A preliminary cost-effectiveness analysis of lung protective ventilation with extra corporeal carbon dioxide removal (ECCO$_2$R) in the management of acute respiratory distress syndrome (ARDS)

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ABSTRACT

Background: Mechanical ventilation (MV) is the cornerstone in the management of the acute respiratory distress syndrome (ARDS). Recent research suggests that decreasing the intensity of MV using lung protective ventilation (LPV) with lower tidal volume (Vt) and driving pressure (ΔP) could improve survival. Extra-corporal CO$_2$ removal (ECCO$_2$R) precisely enables LPV by allowing lower Vt, ΔP and mechanical power while maintaining PaCO$_2$ within a physiologic range. This study evaluates the potential cost-effectiveness of ECCO$_2$R-enabled LPV in France.

Methods: We modelled the distribution over time of ventilated ARDS patients across 3 health-states (alive & ventilated, alive & weaned from ventilation, dead). We compared the outcomes of 3 strategies: MV (no ECCO$_2$R), LPV (ECCO$_2$R when PaCO$_2$ > 55 mmHg) and Ultra-LPV (ECCO$_2$R for all). Patients characteristics, ventilation settings, survival and lengths of stay were derived from a large ARDS epidemiology study. Survival benefits associated with lower ΔP were taken from the analysis of more than 3000 patients enrolled in 9 randomized trials. Health outcomes were expressed in quality-adjusted life years (QALYs). Incremental cost-effectiveness ratios (ICERs) were computed with both Day 60 cost and Lifetime cost.

Results: Both LPV and ULPV as enabled by ECCO2R provided favorable results at Day 60 as compared to MV. Survival rates were increased with the protective strategies, notably with ULPV that provided even more manifest benefits as compared to MV. LPV and ULPV produced +0.162 and + 0.627 incremental QALYs as compared to MV, respectively. LPV and ULPV costs were augmented because of their survival benefits. Nonetheless, ICERs of LPV and ULPV vs. MV were all well below the €50,000 threshold. ULPV also presented with favorable ICERs as compared to LPV (i.e. less than €25,000/QALY).

Conclusions: ECCO$_2$R-enabled LPV strategies might provide cost-effective survival benefit. Additional data from interventional and observational studies are needed to support this preliminary model-based analysis.

1. Background

The Acute Respiratory Distress Syndrome (ARDS) represents an acute inflammatory reaction of the lungs that is present in 10% of total ICU admissions [1]. ARDS very often requires mechanical ventilation and prolongs ICU length of stay (LoS) [2]. In addition, ARDS is associated

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with high in-hospital mortality: 35% to 40% of ARDS patients die within the ICU or the hospital, respectively [1]. Beside the risk of in-hospital mortality, ARDS causes long-term functional disability and impaired quality of life [3,4].

Mechanical ventilation (MV) is a cornerstone in the management of ARDS. Significant progress has been achieved in the ventilatory management of ARDS patients since the landmark ARDS Network trial [5] in which lowering the tidal volume (Vt) to 6 mL/kg of predicted body weight improved survival. However, a growing body of evidence is suggesting that ultra-lung protective ventilation (ultra-LPV) with even lower Vt, lower plateau pressure (Pplat) and thus, lower driving pressure (ΔP), could further improve survival of ARDS patients [5-9]. Driving pressure (ΔP) has indeed been shown to be inversely related to survival in ARDS based on an analysis of more than 3000 patients from 9 clinical trials [7].

However, Vt reduction may induce hypercapnia and its related complications [10-13]. Extra Corporeal Carbon Dioxide Removal ($ECCO_2R$) in association with mechanical ventilation may enable ultra-LPV by allowing lower Vt and ΔP while maintaining $PaCO_2$ within a physiologic range [14].

Recent studies have demonstrated the feasibility of ultra-LPV as enabled by low-flow $ECCO_2R$ in moderate ARDS [15-22]. The aim of this study was to evaluate the potential cost-effectiveness of $ECCO_2R$-enabled ultra-LPV in the setting of the French health-care system.

2. Materials and methods

2.1. Decision problem

We simulated and compared the health outcomes and healthcare costs of 3 different mechanical ventilation strategies for patients diagnosed with moderate ARDS (defined as a PaO_2/FiO_2 ratio comprised between 100 and 200 mmHg) in the ICU. The 3 ventilation strategies considered were:

(1). MV with Vt $\approx$ 7–8 mL/kg PBW and Pplat $\approx$ 20–30 cm H_2O as conventional approach or standard of care that was reported in the LUNG-SAFE study [1];
(2). LPV with Vt $\approx$ 6 mL/kg PBW and Pplat $\approx$ 20–30 cm H_2O + $ECCO_2R$ initiated for patients with $PaCO_2$ > 55 mmHg under LPV before starting $ECCO_2R$ [23,24];
(3). Ultra-LPV with Vt $\approx$ 3–4 mL/kg PBW and Pplat $\approx$ 20–25 cm H_2O + $ECCO_2R$ for all patients [16,21].

2.2. Perspectives

The analysis was performed over a Day 60 and a lifetime horizon from a French hospital and healthcare perspectives. Only direct healthcare costs were thus considered.

2.3. Analytic model

We designed in MS Excel a partitioned survival time model whereby survival curves were extrapolated and areas under those curves were used to estimate the distribution over time of patients across mutually exclusive health states. The 3 mutually exclusive health states that were defined to describe the experience of mechanically ventilated ARDS patients were: Alive and ventilated (AV), alive and non-ventilated, i.e. successfully weaned from ventilation (AnV) and dead (D). The proportion of patients in the AV state was obtained by combining overall survival time and ventilation duration. The proportion of patients in the AnV state was then determined by the difference between the proportion of patient alive minus the proportion of those in the AV state. Multiple episodes of ventilation were not considered given the absence of data to inform such transition. A 6-h cycle was used until Day 60 and a yearly cycle afterwards. The 6-h cycle was applied until Day 60 to better capture the sometimes-rapid evolution of patients during their ICU stays. Health outcomes and healthcare costs were thus accumulated cyclically by health states as the cohort of patients was distributed through the different health states over time. The model schematic is depicted on Fig. 1.

2.4. Baseline characteristics and ventilation settings

Baseline patients' characteristics and ventilation settings, ventilation duration, ICU and hospital lengths of stay (LoS) were all derived from the LUNG SAFE study [1]. This study was a large observational and prospective cohort study carried out from a sample of 459 ICUs from 50 countries. In total, the study reported data from 2377 ARDS patients [1]. Baseline patients' characteristics and ventilation settings are shown in Table 1. For LPV, the positive end-expiratory pressure (PEEP) was assumed to be the same as for MV. For ULPV, PEEP was increased up to 12–13 cm H_2O for moderate ARDS to prevent atelectasis and derecruitment with $ECCO_2R$, further inducing a reduction of ΔP.

2.5. Survival

The survival curve needed for the partitioned survival model was extrapolated using a Weibull regression from the Day 28 survival rate for moderate ARDS reported in the LUNG SAFE study (65%) and an assumed Day 60 survival rate of 60%, observing that survival tends to plateau from Day 30 [25,26]. Survival benefits associated with lower ΔP were taken from the analysis of more than 3000 patients enrolled in 9 randomized trials [7]. This analysis showed that ΔP was the ventilation parameter most strongly associated with survival. The relationship between ΔP and the multivariable relative risk of death in the hospital was extrapolated using a second-order polynomial equation. The extrapolated survival curve and relationships between ΔP and risk of death are shown on Fig. 2.

2.6. Ventilation duration and LoS

The probability of remaining on ventilation was extrapolated from the median and the inter-quartile ranges ventilation duration reported in the LUNG SAFE study using a Weibull regression (Fig. 2). Average ICU and hospital LoS distinguishing between survivors and those who died at hospital were approximated from the median and the inter-quartile ranges reported in the LUNG SAFE study using the approximation methods proposed by Wan et al. [27]. It should be noted that ARDS survivors in the LUNG SAFE study consistently reported longer LoS.

2.7. $ECCO_2R$

The potential shortening of ventilation duration with $ECCO_2R$ (% with successful weaning from ventilation at Day 30) was inferred from a prospective randomized study of lower tidal volume strategy ($\approx$ 3 mL/kg) combined with $ECCO_2R$ vs. "conventional" MV [16]. Considering that $ECCO_2R$ could be run with a renal replacement platform, $ECCO_2R$ complications in the model included major bleeding (MB) and catheter-related bloodstream infection (CRBI). The respective frequencies of these complications were taken from a large clinical study on renal replacement therapy in the ICU [28]. This assumption that MB and CRBI frequencies were nearly like those of renal replacement therapy can be justified by the fact that smaller catheter sizes are used as compared to full-blown extra-corporeal membrane oxygenation (ECMO).

2.8. Health utilities

The utility level during a patient stay in the ICU was set at 0.13 [29]. In case of ventilation during the ICU stay, we assumed the utility would be lower to some extent and assumed a level of 0.10. The utility level
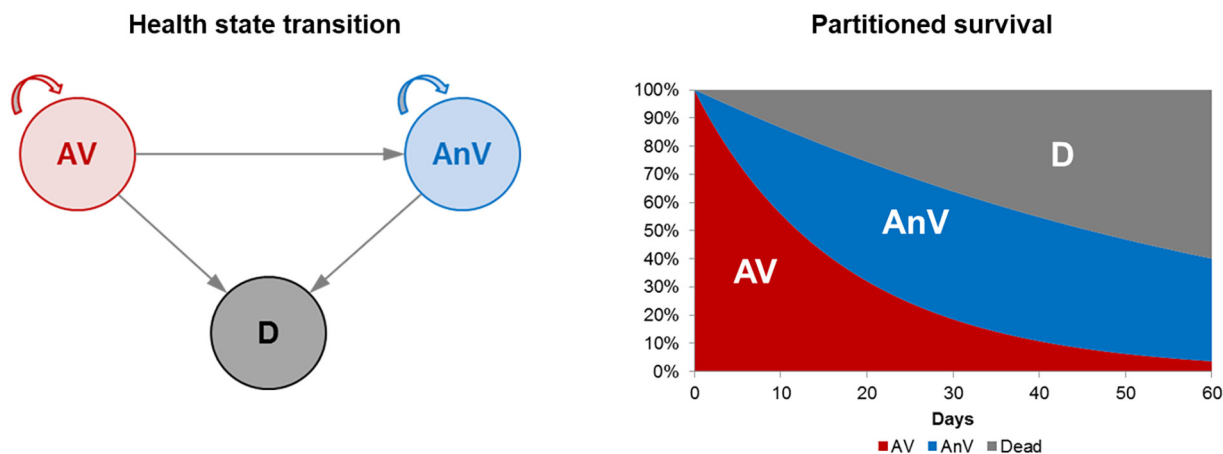
Health state transition

Partitioned survival

Fig. 1. Schematic of the partitioned survival time model. AV: Alive and ventilated; AnV: Alive and non-ventilated i.e., successfully weaned from ventilation; D: dead. All patients start in the AV health state and transition to the AnV and/or the D health states depending on ARDS severity and ventilation strategy.

during hospitalization was set at 0.60 [30]. Regarding health utility evolution over lifetime for ARDS survivors once discharged from hospital, we interpolated the published French population norms based on the EQ-5D index [31]. The interpolation was done continuously over the

18–100 years of age range using a slightly decreasing utility as function of age. The impact of ARDS was then estimated from a quality of life study in ARDS. The study reported a 31.8% reduction at 1-year from age- and sex-matched reference values in EQ-5D score for ARDS

Table 1
Summary of inputs data.

Parameters			Base case	DSA range		PSA distributions	Sources
				Min.	*Max.*		
Moderate ARDS in the ICU							
PaCO2 *(mm Hg)*			45.8	44.9	46.6	NORMAL (45.8;0.4)	[1]
Age *(years)*			62.0	62.0	63.0	NORMAL (62.0;0.3)	[1]
Baseline ventilation settings							
	MV	*PEEP (cm H2O)*	8.7	8.5	9.0	NORMAL (8.7;0.1)	[1]
		Pplat (cm H2O)	24.3	23.6	24.9	NORMAL (24.3;0.3)	[1]
		ΔP	15.6	15.1	15.9		
	LPV	*PEEP (cm H2O)*	8.7	8.5	9.0	NORMAL (8.7;0.1)	Assumption
		Pplat (cm H2O)	22.0	21.0	23.0	NORMAL (22.0;0.5)	Assumption
		ΔP	13.3	12.5	14.0		
	ULPV	*PEEP (cm H2O)*	12.5	12.0	13.0	NORMAL (12.5;0.3)	Assumption
		Pplat (cm H2O)	21.0	20.0	22.0	NORMAL (21.0;0.5)	Assumption
		ΔP	8.5	8.0	9.0		
ECCO$_2$R							
PaCO$_2$ threshold			55.0	50.0	60.0	NORMAL (55.0;2.6)	Assumption
Number of kits			2.0	1.0	3.0	RAND (0.0;0.0)	[21]
Successful weaning at day 30			1.6	1.1	2.1	LOG-NORMAL (1.6;0.3)	[16]
Complications *(%)*	MB		10.5%	8.4%	12.6%	BETA (85.9;731.8)	[27]
	CRBI		7.5%	6.0%	9.0%	BETA (88.8;1094.7)	[27]
Extra ICU days	MB		2.0	0.0	4.0	GAMMA (1.0;2.0)	Assumption
	CRBI		2.0	0.0	4.0	GAMMA (1.0;2.0)	Assumption
Health state utilities							
ICU stay	*Ventilated*		0.10	0.08	0.12	BETA (86.3;777.0)	Assumption
	Non-ventilated		0.13	0.10	0.16	BETA (83.4;558.3)	[28]
Hospital stay			0.60	0.48	0.72	BETA (37.8;25.2)	[29]
Lifetime, adjustement *(%)*			−31.8%	−25.4%	−38.2%	-BETA (65.2;139.8)	[31]
Healthcare costs *(€)*							
ICU stay *(per day)*			3017	2414	3620	GAMMA (1.0;3017.0)	[32,33][a]
Hospital stay *(per day)*			1333	1066	1600	GAMMA (1.0;1333.0)	[32,33][a]
ECCO$_2$R *(per kit)*			3000	2400	3600	GAMMA (1.0;3000.0)	Assumption
MB *(per event)*			10,000	8000	12,000	GAMMA (1.0;3000.0)	Assumption
CRBI *(per event)*			10,000	8000	12,000	GAMMA (1.0;10,000.0)	Assumption
Lifetime *(per year)*			4167	3334	5000	GAMMA (1.0;10,000.0)	[34]
Discounting							
QALYs *(%)*			4.0%	0.0%	6.0%	Not varied	[35]
Costs *(%)*			4.0%	0.0%	6.0%	Not varied	[35]

ΔP: Driving pressure (= Pplat – PEEP); DSA: Deterministic sensitivity analysis; CRBI: Catheter-related bloodstream infection; LPV: Lung-protective ventilation; MB: Major bleeding; MV: Mechanical ventilation, conventional; PaCO2: Partial pressure of carbon dioxide in arterial blood; PEEP: Positive end-expexitory pressure; Pplat: Plateau pressure; PSA: Probabilistic sensitivity analysis; ULPV: Ultra lung-protective ventilation.

[a] Median cost from official inpatient tariffs of CHU Bordeaux [32] and Hospices Civils de Lyon [33].
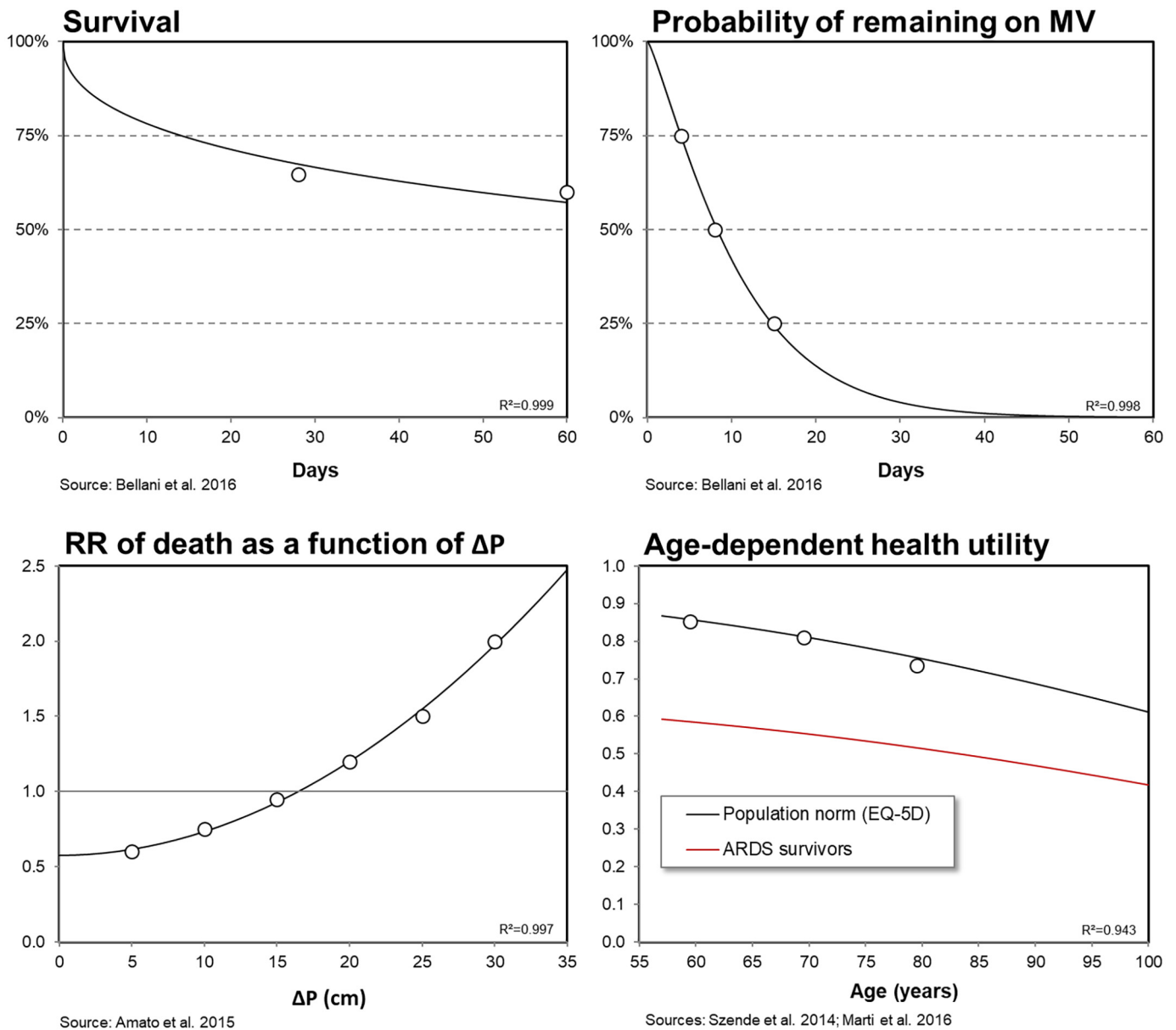
Fig. 2. Survival, ventilation duration and age-dependent health utilities extrapolations.

survivors under the age of 65 years [32]. We assumed this impact would last over the entire remaining lifetime of ARDS survivors (Fig. 2).

2.9. Healthcare costs

Healthcare costs were expressed in € 2018 and included costs of $ECCO_2R$ implementation and complications, ICU and hospital costs for the Day 60 horizon. Whenever possible, costs were documented from published literature or official sources. Both daily costs for an ICU stay (inclusive of MV cost) and a hospital stay (general wards) were taken from the official inpatient 2018 tariffs of 2 large French hospitals [33,34]. For $ECCO_2R$, as a kit allows for 72 h on $ECCO_2R$, we stipulated that 2 kits would be necessary and set the cost of a kit at €3000. In absence of reliable data, we assumed the cost of an $ECCO_2R$ complication (i.e. MB or CRBI) at €10,000. Additionally, we assumed that a complication would incur 2 extra days in the ICU. All costing assumptions were done conservatively. For the lifetime horizon, we assigned a yearly cost to each surviving patient using

the healthcare cost per capita in France [35]. As data were available over the 2009-2015-time frame, the yearly healthcare cost per capita was linearly trended until 2018.

2.10. Base case analysis

Health outcomes, LoS and healthcare costs were simulated and averaged for a cohort of 1000 moderate ARDS patients. Health outcomes were expressed in terms of Day 60 survival, Life Day Gained (LDG) and Quality-adjusted Life-Days (QALDs) for the Day 60 horizon and in Life Year (LY) gained and Quality-adjusted Life-Years (QALYs) gained for the lifetime horizon. Incremental cost-effectiveness ratios (ICERs) expressed as incremental cost-per-LY gained and incremental cost-per-QALY gained were computed to compare the 3 ventilations strategies. All ICERs were computed using both the Day 60 cost and the lifetime cost. Both health outcomes and cost were discounted at 4% per annum, as recommended by the French health technology assessment agency [36].

2.11. Sensitivity analyses

Deterministic one-way sensitivity analyses were carried by varying all model parameters individually within their 95%CI bounds when available or within a ± 20% range, alternatively. Results were presented using Tornado diagrams as appropriate. A probabilistic sensitivity analysis was also performed to appraise the multivariate uncertainty in the model. Utilities and proportions were simulated with a Beta distribution. Costs were simulated with a Gamma distribution. The risk ratio for successful weaning at Day 30 with ECCO₂R was simulated with a Log-Normal distribution. All other parameters were simulated with a Normal distribution. All inputs data and their respective variations and probabilistic distributions used for the sensitivity analyses are summarized in Table 1. Results were presented as scatter plots of pairwise strategies comparisons and cost-effectiveness effectiveness acceptability curves (CEAC) against maximum willingness-to-pay (WTP) thresholds for a QALY ranging from € 0 to €100,000.

3. Results

3.1. Base case

Base case results are presented on Table 2. Both LPV and ULPV as enabled by ECCO₂R provided favorable results for all Day 60 health outcomes as compared to conventional MV. Survival rates were increased with the protective strategies, notably with ULPV that provided even more manifest benefits as compared to MV. Consequently, LoS were slightly increased with the protective strategies reflecting the greater proportion of survivors. Day 60 costs were increased with LPV and ULPV due to the cost of ECCO₂R per se and, to a lesser extent, to the management of its potential complications and to the somewhat longer LoS that LPV and ULPV entailed due to extended survival. Using Day 60 survival and cost only, the incremental cost per additional life saved were €57,024 for LPV vs. MV, €82,314 for ULPV vs. MV and €104,963 for ULPV vs. LPV, respectively.

Regarding lifetime cost-effectiveness outcomes, MV yielded 7.393 LYs and 2.595 QALYs. In comparison, LPV and ULPV produced 8.204 (+0.811) and 9.110 (+1.716) LYs, respectively. This resulted in higher QALYs gains as compared to MV, with 2.711 (+0.176) and 3.203 (+0.609) QALYs for LPV and ULPV, respectively. LPV and ULPV lifetime costs were also augmented because of their survival benefits. ICERs of LPV and ULPV vs. MV were all well below the €50,000 WTP threshold. The greatest ICER was for LPV vs. MV with lifetime cost and QALY (+€27,772/QALY) and the lowest ICER was for LPV vs. MV with Day 60 cost and LY (+€4407/LY). ULPV also presented with favorable ICERs as compared to LPV in both cost scenarios (less than €25,000/QALY).

3.2. Sensitivity analyses

Fig. 3 displays the pairwise scatter plots obtained from the multiway probabilistic sensitivity analyses. ULPV consistently shown greater costs and health benefits as compared to MV or LPV. Difference was less marked for LPV vs. MV. Fig. 4 shows the CEAC for each strategy, indicating the probabilities that a strategy is cost-effective for a range of maximum WTP thresholds. ULPV becomes the strategy with the highest probability of cost-effectiveness as from a WTP of ≈ €22,500 per QALY.

Fig. 5 shows the Tornado diagrams from the one-way deterministic sensitivity analyses on the ICERs comparing ULPV vs. LPV. Regardless the outcome measure used, LY or QALY, ICERs variations was within a ± 20% range only. The most influential parameter on both ICERs was the number of ECCO₂R kits used in moderate ARDS.

Table 2
Base case results.

| Outcomes	Ventilation strategies			Incremental analyses		
	MV	LPV	ULPV	LPV- MV	ULPV-MV	ULPV-LPV
Day 60						
Survival at day 60 (%)	57.1%	63.4%	70.4%	+6.3 pp	+13.3 pp	+7.0 pp
LDs	41.4	44.2	47.2	+2.8	+5.8	+3.1
Ventilated	8.7	6.8	4.7	−1.9	−4.0	−2.1
Non-ventilated	32.7	37.3	42.5	+4.7	+9.8	+5.2
QALDs	18.4	20.0	21.7	+1.6	+3.4	+1.8
LoS (days)						
ICU	12.1	12.3	12.5	+0.2	+0.4	+0.2
Hospital	19.0	19.8	20.8	+0.9	+1.9	+1.0
Costs						
ECCO₂R	€ 0	€ 1616	€ 6000	+€ 1616	+€ 6000	+€ 4384
ICU	€ 36,506	€ 37,035	€ 37,626	+€ 529	+€ 1121	+€ 591
Hospital (Non-ICU)	€ 9140	€ 10,084	€ 11,138	+€ 944	+€ 1998	+€ 1054
ECCO₂R complications	€ 0	€ 485	€ 1800	+€ 485	+€ 1800	+€ 1315
Total	€ 45,646	€ 49,219	€ 56,564	+€ 3574	+€ 10,919	+€ 7345
Lifetime						
LYs (undiscounted)	7.393	8.204	9.110	+0.811	+1.716	+0.905
QALYs	2.595	2.771	3.203	+0.176	+0.609	+0.432
Lifetime cost	€ 19,816	€ 21,143	€ 24,416	+€ 1328	+€ 4600	+€ 3272
Total cost	€ 65,462	€ 70,363	€ 80,980	+€ 4901	+€ 15,519	+€ 10,617
Cost-effectiveness						
Day 60 cost only						
Cost/LY	€ 6174	€ 5999	€ 6209	+€ 4407	+€ 6362	+€ 8112
Cost/QALY	€ 17,592	€ 17,762	€ 17,657	+€ 20,250	+€ 17,935	+€ 16,990
Lifetime cost						
Cost/LY	€ 8854	€ 8576	€ 8889	+€ 6044	+€ 9042	+€ 11,726
Cost/QALY	€ 25,229	€ 25,391	€ 25,279	+€ 27,772	+€ 25,491	+€ 24,559

pp: percentage point; QALD: Quality-adjusted life-day; QALY: Quality-adjusted life-year; LD: Life-day; LoS: Length of stay; LPV: Lung-protective ventilation; LY: Life-year; MV: Mechanical ventilation; ULPV: Ultra lung-protective ventilation.

4. Discussion

We designed a partitioned survival model over patients' lifetime to assess the value of LPV and ULPV strategies as enabled by the addition of ECCO₂R in the management of ARDS. Our findings suggest that in moderate ARDS LPV and ULPV represents cost-effective ventilation strategies when compared to the conventional MV approach. The decrease of ΔP with LPV and ULPV would indeed provide survival benefit and shorten ventilation duration. All of this would be achieved by maintaining patient's PaCO2 within physiologic ranges and thus minimizing the risk of hypercapnia and its related complications [12].

Increased survival is nonetheless associated with longer LoS and causes somewhat higher costs, but our analysis suggests that the incremental survival benefit seems worth the incremental cost with ICERs remaining within acceptable ranges. The potential economic benefit of protective ventilation could be furthered in future research by broadening the perspective of the analysis. Indeed, typical patients are in the range of 60 years of age and still belong to the economically active population. Better preservation of life when ARDS occurs has more than surely the potential to generate broader economic returns.

LPV vs. MV
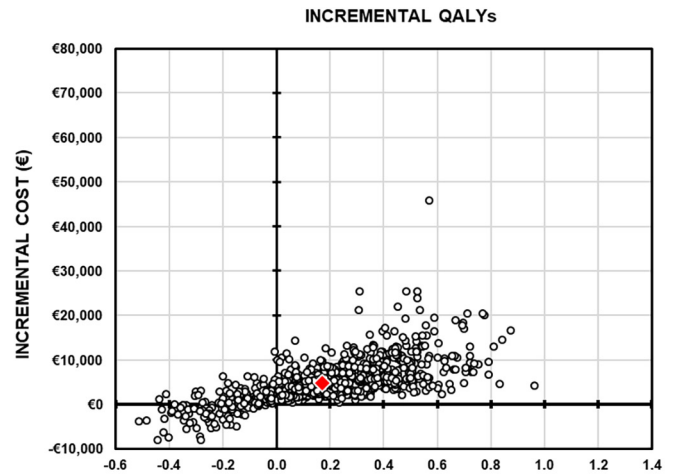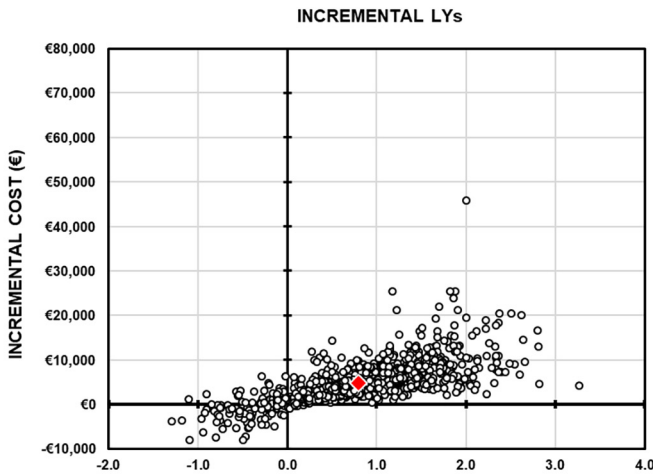
ULPV vs. MV
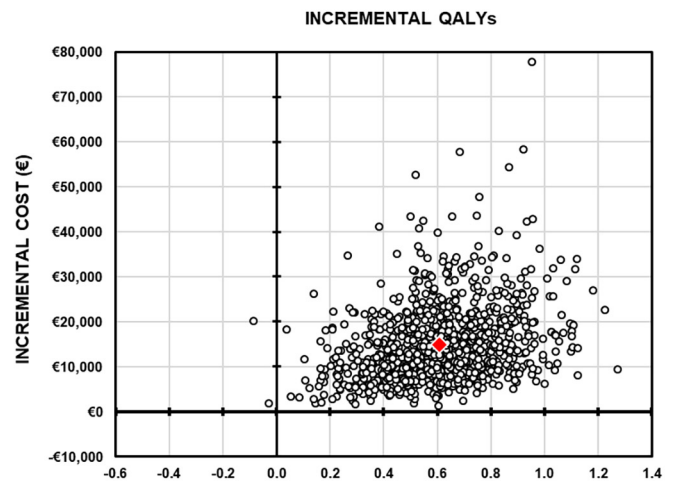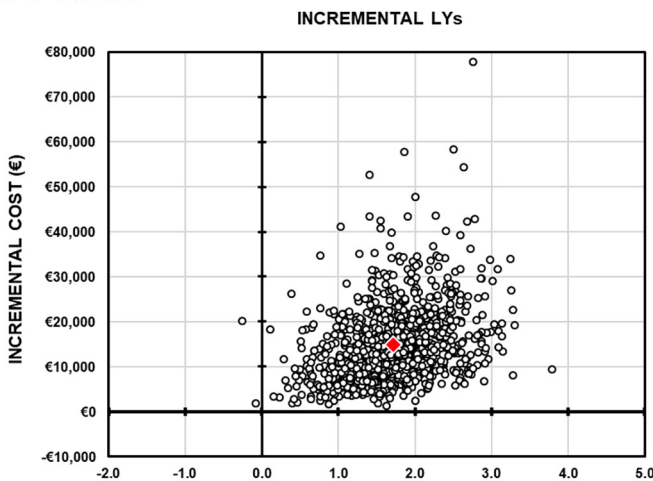
ULPV vs. LPV

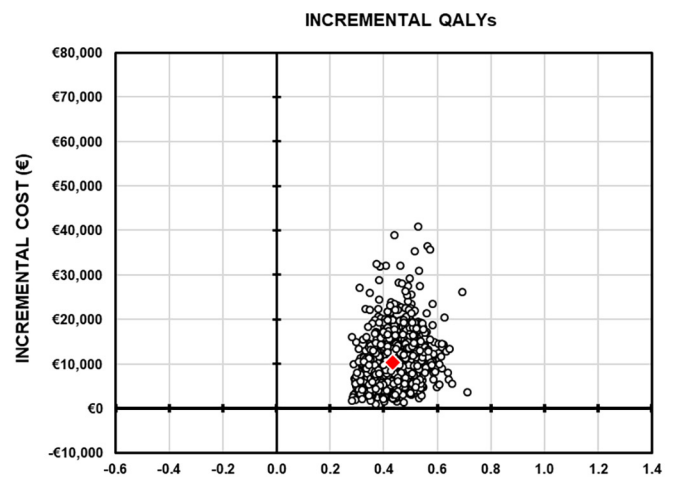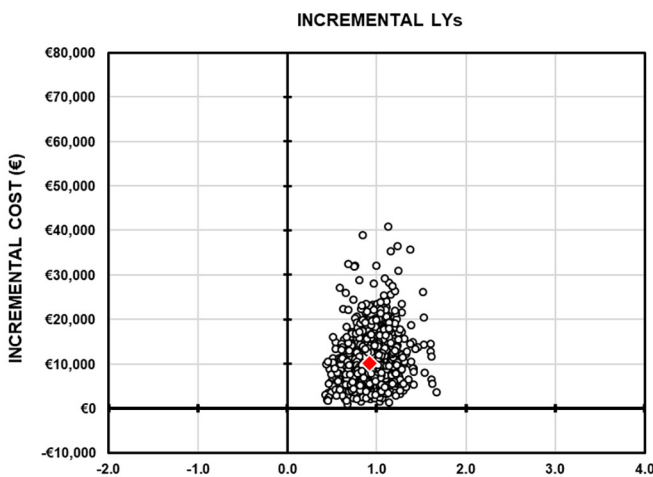**Fig. 3.** Scatter plots from the multi-way probabilistic sensitivity analyses for each comparison.

In our analysis, both the protective (i.e. Vt ≈ 6 mL/kg PBW to keep Pplat between 20 and 30 cm H_2O + $ECCO_2R$ if $PaCO_2$ > 55 mmHg) and the ultra-protective (i.e. Vt ≈ 3–4 mL/kg PBW to keep Pplat between 20 and 25 cm H_2O + $ECCO_2R$) ventilation strategies were defined on the basis of recent feasibility studies and experts consensus, and were not based on clinical evidence supporting their use. Admittedly, optimal ventilation strategies with $ECCO_2R$ are still a matter of intense research and the definition of such strategies should be cautiously treated.

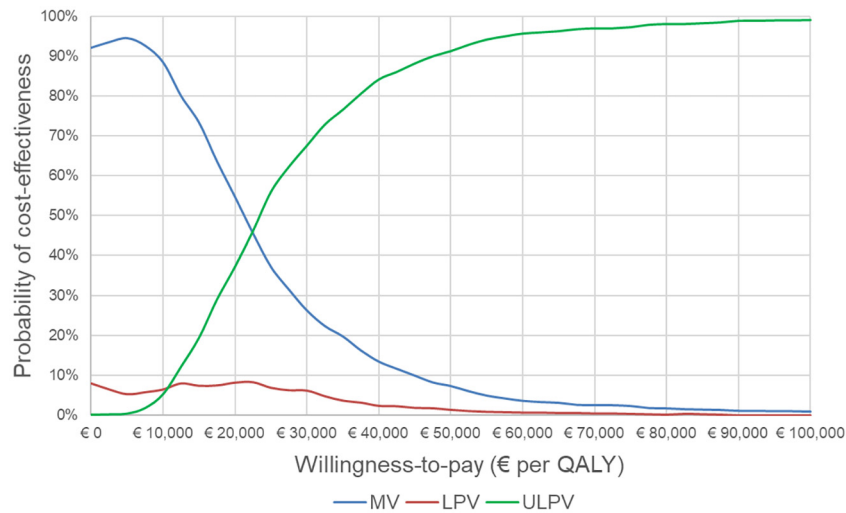**Fig. 4.** Cost-effectiveness acceptability curves comparing the MV, LPV and ULPV strategies.

To our knowledge, this study is the first that has intended to estimate the cost-effectiveness of both LPV and ULPV strategies. Our results add an economic perspective to the use of ECCO$_2$R and complement the results of clinical studies that have demonstrated both the feasibility and the clinical value of the use of ECCO$_2$R in the management of ARDS [15-19,21]. Cooke et al. also reported that LPV was a highly cost-effective ventilation strategy [37]. Based on a decision-analytic model, the authors showed that a hypothetical intervention aimed at improving LPV adherence at the ICU level would generate 0.62 additional QALYs (4.83 QALYs for LPV vs. 4.21 QALYs for non-LPV care) with an ICER of $11,690/QALY gained (expressed in $2008). Few other studies have assessed the cost-effectiveness of MV vs. non-MV but did not necessarily intend to document the cost-effectiveness of more recent and highly protective strategies as enabled by ECCO$_2$R [2,38].

Many parameters of our model were informed by sound evidence. The LUNG SAFE study, a large international study reporting a wealth of information from 2377 ARDS patients, was used to document baseline characteristics, MV ventilation settings and corresponding LoS and survival outcomes [1]. However, it should be kept in mind there are limitations regarding the use of the LUNG SAFE study to define the MV comparator in our analysis. In LUNG SAFE, plateau pressure was not monitored in 60% of ventilated ARDS and a sizeable proportion of patients had a plateau pressure above 30 cm H$_2$O. The risk is thus that our analysis may overestimate the effect size of the benefit associated to ECCO$_2$R.

We used the relationship between ΔP and risk of hospital mortality demonstrated by Amato et al. from 3562 ARDS patients enrolled in nine randomized trials [7]. Of interest, The LUNG SAFE investigators also noticed an inverse relationship between ΔP and the risk of hospital death. They reported for instance that patients with a ΔP greater than 14 cm H$_2$O on day 1 of ARDS had a higher risk of hospital mortality [1]. Moreover, the prediction of ΔP reduction as enabled by ECCO$_2$R using alveolar dead space fraction and respiratory system compliance may allow increased mortality benefit, and reduced sample size and screening size requirements to enrich future clinical trials of ECCO$_2$R for ULPV in ARDS [39,40].

Nonetheless, our approach hypothesized that very low Vt as enabled by ECCO$_2$R prospectively could achieve similar outcomes to that retrospectively observed in studies among ARDS patients with variable ΔP, including studies that did not employ ECCO$_2$R. While ΔP is an important predictor of death in ARDS, it remains uncertain whether ventilator strategies that attempt to minimize this parameter will achieve better outcomes than traditional MV. This should be kept in mind in the interpretation of our analysis to modern ventilation practice and further

emphasizes the need for interventional and observational studies with that regard.

We had difficulties to identify reliable and published sources for some of the cost estimates. In our analysis, protective ventilation followed the approach protocolized in the SUPERNOVA study [21]. As there are multiple ways to deliver ECCO$_2$R, we assumed low flow veno-venous ECCO$_2$R vascular access, as integrated on a continuous renal replacement therapy device. In this condition, we assumed that 2 ECCO$_2$R kits would be necessary, whose cost was hypothesized at €3000 per kit. It should be kept in mind that alternative ways of delivering ECCO$_2$R could lead to other cost estimate. We also did not account for the potential costs of clotting as well as manpower and training that might be needed for the implementation and supervision of ECCO$_2$R.

However, this limitation on cost estimates must be nuanced as we have used a rather conservative approach to compute ICU and hospital costs. By applying a fix cost per day spend in the ICU and the hospital, ARDS survivors who tend to have longer LoS as suggested by the LUNG SAFE study were attributed a greater overall cost in our analysis. Some studies conducted in various ICU patients' population have evidenced that this is not necessarily the case. Even if ICU survivors tend to have longer ICU LoS, their overall ICU cost could be lower [41]. This is at least partly explained by the fact that their cost per day in the ICU gradually declines during their stay [42-44].

Moreover, as a main limit of our analysis, we had to rely on relatively sparse evidence for what appeared as a key parameter of the model: the impact that ECCO$_2$R could have on the potential shortening of ventilation duration. We have used the results from the prospective randomized Xtravent-study suggesting that ARDS patients with a PaO$_2$/FiO$_2$ ratio below 150 mmHg and receiving ECCO$_2$R were 2.1 times more likely at Day 30 to be successfully weaned from ventilation as compared to controls [16] to inform this parameter. Though this study demonstrated an effect as a ratio of 2.1, we have conservatively used this value as the best-case assumption. In the absence of any other information, the lower or worst-case was set at 1.1 (nearly no effect) and the base case value at 1.6 (median point). Finally, this parameter did not emerge in the deterministic sensitivity analyses as so impactful on the ICERs, which remained below the €30,000 threshold in the worst case (Fig. 5). Therefore, cost-effectiveness of ECCO$_2$R was still granted even with very minimal effect on the shortening of ventilation duration.

This observation stresses the interest of modeling. First, to overcome the lack of direct information by combining multiple sources of data and assumptions. Second, to guide eventual future research. In effect, it should be kept in mind that our model is a preliminary approach

ICER LYs

Upper ■ Lower ■

€ 8,000   € 10,000   € 12,000   € 14,000   € 16,000

ECCO2R number of kits in moderate ARDS — € 9,305 ... € 14,148

LPV setting in moderate ARDS - Pplat (cm H2O) — € 10,200 ... € 14,094

RR of death as function of ΔP — € 10,432 ... € 13,668

ULPV setting in moderate ARDS - Pplat (cm H2O) — € 10,763 ... € 13,234

ECCO2R cost (per kit) — € 10,758 ... € 12,695

PaCO2 threshold for ECCO2R use with LPV in moderate ARDS (mm Hg) — € 10,735 ... € 12,356

Lifetime cost (per year) — € 11,004 ... € 12,449

ULPV setting in moderate ARDS - PEEP (cm H2O) — € 11,196 ... € 12,389

Discounting costs (%) — € 11,485 ... € 12,534

LPV setting in moderate ARDS - PEEP (cm H2O) — € 11,370 ... € 12,323

ICER QALYs

Upper ■ Lower ■

€ 15,000   € 20,000   € 25,000   € 30,000   € 35,000

ECCO2R number of kits in moderate ARDS — € 19,489 ... € 29,630

Discounting QALYs (%) — € 20,930 ... € 25,921

Health utility decrease vs. population norm (%) — € 22,476 ... € 27,068

LPV setting in moderate ARDS - Pplat (cm H2O) — € 22,716 ... € 27,024

ECCO2R cost (per kit) — € 22,531 ... € 26,588

PaCO2 threshold for ECCO2R use with LPV in moderate ARDS (mm Hg) — € 22,484 ... € 25,877

Lifetime cost (per year) — € 23,046 ... € 26,073

ULPV setting in moderate ARDS - Pplat (cm H2O) — € 23,337 ... € 26,312

RR of death as function of ΔP — € 23,470 ... € 25,953

Discounting costs (%) — € 24,054 ... € 26,251

Fig. 5. Tornado diagram from the one-way deterministic sensitivity analyses on the ICERs comparing ULPV vs. LPV strategies.

whose findings need to be completed as more data become available on ECCO$_2$R. We have identified the potential effect of adding ECCO$_2$R on the reduction of ventilation duration as a main source of uncertainty. It is thus advisable that the design of future interventional or observational studies pay attention to proper collection of ventilation duration data with or without ECCO$_2$R-enabled LPV or ULPV.

5. Conclusions

Our analysis suggests that ECCO$_2$R-enabled LPV and ULPV strategies might provide cost-effective survival benefit in moderate ARDS. Additional data from interventional and observational studies are needed to support this preliminary model-based analysis.

Declaration of Competing Interest

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