Anticoagulation des patients COVID : risque hémorragique et thrombotique

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Conflits d’intérêt

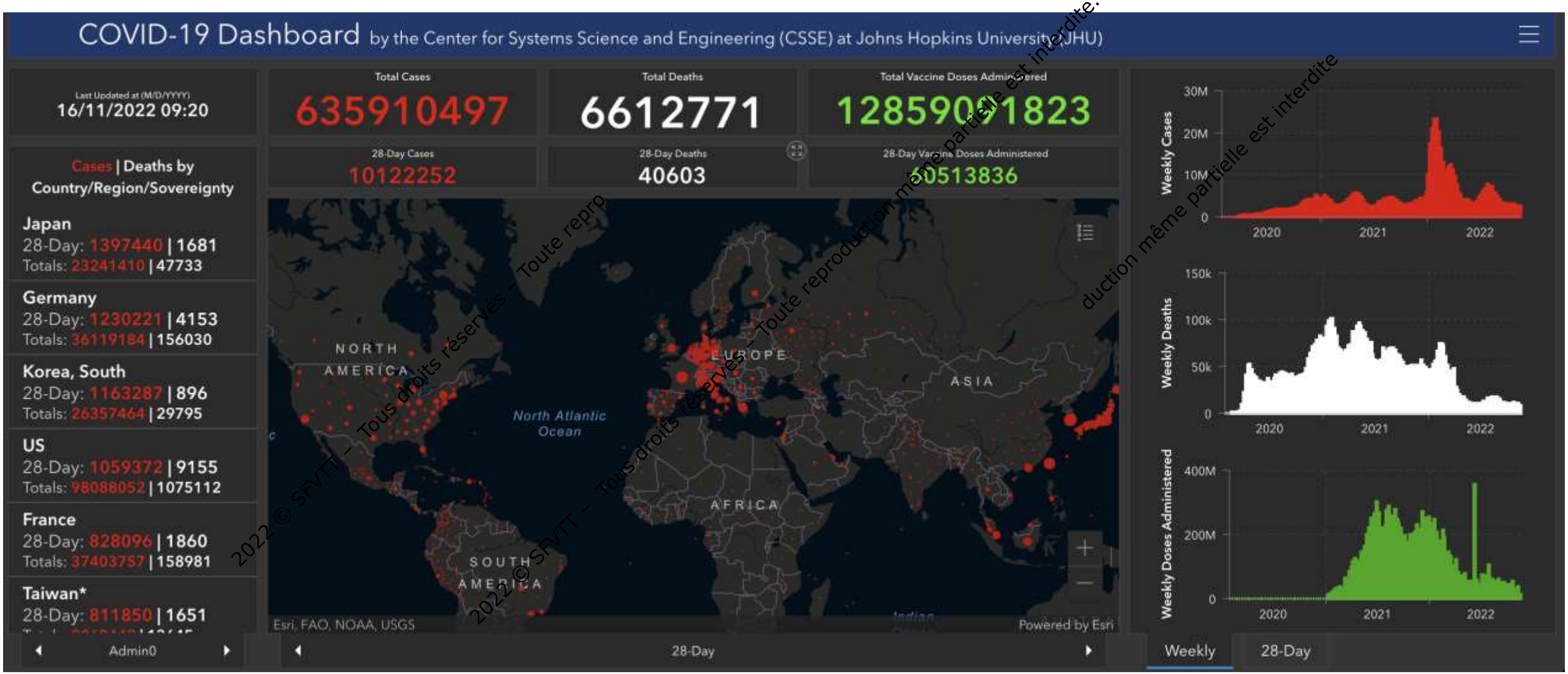
Industriels

- LFB: financement du PRI HEMOSTVAD
- Braun: financement protocole de recherche expérimentale
- Sanofi: symposium SFAR 2021

Académiques

- Membre du GIHP
- Coordinateur du GERAP

Introduction



Quelle était la situation lors de la 1ère vague?

Introduction

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	Non-COVID-19-ARDS (n = 145)	COVID-19-ARDS (n = 77)	OR [95% IC]	p
Thrombo-embolic complications - n (%)	14 (6.0)	27 (18.0)	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

Helms and al. ICM 2020

Physiopathologie

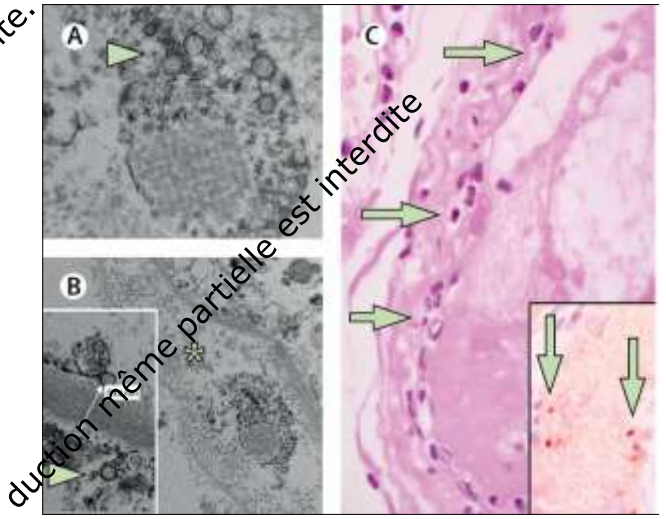
<u>Atteinte endothéliale</u> +++

- Infection directe de l'endothélium par le SARS-CoV-2
- Sécrétion de VWF et de FVIII: effet pro-coagulant

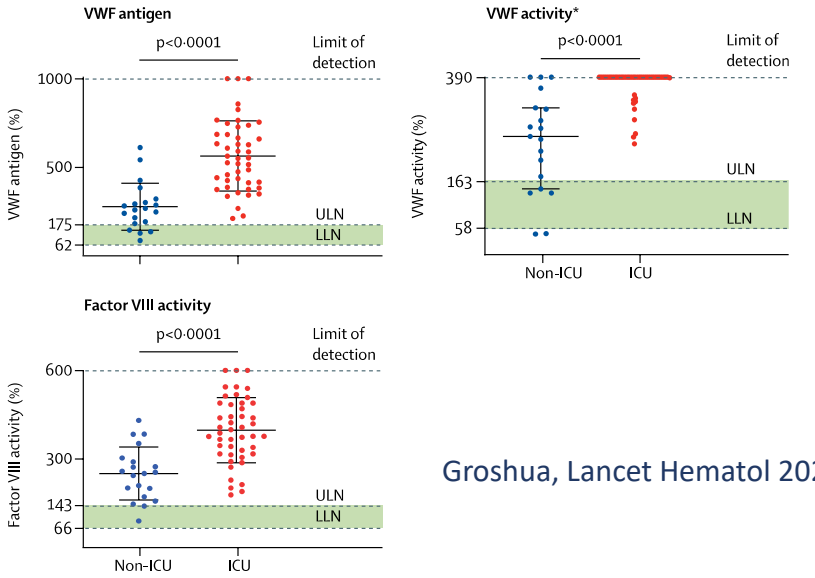
Varga, Lancet 2020; Escher Thromb Res 2020; De Cristofaro Blood Coag Fib, 2021

- Sécrétion d'angiopoïetine 2: vasoconstriction

Smadja, Angiogenesis 2020



Varga, Lancet 2020

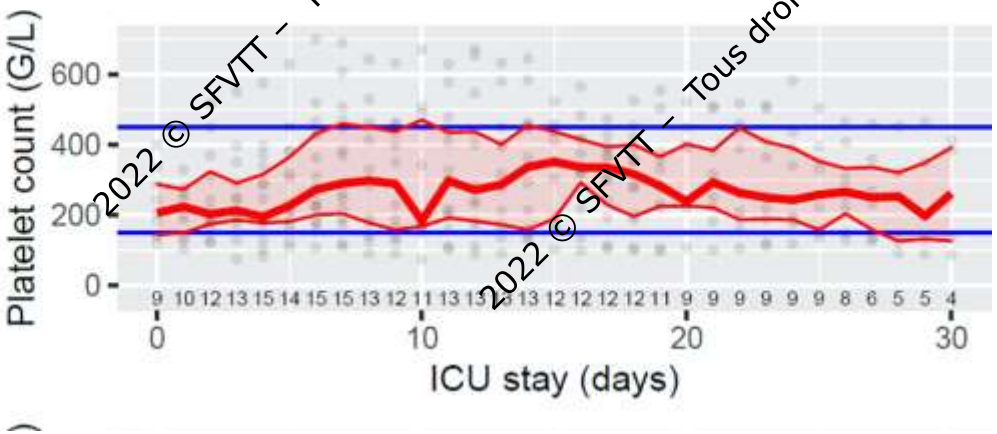


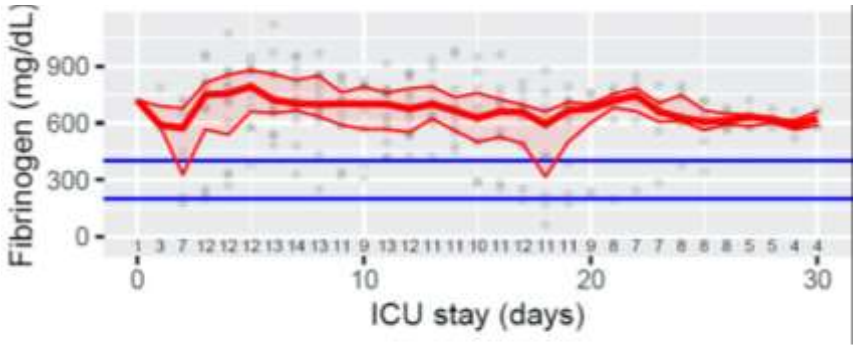
Groshua, Lancet Hematol 2021

Physiopathologie

Activation des voies de la coagulation

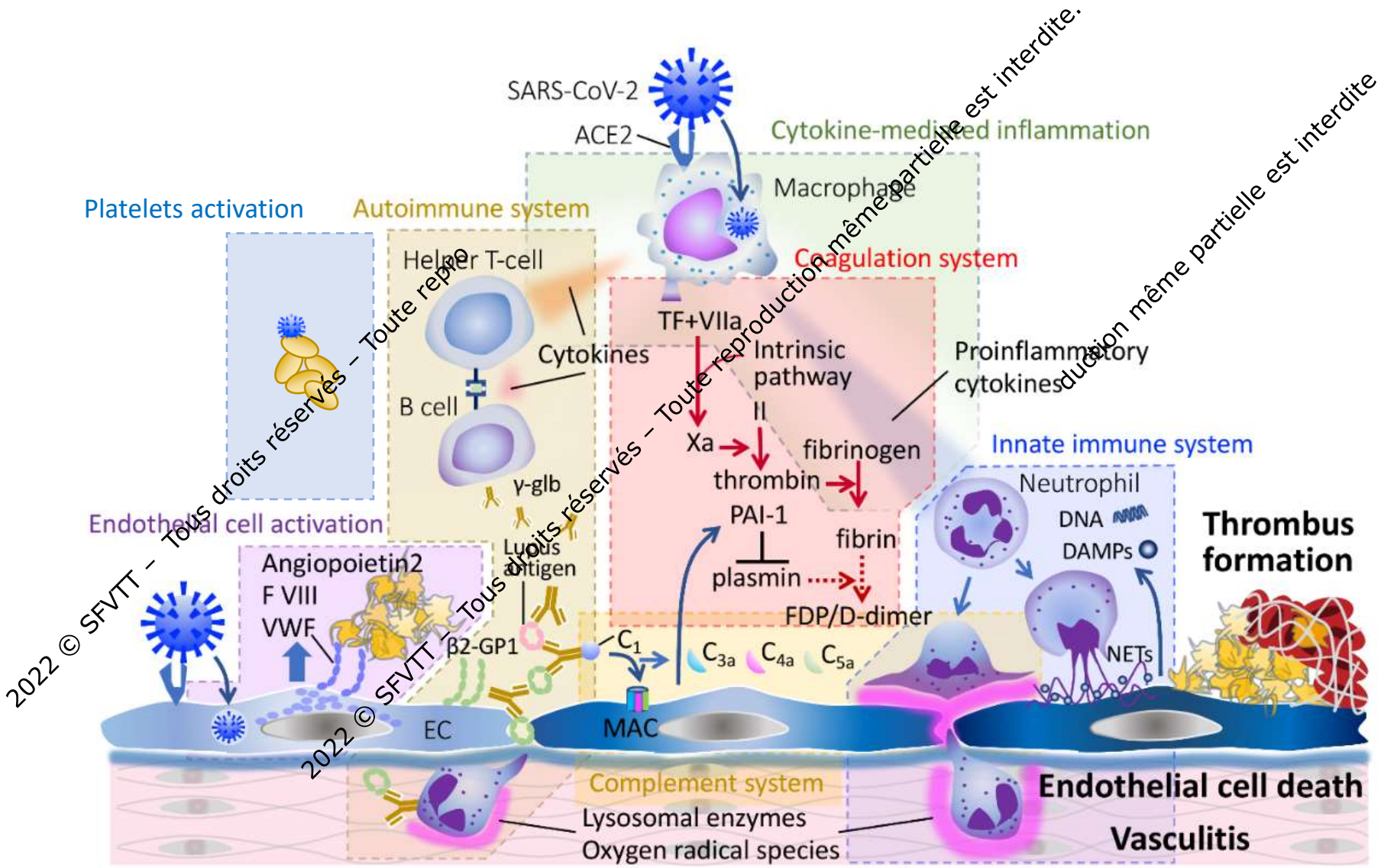
- Activation de la voie extrinsèque via la sécrétion de FT par macrophages/monocytes et endothélium activé
- Activation de la phase contacte
- Dépôts de fibrine intra alvéolaire ++
- Activation de la fibrinolyse = D-dimères (FdR indépendant de mortalité)





Hardy, Thromb Res, 2020

Physiopathologie



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Adapted from Iba, JCM 2021

Risque thrombotique

Evènements thromboemboliques

Lieu d'hospitalisation	Incidence
Service de médecine	**7,1 % (4,8-9,8)**
Réanimation	27,9 % (22,1-34,1)

Jimenez and al, Chest 2020

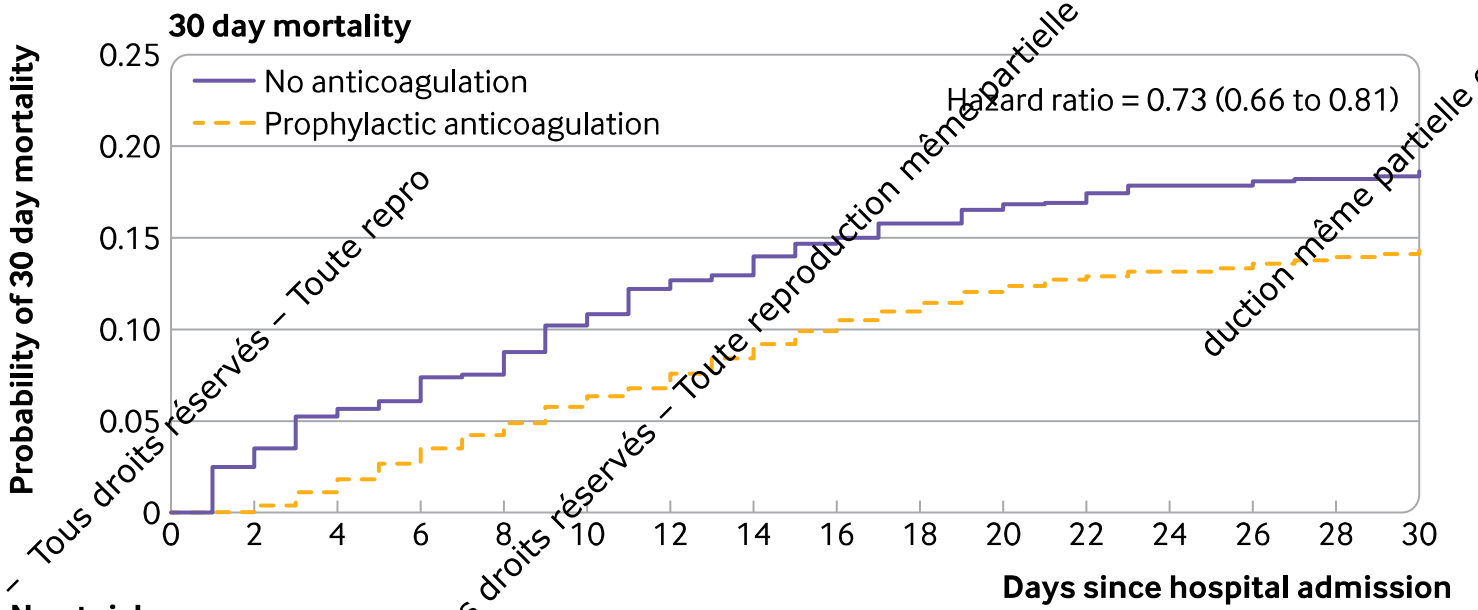
Table 2: Pooled Incidence of PE and DVT according to Study Characteristics

Parameter	Incidence (%)	Heterogeneity*
PE		
Overall	16.5 (11.6, 22.9)	NA
Study design		
Retrospective (n = 20)	15.5 (10.4, 22.6)	<.001, 0.93
Prospective (n = 2)	25.1 (11.1, 47.2)	<.001, 0.93
Study population†		
Non-ICU or various (n = 12)	10.5 (5.1, 20.2)	<.001, 0.95
ICU or critically ill patients (n = 18)	24.7 (18.6, 32.1)	<.001, 0.82

Suh and al, Radiology 2020

Anticoagulation

Surmortalité en l'absence d'anticoagulation



No at risk

No anticoagulation

2141 2087 2039 2010 1980 1922 1880 1864 1826 1803 1787 1779 1759 1759 1750 1748

Prophylactic anticoagulation

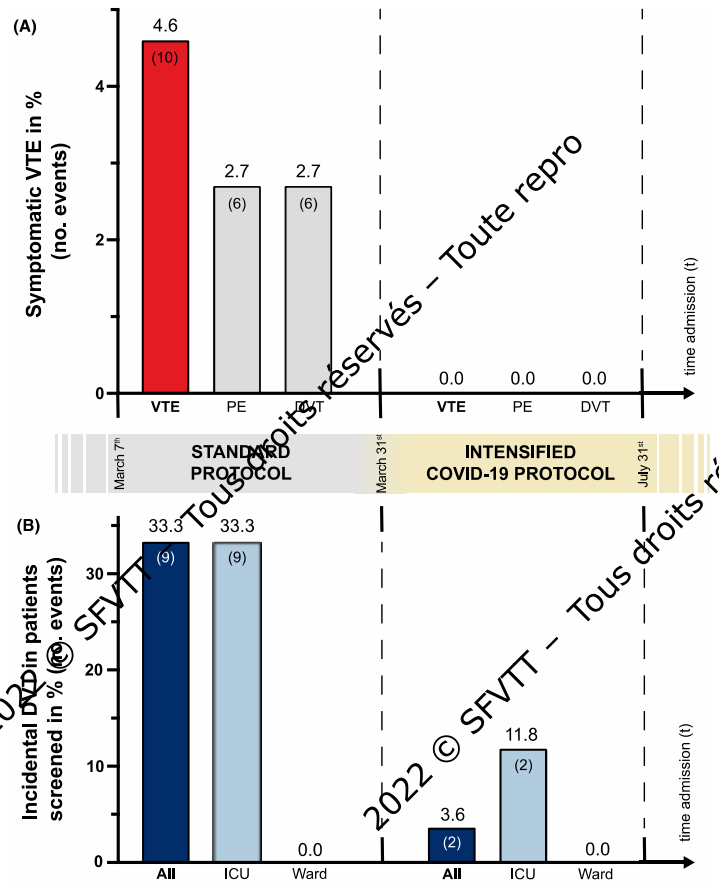
2156 2134 2131 2097 2064 2031 2008 1974 1946 1918 1895 1881 1873 1867 1858 1852

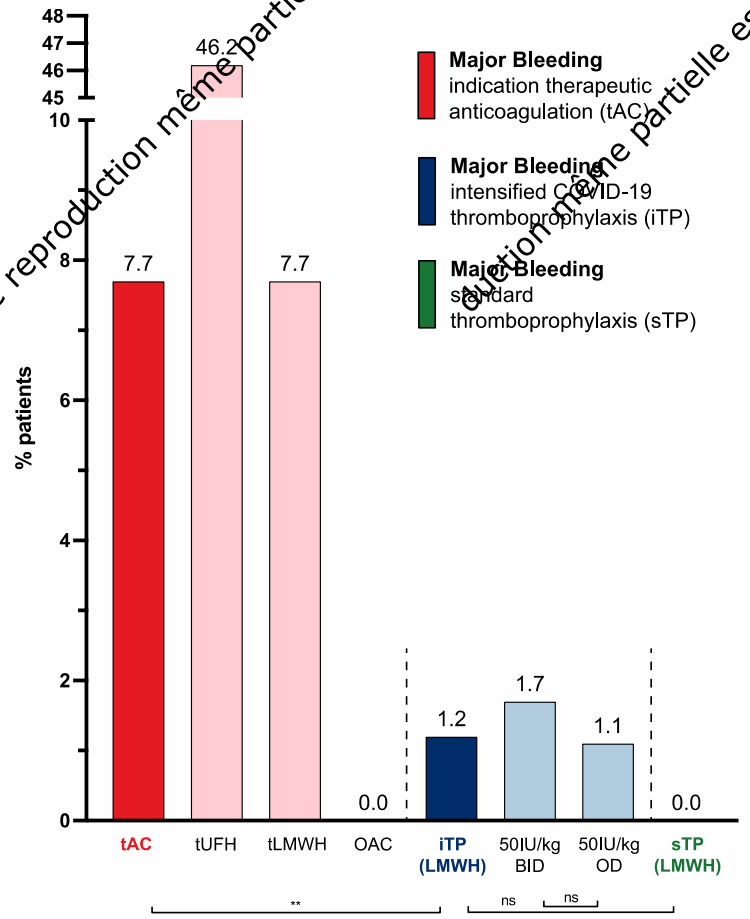
Rentsch, BMJ 2021

Etude observationnelle, score de propension

Anticoagulation

Bénéfice d'une dose renforcée?



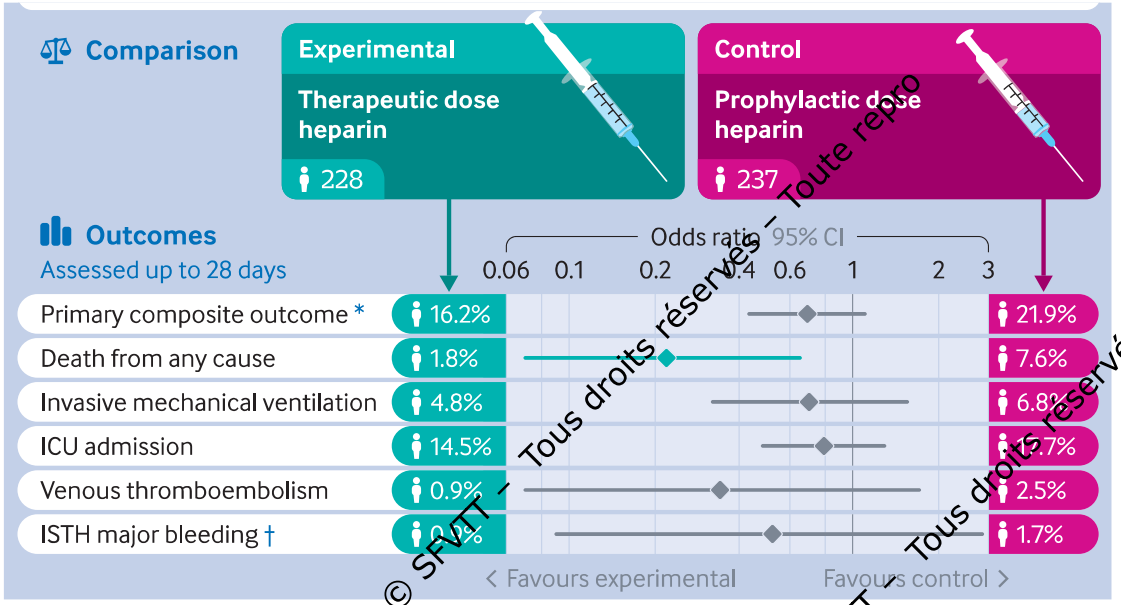


Engelen, RPTH 2021

Anticoagulation

Bénéfice d'une dose renforcée?

RAPID Trial



Scholzberg, BMJ 2021

Essai randomisé contrôlé
AC jusqu'à J28

HEP-COVID study

Table 2. Clinical Outcomes During the 30-Day Postrandomization Phase

Outcome	No./total No. (%) Therapeutic dose (n = 129)	Standard dose (n = 124)	RR (95% CI)	*P* value[a]
Primary efficacy outcome				
VTE, ATE, or death	37/129 (28.7)	52/124 (41.9)	0.68 (0.49-0.96)	.03
Non-ICU stratum	14/84 (16.7)	31/86 (36.1)	0.46 (0.27-0.81)	.004
ICU stratum	23/45 (51.1)	21/38 (55.3)	0.92 (0.62-1.39)	.71
VTE + ATE	14/129 (10.9)	36/124 (29.0)	0.37 (0.21-0.66)	<.001
Death	25/129 (19.4)	31/124 (25.0)	0.78 (0.49-1.23)	.28

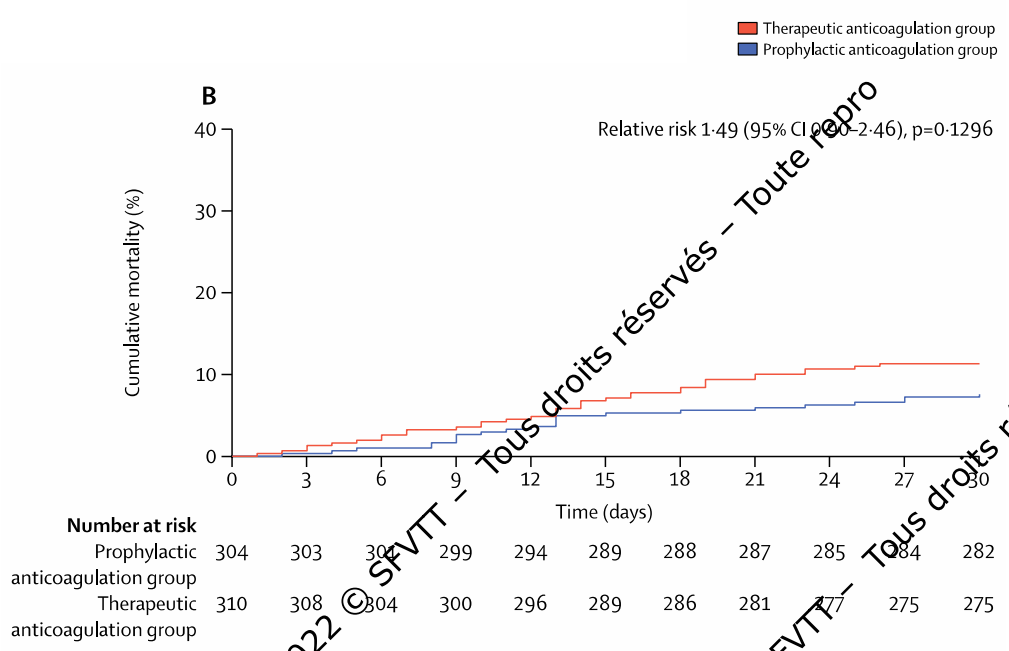
Spyropoulos, JAMA internal med, 2021

Pas de bénéfice chez les patients de réanimation
38% d'anticoagulation à dose intermédiaire dans le groupe standard

Anticoagulation

Bénéfice d'une dose renforcée?

ACTION Trial

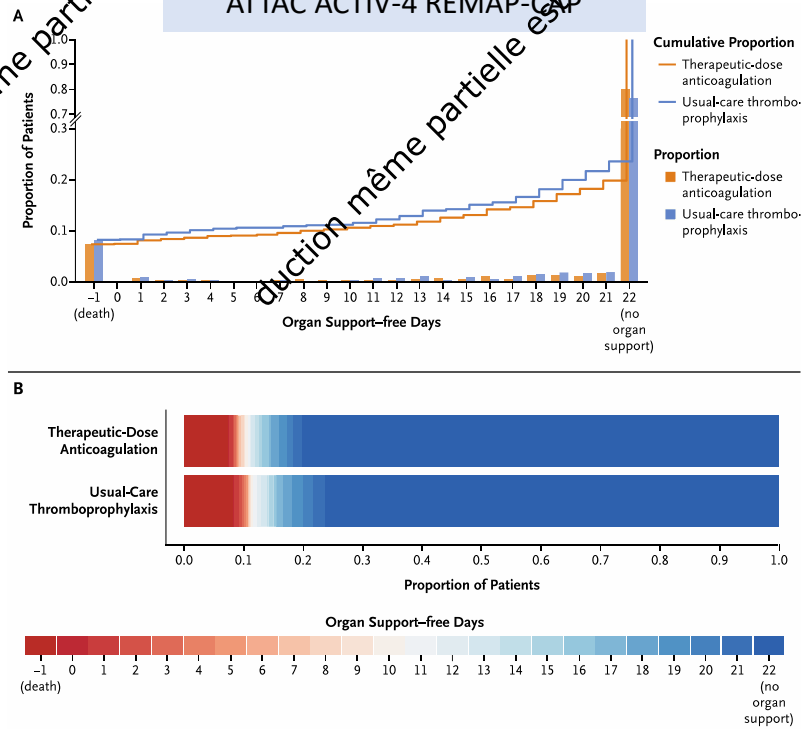


Lopes, The Lancet 2021

Etude randomisée contrôlée

Groupe thérapeutique : 90% sous rivaroxaban
Durée du traitement: 30 jours !

ATTAC ACTIV-4 REMAP-CAP



NEJM 2021

Etude randomisée contrôlée

Bénéfice à AC curative chez les patients peu sévère
Durée: 14 jours

Risque thrombotique - réanimation

Evènements thromboemboliques

Lieu d'hospitalisation	Incidence
Service de médecine	7,1% (4,8-9,8)
Réanimation	**27,9% (22,1-34,1)**

Jimenez and al, Chest 2020

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Suh and al, Radiology 2020

Anticoagulation

Diminution de l'incidence des complications thrombotiques

TABLE 4] Summary of Cox Model for the Effect of High-Dose Prophylactic Anticoagulation on TCs

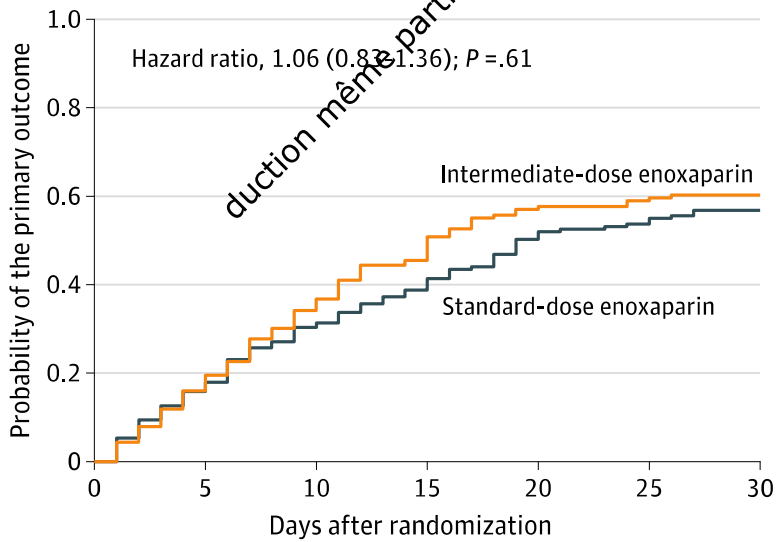
Population	Model	Factor	Coefficient (SE)	HR (95% CI)	*P* Value
TC all thrombosis (53 events, 1,104 observations, 245 patients)					
	Univariate Cox model				
		HPA	−0.243 (0.112)	0.785 (0.646-0.952)	.01
	Adjusted Cox model				
		HPA	−0.208 (0.115)	0.813 (0.663-0.996)	.05
		RRT	0.687 (0.308)	1.988 (1.083-3.648)	.03
		ECMO	0.254 (0.401)	1.290 (0.577-2.881)	.54
		Pao_2 to Fio_2 ratio	−0.002 (0.004)	0.998 (0.989-1.007)	.67
	Weighted Cox model				
		HPA	−0.332 (0.152)	0.718 (0.532-0.967)	.03
	Weighted and Adjusted Cox model				
		HPA	−0.217 (0.112)	0.804 (0.653-0.990)	.04
		RRT	0.671 (0.308)	1.957 (1.056-3.627)	.03
		ECMO	0.173 (0.405)	1.189 (0.514-2.751)	.69
		Pao_2 to Fio_2 ratio	−0.002 (0.004)	0.998 (0.989-1.007)	.64

Etude observationnelle, score de propension

Tacquard et al, Chest 2021

Pas d'effet sur la mortalité??

Figure 2. Primary Outcome in the Prespecified Primary Cohort in a Study of the Effect of Intermediate-Dose vs Standard-Dose Prophylactic Among Patients With COVID-19 Admitted to the Intensive Care Unit



Etude randomisée contrôlée

INSPIRATION trial, JAMA 2021

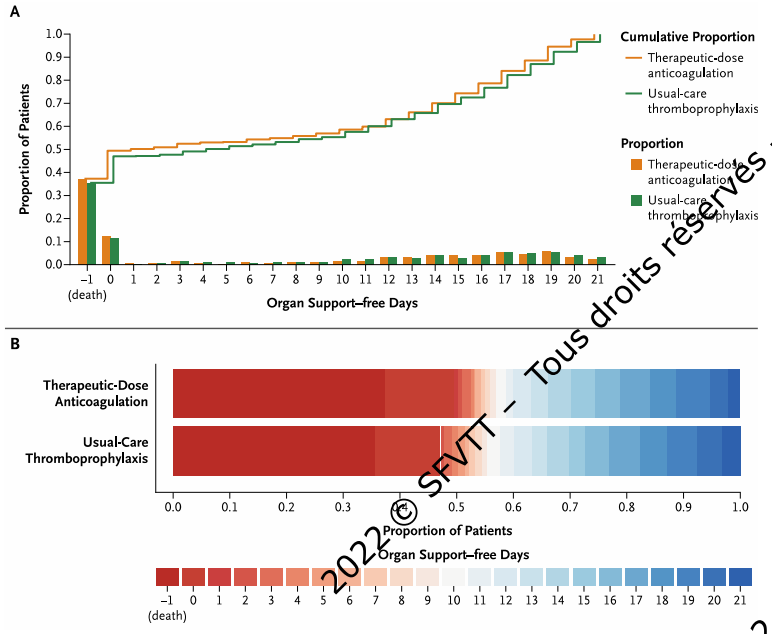
Seulement 3% d'ETEV
40 % de mortalité
Durée médiane de séjour: 6 jours!
Nombre de patients ventilés: 20%
Problème d'adéquation de moyen??

Anticoagulation

ORIGINAL ARTICLE

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

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



Pas d'AC à dose thérapeutique a tout le monde !

59,6 % des patients du groupe contrôle sont sous AC renforcée
Dont 6% sous AC à dose thérapeutique

Table S1 – Anticoagulation Regimens

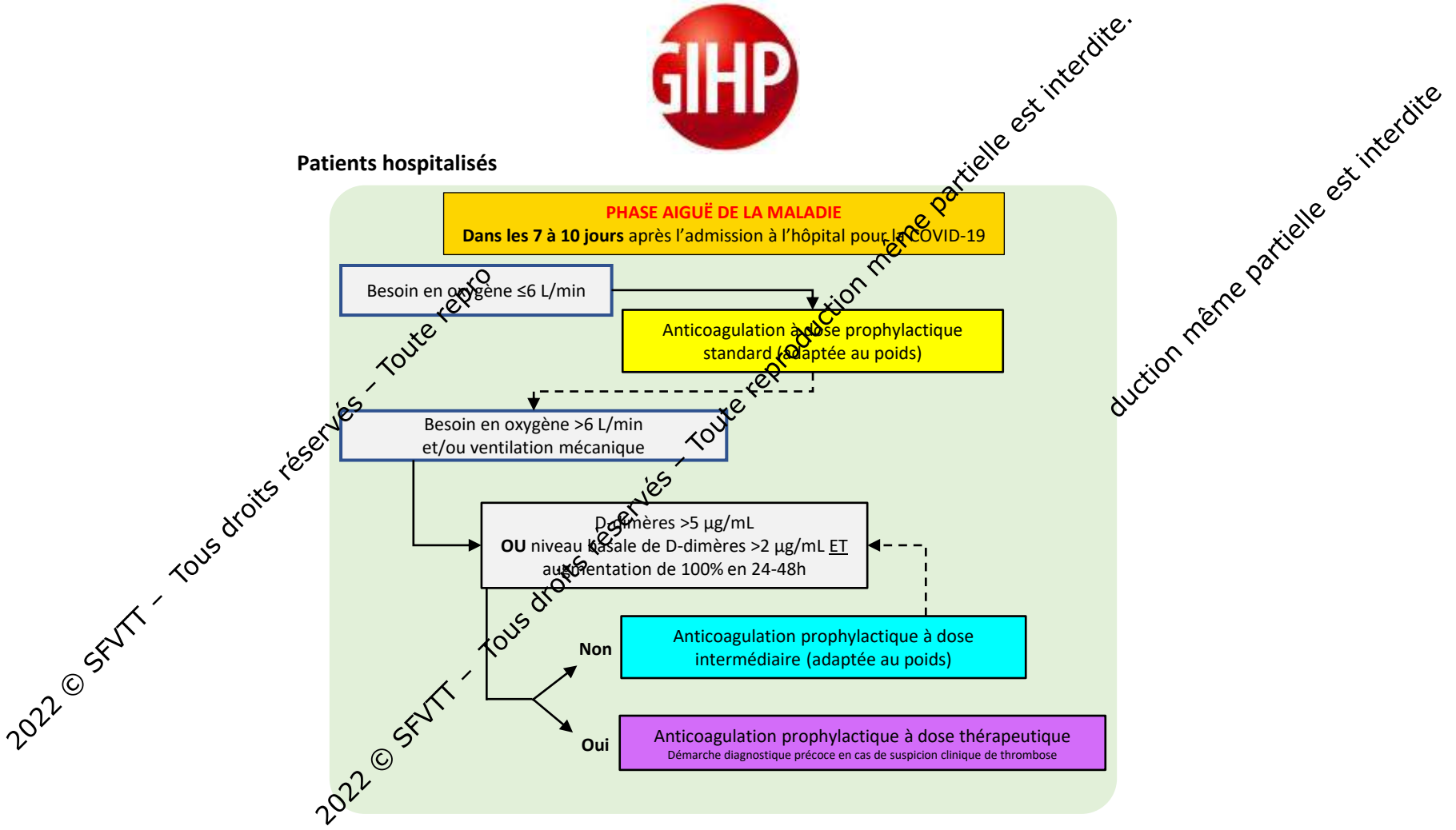
	Therapeutic-dose anticoagulation N=536	Usual care pharmacological thromboprophylaxis N=567
Anticoagulant drug – n (%)[a]	N=519	N=551
Enoxaparin	252 (48.6)	287 (52.1)
Dalteparin	175 (33.7)	181 (32.8)
Tinzaparin	35 (6.7)	28 (5.1)
Subcutaneous unfractionated heparin	7 (1.3)	25 (4.5)
Intravenous unfractionated heparin	50 (9.6)	6 (1.1)
Fondaparinux	0 (0)	0 (0)
Direct oral anticoagulant	0 (0)	1 (0.2)
None	6 (1.2)	24 (4.4)
Other	1 (0.2)	4 (0.7)
Post-randomization dosage equivalents[a]	N=469	N=493
Low dose thromboprophylaxis	16 (3.4)	199 (40.4)
Intermediate dose thromboprophylaxis	50 (8.3)	255 (51.7)
Subtherapeutic dose anticoagulation	39 (8.3)	9 (1.8)
Therapeutic dose anticoagulation	364 (77.6)	30 (6.1)

[a] Data reported reflects those in whom specific dosing information was available at the time the dataset was locked for analysis; drug and dose reported are those prescribed on post-randomization day 1

ATTAC ACTIV-4 REMAP-CAP, NEJM

Etude randomisée contrôlée

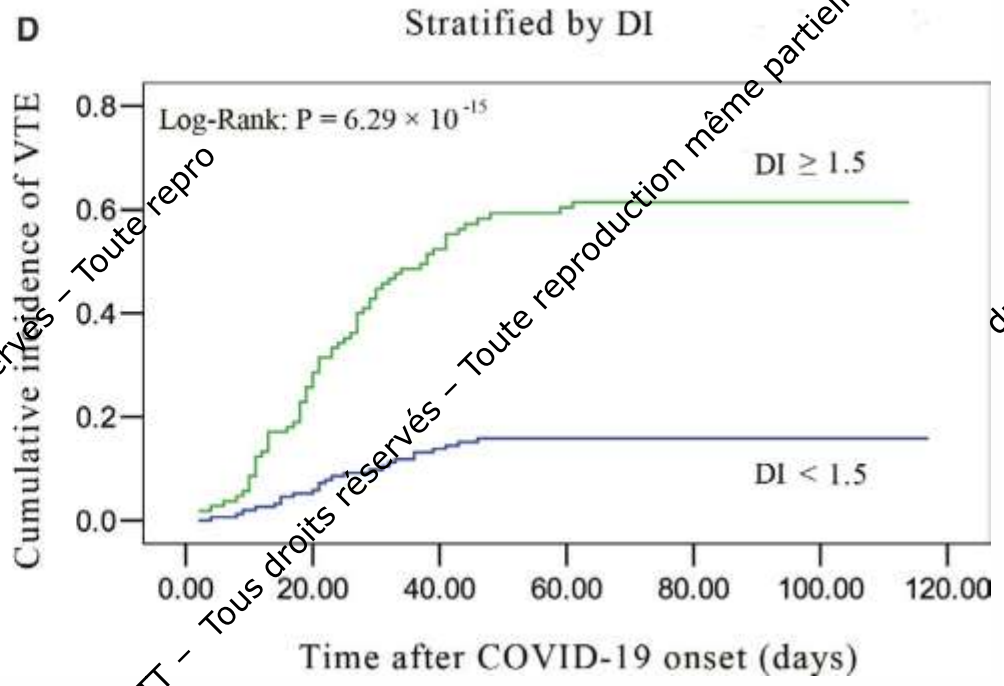
Propositions du GIHP



Godon et al, ACCPM 2021

Anticoagulation

Augmentation brutale des Ddi fortement associée aux évènements thrombotiques

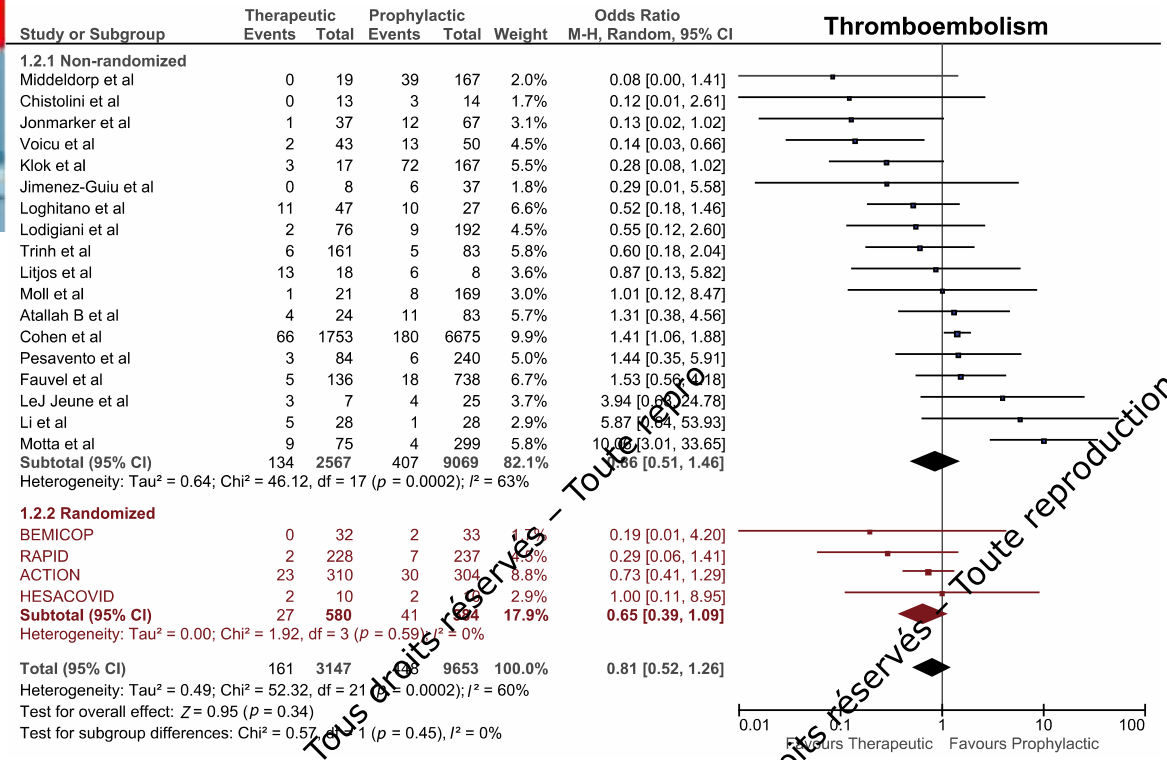


Etude observationnelle

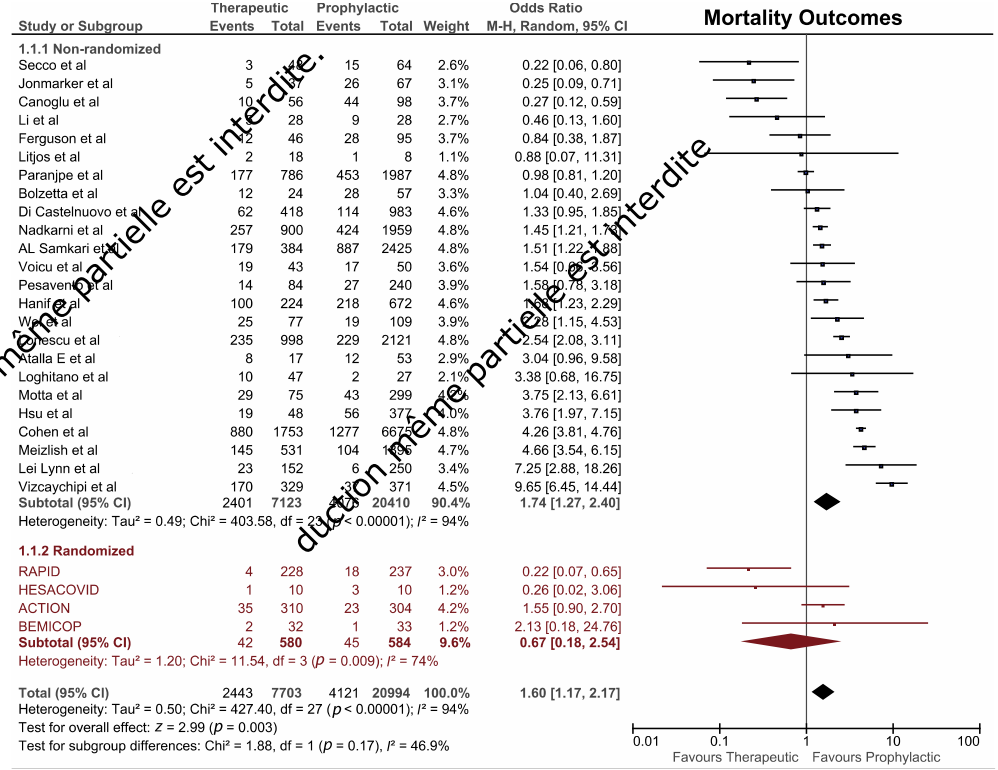
Li et al, JTH 2020

Prévalence très élevée des évènements thrombotiques dans cette sous-catégorie de patients

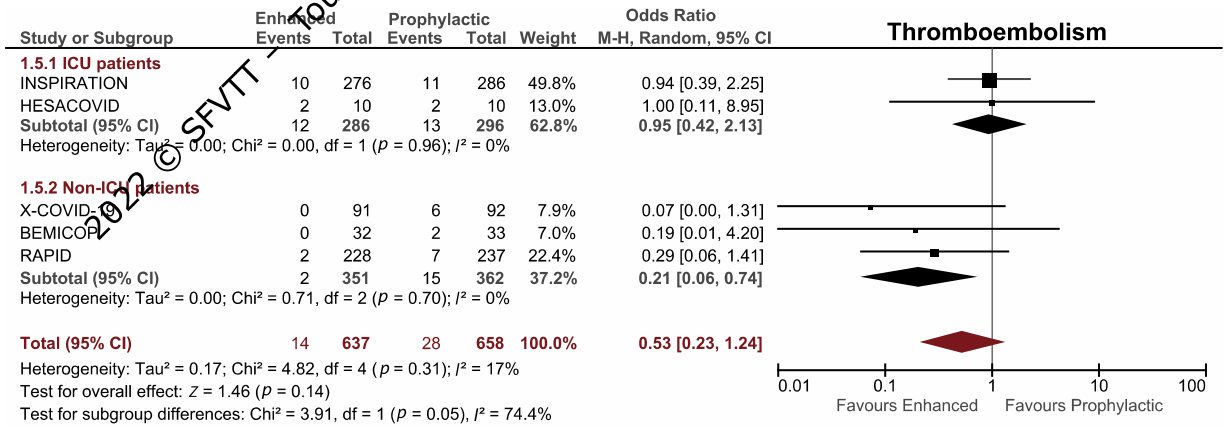
Méta-analyses



Study or Subgroup	Therapeutic Events	Total	Prophylactic Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 Non-randomized						
Middeldorp et al	0	19	39	167	2.0%	0.08 [0.00, 1.41]
Chistolini et al	0	13	3	14	1.7%	0.12 [0.01, 2.61]
Jonmarker et al	1	37	12	67	3.1%	0.13 [0.02, 1.02]
Voicu et al	2	43	13	50	4.5%	0.14 [0.03, 0.66]
Klok et al	3	17	72	167	5.5%	0.28 [0.08, 1.02]
Jimenez-Guiu et al	0	8	6	37	1.8%	0.29 [0.01, 5.58]
Loghitano et al	11	47	10	27	6.6%	0.52 [0.18, 1.46]
Lodigiani et al	2	76	9	192	4.5%	0.55 [0.12, 2.60]
Trinh et al	6	161	5	83	5.8%	0.60 [0.18, 2.04]
Litjos et al	13	18	6	8	3.6%	0.87 [0.13, 5.82]
Moll et al	1	21	8	169	3.0%	1.01 [0.12, 8.47]
Atallah B et al	4	24	11	83	5.7%	1.31 [0.38, 4.56]
Cohen et al	66	1753	180	6675	9.9%	1.41 [1.06, 1.88]
Pesavento et al	3	84	6	240	5.0%	1.44 [0.35, 5.91]
Fauvel et al	5	136	18	738	6.7%	1.53 [0.56, 4.18]
LeJ Jeune et al	3	7	4	25	3.7%	3.94 [0.60, 24.78]
Li et al	5	28	1	28	2.9%	5.87 [0.64, 53.93]
Motta et al	9	75	4	299	5.8%	10.08 [3.01, 33.65]
Subtotal (95% CI)	134	2567	407	9069	82.1%	0.86 [0.51, 1.46]
Heterogeneity: Tau² = 0.64; Chi² = 46.12, df = 17 (p = 0.0002); I^2 = 63%						
1.2.2 Randomized						
BEMICOP	0	32	2	33	4.1%	0.19 [0.01, 4.20]
RAPID	2	228	7	237	13.8%	0.29 [0.06, 1.41]
ACTION	23	310	30	304	18.8%	0.73 [0.41, 1.29]
HESACOVID	2	10	2	10	2.9%	1.00 [0.11, 8.95]
Subtotal (95% CI)	27	580	41	584	17.9%	0.65 [0.39, 1.09]
Heterogeneity: Tau² = 0.00; Chi² = 1.92, df = 3 (p = 0.59); I^2 = 0%						
Total (95% CI)	161	3147	448	9653	100.0%	0.81 [0.52, 1.26]
Heterogeneity: Tau² = 0.49; Chi² = 52.32, df = 21 (p = 0.0002); I^2 = 60%						
Test for overall effect: Z = 0.95 (p = 0.34)						
Test for subgroup differences: Chi² = 0.57, df = 1 (p = 0.45), I^2 = 0%						



Study or Subgroup	Therapeutic Events	Total	Prophylactic Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Non-randomized						
Secco et al	3	44	15	64	2.6%	0.22 [0.06, 0.80]
Jonmarker et al	5	37	26	67	3.1%	0.25 [0.09, 0.71]
Canoglu et al	10	56	44	98	3.7%	0.27 [0.12, 0.59]
Li et al	3	28	9	28	2.7%	0.46 [0.13, 1.60]
Ferguson et al	12	46	28	95	3.7%	0.84 [0.38, 1.87]
Litjos et al	2	18	1	8	1.1%	0.88 [0.07, 11.31]
Paranjpe et al	177	786	453	1987	4.8%	0.98 [0.81, 1.20]
Bolzetta et al	12	24	28	57	3.3%	1.04 [0.40, 2.69]
Di Castelnuovo et al	62	418	114	983	4.6%	1.33 [0.95, 1.85]
Nadkarni et al	257	900	424	1959	4.8%	1.45 [1.21, 1.74]
AL Samkari et al	179	384	887	2425	4.8%	1.51 [1.22, 1.88]
Voicu et al	19	43	17	50	3.6%	1.54 [0.68, 3.56]
Pesavento et al	14	84	27	240	3.9%	1.58 [0.78, 3.18]
Hanif et al	100	224	218	672	4.6%	1.66 [1.23, 2.29]
Wu et al	25	77	19	109	3.9%	2.28 [1.15, 4.53]
Ionescu et al	235	998	229	2121	4.8%	2.54 [2.08, 3.11]
Atalla E et al	8	17	12	53	2.9%	3.04 [0.96, 9.58]
Loghitano et al	10	47	2	27	2.1%	3.38 [0.68, 16.75]
Motta et al	29	75	43	299	4.6%	3.75 [2.13, 6.61]
Hsu et al	19	48	56	377	4.0%	3.76 [1.97, 7.15]
Cohen et al	880	1753	1277	6675	4.8%	4.26 [3.81, 4.76]
Meizlish et al	145	531	104	1996	4.7%	4.66 [3.54, 6.15]
Lei Lynn et al	23	152	6	250	3.4%	7.25 [2.88, 18.26]
Vizcaychipi et al	170	329	31	371	4.5%	9.65 [6.45, 14.44]
Subtotal (95% CI)	2401	7123	4121	20410	90.4%	1.74 [1.27, 2.40]
Heterogeneity: Tau² = 0.49; Chi² = 403.58, df = 23 (p < 0.00001); I^2 = 94%						
1.1.2 Randomized						
RAPID	4	228	18	237	3.0%	0.22 [0.07, 0.65]
HESACOVID	1	10	3	10	1.2%	0.26 [0.02, 3.06]
ACTION	35	310	23	304	4.2%	1.55 [0.90, 2.70]
BEMICOP	2	32	1	33	1.2%	2.13 [0.18, 24.76]
Subtotal (95% CI)	42	580	45	584	9.6%	0.67 [0.18, 2.54]
Heterogeneity: Tau² = 1.20; Chi² = 11.54, df = 3 (p = 0.009); I^2 = 74%						
Total (95% CI)	2443	7703	4121	20994	100.0%	1.60 [1.17, 2.17]
Heterogeneity: Tau² = 0.50; Chi² = 427.40, df = 27 (p < 0.00001); I^2 = 94%						
Test for overall effect: Z = 2.99 (p = 0.003)						
Test for subgroup differences: Chi² = 1.88, df = 1 (p = 0.17), I^2 = 46.9%						

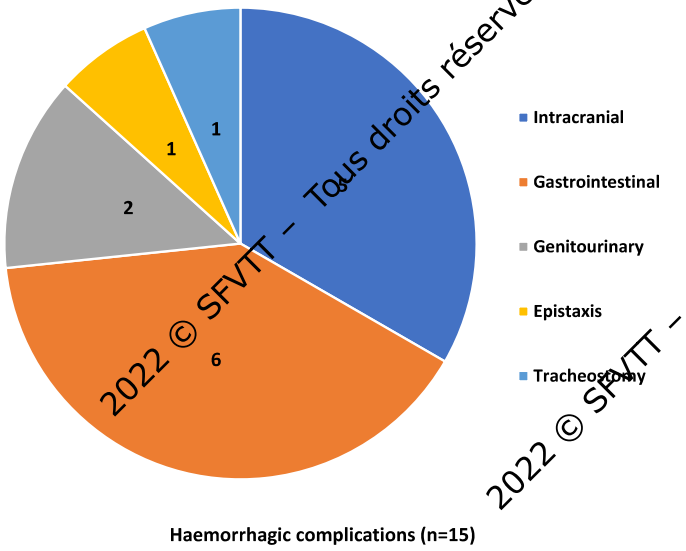


Study or Subgroup	Enhanced Events	Total	Prophylactic Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.5.1 ICU patients						
INSPIRATION	10	276	11	286	49.8%	0.94 [0.39, 2.25]
HESACOVID	2	10	2	10	13.0%	1.00 [0.11, 8.95]
Subtotal (95% CI)	12	286	13	296	62.8%	0.95 [0.42, 2.13]
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (p = 0.96); I^2 = 0%						
1.5.2 Non-ICU patients						
X-COVID-19	0	91	6	92	7.9%	0.07 [0.00, 1.31]
BEMICOP	0	32	2	33	7.0%	0.19 [0.01, 4.20]
RAPID	2	228	7	237	22.4%	0.29 [0.06, 1.41]
Subtotal (95% CI)	2	351	15	362	37.2%	0.21 [0.06, 0.74]
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 2 (p = 0.70); I^2 = 0%						
Total (95% CI)	14	637	28	658	100.0%	0.53 [0.23, 1.24]
Heterogeneity: Tau² = 0.17; Chi² = 4.82, df = 4 (p = 0.31); I^2 = 17%						
Test for overall effect: Z = 1.46 (p = 0.14)						
Test for subgroup differences: Chi² = 3.91, df = 1 (p = 0.05), I^2 = 74.4%						

Risque hémorragique

- Incidence globale: 7,8 % [2,6-15,3]
- Anticoagulation à dose intermédiaire/curative 21,4 % [13,2-31,7] *vs.* standard 4,7 % [1,9-8,7]
- Service 5,6 % [1,9-10,9] *vs.* réa 4,4 % [1,1-9,3]

Jimenez and al, CHEST 2020



Bleeding complications within the first 2 weeks of ICU hospitalization

ICU: intensive care unit; PRBC: packed red blood cells

		N = 39 patients (%)
GUSTO Scale	Type of bleeding complications	
All bleeding events		53 (100)
Severe bleeding		
	Intracranial hemorrhage	4 (7,5)
	Hemorrhagic shock	7 (13,2)
	Fatal hemorrhage	1 (1,9)
Moderate bleeding		
	Gastro-intestinal hemorrhage requiring hemostatic intervention	4 (7,5)
	Other hemorrhage requiring hemostatic intervention	8 (15,1)
	Transfusion of at least 2 PRBC or decrease of at least 2 g/dL hemoglobin within 24 hours	29 (54,7)

Shah and al, Crit, Care 2020

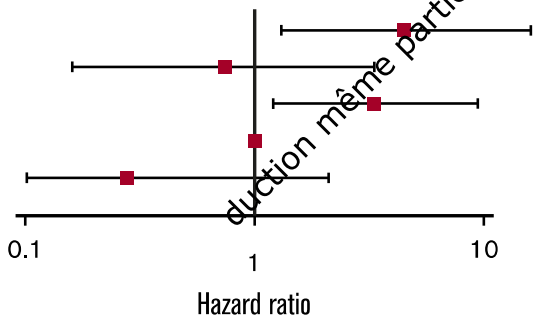
Tacquard and al, CHEST 2020

Risque hémorragique

Haemorrhagic risk factors

Bleed within 90 days of admission

	Bleed	No Bleed	HR (95% CI)	p
Age > 70 yrs	12	151	4.5 (1.3 - 16)	**<0.001**
Antiplatelet (prior to admission)	2	60	0.74 (0.16-3.3)	0.68
Anticoagulant (prior to admission)	6	52	3.3 (1.2-9.4)	**0.03**
Platelet count on admission	219.7	189.1	1 (0.99-1)	0.14
HDU or ICU care	1	66	0.28 (0.04 - 2.1)	0.14



Salisbury and al, Blood Adv 2020

BMI (OR 0,87 [0,78-0,97] p=0,02)

ECMO support (OR 6,26 [2,31-17,01] p<0,001)

Tacquard and al, CHEST 2020

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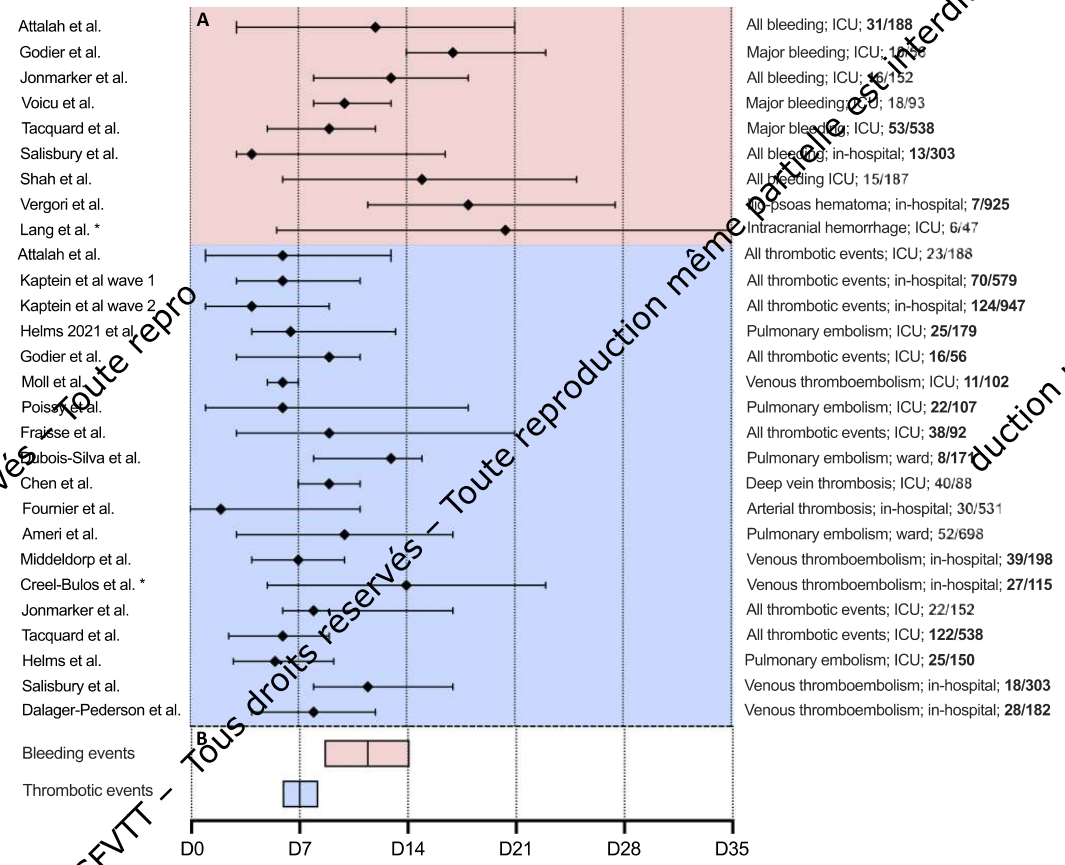
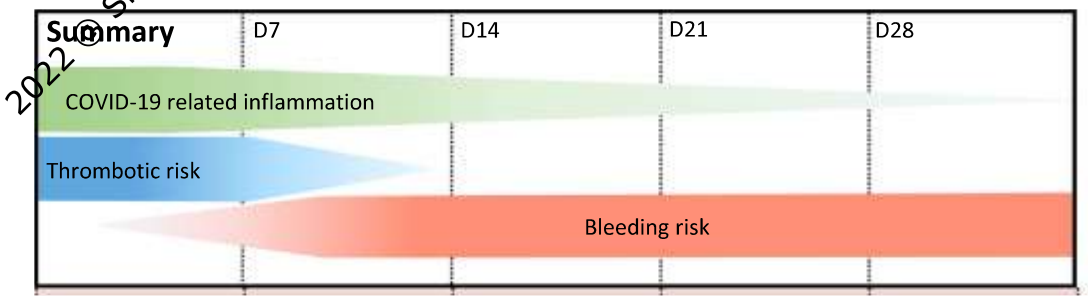
Evolution temporelle

Attention au risque hémorragique!

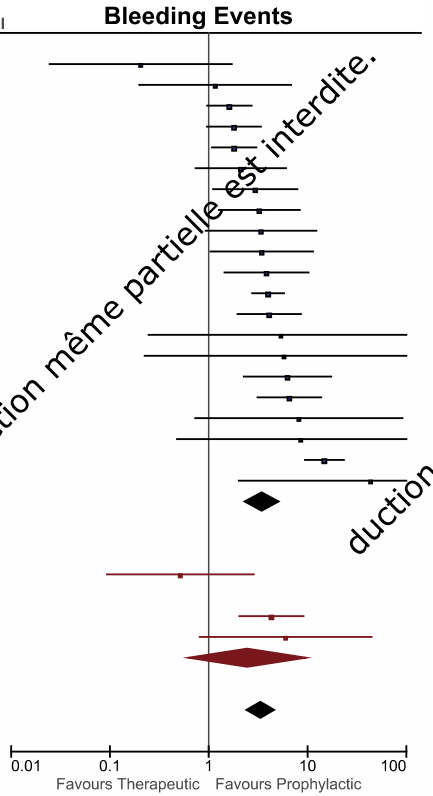
Tacquard et al, ACCPM 2021



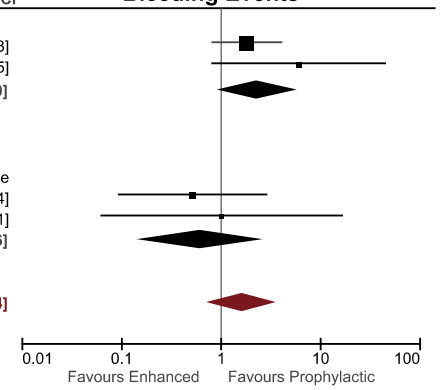


Méta-analyses

Study or Subgroup	Therapeutic Events	Total	Prophylactic Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.3.1 Non-randomized						
Jonmarker et al	1	37	8	67	2.2%	0.20 [0.02, 1.71]
Loghitano et al	4	47	2	27	2.8%	1.16 [0.20, 6.81]
Paranjpe et al	24	786	38	1987	6.6%	1.62 [0.96, 2.71]
Trinh et al	51	161	17	83	6.2%	1.80 [0.96, 3.37]
Nadkarni et al	27	900	33	1959	6.6%	1.81 [1.08, 3.02]
Voicu et al	11	43	7	50	4.7%	2.11 [0.74, 6.05]
Musoke et al	11	102	7	178	4.9%	2.95 [1.11, 7.88]
Lei Lynn et al	13	152	7	250	5.1%	3.25 [1.27, 8.33]
Atallah B et al	5	24	6	83	3.9%	3.38 [0.93, 12.25]
Shah et al	5	31	8	151	4.2%	3.44 [1.04, 11.33]
Ferguson et al	12	46	8	95	4.9%	3.84 [1.44, 10.21]
Lonescu et al	81	998	46	2121	7.0%	3.98 [2.75, 5.77]
Pesavento et al	18	84	15	240	5.8%	4.09 [1.96, 8.56]
Li et al	2	28	0	28	1.2%	5.38 [0.25, 117.25]
Jimenez-Guiu et al	1	20	0	37	1.1%	5.77 [0.22, 148.35]
Hsu et al	7	48	10	377	4.8%	6.27 [2.26, 17.35]
Hanif et al	22	224	11	672	5.8%	6.54 [3.12, 13.73]
Motta et al	2	75	1	299	1.8%	8.16 [0.73, 91.2
Kessler et al	10	65	0	22	1.4%	8.51 [0.48, 151.1
AL Samkari et al	60	384	30	2425	6.8%	14.78 [9.40, 23.26]
Moll et al	2	21	0	169	1.2%	43.46 [2.01, 938.42]
Subtotal (95% CI)	369	**4276**	254	**11320**	**89.0%**	**3.45 [2.32, 5.13]**
Heterogeneity: Tau² = 0.49; Chi² = 75.93, df = 20 (p < 0.00001); I^2 = 74%						
1.3.2 Randomized						
RAPID	2	228	4	237	2.9%	0.52 [0.09, 2.84]
BEMICOP	0	32	0	33		Not estimable
ACTION	36	310	9	304	5.8%	4.31 [2.04, 9.11]
HESACOVID	6	10	2	10	2.4%	6.00 [0.81, 44.35]
Subtotal (95% CI)	44	**580**	15	**584**	**11.0%**	**2.52 [0.64, 9.89]**
Heterogeneity: Tau² = 0.91; Chi² = 5.37, df = 2 (p = 0.07); I^2 = 63%						
Total (95% CI)	413	**4856**	269	**11904**	**100.0%**	**3.35 [2.31, 4.85]**
Heterogeneity: Tau² = 0.47; Chi² = 81.41, df = 23 (p < 0.00001); I^2 = 72%						
Test for overall effect: Z = 6.40 (p < 0.00001)						
Test for subgroup differences: Chi² = 0.19, df = 1 (p = 0.67), I^2 = 0%						

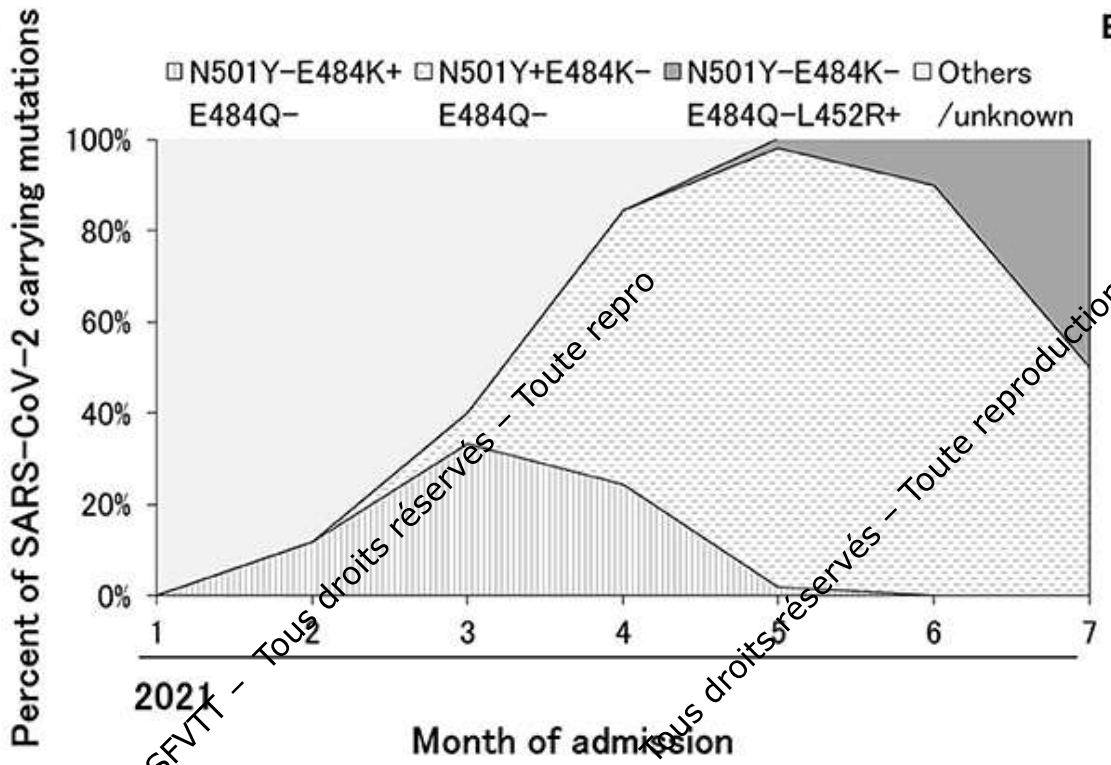


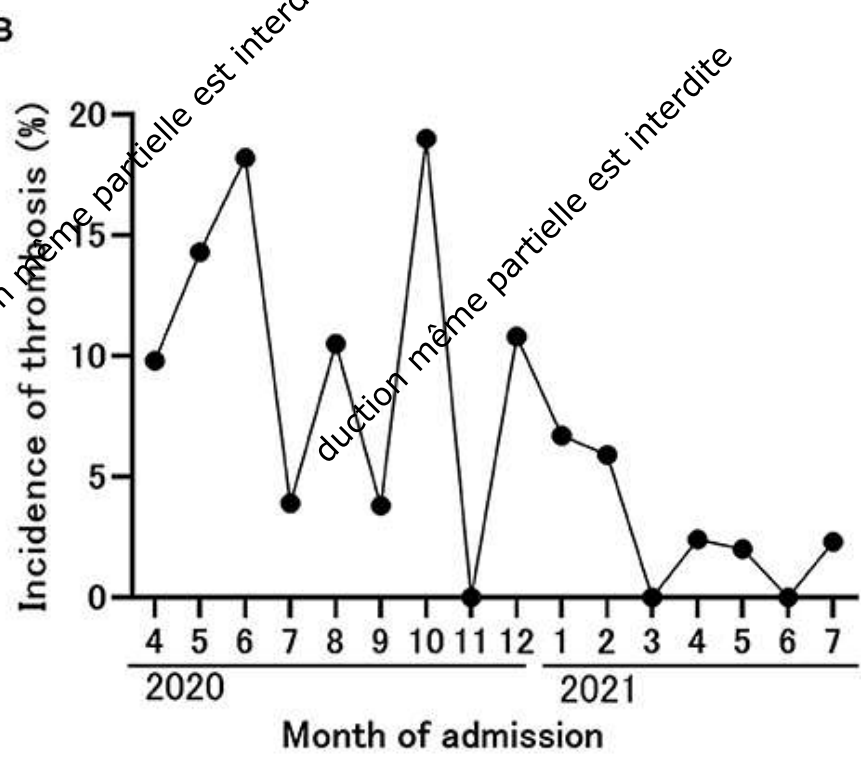
Study or Subgroup	Enhanced Events	Total	Prophylactic Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.6.1 ICU patients						
INSPIRATION	17	276	10	286	58.1%	1.81 [0.81, 4.03]
HESACOVID	6	10	2	10	14.6%	6.00 [0.81, 44.35]
Subtotal (95% CI)	23	**286**	12	**296**	**72.8%**	**2.29 [0.90, 5.80]**
Heterogeneity: Tau² = 0.11; Chi² = 1.19, df = 1 (p = 0.28); I^2 = 16%						
1.6.2 Non-ICU patients						
BEMICOP	0	32	0	33		Not estimable
RAPID	2	228	4	237	19.3%	0.52 [0.09, 2.84]
X-COVID-19	1	91	1	92	8.0%	1.01 [0.06, 16.41]
Subtotal (95% CI)	3	**351**	5	**362**	**27.2%**	**0.62 [0.14, 2.66]**
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (p = 0.69); I^2 = 0%						
Total (95% CI)	26	**637**	17	**658**	**100.0%**	**1.62 [0.72, 3.64]**
Heterogeneity: Tau² = 0.13; Chi² = 3.56, df = 3 (p = 0.31); I^2 = 16%						
Test for overall effect: Z = 1.16 (p = 0.25)						
Test for subgroup differences: Chi² = 2.20, df = 1 (p = 0.14), I^2 = 54.5%						



Et maintenant?

Evolution du risque thrombotique



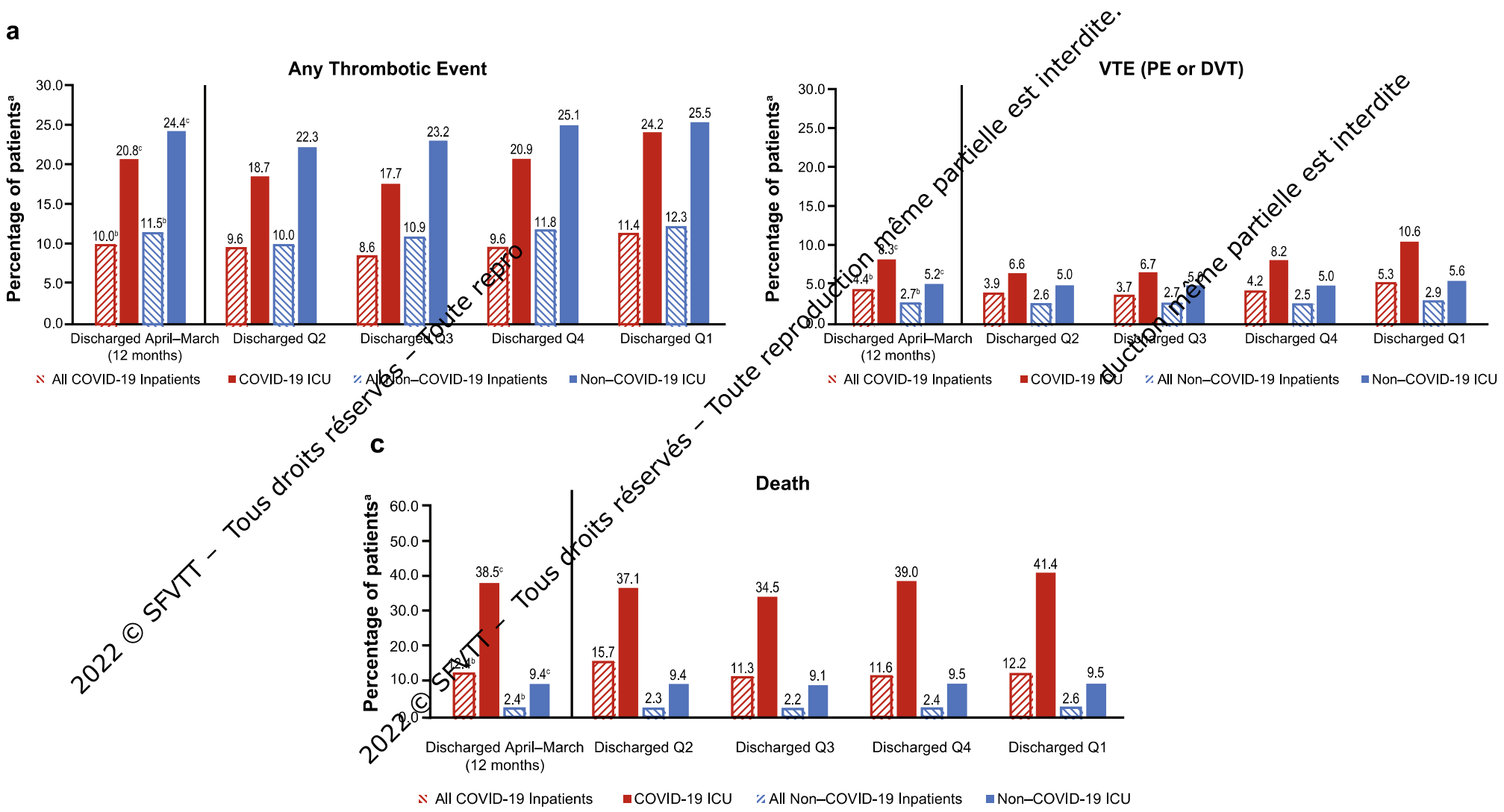


Augmentation progressive du niveau d'anticoagulation

AC thérapeutique 6,6% -> 19%

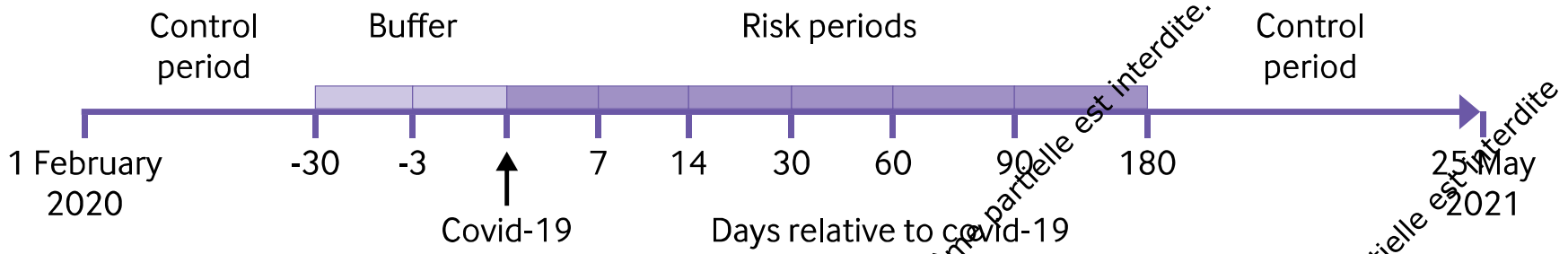
Oba, Frontiers immunol 2021

Evolution du risque thrombotique

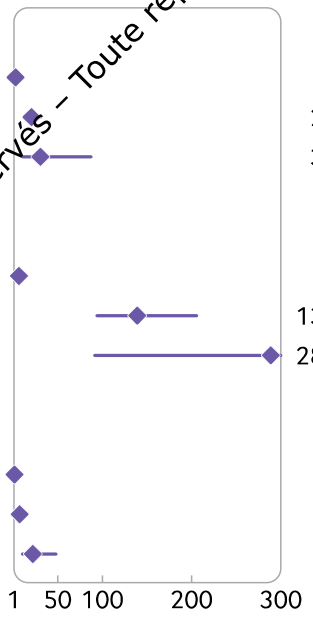


Deitelzweig, J, Thromb, Thrombo 2022

Evolution du risque thrombotique



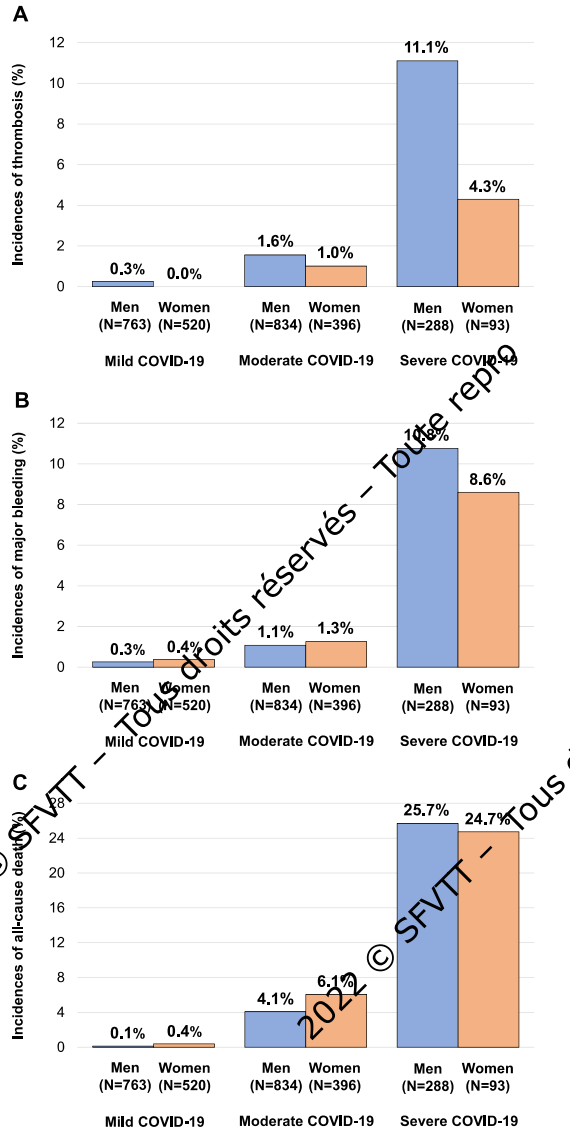
Outcome/ covid-19 severity	No of events (%)	Risk ratio (95% CI)	Risk ratio (95% CI)	P value
Deep vein thrombosis (n=4 967 398)				
Negative	267 (0.01)		1 (ref)	
Mild	155 (0.02)		2.80 (2.26 to 3.47)	<0.001
Admitted to hospital	163 (0.36)		20.21 (13.07 to 31.25)	<0.001
Admitted to ICU	83 (1.18)		30.58 (10.57 to 88.46)	<0.001
Pulmonary embolism (n=4 967 398)				
Negative	171 (0.004)		1 (ref)	-
Mild	23 (0.02)		6.77 (5.43 to 8.45)	<0.001
Admitted to hospital	1037 (2.27)		139.16 (94.32 to 205.31)	<0.001
Admitted to ICU	485 (6.87)		289.38 (91.55 to 914.73)	<0.001
Bleeding (n=4 643 423)				
Negative	1 292 (0.04)		1 (ref)	-
Mild	349 (0.04)		1.03 (0.91 to 1.17)	0.64
Admitted to hospital	467 (1.18)		7.40 (6.00 to 9.12)	<0.001
Admitted to ICU	186 (2.85)		22.68 (10.67 to 48.2)	<0.001



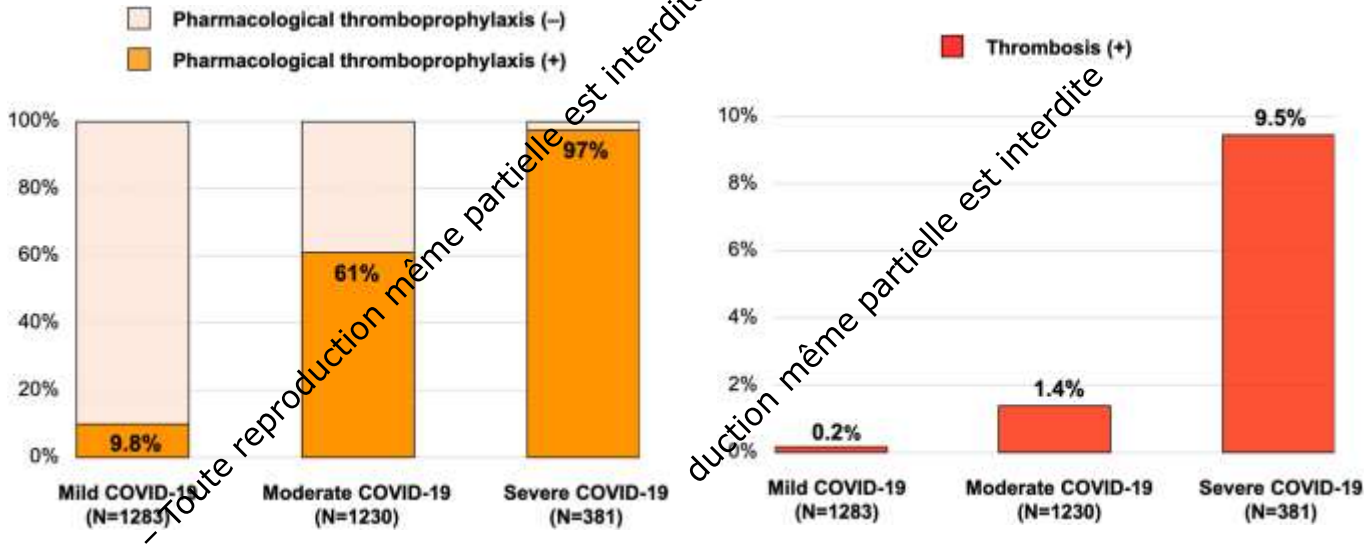
Katsoularis, BMJ 2022

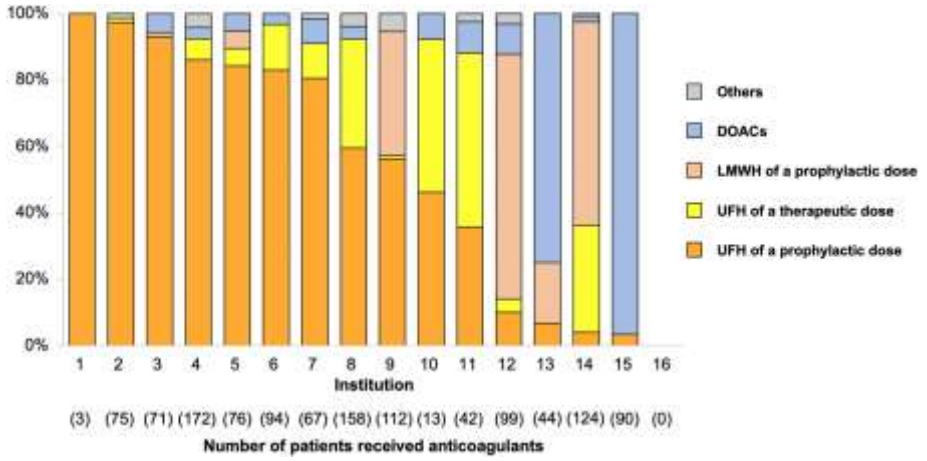
Risque thrombotique - réanimation

4/5ème vague



Yamashita, Thromb, Res, 2022





Nishimoto, J, Cardiol 2022

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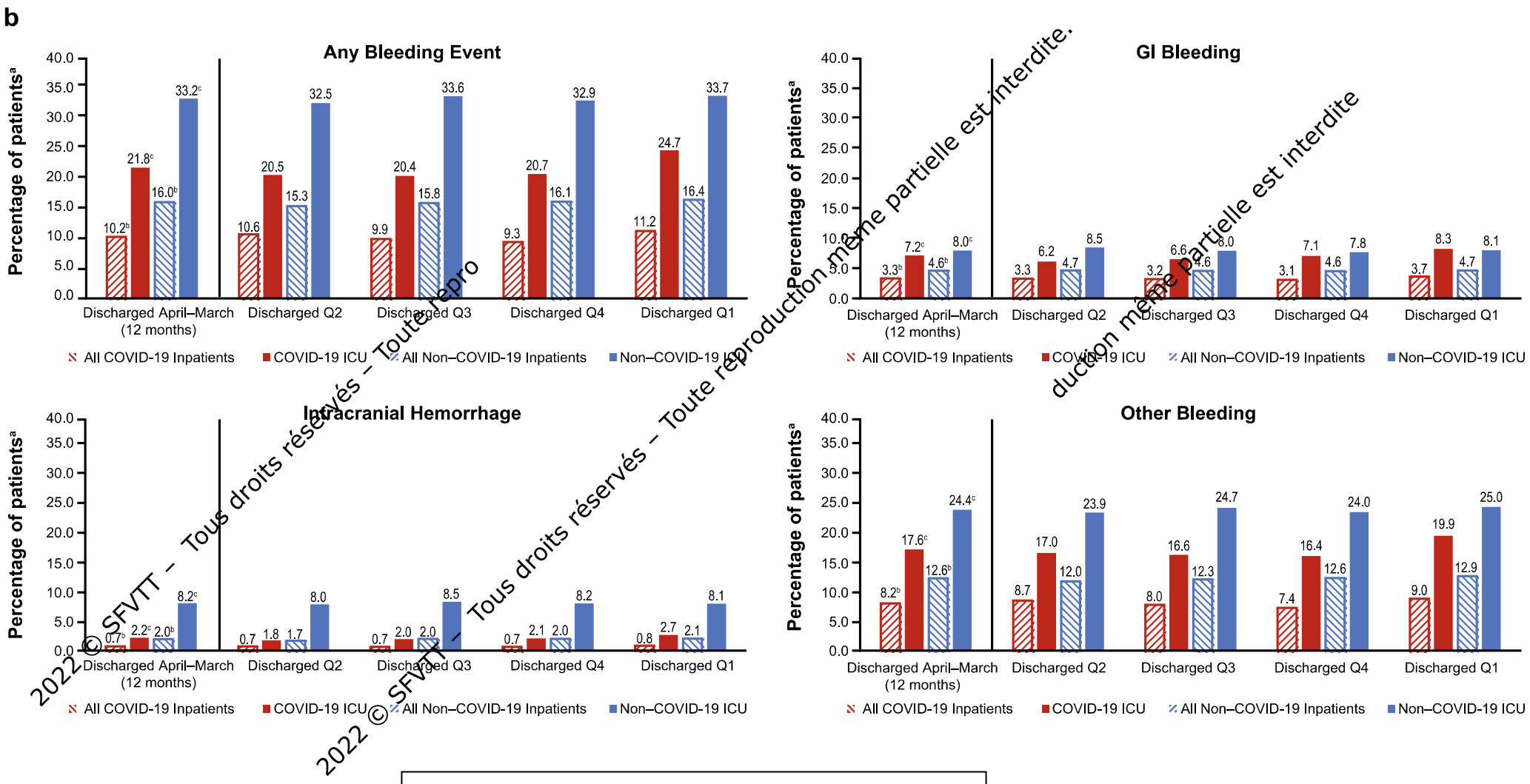
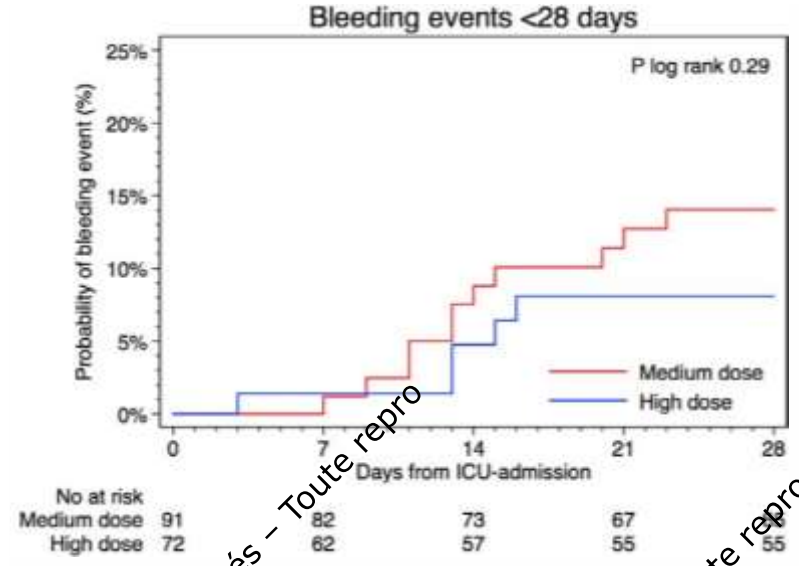
Risque hémorragique



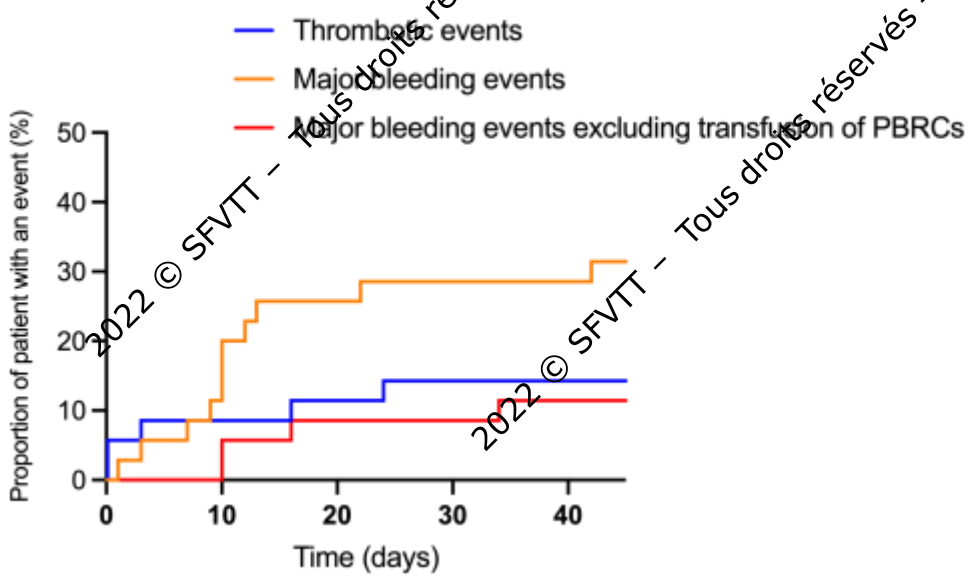
Pas de données sur le niveau d'anticoagulation

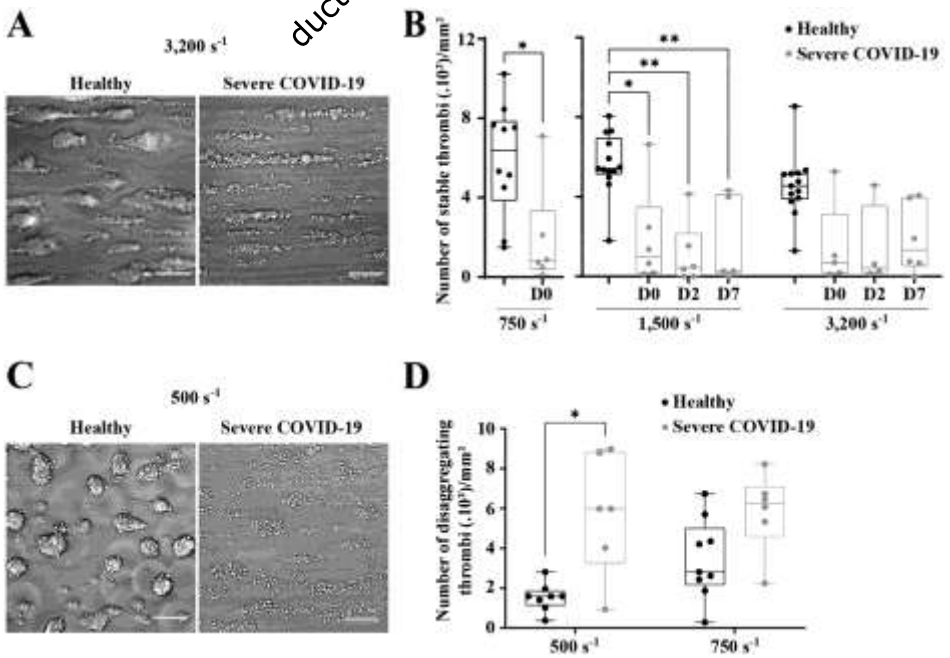
Deitelzweig, J, Thromb, Thrombo 2022

Risque hémorragique



Jonmarker, Acta Anesth, Scnad, 2022





Tacquard, Thromb Res 2022

Conclusion

- Risque thrombotique élevé au cours de la COVID-19 d'autant plus que le patient est sévère
- **COVID-19 = thrombose?** ou **obésité + inflammation + hypoxémie = thrombose?**
- Tous les patients atteints d'une COVID-19 à la phase aiguë doivent être à minima traités par thromboprophylaxie pharmacologique à dose standard
- Probable intérêt à majorer la dose chez des patients sélectionnés
- Ne pas négliger le risque hémorragique et savoir désescalader rapidement
- **Les risques thrombotique et hémorragiques sont mal connus pour les nouveaux variants!**

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Merci pour votre attention

Quelles sont vos questions?

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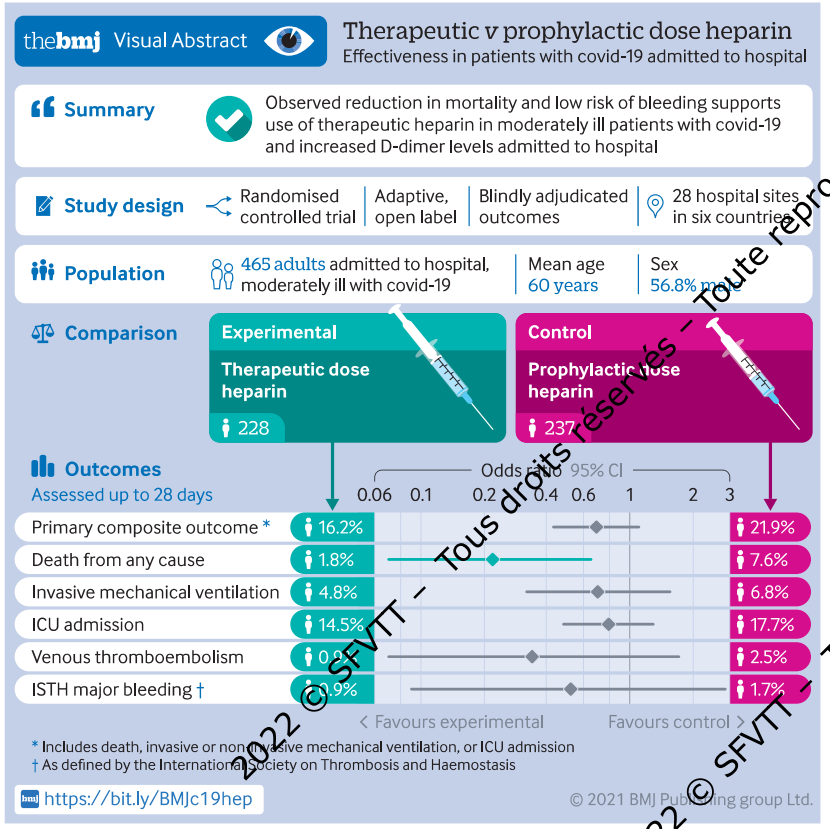
Anticoagulation

RAPID trial



Scholzberg, BMJ 2021

Essai randomisé contrôlé
AC jusqu'à J28

HEP-COVID

Table 2. Clinical Outcomes During the 30-Day Postrandomization Phase

Outcome	No./Total No. (%) Therapeutic dose (n = 129)	Standard dose (n = 124)	RR (95% CI)	*P* value[a]
Primary efficacy outcome				
VTE, ATE, or death	37/129 (28.7)	52/124 (41.9)	0.68 (0.48-0.96)	.03
Non-ICU stratum	14/84 (16.7)	31/86 (36.1)	0.46 (0.27-0.81)	.004
ICU stratum	23/45 (51.1)	21/38 (55.3)	0.93 (0.62-1.39)	.71
VTE + ATE	14/129 (10.9)	36/124 (29.0)	0.37 (0.21-0.66)	<.001
Death	25/129 (19.4)	31/124 (25.0)	0.78 (0.49-1.23)	.28
Secondary efficacy outcomes				
Primary efficacy outcome at day 14	30/129 (23.3)	45/124 (36.3)	0.64 (0.43-0.95)	.02
Progression to ARDS	11/127 (8.7)	6/121 (5.0)	1.75 (0.67-4.58)	.25
Rehospitalization	1/129 (0.8)	3/124 (2.4)	0.32 (0.03-3.04)	.36
Intubation	17/122 (13.9)	21/121 (17.4)	0.80 (0.45-1.45)	.46
ECMO	1/129 (0.8)	1/124 (0.8)	0.96 (0.06-15.20)	>.99
Nonfatal cardiac arrest	0	2/124 (1.6)	0.19 (0.01-3.97)	.24
Acute kidney injury[b]	17/129 (13.2)	12/124 (9.7)	1.36 (0.68-2.73)	.38
New-onset atrial fibrillation	4/129 (3.1)	5/124 (4.0)	0.77 (0.21-2.80)	.75
Principal safety outcome				
Major bleeding	6/129 (4.7)	2/124 (1.6)	2.88 (0.59-14.02)	.28
Non-ICU stratum	2/84 (2.4)	2/86 (2.3)	1.02 (0.15-7.10)	>.99
ICU stratum	4/45 (8.9)	0	7.62 (0.42-137.03)	.12

Abbreviations: ARDS, acute respiratory distress syndrome; ATE, arterial thromboembolism; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; RR, relative risk; VTE, venous thromboembolism.

[a] Modified intention-to-treat population (2-sided *P* value for superiority).

[b] Acute kidney injury defined as (1) increase in serum creatinine by 0.3 mg/dL or greater within 48 hours, (2) increase in serum creatinine by a factor of 1.5 times baseline or greater, or (3) decrease in urine volume to less than 0.5 mg/kg/h for 6 hours per Kidney Disease: Improving Global Outcomes standard definition.

Spyropoulos, JAMA internal med, 2021

HEP-COVID study
Pas de bénéfice chez les patients de réanimation
38% d'anticoagulation à dose intermédiaire dans le groupe standard