Quelle oxygénation initiale pour les patients immunodéprimés en insuffisance respiratoire aiguë hypoxémiante ?

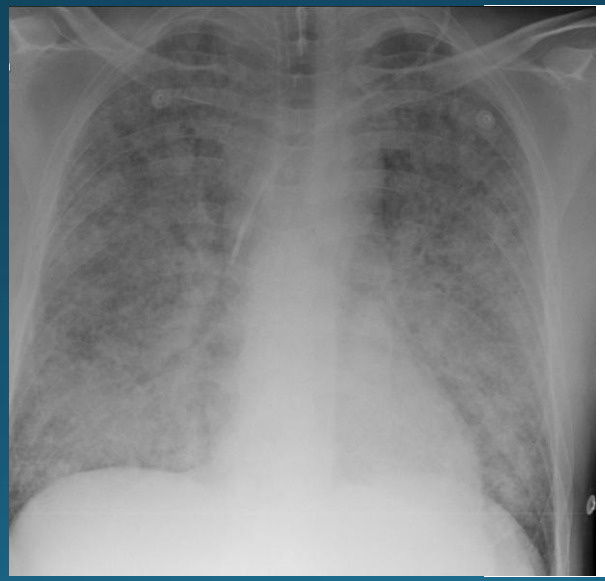
Liens et conflits d'intérêt

	Mon hôpital	Mon groupe de Recherche	Moi
Gilead		+	+
Alexion		+	+
Ablynx		+	+
MSD	+		
Jazz		+	
Fisher & Payckle	+	+	
Baxter		+	+

Acute Respiratory failure

❶

❷



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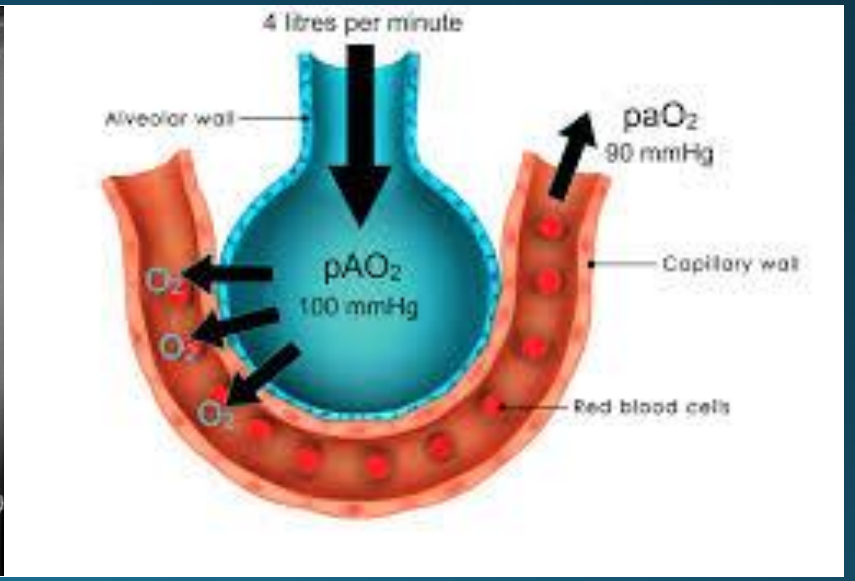


Patients immunodéprimés en Réanimation

30%

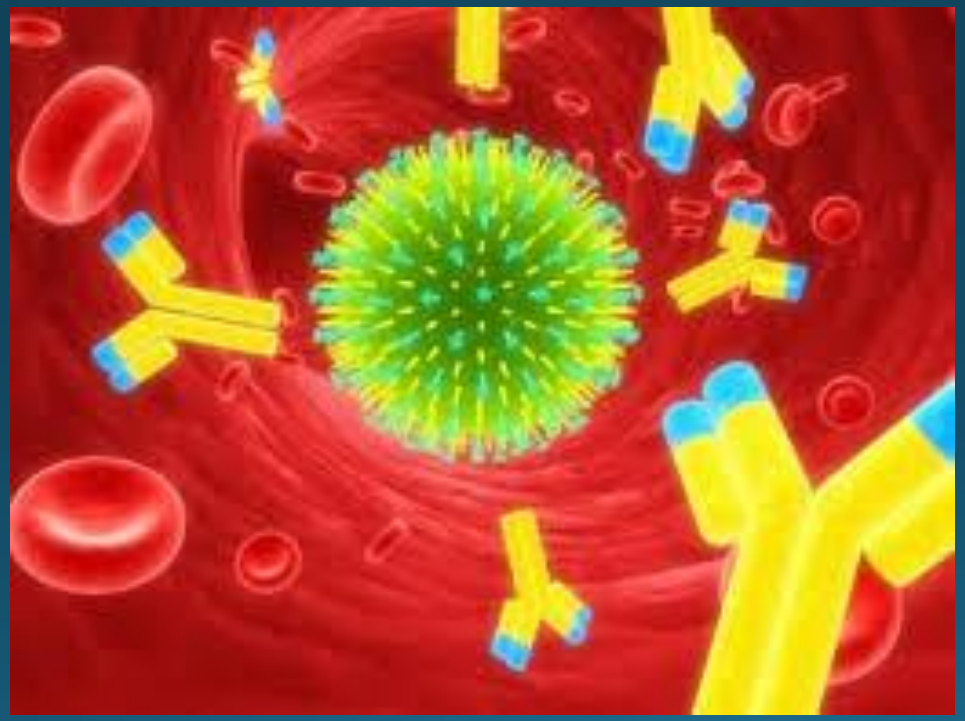
70 %

35-70 %

Immunodéprimés

Oncologie

Hématologie/
BMT



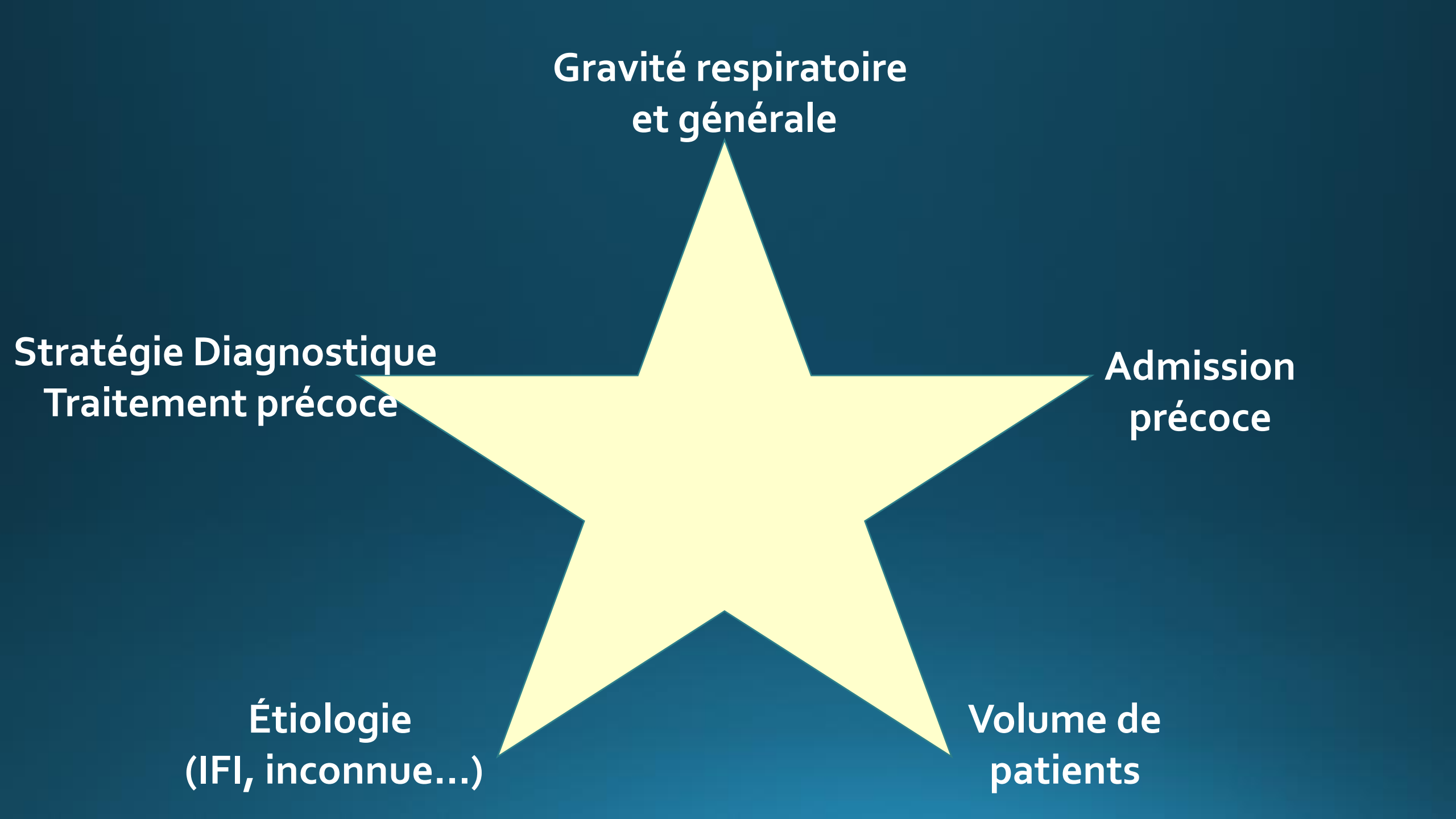
Hématologie

Transplantation

Médicaments

DI primitifs

(VIH)


Gravité respiratoire
et générale
Admission
précoce
Volume de
patients
Étiologie
(IFI, inconnue…)
Stratégie Diagnostique
Traitement précoce

La stratégie d'oxygénation initiale a-t-elle un impact sur le devenir des patients ?

(et si oui, est ce dans le sens où une bonne stratégie améliore le pronostic ou bien est ce qu'une mauvaise stratégie puisse l'aggraver ?)

1. ID vs. Non immunodéprimés

Trois raisons de penser différemment

Trois raisons de penser différemment

1. Taux d'évènements différents
   a. Intubation, mortalité, échec
   b. Mortalité en cas d'échec

2. Nécessité d'identifier l'étiologie de l'IRA
   a. 5-25% de patients sans diagnostic: surmortalité
   b. Stratégie diagnostique tronquée dans 70% des cas

3. Trajectoires différentes
   a. Confort ? Quand on vient de recevoir un diagnostic difficile
   b. Dyspnée? quand on a une maladie pulmonaire ou ORL?
   c. Tachypnée? 50% de patients avec SOFA>6, 50% d'acidose, 30% d'AKI etc…

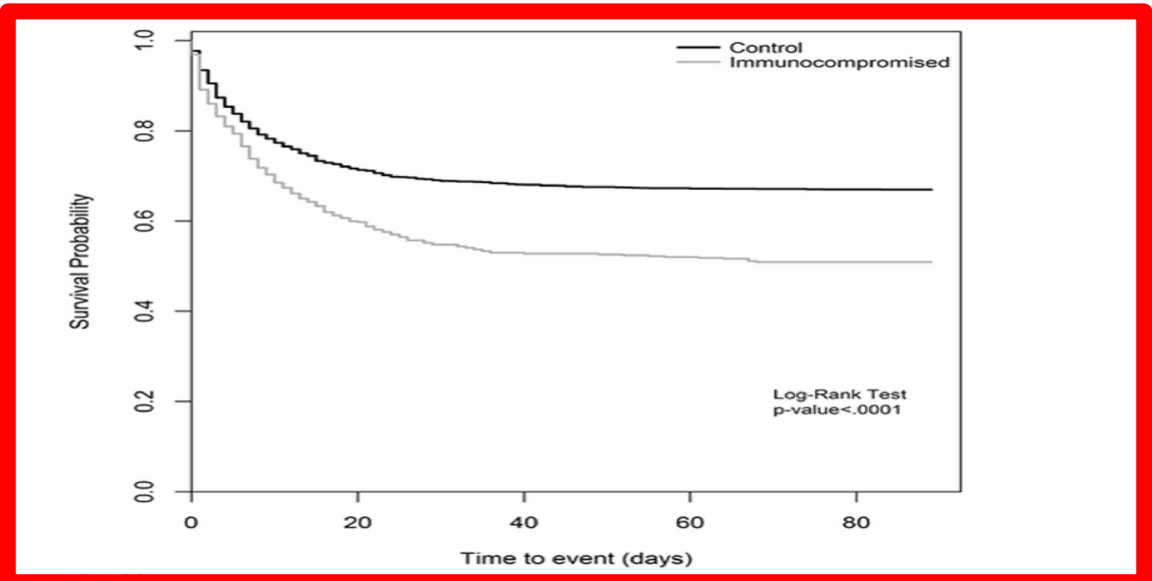
RESEARCH Open Access

Immunocompromised patients with acute respiratory distress syndrome: secondary analysis of the LUNG SAFE database

Andrea Cortegiani[1*], Fabiana Madotto[2], Cesare Gregoretti[1], Giacomo Bellani[3,4], John G. Laffey[5,6,7], Tai Pham[6,7], Frank Van Haren[8,9], Antonino Giarratano[1], Massimo Antonelli[10], Antonio Pesenti[11,12], Giacomo Grasselli[11], LUNG SAFE Investigators and the ESICM Trials Group

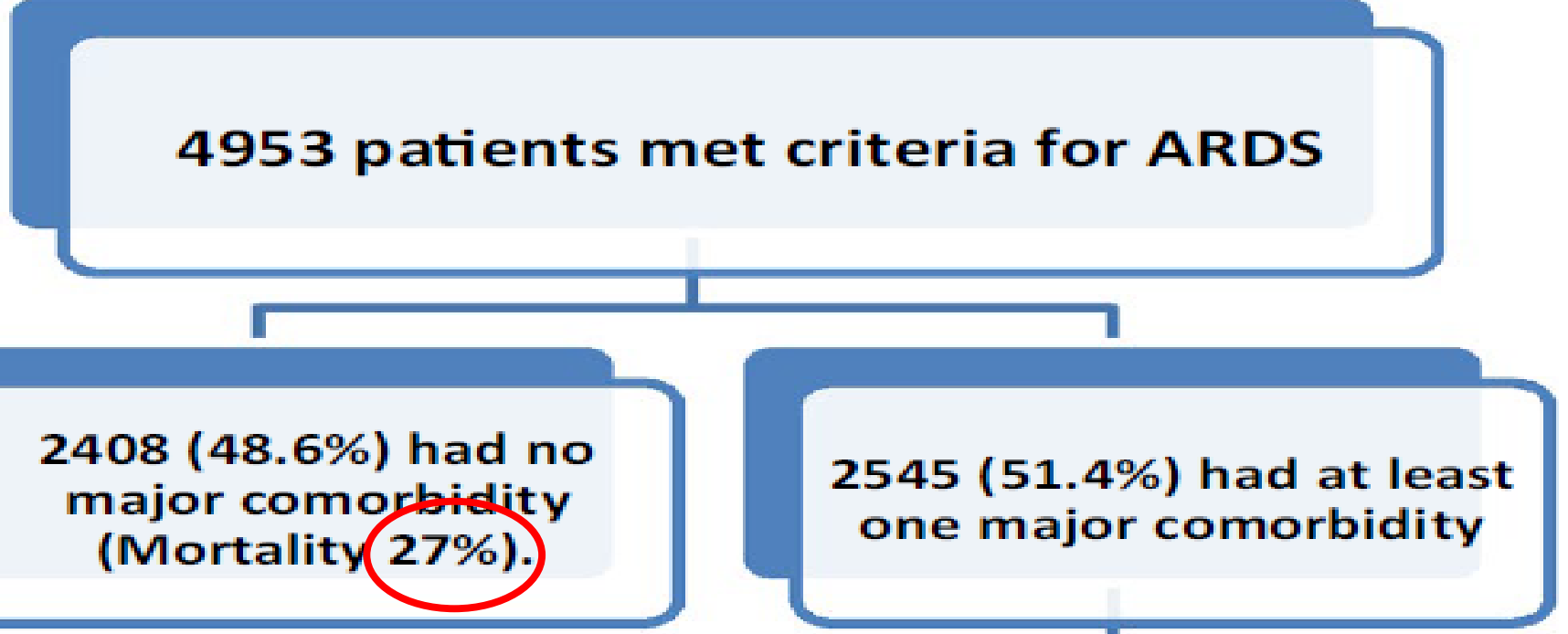
Cortegiani *et al. Critical Care* (2018) 22:157
https://doi.org/10.1186/s13054-018-2079-9

2229 immunocompetent patients (79.2%)



584 immunocompromised patients (20.8%)

Clinical endpoints	Control ($n = 2229$)	Study ($n = 584$)	p Value
IMV during ICU stay, n (%)	1874 (84.1)	462 (79.1)	**0.0044**
NIV success during ICU stay, n (%)	212 (9.5)	63 (10.8)	0.3551
NIV failure during ICU stay, n (%)	143 (6.4)	59 (10.1)	**0.0021**
Duration of mechanical ventilation, d, median (Q_1–Q_3)	8.0 (4.0–15.0)	8.0 (4.0–14.0)	0.4213
Progression/regression of ARDS[a], n (%)			0.5613
No change	824 (41.7)	201 (39.6)	
Progression	214 (10.8)	55 (10.8)	
Regression	422 (21.3)	123 (24.2)	
Resolution	518 (26.2)	129 (25.4)	
Limitation of life-sustaining measures, n (%)			
Decision to withhold life-sustaining measures	415 (18.6)	158 (27.1)	**< 0.0001**
Decision to withdraw life-sustaining measures	356 (16.0)	129 (22.1)	**0.0005**
Decision to withhold or withdraw life-sustaining measures	507 (22.7)	195 (33.4)	**< 0.0001**
ICU mortality[b], n (%)	698 (31.3)	266 (45.5)	**< 0.0001**
Hospital mortality[c], n (%)			
All patients	804 (36.2)	304 (52.4)	**< 0.0001**
Patients with limitations of life-sustaining measures[d]	419 (82.6)	173 (88.7)	**0.0473**



Comorbid condition	N patients (%)	Day-28 Mortality
Chronic respiratory diseases	948 (19.1%)	31%
Chronic heart disease	673 (13.6%)	44%
Solid tumors	628 (12.7%)	43%
Liver cirrhosis	357 (7.2%)	45%
Drug related immunodeficiency	256 (5.2%),	36%
Hematological malignancies	(n=248, 5%)	56%
HIV infection	104 (2.1%)	31%

The Price of Undertermined ARF etiology

Authors	Reference	Population	Prevalence	Impact on outcomes
Masur	Medicine 1991	AIDS	**/**	(autopsy study)
Ewig	ERJ 1998	Hematology	**31%**	Not evaluated
Gruson	ERJ 1999	BMT	**58%**	**Increased mortality**
Rano	Thorax 2001	All IC patients	**19%**	Not evaluated
Rano	Chest 2002	All IC patients	**22%**	**Increasd mortality if time to diagnosis > 5d**
Danès	JCM 2002	All IC patients	**16%**	Not evaluated
Azoulay	Medicine 2004	Cancer	**21%**	**Increased mortality**
Contejean	AIC 2016	Hematology	**12.9%**	**Increased mortality**
Azoulay	ICM 2017	All IC patients	**13.2%**	**Increased mortality**

Lemiale *et al. Critical Care* (2015) 19:380
DOI 10.1186/s13054-015-1097-0

CRITICAL CARE

RESEARCH Open Access

The effects of a 2 h trial of high flow

	HFNO group (n = 52)	Venturi mask group (n = 48)	*P* value
Primary endpoint			
Number (%) of patients requiring mechanical ventilation	8 (15 %)	4 (8 %)	0.36
Noninvasive mechanical ventilation	6[a]	3[a]	
Invasive mechanical ventilation	4	2	
Secondary endpoints, median [25th–75th percentile]			
Discomfort VAS score[b] at 120 min	3 [1–5]	3 [0–5]	0.88
Dyspnea VAS score[b] at 120 min	3 [2 – 6]	3 [1–6]	0.87
Thirst VAS score[b] at 120 min	6 [3–8]	6 [5 – 9]	0.40
Respiratory rate at 120 min, breaths/min	25 [22–29]	25 [21–31]	
Heart rate at 120 min, beats/min	98 [90–110]	99 [83–112]	0.43

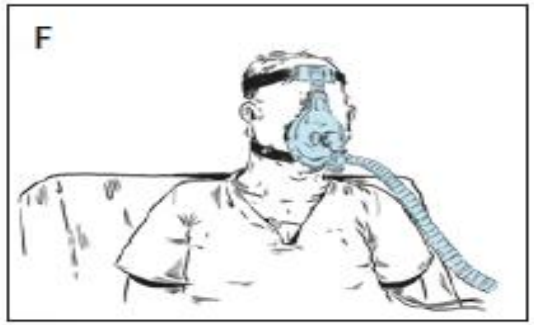
2. Quel est le menu?

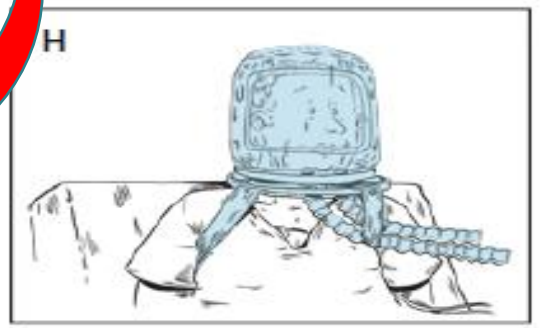
Standard oxygen

High-flow oxygen therapy

VS.

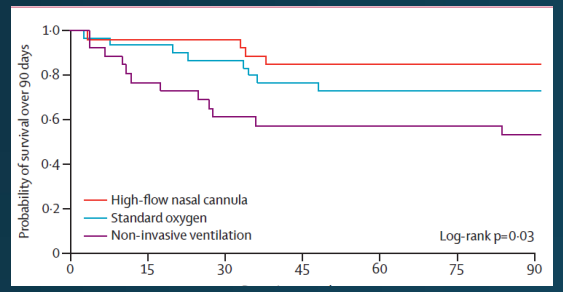
Non-invasive ventilation





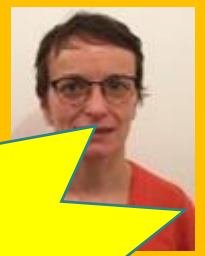
Intubation and mechanical ventilation

Noninvasive ventilation: *Not an option anymore*

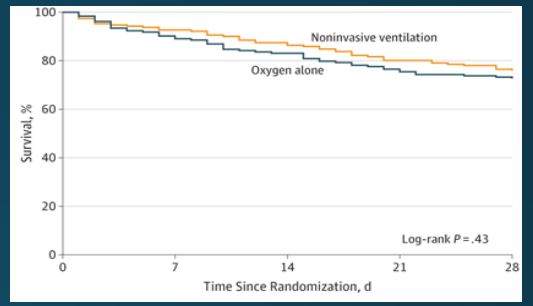


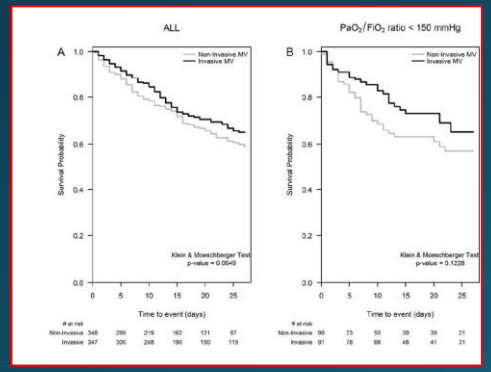
FLORALI

iVNIctus



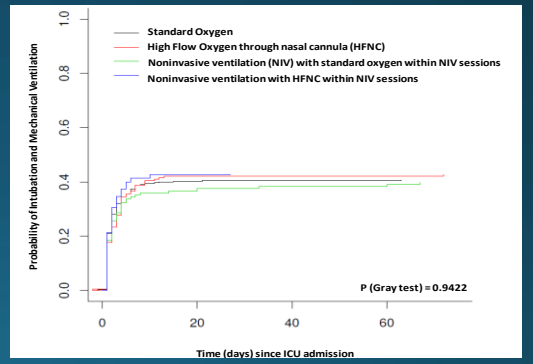
Hypercapnia
CPO
Atelectasis?
DAH?
Transient infiltrates?





LUNGS

RAIM



Helmet?

Standard oxygen: the best comparator?

Standard Oxygen

- Small prongues or mask
- Venturi

High Flow Oxygen

- 50-60L/min
- FiO2 for 92<Sp02<95

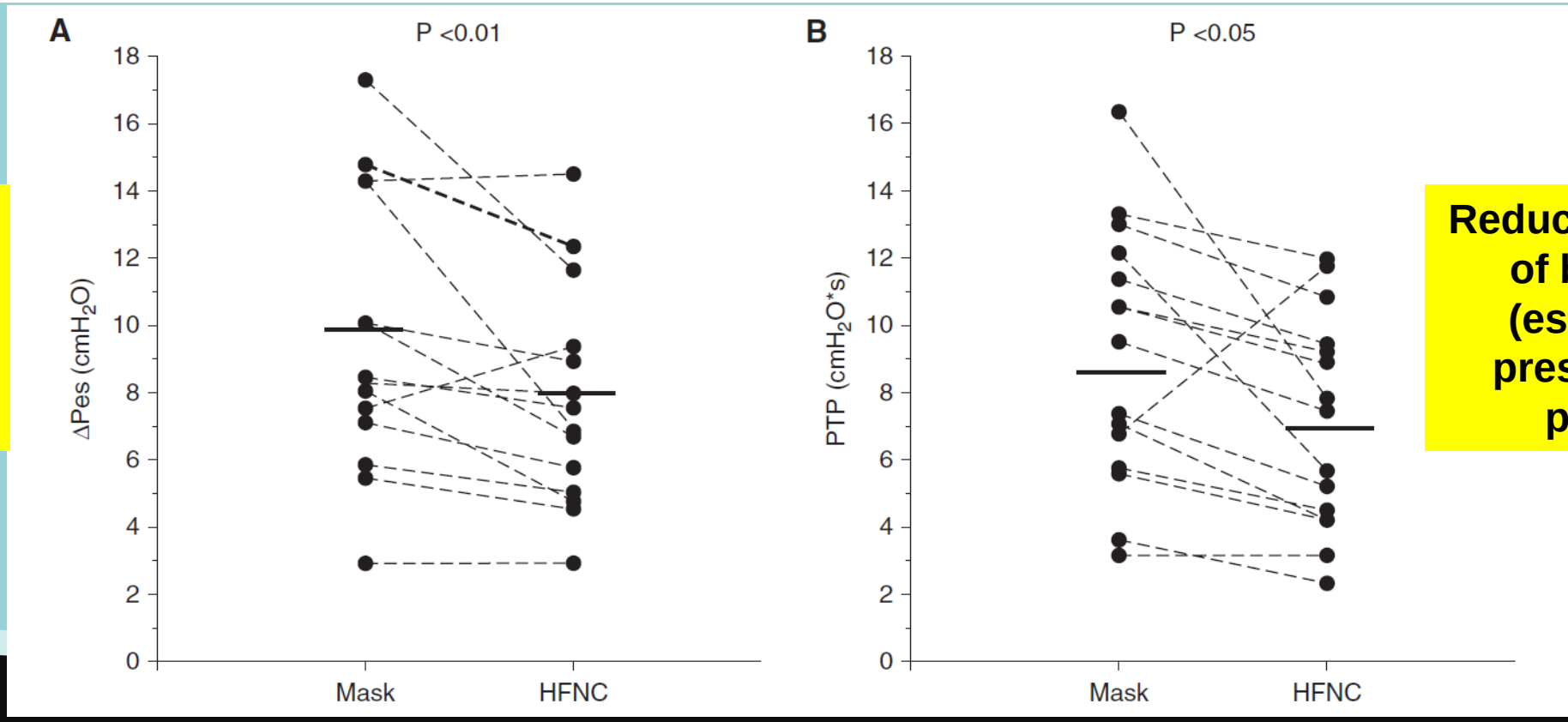
ORIGINAL ARTICLE Am J Respir Crit Care Med Vol 195, Iss 9, pp 1207–1215, May 1, 2017

HFNC delivered at 40 L/min vs. standard nonocclusive facial mask at 12 L/min

Physiologic Effects of High-Flow Nasal Cannula in Acute Hypoxemic Respiratory Failure

Tommaso Mauri[1,2], Cecilia Turrini[1,3], Nilde Eronia[4], Giacomo Grasselli[1], Carlo Alberto Volta[3], Giacomo Bellani[4,5], and Antonio Pesenti[1,2]

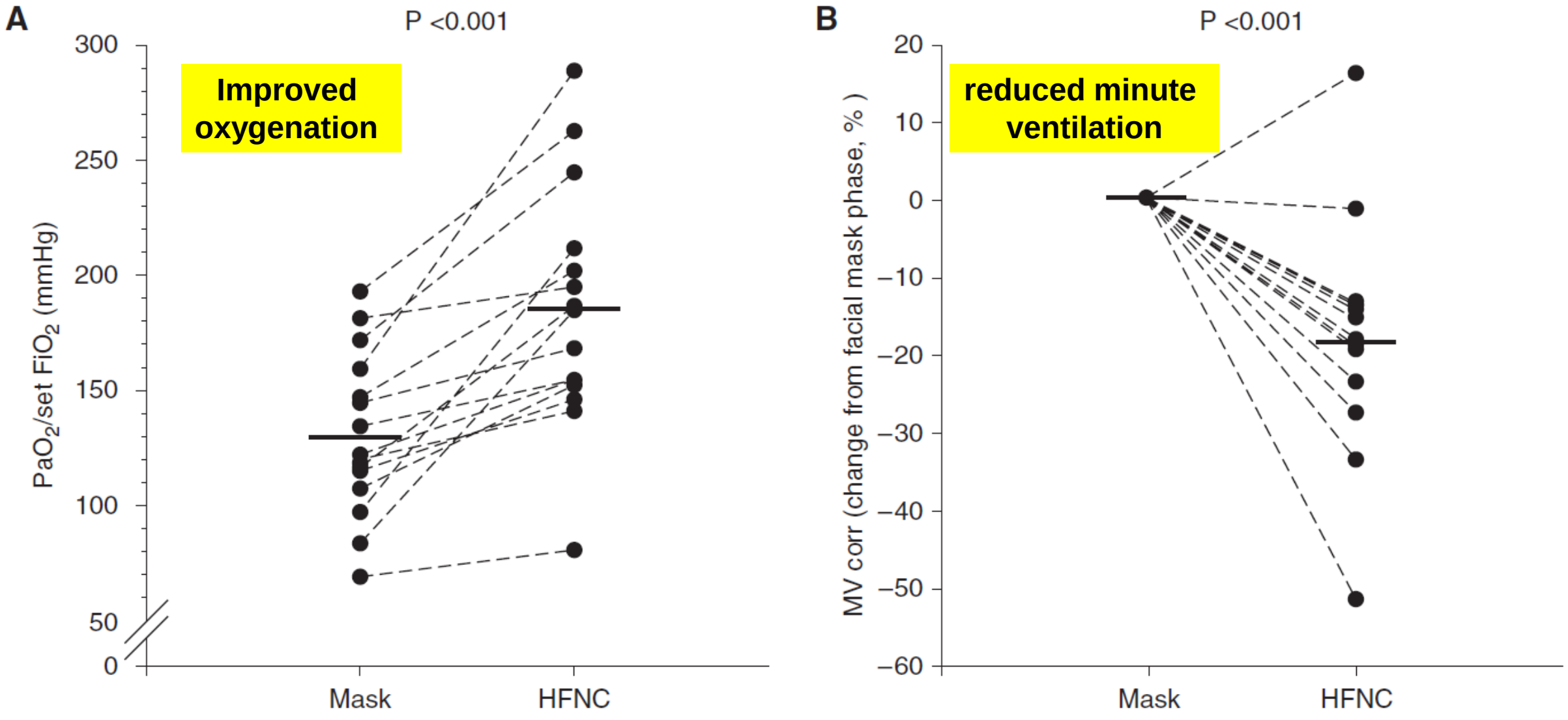
Reduction of inspiratory effort (red negative swings of Es pressure

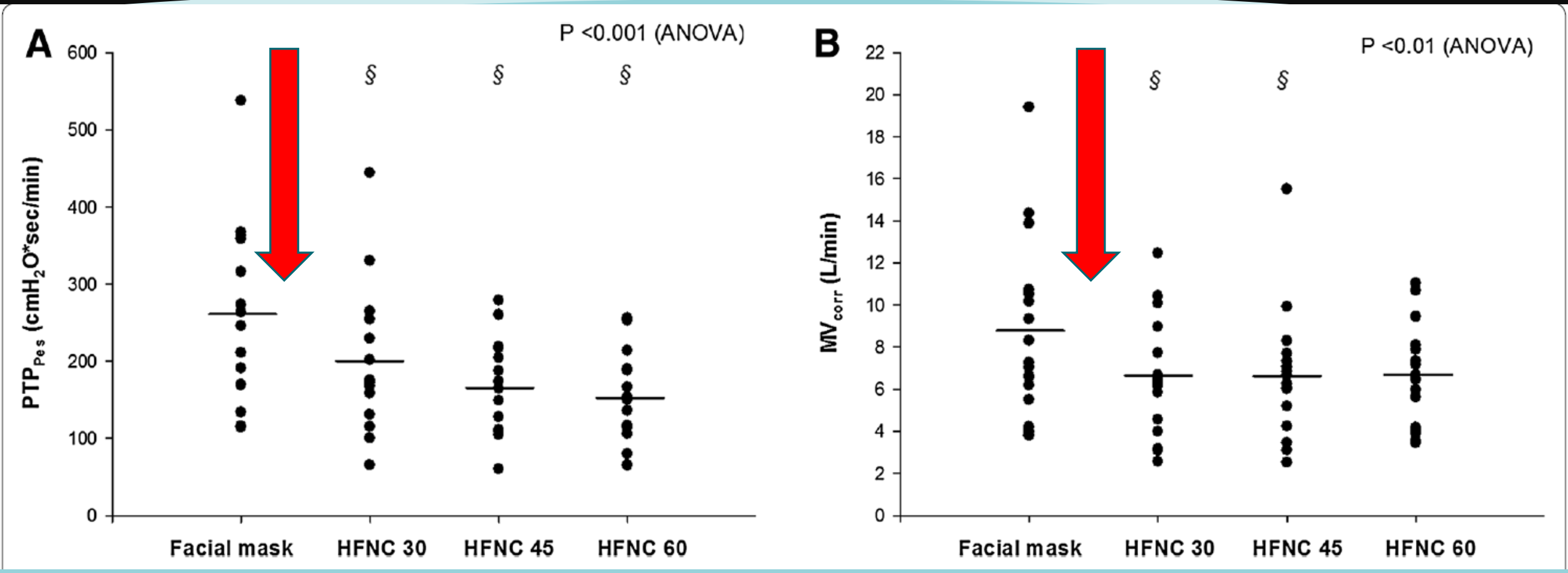


Reduction of work of breathing (esophageal pressure-time product)

Am J Respir Crit Care Med Vol 195, Iss 9, pp 1207–1215, May 1, 2017

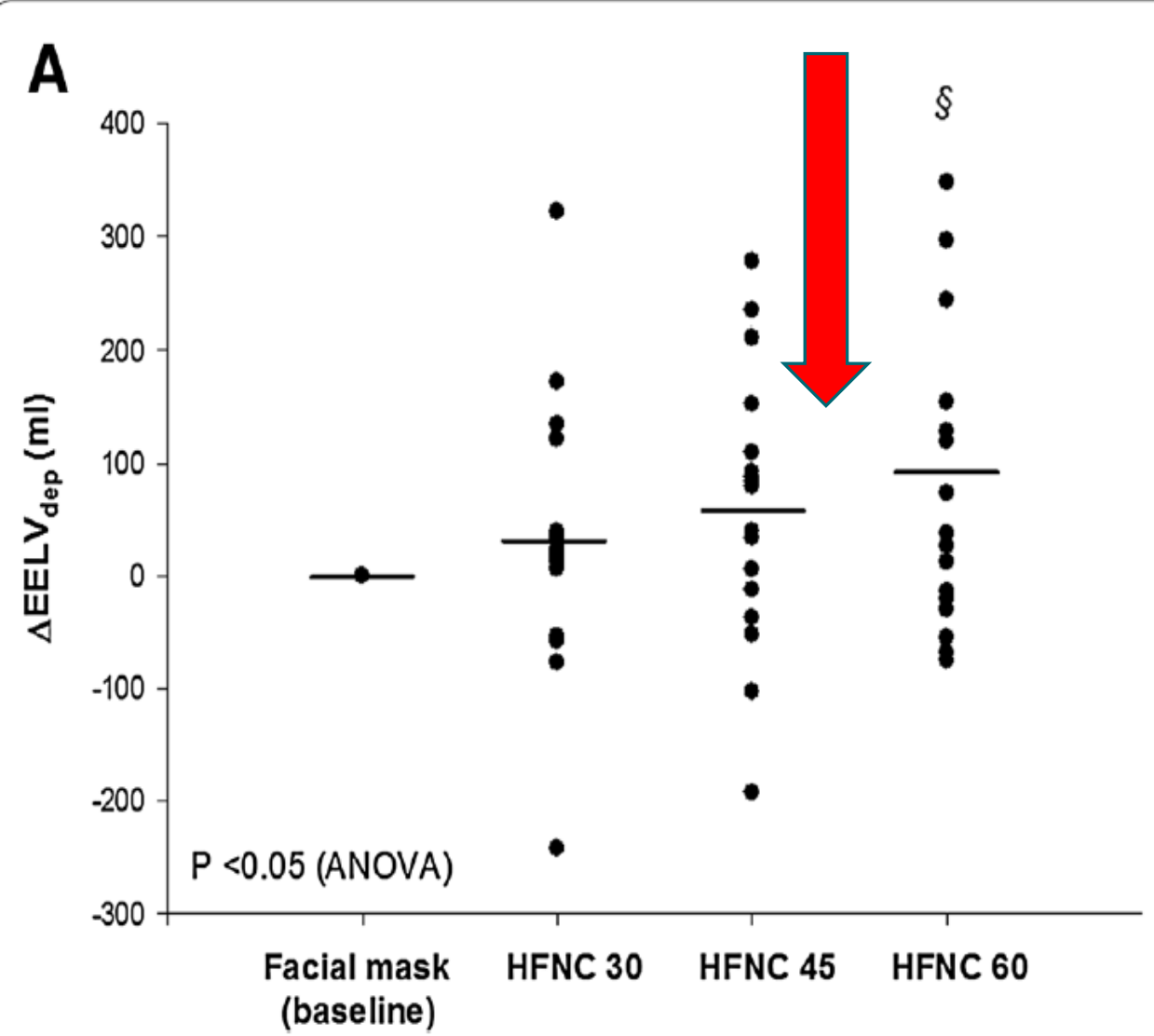
HFNC delivered at 40 L/min vs. standard nonocclusive facial mask at 12 L/min

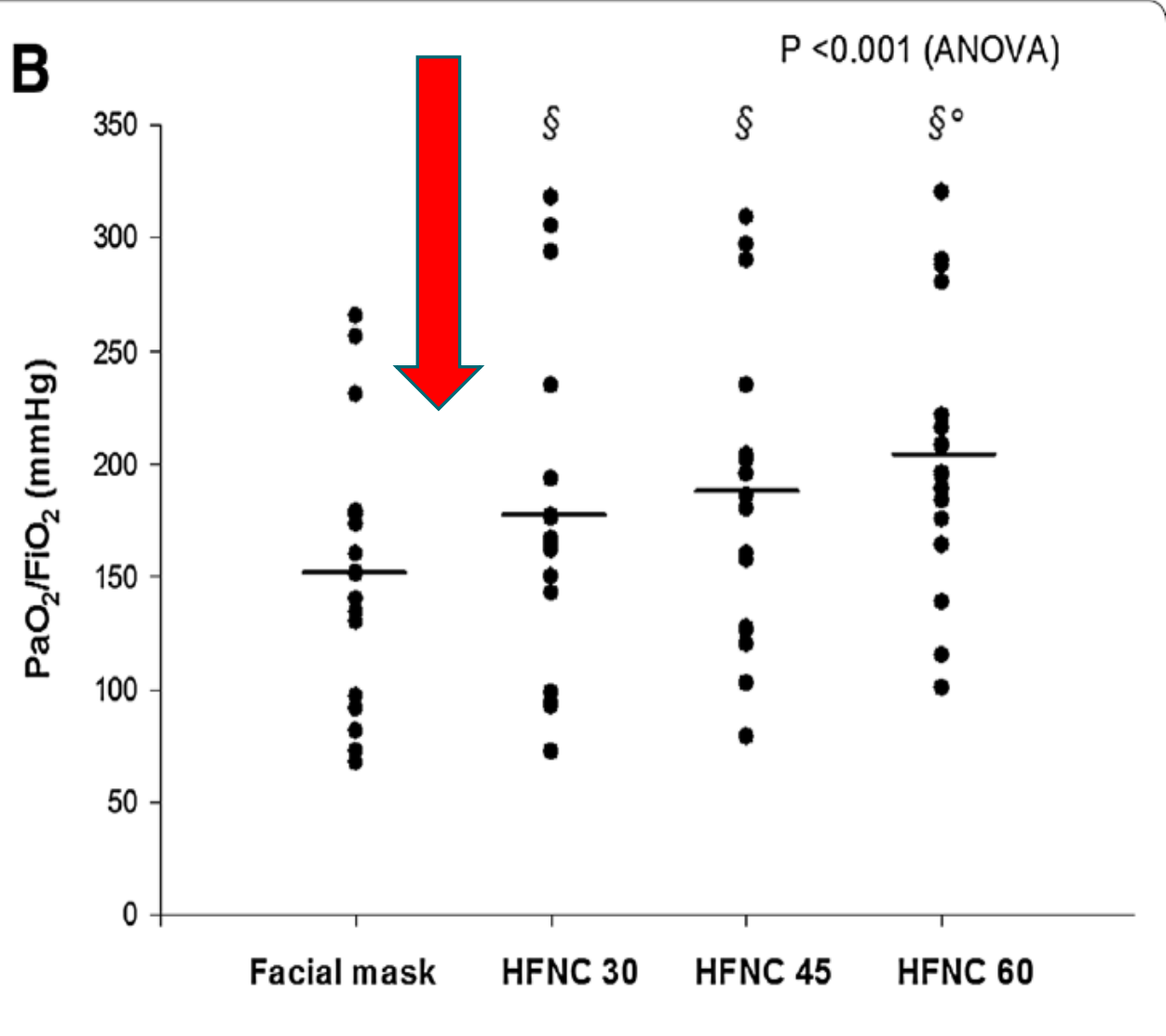




inspiratory effort

CO2 « clearance »





Changes in lung aeration

PaO2 / Fi02

Quel comparateur?

	iVNIctus JAMA 2015-CCM2017	Florali NEJM2015-LRM 2016	Efraim ICM 2017
	RCT N=374	RCT N=300 (82 ID)	Cohorte N=1611 (915 non intubés)
O2 Standard	NS par rapport HFNC	NS par rapport HFNC	NS par rapport à la VNI
HFNC	NS par rapport O2	NS par rapport O2	Presque supériorité par rapport à l'O2 sur l'IOT mais NS sur la mortalité

Effect of non-invasive oxygenation strategies in immunocompromised patients with severe acute respiratory failure: a post-hoc analysis of a randomised trial

Jean-Pierre Frat, Stéphanie Ragot, Christophe Girault, Sébastien Perbet, Gwénael Prat, Thierry Boulain, Alexandre Demoule, Jean-Damien Ricard, Rémi Coudroy, René Robert, Alain Mercat, Laurent Brochard, Arnaud W Thille, for the REVA network

Of the 8
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Intubati
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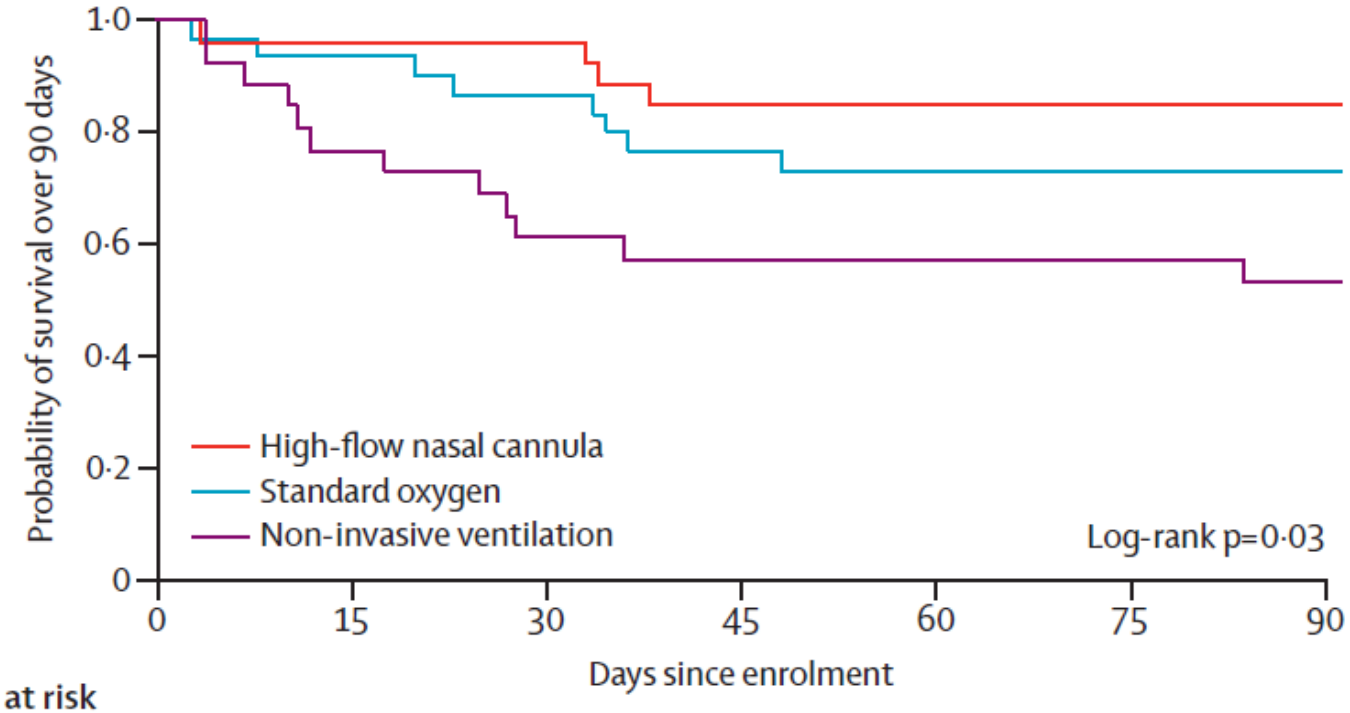
HFN
NIV

OR for i
OR for i

After m **h endotracheal**
int **e therapy.**



Number at risk							
High-flow nasal cannula group	26	25	25	22	22	22	22
Standard oxygen group	30	28	26	23	22	22	22
Non-invasive ventilation group	26	20	16	15	14	14	13

Méta-analyses: je n'en montrerai pas

- Il y en a beaucoup
- Mélange de RCT et d'études rétrospectives
- ID avec non ID
- Critères de jugement
- Hétérogénéité +++

3. Essai randomisé HIGH

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of High-Flow Nasal Oxygen vs Standard Oxygen on 28-Day Mortality in Immunocompromised Patients With Acute Respiratory Failure

The HIGH Randomized Clinical Trial

Elie Azoulay, MD, PhD; Virginie Lemiale, MD; Djamel Mokart, MD, PhD; Saad Nseir, MD, PhD; Laurent Argaud, MD, PhD; Frédéric Pène, MD, PhD; Loay Kontar, MD; Fabrice Bruneel, MD; Kada Klouche, MD, PhD; François Barbier, MD, PhD; Jean Reignier, MD, PhD; Lilia Berrahil-Meksen, MD; Guillaume Louis, MD; Jean-Michel Constantin, MD, PhD; Julien Mayaux, MD; Florent Wallet, MD; Achille Kouatchet, MD; Vincent Peigne, MD; Igor Théodose, MS; Pierre Perez, MD; Christophe Girault, MD; Samir Jaber, MD, PhD; Johanna Oziel, MD; Martine Nyunga, MD; Nicolas Terzi, MD, PhD; Lila Bouadma, MD, PhD; Christine Lebert, MD; Alexandre Lautrette, MD, PhD; Naike Bigé, MD, PhD; Jean-Herlé Raphalen, MD; Laurent Papazian, MD, PhD; Michael Darmon, MD, PhD; Sylvie Chevret, MD, PhD; Alexandre Demoule, MD, PhD

IMPORTANCE High-flow nasal oxygen therapy is increasingly used for acute hypoxemic respiratory failure (AHRF).

OBJECTIVE To determine whether high-flow oxygen therapy decreases mortality among immunocompromised patients with AHRF compared with standard oxygen therapy.

DESIGN, SETTING, AND PARTICIPANTS The HIGH randomized clinical trial enrolled 776 adult immunocompromised patients with AHRF (Pao_2 <60 mm Hg or Spo_2 <90% on room air, or tachypnea >30/min or labored breathing or respiratory distress, and need for oxygen ≥6 L/min) at 32 intensive care units (ICUs) in France between May 19, 2016, and December 31, 2017.

INTERVENTIONS Patients were randomized 1:1 to continuous high-flow oxygen therapy (n = 388) or to standard oxygen therapy (n = 388).

MAIN OUTCOMES AND MEASURES The primary outcome was day-28 mortality. Secondary outcomes included intubation and mechanical ventilation by day 28, Pao_2:Fio_2 ratio over the 3 days after intubation, respiratory rate, ICU and hospital lengths of stay, ICU-acquired infections, and patient comfort and dyspnea.

RESULTS Of 778 randomized patients (median age, 64 [IQR, 54-71] years; 259 [33.3%] women), 776 (99.7%) completed the trial. At randomization, median respiratory rate was 33/min (IQR, 28-39) vs 32 (IQR, 27-38) and Pao_2:Fio_2 was 136 (IQR, 96-187) vs 128 (IQR, 92-164) in the intervention and control groups, respectively. Median SOFA score was 6 (IQR, 4-8) in both groups. Mortality on day 28 was not significantly different between groups (35.6% vs 36.1%; difference, −0.5% [95% CI, −7.3% to +6.3%]; hazard ratio, 0.98 [95% CI, 0.77 to 1.24]; P = .94). Intubation rate was not significantly different between groups (38.7% vs 43.8%; difference, −5.1% [95% CI, −12.3% to +2.0%]). Compared with controls, patients randomized to high-flow oxygen therapy had a higher Pao_2:Fio_2 (150 vs 119; difference, 19.5 [95% CI, 4.4 to 34.6]) and lower respiratory rate after 6 hours (25/min vs 26/min; difference, −1.8/min [95% CI, −3.2 to −0.2]). No significant difference was observed in ICU length of stay (8 vs 6 days; difference, 0.6 [95% CI, −1.0 to +2.2]), ICU-acquired infections (10.0% vs 10.6%; difference, −0.6% [95% CI, −4.6 to +4.1]), hospital length of stay (24 vs 27 days; difference, −2 days [95% CI, −7.3 to +3.3]), or patient comfort and dyspnea scores.

CONCLUSIONS AND RELEVANCE Among critically ill immunocompromised patients with acute respiratory failure, high-flow oxygen therapy did not significantly decrease day-28 mortality compared with standard oxygen therapy.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT02739451.

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Editorial
Supplemental content

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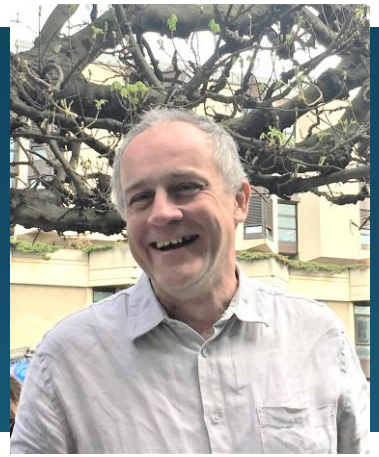
776 adult immunocompromised patients with AHRF at 32 ICUs in France between May 19, 2016, and December 31, 2017

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of High-Flow Nasal Oxygen vs Standard Oxygen on 28-Day Mortality in Immunocompromised Patients With Acute Respiratory Failure

The HIGH Randomized Clinical Trial



Elie Azoulay, MD, PhD; Virginie Lemiale, MD; Djamel Mokart, MD, PhD; Saad Nseir, MD, PhD; Laurent Argaud, MD, PhD; Frédéric Pène, MD, PhD; Loay Kontar, MD; Fabrice Bruneel, MD; Kada Klouche, MD, PhD; François Barbier, MD, PhD; Jean Reignier, MD, PhD; Lilia Berrahil-Meksen, MD; Guillaume Louis, MD; Jean-Michel Constantin, MD, PhD; Julien Mayaux, MD; Florent Wallet, MD; Achille Kouatchet, MD; Vincent Peigne, MD; Igor Théodose, MS; Pierre Perez, MD; Christophe Girault, MD; Samir Jaber, MD, PhD; Johanna Oziel, MD; Martine Nyunga, MD; Nicolas Terzi, MD, PhD; Lila Bouadma, MD, PhD; Christine Lebert, MD; Alexandre Lautrette, MD, PhD; Naike Bigé, MD, PhD; Jean-Herlé Raphalen, MD; Laurent Papazian, MD, PhD; Michael Darmon, MD, PhD; Sylvie Chevret, MD, PhD; Alexandre Demoule, MD, PhD

Objective

- To determine whether HFNC compared to standard oxygen decreases mortality in immunocompromised patients with ARF.

- Randomized clinical trial enrolling 776 adult immunocompromised patients with ARF at 32 ICUs in France between May 19, 2016 to December 31, 2017.

- Patients were randomized 1:1 to either continuous high-flow oxygen therapy (n=388), or to standard oxygen (n=388)

Inc/Excl Criteria

Inclusion criteria

- ICU admission
- Age ≥18 years
- ARF with PaO_2<60 mmHg or SpO_2<90% on room air, or tachypnea >30/minute or labored breathing or respiratory distress
- Need for oxygen therapy ≥6 L/min
- Known immunosuppression (not AIDS)
- Written informed consent

Exclusion Criteria

- imminent death
- refusal of study participation
- anatomical factors
- hypercapnia ($PaCO_2$≥50 mmHg)
- isolated cardiogenic pulmonary edema
- pregnancy or breastfeeding
- No coverage by a healthcare insur. system
- surgery within the last 6 days

Stratification at randomization

- Randomization was stratified on
  - study center,
  - oxygen flow rate at randomization (> or ≤9 L/min),
  - need for vasopressors,
  - and time since ICU admission (≤2 vs. ≥3 days),

Intervention

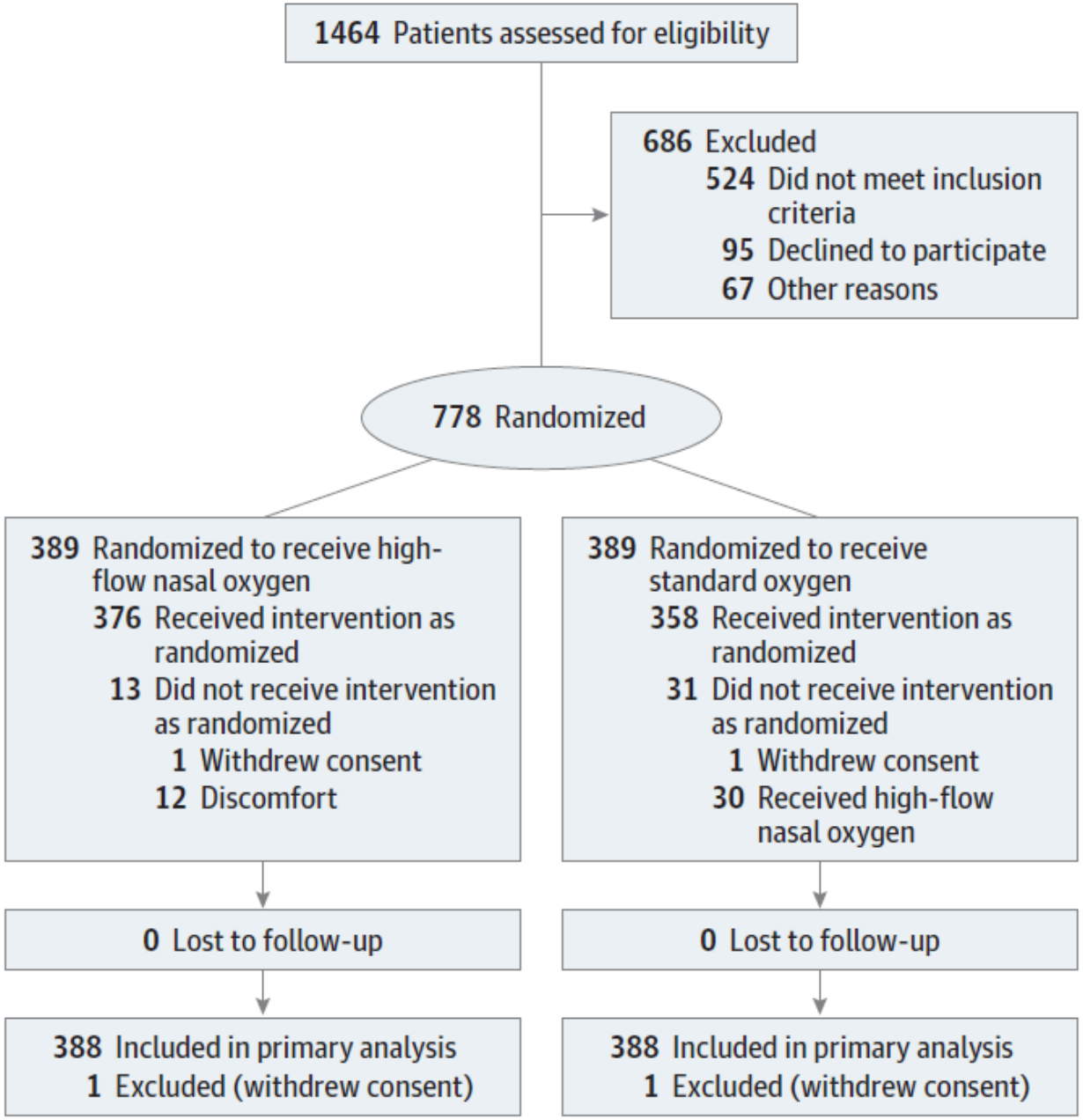
- Standard oxygen (control) group:
  - oxygen was delivered via any device or combination of devices. Oxygen flow was set to achieve $SpO_2 \geq 95\%$.
- In the intervention group,
  - O2 was delivered only by continuous HFNC, initiated at 50 L/min and 100% FiO_2, with a subsequent flow rate increase to achieve $SpO_2 \geq 95\%$, up to at least 50 L/min within the first three days then up to 60 L/min as needed. FiO_2 was tapered as possible while maintaining $SpO_2 \geq 95\%$.
- NIV used only if hypercapnia or pulmonary edema.

Study outcomes

- The primary endpoint was mortality within 28 days after randomization.

- 778 patients (389 in each group) were required
  - Expected day-28 mortality rate in the standard oxygen group : 30%
  - Decrease to 20% in the high-flow oxygen therapy group,
  - with α set at 5%, power 90%
- Interim analysis performed after 100 deaths.
- Intent-to-treat approach.

Figure 1. Flow of Patients Through the HIGH Trial



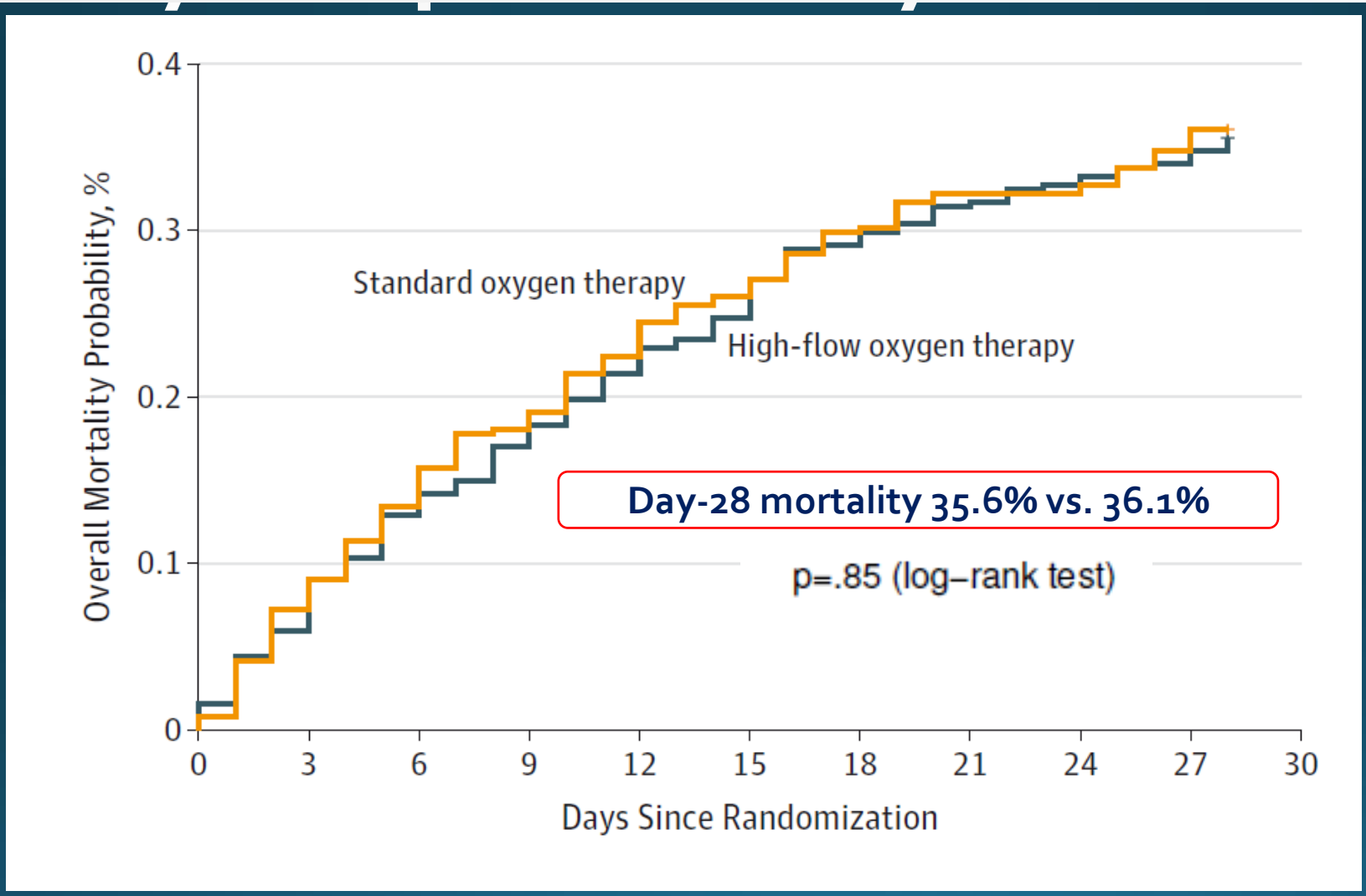
778 randomized

776 included in the primary analysis

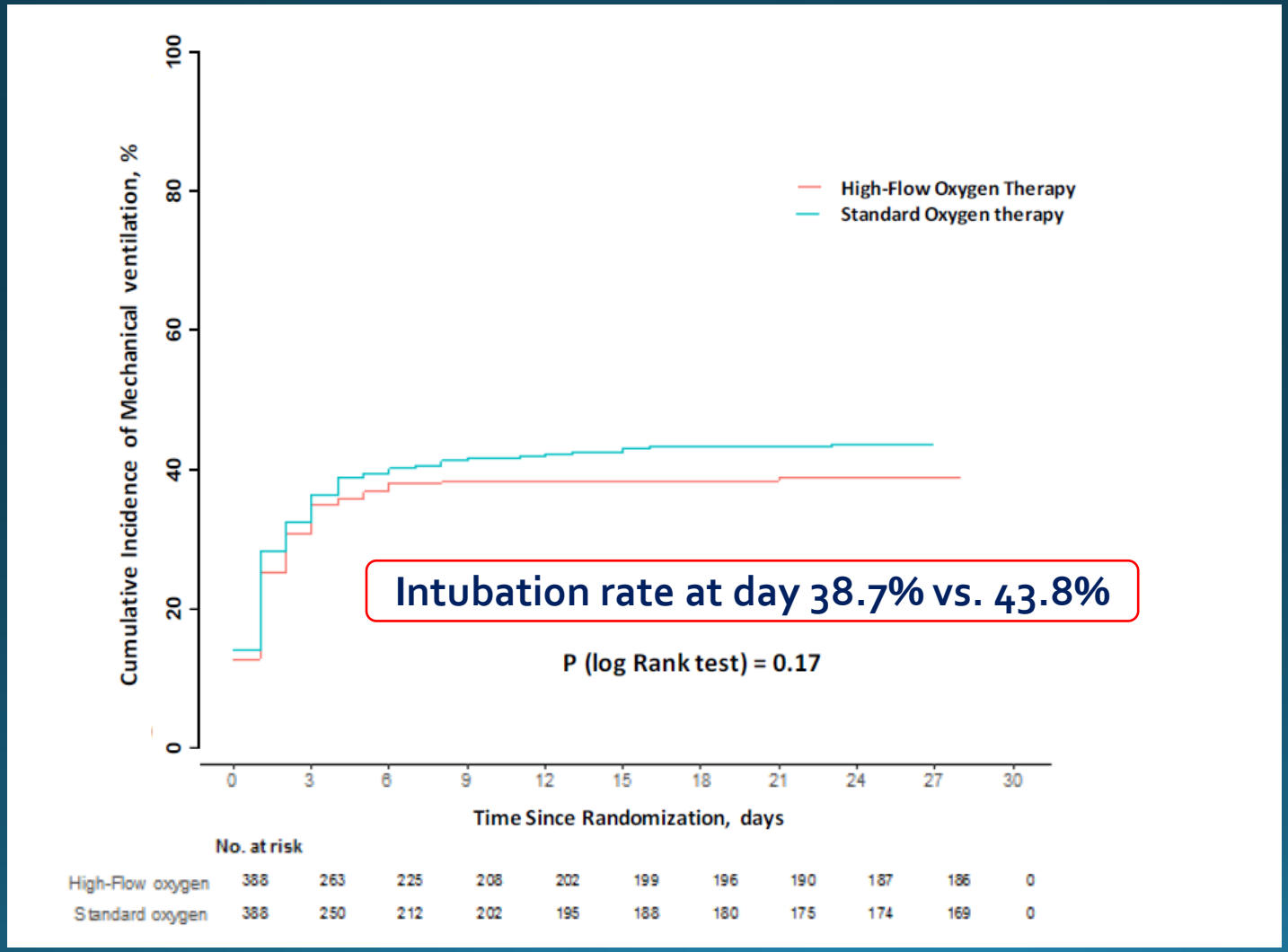
0 lost to follow up

	High-flow oxygen therapy, (N=388)	Standard Oxygen, (N=388)
Age (years, median)	64 [55-70]	63 [56-71]
Charlson comorbidity index	5 (4-7)	5 (3-7)
Underlying conditions		
Cancer	294 (75.8)	319 (82.2)
Hematological malignancies	167 (43.0)	181 (46.6)
Solid tumors	127 (32.7)	138 (35.6)
Immunosuppressive drugs	133 (34.3)	135 (34.8)
For non-transplant-related reasons	89 (22.9)	98 (25.2)
After solid organ transplantation	44 (11.3)	37 (9.5)
SOFA[c] at randomization	6 [4-8]	6 [4-8]
Vasopressors at randomization	33 (8.5)	39 (10.0)
Full-code management	308 (79.4)	309 (79.6)
Overall PaO_2/FiO_2 ratio at randomization	136 [96-187]	128 [92-164]

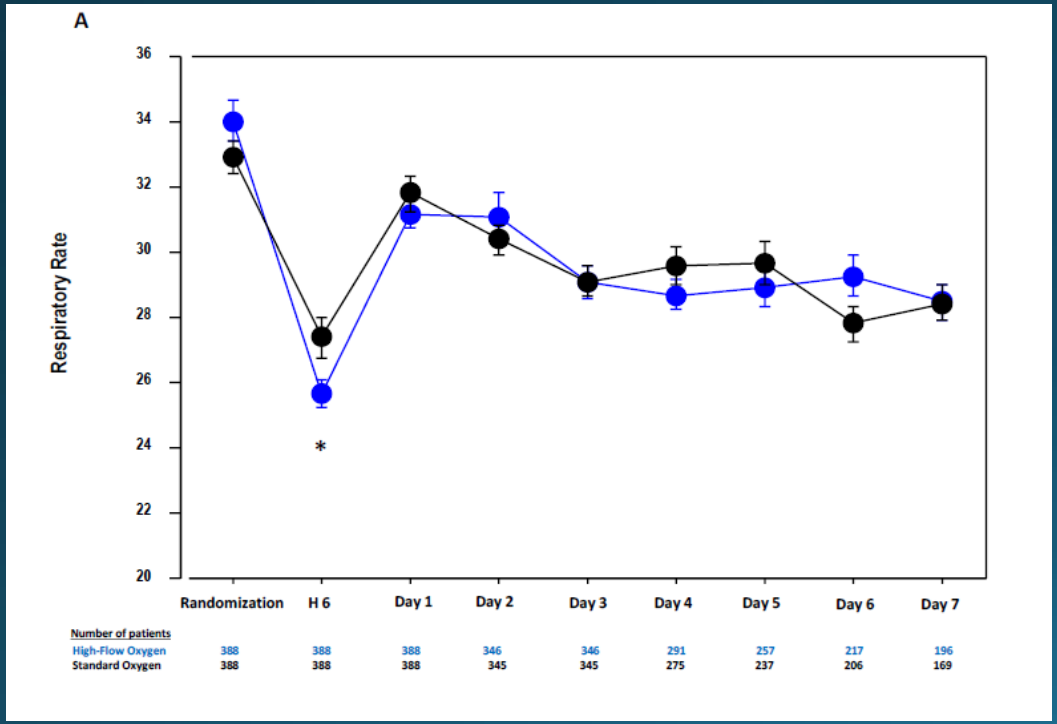
Primary endpoint – Day 28 mortality

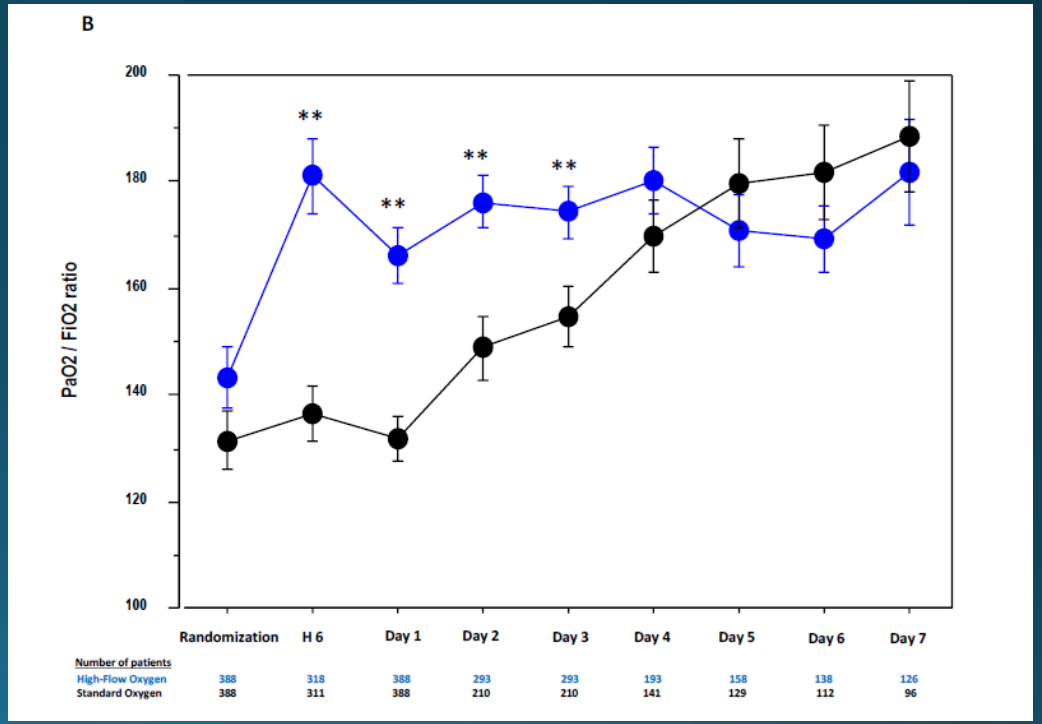


Cumulative incidence of intubation during the first 28 days after randomization

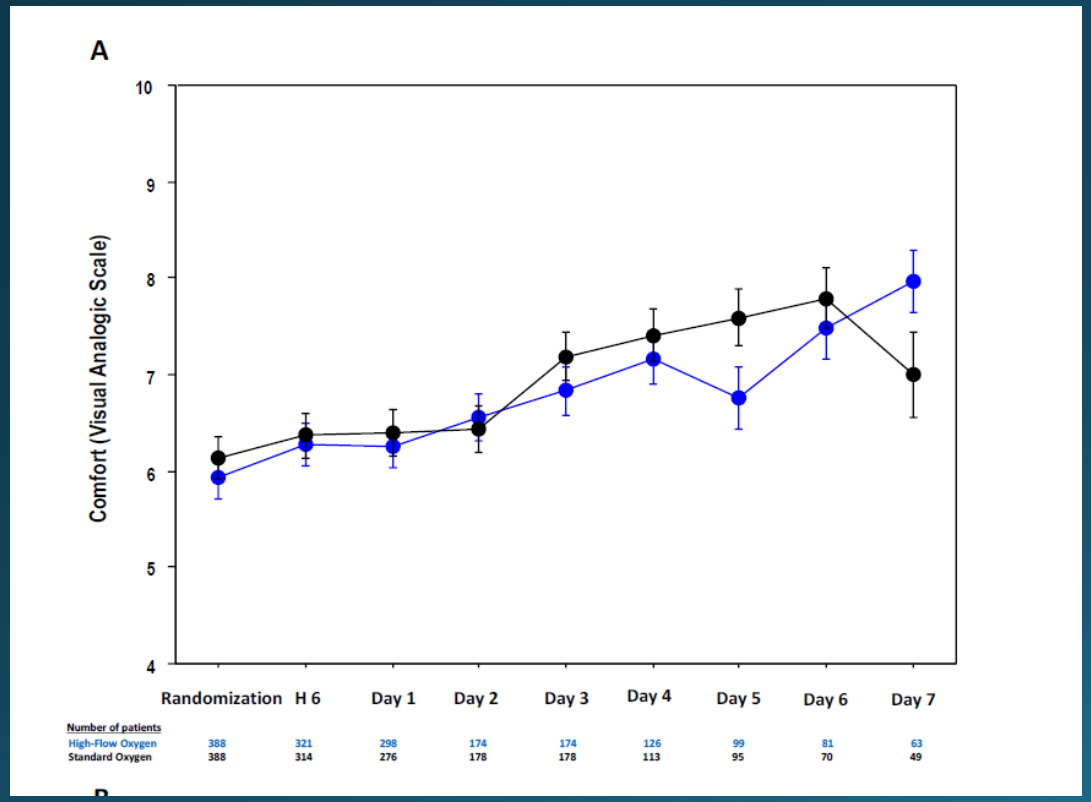


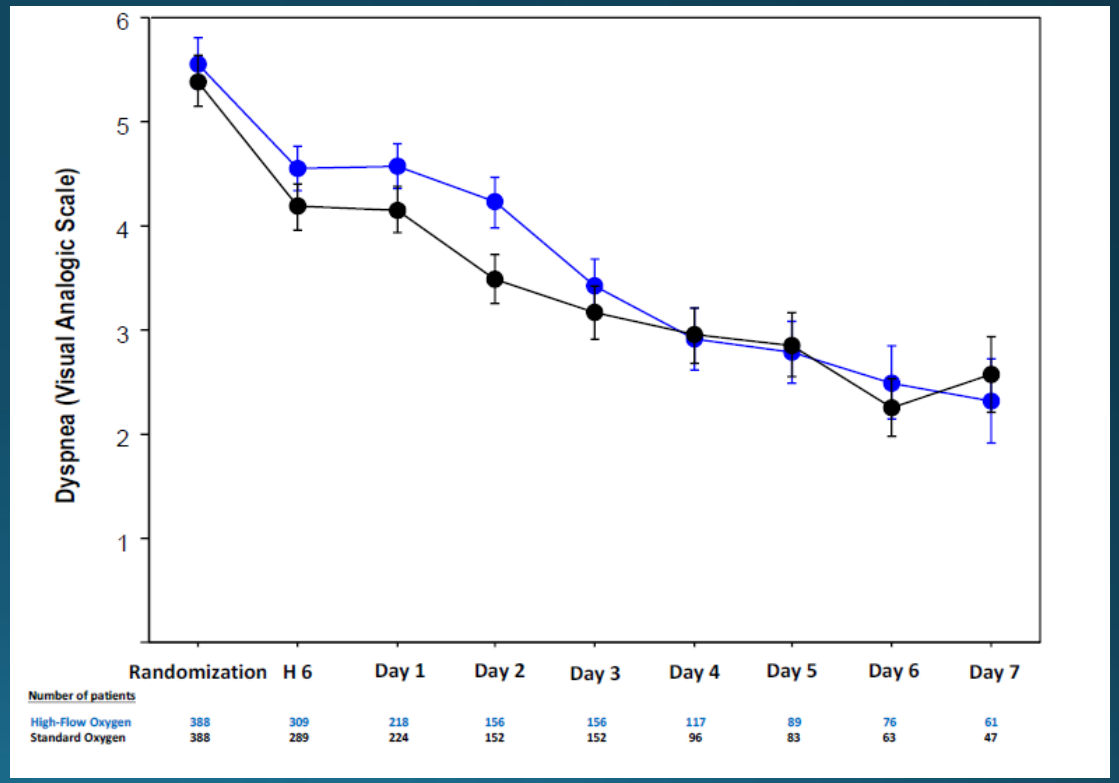
Respiratory rate (panel A) and PaO2/FiO2 ratio (panel B) over the first seven days following randomization





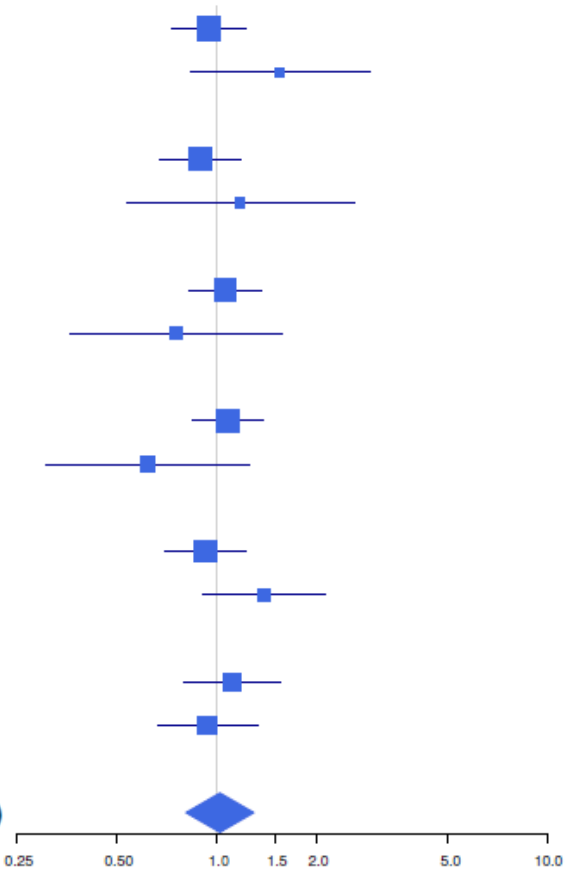
Visual analog scale scores for comfort (panel A) and dyspnea (panel B) during the seven days following randomization





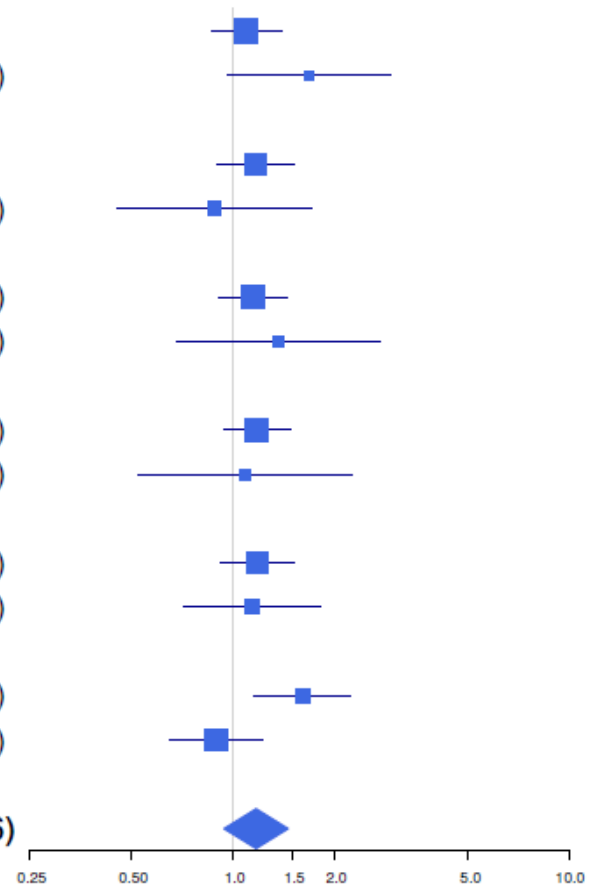
Post Hoc Outcomes - Mortality

Subset	HPNO 28 day deaths/Pts	O2 standard 28 day deaths/Pts	HR (95%CI)	Interaction p–value
Strate				
D0–D1	120/321	118/330	0.95 (0.74;1.22)	
>=D2	18/67	22/58	1.55 (0.83;2.9)	0.15
PAO2 FiO2				
<200	99/237	95/251	0.89 (0.68;1.19)	
>=200	16/65	10/35	1.18 (0.54;2.6)	0.52
Debit O2				
<9	122/348	127/347	1.06 (0.83;1.36)	
>9	16/40	13/41	0.76 (0.36;1.57)	0.39
Catecholamines				
no	121/355	126/349	1.08 (0.84;1.39)	
yes	17/33	14/39	0.62 (0.31;1.26)	0.15
Unknown Diagnosis				
no	99/297	95/303	0.93 (0.7;1.23)	
yes	39/91	45/85	1.39 (0.9;2.13)	0.12
Hematological malignancy				
no	66/199	72/198	1.11 (0.79;1.55)	
yes	64/167	65/181	0.94 (0.67;1.33)	0.5
All patients			**1.02 (0.81;1.29)**	



Post Hoc Outcomes - Intubation

Subset	HPNO 28 day MV/Pts	O2 standard 28 day MV/Pts	HR (95%CI)	Interaction p–value
Strate				
D0–D1	128/321	142/330	1.1 (0.87;1.4)	
>=D2	22/67	28/58	1.69 (0.96;2.95)	0.17
PAO2 FiO2				
<200	99/237	117/251	1.17 (0.9;1.53)	
>=200	27/65	13/35	0.88 (0.46;1.71)	0.44
Debit O2				
<9	136/348	151/347	1.15 (0.91;1.45)	
>9	14/40	19/41	1.37 (0.68;2.72)	0.65
Catecholamines				
no	137/355	154/349	1.18 (0.94;1.49)	
yes	13/33	16/39	1.09 (0.52;2.26)	0.83
Unknown Diagnosis				
no	114/297	135/303	1.18 (0.92;1.52)	
yes	36/91	35/85	1.15 (0.72;1.82)	0.9
Hematological malignancy				
no	61/199	89/198	1.61 (1.16;2.23)	
yes	78/167	77/181	0.89 (0.65;1.22)	0.01
All patients			**1.17 (0.94;1.46)**	



Other secondary endpoints

Number (%) or median	High-flow oxygen therapy (N=388)	Standard oxygen (N=388)	P value
ICU-acquired infection	39 (10.0)	41 (10.6)	0.91
ICU mortality	123 (31.7)	122 (31.4)	0.64
Hospital mortality	160 (41.2)	162 (41.7)	0.77
ICU length of stay, days	8 (4-14)	6 (4-13)	0.07
Hospital length of stay, days	24 [14-40]	27 [15-42]	0.60

In conclusion

- Compared to standard oxygen, high-flow oxygen therapy did not significantly improve day-28 mortality in immunocompromised patients with ARF.
- No safety issue could be raised from this large trial, making the two oxygenation strategies interchangeable.
- Further analyses are ongoing to identify patients likely to benefit from high-flow oxygen therapy.

Ou en sommes nous aujourd'hui?

- Toute seule, l'oxygénation a de faibles chances de changer la mortalité.
- Insérer la stratégie d'oxygénation dans une prise en charge globale
- Identifier les patients avec réponse favorable à l'HF et comprendre si des critères de jugement précoces sont prédictifs de l'intubation / mortalité
- Reconnaître la relation complexe entre l'étiologie de l'IRA et la réponse à l'oxygène (trajectoire)
- Comprendre ce que deviennent les patients après l'intubation et refuser de tenir compte des séries ou la mortalité des intubés est trop haute.

Thank you for your attention

	High-flow oxygen therapy, (N=388)	Standard Oxygen, (N=388)
Immediately before randomization		
Respiratory rate	33 [28-39]	32 [27-38]
Standard oxygen only	311 (80.1)	334 (86.1)
Oxygen flow (L/min, median	10 [6-15]	10 [6-15]
PaO_2 on standard oxygen	81 [65-111]	75 [65-93]
Estimated PaO_2/FiO_2 ratio	120 [86-164]	114 [82-149]
Noninvasive ventilation	25 (6.4)	18 (4.6)
High-flow oxygen therapy	52 (13.4)	36 (9.3)
Calculated PaO_2/FiO_2 (noninvasive ventilation or high-flow oxygen therapy, median	117 [87-173]	108 [76-167]
Overall PaO_2/FiO_2 ratio at randomization	136 [96-187]	128 [92-164]