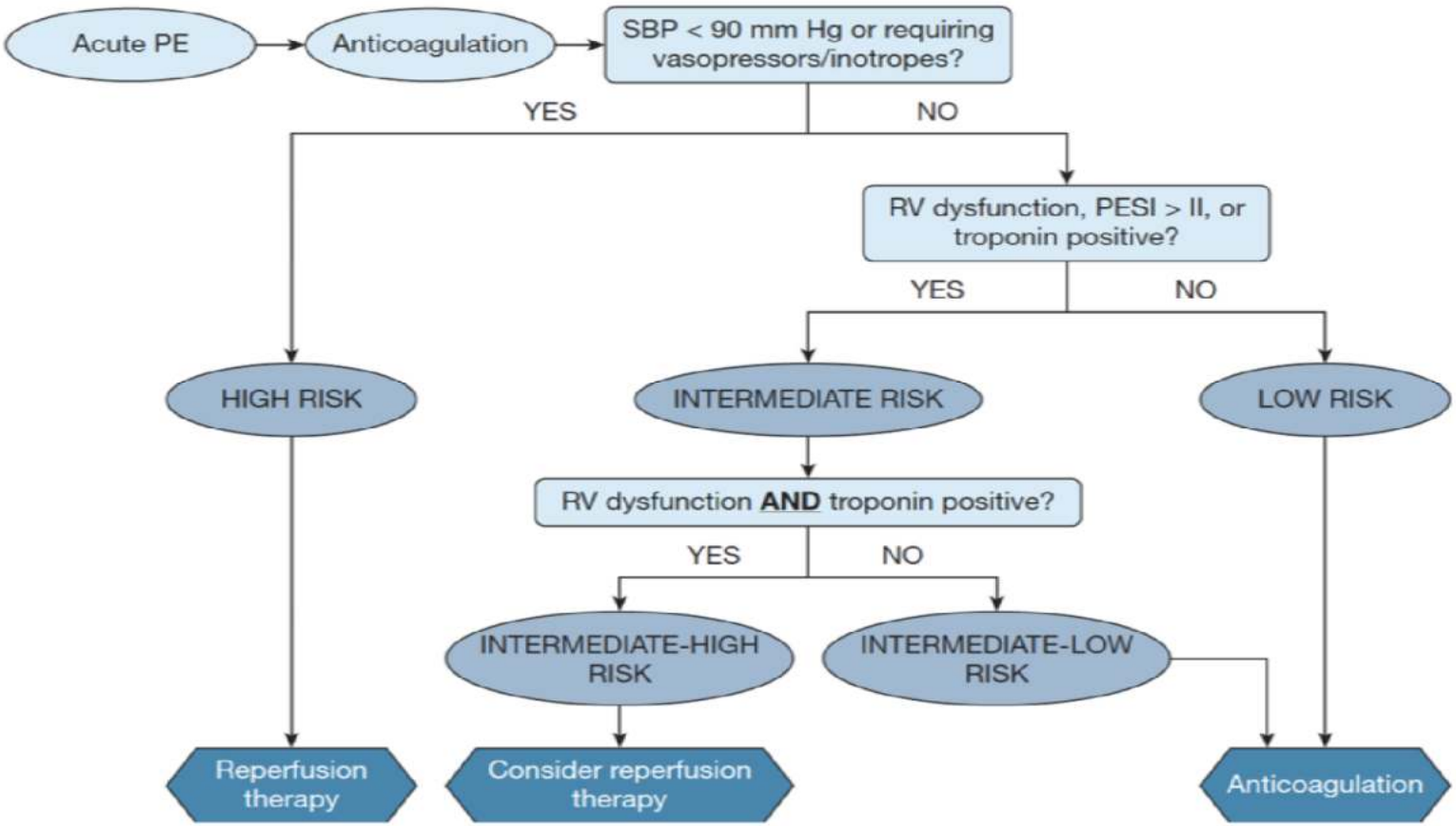
Postdischarge venous thromboembolism following hospital admission with COVID-19

Roberts LN et al. Blood. 2020;136(11):1347-1350

- La proportion de patients COVID-19 qui développent une MTE après leurs sortie est de 4,8 pour 1000 sorties (42 jours après la sortie) comparable au patients médicaux (3,1 pour 1000 sorties)
  - Pas d'indication à l'extension de la thromboprophylaxie à la sortie chez tous les patients
  - Seul les patients à haut risque (*mobilité réduite, cancer, antécédents de MTE, IMC>30Kg/m^2, D-Dimer > 2 fois le niveau supérieur de la normale, Sujets âgés > 75 ans, Réanimation, thrombophilie*) et ayant un faible risque de saignement peuvent avoir une extension de la thromboprophylaxie
  - Durée ≥ 14 j jusqu'à 30 jours.

Anticoagulation curative

- Médicament dépend de
  - Fonction rénale et hépatique
  - Throbocytopénie
  - Tractus digestif
- Hôpital : HBPM
- Hors hôpital : anticoagulation orale (interaction médicamenteuse)
- Durée de traitement ≥ 3 mois


Acute PE
Anticoagulation
SBP < 90 mm Hg or requiring vasopressors/inotropes?
YES
NO
RV dysfunction, PESI > II, or troponin positive?
YES
NO
HIGH RISK
INTERMEDIATE RISK
LOW RISK
RV dysfunction AND troponin positive?
YES
NO
INTERMEDIATE-HIGH RISK
INTERMEDIATE-LOW RISK
Reperfusion therapy
Consider reperfusion therapy
Anticoagulation

Merci pour votre attention