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ORIGINAL RESEARCH

Comparison between traditional and goal directed perfusion in cardiopulmonary by-pass. A differential cost analysis in US

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ABSTRACT

OBJECTIVES: High oxygen delivery (DO2) during cardiopulmonary bypass (CPB) is associated with better renal outcome in cardiac surgery. Traditional perfusion (TP) techniques, targeted on body surface area and CPB temperature, achieves high DO2 in about 50% of the cases while a goal directed perfusion (GDP) approach can lead to more than 90% of cases achieving high DO2 with a consequent reduction in Acute Kidney Injury (AKI) rate of about 40%. Aim of this study is to perform an economic evaluation of GDP strategy with respect to TP in US. METHODS: A Discrete Event Simulation model was developed to compare TP and GDP strategy in patients undergoing CPB. The patient's pathways from operation to discharging from hospital was simulated: AKI incidence, in-hospital mortality, hospital length of stay, transfusions were correlated to probability to achieve high DO2 target using published correlations. National perspective was adopted to calculate costs associated to each event while GDP strategy was exploited the introduction of Sorin Heartlink (HL) Card/GDP Card and Sorin Connect (electronic data management system). RESULTS: GDP strategy saved more than 3 days in hospital and 11% of AKI episodes. The cost-saving is $ 3,137 (95% CI: 1,122-4,951); the cost of HL Card/GDP Card+Connect ($ 180, 95% CI: 113-249) is more than offset by savings in hospital stay that result the main driver in cost ($ 3,222, 95% CI: 1,235-4,950). Deterministic sensitivity analysis shows that the total savings are mainly influenced by nadir haematocrit during CPB and hospital LOS/cost per day both in ICU and in ward. CONCLUSIONS: GDP seems to improve significantly the main outcomes related to CPB surgery, when compared to TP techniques. Additional costs due to perform GDP strategy have no impact on the total cost since completely offset by the savings in hospital cost.

Keywords

Cardiopulmonary bypass; Traditional perfusion; Goal directed perfusion

INTRODUCTION

Oxygen delivery (DO2) and carbon dioxide production (VCO2) during cardiopulmonary bypass (CPB) are associated with renal outcome in cardiac surgery [1,2]. Nadir DO2 below the threshold of 262-272 ml/min/m^2 and DO2/VCO2 ratio lower than 5.0 are linked to an increased incidence of acute kidney injury (AKI) after cardiac operations [1].

Data collected in [2] shows that 693 patients reached the DO2 target among 1,048 patients undergoing CPB with a traditional perfusion strategy. Such patients were divided in two groups according to HCT level; as anticipated by physiology (see Appendix A), results show that the probability to achieve the DO2 goal resulted higher among patients with HCT> 26% (640 of 753 patients) than in patients with HCT< 26% (53 of 293 patients).

Sorin HeartLink™ is the first and unique perfusion system automatically integrating perfusion data, patient parameters and product information to enable implementation of Goal Directed Perfusion (GDP) adapting adequacy of perfusion to the patient.

Hypothesis of the Goal dIrected perFusion Trial (GIFT) protocol is that a GDP approach can raise this percentage to more than 90% of cases, with a consequent reduction in the AKI rate of about 40% [3].

Aim of this project is to perform an economic evaluation of the consequences of GDP strategy in US, through the construction, validation, and analysis of an *ad hoc* simulation model based on estimation of goal-achievement rate (DO2 value over the threshold of 272 ml/min/m^2) with and without GDP and the correlations between main clinical out-

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comes (AKI incidence, in-hospital mortality, hospital length of stay, transfusions) and DO2 over the critical threshold. All possible patient pathways during the peri- and post-operative period were considered in order to estimate management of adverse events, hospital stay and related resource consumption costs.

METHODS

Model structure

A patient-level simulation model was developed incorporating baseline outcomes rates and comparative efficacy data from published literature, and US hospital cost data.

The model simulates two treatment alternatives for patients undergoing CPB: traditional perfusion (TP – targeted on BSA and CPB temperature) and goal-directed perfusion (GDP – specifically aimed at maintaining DO2 over the critical threshold). GDP is allowed by an integrated monitoring system (Sorin GDP™ Monitor) displaying DO2 and DO2/VCO2 values in a quasi-continuous mode: the perfusionist can immediately react to lowering DO2 by increasing pump flow, as a primary intervention.

The model was structured as a decision analytic Discrete Event Simulation (DES); in a DES changes in the individuals' state are modelled over time, in terms of events that occur and their consequences. This strategy is preferable to the Markov methodology in representing clinical conditions that are neither chronic nor characterized by recurrent events occurring at fixed time intervals, like in patients analysed here.

According to this technique, each iteration of the simulation represents a unique patient, who is sent simultaneously through both treatment arms of the model. The parameters of each iteration are drawn from their distributions, allowing representation of the individual variability in the outcomes of the simulated population. The simulation steps are qualitatively common for both treatment arms, which however differ in the probability of the events considered, and for the time-to-event distributions.

The patient's pathway (Table I) is detailed below.

During CPB:

- Each patient is characterized by sampling a nadir haematocrit (HCT) value; this is independent of the perfusion strategy considered.
- According to the HCT level (> or < 26%), patients reach DO2 target with a probability that depends on the perfusion strategy.
- According to transfusion protocol (depending on HCT level) patients can receive packed red cells (PRCs).
- Patients are at risk of renal adverse events:
  - AKI, with probabilities depending on DO2 level (target reached or not).
  - Renal failure needing RT (only for patients experiencing AKI) with probabilities that also depend on DO2 level (target reached or not).

Post CPB:

- During the post-operative period, patients can die with probability that depends on renal complications (AKI or not) and can receive PRCs.
- Post-operative length of stay (LOS) in ICU depends on DO2 level during CPB.
- LOS in ward (only for patients discharged alive from ICU) depends on DO2 level during CPB.

The hospital perspective was adopted when calculating costs associated to each state and to evaluate the differential economic impact of GDP vs TP. Only potentially differential costs were considered in the analyses so the total cost calculated in the simulation represents the sum of these cost items.

Half-cycle correction was applied to LOS in ICU and to number of PRCs post-CPB for patients dying in ICU.

Event	Depending on
During CPB surgery	
Reaching DO2 target	HCT, P*
PRCs transfused	HCT
Renal disease (AKI)	DO2
AKI needing of RT	DO2
In ICU (post-CPB)	
LOS	DO2
PRCs transfused	HCT
Death	AKI
In ward	
LOS	DO2

Table I. *Events evaluated during the simulation*
* perfusion strategy (traditional or GDP)
AKI = acute kidney injury; HCT= nadir haematocrit; LOS = length of stay; PRCs = packed red cells

Input parameters

Clinical parameters not depending on DO2 level

The lowest haematocrit during CPB was taken from a retrospective analysis on data from 5,000 consecutive cardiac operations with CPB performed on adults (1994 to 2000) [4]. For each modelled patient, a nadir

Parameters	Values		Sources
Nadir HCT on CPB (%) [mean (SD)]	21.4 (4.2)		[4]
Probability to achieve DO2 goal (%)	**High HCT**	**Low HCT**	
With TP	85	18	[2]
With GDP	100	90	Elaborated from [3]
	With AKI	**w/o AKI**	
Operative mortality (%)	11.9	1.2	Elaborated from [5], see Table IA in Appendix B
Transfusion protocol	**During CPB**	**Post CPB (in ICU)**	
PRC units [mean (SD)]	1.7 (2.0)	1.1 (1.4)	Elaborated from [1]*, [6]
Transfusion rate (%)			[3]
• HCT< 19%	100	100	Mandatory
• HCT< 24%	50	50	PRC allowed
• HCT< 30%	0	25	Admitted based on physician's judgment only during CPB
• Other	0	0	PRC prohibited

Table II. *Clinical input values not depending on DO2 level, directly*
*Gamma distribution was fitted on median (1) and interquartile range (2) of PRCs to estimate mean and SD used in the model

HCT value was sampled from a gamma distribution fitted on mean and SD reported in the article (Table II).
Probability to achieve the DO2 target with traditional perfusion was elaborated from [2] as explained in the Introduction while for the GDP strategy we supposed the 100% of success for patients with nadir HCT> 26% during CPB and 90% otherwise (Table II).
The relationship between AKI incidence and post-operative mortality was investigated, using logistic regression modelling, in a multicentre cohort study on 3,500 adult patients undergoing cardiac surgery at 7 hospitals during 2004 [5]. Three thresholds of AKI were selected to evaluate mortality rates: > 25%, > 50%, and > 75% decrease in estimated glomerular filtration rate (eGFR) within 1 week of surgery. Since in this study eGFR was estimated using the Cockcroft-Gault formula, an eGFR decrease greater than 33% coincides with the definition of AKI in the GIFT protocol (i.e. > 50% increase in serum creatinine, see Appendix B for calculation details). Assuming that patients with eGFR decrease 25-50% were uniformly distributed (i.e. one third between 25-33% and 2 thirds between 33-50%), post-operative mortality results in 11.9% and 1.2% for patients experiencing and not experiencing AKI, respectively (Tabel II).
During CPB, according to current practice and the GIFT protocol, transfusions are mandatory below a HCT of 18% and generally prohibited for an HCT > 21%. However, based on the individual judgment that the patient is actually in need for packed red cells, transfusions are allowed between an HCT of 22% and 24%. Transfusions are always prohibited for an HCT > 24%. After CPB, transfusions are mandatory if HCT < 18%, allowed for HCT between 19% and 23% and generally prohibited otherwise. However for HCT between 24% and 30%, transfusions are admitted based on physician's judgment. In order to simulate this uncertainty in the model, we chose a probability of 50% to be transfused for allowed transfusions and 25% for transfusions admitted based on physician's judgment.
Numbers of PRCs transfused during CPB and after CPB (in ICU) were sampled from gamma distributions fitted on mean and SD reported in [1] and [6], respectively (Table II).

Clinical input parameters depending on DO2 level

A retrospective analysis of data prospectively collected at two different institutions [1] shows that hospital and ICU length of stay (LOS) and renal disease (AKI) are correlated with the DO2 level during CPB (Table III). Length of stay in ward was calculated starting from hospital and ICU LOS according to mortality and AKI rate; in fact the mean value of this outcome is not the difference between mean time spent in hospital and in ICU, since some patients die in ICU (and mortality depends on experiencing or not renal disease).
Risk of renal disease in patients with low DO2 during CPB results more than double

Parameters	High DO2	Low DO2	Source
Length of stay (days) [mean(SD)]			
Total in hospital	12.4 (12.1)	17.6 (14.1)	[1]
• in ICU	2.5 (4.4)	4.2 (8.7)	[1]
• in ward	10.2 (11.4)	13.9 (11.2)	Elaborated from hospital/ICU LOS according to mortality and AKI rate (see Appendix C)
Renal disease – AKI (%)	12.1	29.8	Reported in [3], elaborated from [1]
• of which needing RT	9.9	18.8	RT rate reported in [2] rescaled to total AKI rate

Table III. *Clinical input values depending on DO2 level*

the risk in patients reaching the target [1,3]. The need for replacement therapy among patients experiencing AKI, elaborated from [2], results about 10% in patients reaching the DO2 target, while it is almost 20% in patients not reaching the target. Altogether, this implies the hypothesis that low DO2 is associated with more frequent and also more severe renal injury.

Costs were elaborated in a previous analysis on patients undergoing aortic valve replacement (AVR) [7]. All of the data are the national average costs for Medicare discharges associated with ICD-9-CM procedure code 35.22 for fiscal year (FY) 2013 and does not include Medicare Advantage health maintenance organizations (HMO) utilization. The national costs were calculated using the national average cost-to-charge ratios for 19 departments published by Medicare in the 2015. Statistical outliers were removed at the DRG level. Average length of stay overall and broken out by routine and ICU beds is included.

The cost for a hospital stay was made up of the cost of the ICU in which the patient spends the days immediately after the surgical procedure plus the cost of the standard ward which hosts the patient after the critical post-operative phase has been completed. The cost of hospital haemodialysis treatment was included as a complication cost for patients that developed renal failure. It was defined as the additional charges/day for continuous replacement therapy (CRT) in the ICU to avoid double counting in ICU costs. An official blood bag tariff was taken as a proxy of the real cost for the collection, transportation and storage of patient blood. Unit cost summarized in Table IV, (they were not updated since calculated using tariffs).

Cost items	Unit cost
Renal replacement therapy ($/day)	978.10
ICU ($/day)	1,303.45
Ward ($/day)	779.98
PRC unit transfused ($)	295.94

Table IV. *Unit costs used in the model*

The cost of GDP strategy was calculated considering the introduction of Sorin Heartlink (HL) Card/GDP Card and Sorin Connect (electronic data management system); for every cost the worst case (i.e. higher possible price) was considered: cost of the card was $ 150.00 for US and cost of Connect per patient, calculated dividing the total hospital cost for GDP Monitors (assuming three systems per hospital) by the number of cases per HL Card/GDP Card and the Connect lifetime (10 years), results in $ 29.87.

Simulation technique

Base-case

The simulation technique used for the calculation of base-case results is a so-called micro-simulation or patient-level simulation. According to this technique, each iteration of the simulation represents a unique patient, which runs through both arms of the model (TP and GDP strategies). The parameters of each iteration are drawn from their distributions, allowing the representation of the individual variability in the outcomes of the simulated population. Patient-level parameters and their distributions are presented in Appendix D.

Probabilistic sensitivity analysis

While the micro-simulation takes into account the variability in the population, the probabilistic sensitivity analysis (PSA) allows considering the uncertainty on key parameters and its effect on the estimated outcomes. This is obtained by a two level Monte Carlo simulation: the inner loop (1,000 iterations) is the patient-level simulation, which is averaged and repeated 1,000 times (outer loop) to perform PSA on key model parameters. In the absence of reliable data on their uncertainty, we set a standard deviation of 20% of their mean value, and attributed adequate distributions according to the type of

data (i.e. gamma distributions for costs data and beta distributions for probabilities). For each cost item, the mean value (depending on the selected country) was multiplied by a gamma distributed factor with mean 1 and SD equal to 20%. The parameters on which the PSA is conducted and their distributions are presented in Appendix C.

Deterministic sensitivity analysis

A deterministic (one-way) sensitivity analysis (DSA) was performed in order to test the sensitivity of result to variations of base-case estimates. A variation of ±20% was considered for each parameter except nadir HCT during CPB that varies between -10% (to avoid unrealistic lower HCT values) and +35% (to take into account higher HCT values reported in recent surgical series) and probability to achieve the DO2 goal (±5%) to avoid probabilities higher than 100%.

Further analyses

Since the nadir HCT and the DO2 level are the center point of the simulation we studied the cost difference (GDP vs. TP strategy) in the worst case for GDP efficacy (+35% in the distribution of nadir HCT) for different values of the probability to achieve the DO2 target with GDP for patients with HCT < 26% (such probability was varied between 20% and 90%).

RESULTS

Outcomes and costs resulting from 10,000 simulated patients are shown in Table V and Table VI as mean and 95% confidence interval (calculated from PSA).

In the GDP strategy more than 90% of patients reach the DO2 target while in TP strategy less than 30%. Renal disease incidence is lower with respect to traditional perfusion both in terms of AKI episodes (11% AKI episodes saved) and need for RRT (2.5% dialysis procedures saved). Reduction in operative mortality (3.6 with TP vs 2.5% with GDP) causes the small increment in PRCs transfused (post CPB) with GDP strategy; this is due to the so called paradox effect: there are more patients alive in ICU which can be transfused. On average, GDP strategy saves more than 3 days in hospital, of which about 1 ICU day.

Total cost with TP results in about $ 15,300 while GDP reduces the total cost by more than $ 3,000. For both strategies the main driver is the hospital cost, of which almost one third is due to ICU stay. Furthermore, the cost of GDP strategy (Sorin GDP™ Monitor and Sorin Connect™) is completely offset by the saving in hospital stay (more than $ 3,000).

Main outcomes reduction, hospital and total savings result statistically significant since the 95% confidence intervals do not cross the zero boundary. Choosing hospital stay reduc-

Outcome [Mean (95% CI)]	TP strategy	GDP strategy	Delta (GDP vs. TP)
DO2 target achieved (%)	26.9 (19.6-35.4)	91.4 (64.8-100.0)	-64.4 (-93.2--36.4)
Hospital stay (days)	16.15 (15.05-17.05)	12.77 (11.22-14.36)	3.38 (1.53-4.99)
• ICU stay (days)	3.63 (3.16-4.16)	2.52 (2.06-3.14)	1.11 (0.40-1.72)
AKI episode (%)	24.5 (15.7-34.5)	13.6 (6.5-20.7)	10.9 (1.3-21.8)
• Need for RRT (%)	4.2 (1.8-7.1)	1.7 (0.0-3.1)	2.5 (0.2-5.7)
Operative mortality (%)	3.6 (1.8-5.9)	2.5 (1.1-4.1)	1.1 (-0.2-2.7)
PRC transfused (n.)	2.48 (2.0-2.92)	2.49 (2.0-2.93)	0.01 (0.00-0.01)

Table V. *Comparison between traditional and goal directed perfusion: mean results from base case (10,000 simulated patients) while the 95% CI is calculated from PSA (1,000 x 1,000 simulation)*

	Costs ($) [Mean (95% CI)]		
	TP strategy	GDP strategy	Savings (GDP vs TP)
Hospital stay	14,499 (10,098-18,755)	11,276 (7,607-15,060)	3,222 (1,235-4,950)
• ICU stay	4,737 (2,773-6,772)	3,285 (1,846-4,939)	1,452 (357-2,403)
Renal complication	134 (1-340)	37 (-28-114)	97 (-39-294)
Transfusion	734 (441-1,021)	737 (443-1,025)	-3 (-7-1)
GDP monitor*	NA	180 (113-249)	-180 (-249--113)
Total cost	**15,367 (10,985-19,670)**	**12,230 (8,528-16,055)**	**3,137 (1,122-4,951)**

Table VI. *Resulting cost for traditional and goal directed perfusion: mean results from base case (10,000 simulated patients) while the 95% CI is calculated from PSA (1,000 x 1,000 simulation)*
*HL Card/GDP Card+Connect

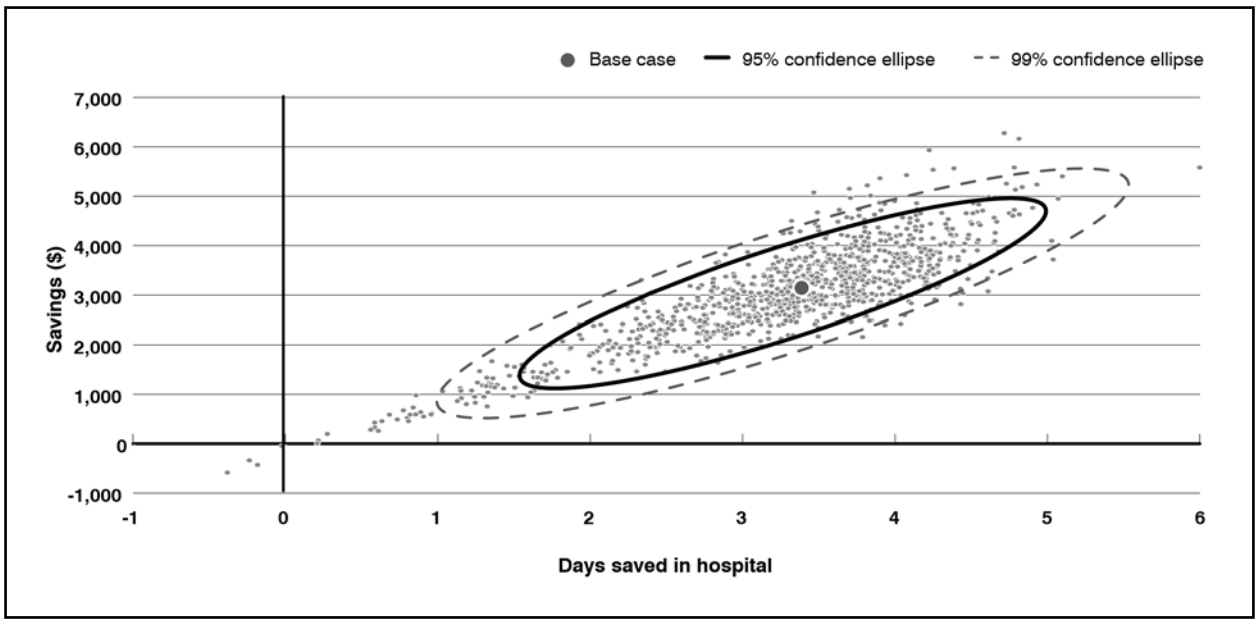

Figure 1. *Cost-effectiveness plane (GDP vs. TP strategy): red point represent base case simulation result while light blue points are the 1,000 simulation in the PSA; continuous and dashed lines represent 95% and 99% confidence ellipses, respectively*

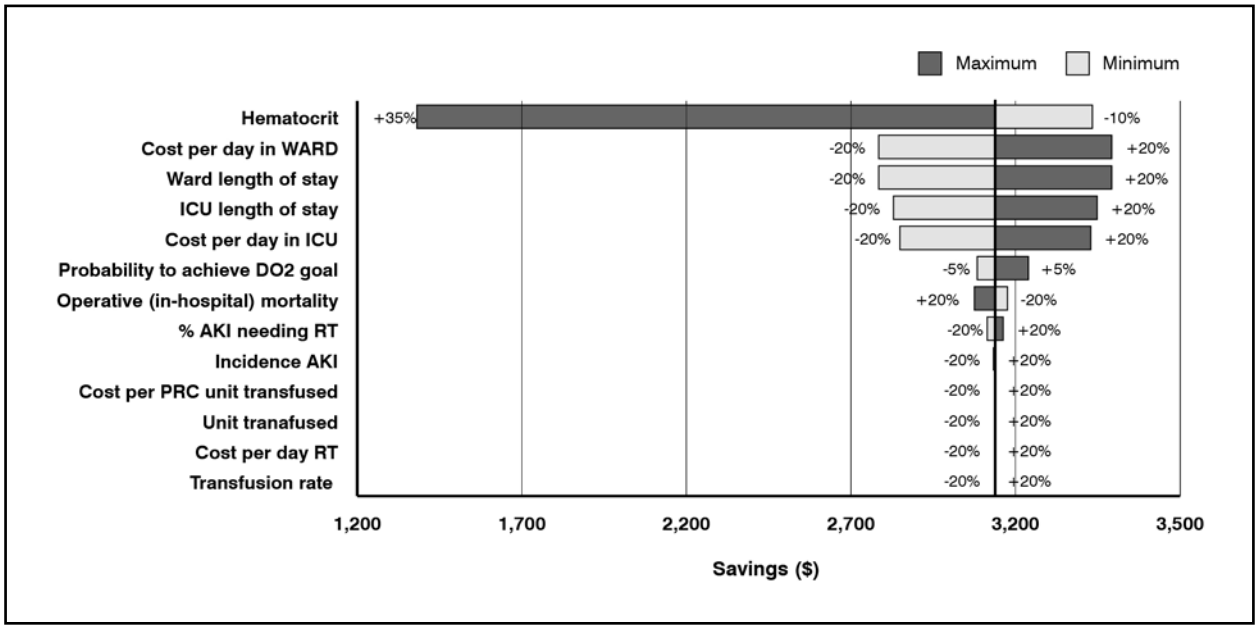

Figure 2. *Deterministic sensitivity analysis – tornado diagram for saving in US (GDP vs. TP strategy)*

tion as effectiveness measure, GDP strategy results cost-effectiveness in more than 95% of cases (Figure 1). In particular both 95% and 99% confidence ellipses lie in the first quadrant of the cost-effectiveness plane (less hospital stay and more cost savings), completely.

Total saving is mostly influenced by nadir haematocrit and, to a lesser extent, by hospital length of stay and hospital cost per day, both in ICU and ward (Figure 2). In particular DSA results show that GDP is more cost-saving for patients with lower nadir HCT, for longer hospital stays and in structures with higher hospital costs.

Analysis on the probability to achieve the DO2 target shows that GDP strategy remains cost-saving also with worse hypothesis of GDP efficacy in a population with higher nadir HCT values (Figure 3). In the worst case, with a 20% probability of success of GDP strategy, a saving of almost $ 400 per case is still possible.

DISCUSSION

Innovation in the delivery of modern healthcare is challenging and profitable; a win-win situation where efficient outcomes are encountered, is valuable and infrequent.

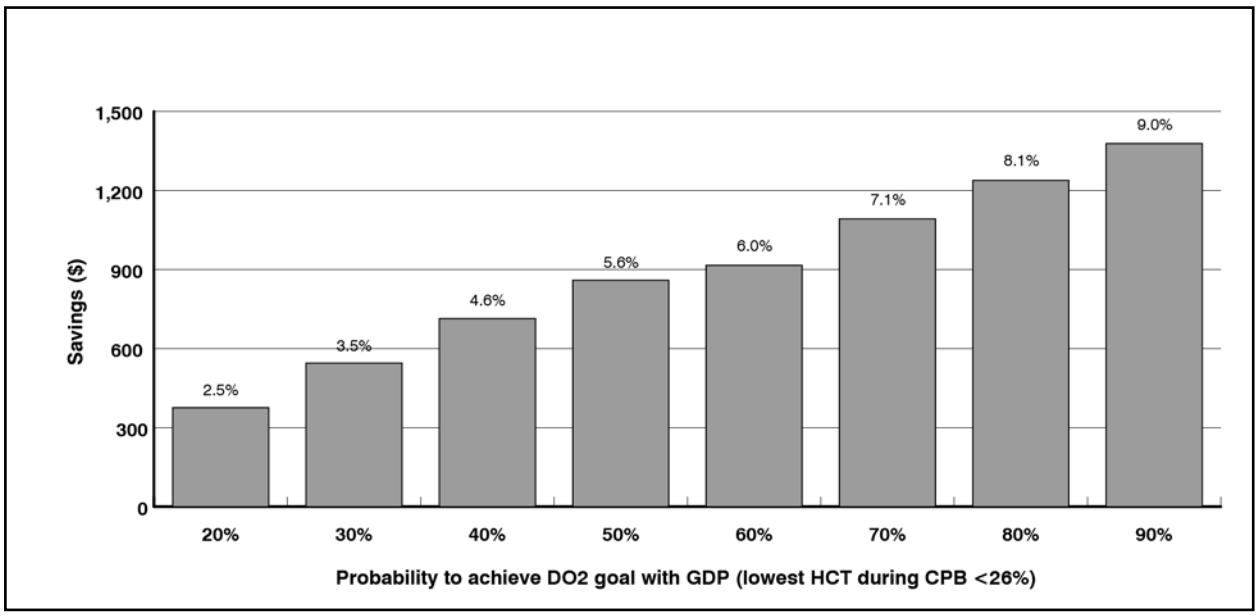

Figure 3. *Savings with respect to different hypothesis of GDP efficacy to achieve DO2 target during CPB in low HCT patients in the worst case for GDP efficacy (+35% for nadir HCT distribution). Light red bar represents saving with GDP base case efficacy*

Just by delivering the right information at the right time during surgery, directing perfusion decisions, undesirable and costly clinical outcomes could be avoided. Assuming that with GDP, compared to TP, the probability to achieve DO2 goal would dramatically increase, on average $ 3,137 per patient (95% CI: 1,122-4,951) could be saved. On average 3.38 ward days (95% CI: 1.53-4.99) and 1.11 ICU days (95% CI: 0.40-1.72) would be avoided per patient. Hence, the intuitive cost driver, intervention cost, was offset mainly by the avoided costs of hospital stay. Reducing the incidence of AKI episodes, and then the need for RRT, also impacted the encountered savings but to a much lesser extent.

Presented sensitivity analysis confirms the cost-effectiveness of GDP. In the DSA, when input parameters were varied to a minimum and a maximum value, the total savings per patient remained in favour of GDP. This savings was more sensitive by the HCT values as the expected gain is expected to be more with those lower HCT values. Then, ward and ICU stays/costs also impacted the amount of savings. All other input clinical parameters like probability of achieving DO2 targets or hospital mortality do not seem to impact the economic outcomes. Similiarly, assumed cost drivers related to AKI or PRC unit perfusion have ignorable impact. Furthermore, in order to invistigate the relationship between the probability of achieving DO2 goal with GDP when HCT distribution is assumed to be 35% above the base case value: the expected benefit is lower ($ 1,378), we varied this probability from 90% to as low as 20% and the cost savings was still realizable.

In summary, savings on the microlevel, patient level or operating theater level, or macrolevel (regional or national) could be considerable.

Estimated results seem comparable with previous economic analyses. A recent study [8], analyzing 953 patients with diabetes mellitus and multivessel coronary artery disease undergoing CABG with standard techniques, estimates a total cost of about $ 19,500 (excluding precedural costs and physician fees not considered in this analysis); value calculated in [8] is higher since it includes also ancillary services. In a less recent paper [9], the direct costs for 4698 patients undergoing CABG at 5 US hospital amount to $ 12,800; a lower results may be due to a shorter hospital LOS (8.7 days). Other two studies reported a mean cost (excluding physician fees) of $ 15,713 [10] and $ 20,574 [11] (2000 US dollars).

CONCLUSION

Few interventions have positive impact on clinical outcomes and costs. This economic forecast suggests that even when the probability of achieving DO2 goal with GDP is challenged below plausible values, GDP remains a cost-effective strategy. Thus, early uptake of such innovative intervention is endorsed until such benefits are empirically quantified and cost savings are realized. Furhtermore, saving is mostly influenced by hospital LOS, cost per day both in ICU and in ward, and nadir HCT during CPB and additional costs due to perform GDP strategy have no impact on the total cost since completely offset by the savings in hospital cost.

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APPENDIX A

The DO2 formula

DO2 is the amount of oxygen delivered to the whole body from the lungs/oxygenators. It is defined by the formula

$$DO2 = 10 \times Qb \times \left(1.36 \times \frac{HCT}{2.94} \times S_aO_2 + 0.003 \times p_aO_2\right)$$

where Qb is the total blood flow or cardiac output, HCT is the haematocrit level, is the arterial saturation, is the arterial tension and 0.003 is the solubility coefficient of oxygen in human plasma.

APPENDIX B

Relation between serum creatinine and eGFR

In the GIFT protocol, AKI is defined according to AKIN criteria [12] as:

$$\text{EQ 1} \qquad Sc_{PO} > 1.5\ Sc_B$$

where Sc_{PO} is the post-operative serum creatinine and Sc_B is the value at baseline. In [5] AKI is defined as a decrease greater than 50% in eGFR within one week of surgery, that is:

$$\text{EQ 2} \quad \frac{eGFR(B) - eGFR(PO)}{eGFR(B)} > 50\%$$

where eGFR is calculated at baseline (B) and post CPB (PO). We find the relation between definitions (EQ 1) and (EQ 2); since eGFR in [5] is estimated using the Cockcroft-Gault formula [13] we have:

$$\text{EQ 3} \quad eGFR = \frac{(140\text{-Age}) \times W}{72 \times Sc} \times (0.85 \text{ if female})$$

where Sc is the serum creatinine valued expressed in mg/dl, the age is measured in years and W is the real weight if BMI is normal (between 18.5 and 25) otherwise is calculated as the ideal BMI (18.5 if BMI < 18.5 and 25 if BMI > 25) multiplied by the square of height.
For each patient, we can consider age and weight constant since the observational time is about a week, than (EQ 3) is simply:

$$\text{EQ 4} \quad eGFR = \frac{A}{Sc}$$

where the constant A contains all information on age, weight and sex.
Using definition (EQ 4), we can re-write (EQ 2) for a general reduction β:

$$Sc_{PO} > \frac{Sc_B}{1 - \beta}$$

$$\frac{Sc_{PO} - Sc_B}{Sc_{PO}} > \beta$$

$$Sc_{PO} - Sc_B > \beta\, Sc_{PO}$$

$$\frac{A/Sc_B - A/Sc_{PO}}{A/Sc_B} > \beta$$

If we want , we have to fix β=33%.
Using this threshold we can calculate mortality rate for patient experiencing and not experiencing AKI from analysis reported in [5].

Decrease in eGFR (%)	Deaths (n.)	Patients (n.)	AKI episode	Mortality rate (%)
< 25%	25	2631	NO	1.2
25-50%	25	601		
25-33%	8	200	YES	11.9
33-50%	17	401		
50-75%	12	109		
> 75%	46	119		

Table IA. *Elaboration of post-operative mortality based on [5]*

APPENDIX C

Calculation of the length of stay distribution in ward (post ICU)

For each simulated patient, the total time spent in hospital is defined as the sum of LOS in ICU and LOS in ward (if patient was discharged alive from ICU). Furthermore, according to our model, mortality in ICU depends on experiencing an AKI episode. Figure 1A shows the decisional tree for calculation of hospital LOS, the structure is the same both for patient achieving and not achieving the DO2 target.

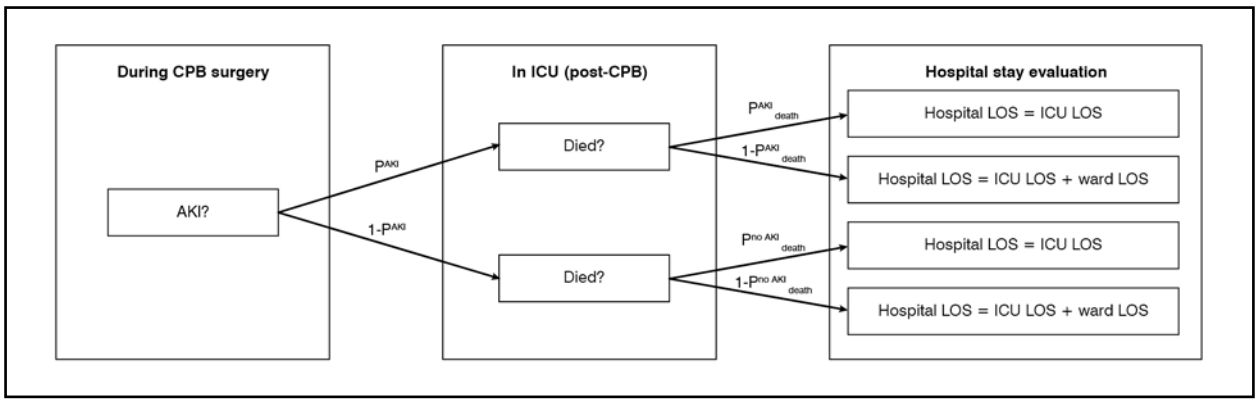

Figure 1A. *Decisional tree for calculation of hospital length of stay*

The distribution of LOS in ward was calculated using bootstrap method:

- 10,000 patients were simulated (both with DO2 target achieved and not achieved) sampling AKI rate, mortality and LOS in ICU from distributions fitted on data reported in Table I and Table II.
- Time spent in ward was sampled from a gamma distribution with parameters α and β unknown.
- α and β was calculated imposing that the resulting hospital LOS distribution was a gamma distribution fitted on mean and SD reported in Table II.

APPENDIX D

Parameter distributions

	Mean	SD	α	λ*	Distribution
Haematocrit	21.4	4.2	20.19	74.16	Beta
ICU length of stay					
High DO2	2.5	4.4	0.32	7.74	Gamma
Low DO2	4.2	8.7	0.23	18.02	Gamma
Ward length of stay					
High DO2	10.39	11.45	0.82	12.63	Gamma
Low DO2	14.60	11.01	1.76	8.30	Gamma
Unit transfused					
During CPB	1.7	2.0	0.72	2.35	Gamma
Post CPB	1.1	1.4	0.60	1.80	Gamma

Table IIA. *Parameters and distribution sampled in the base case simulation (patients-level parameters)*
*For beta distribution, the second parameters is usually named β

Prob. to achieve DO2 goa	Mean	SD	α	β	Mean	SD	α	β	Distribution
	TP strategy				GDP strategy				
HCT> 26%	85	17	2.90	0.51					beta
HCT< 26%	18	3.6	20.32	92.57	90	18	1.60	0.18	beta
	High DO2				Low DO2				
Incidence AKI (%)	12.1	2.42	21.85	158.76	29.8	5.96	17.25	40.64	beta
% AKI needing RT	9.9	1.98	22.43	204.10	18.8	3.76	20.11	86.87	beta
Transfusion rate (%)	During CPB				Post CPB				
HCT< 24%	50	10	12.00	12.00	50	10	12.00	12.00	beta
HCT< 30%					25	5	18.50	55.50	beta
	With AKI				w/o AKI				
Operative mortality (%)	25.4	5.08	18.39	53.89	1.5	0.31	24.60	1,565	beta

Table IIIA. *Parameters and distribution sampled in the PSA (outer loop parameters)*