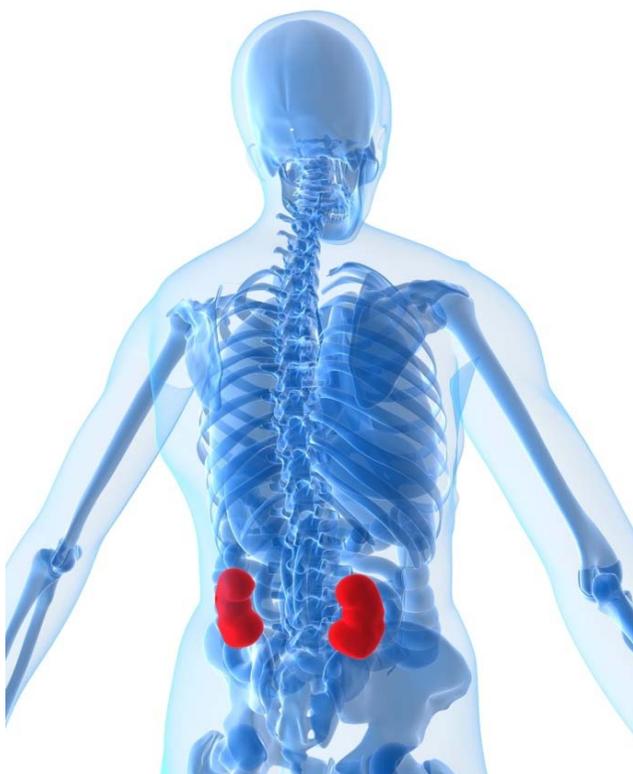


MACHINE PERFUSION IN KIDNEYS FROM DECEASED DONORS – A RAPID ASSESSMENT



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LORENA SAN MIGUEL, DOMINIQUE ROBERFROID, SABINE STORDEUR, NATHALIE SWARTENBROEKX



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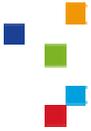


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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
CI	Confidence Interval
CI _s	Cold ischemia
CS	Cold Storage
DBD	Donation after Brain Death
DCD	Donation after Cardiac Death
DGF	Delayed Graft Function
ECD	Expanded Criteria Donor
EMPT	European Machine Perfusion Trial
ESRD	End Stage Renal Disease
HR	Hazard Ratio
HTA	Health Technology Assessment
HTK	Histidine-tryptophan-ketoglutarate
ICER	Incremental Cost Effectiveness Ratio
LOS	Length of Stay
LYS	Life Years Saved
MA	Meta Analysis
MP	Machine Perfusion
NICE	National Institute for Health and Clinical Excellence
OPTN	Organ Procurement and Transplantation Network
PNF	Primary Non Function
PPART	Pulsatile Perfusion in Asystolic Donor Renal Transplantation
QALYs	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Clinical Trial
RR	Risk Ratio
RRT	Renal Replacement Therapy
SCD	Standard Criteria Donors
SCS	Static Cold Storage



■ SCIENTIFIC REPORT

1 BACKGROUND

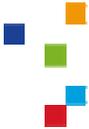
1.1 Scope of the study

End stage renal disease (ESRD) is a severe condition in which kidneys can no longer function properly.¹ Diabetes and hypertension are amongst the main causes of this disease, and prevalence rates are increasing steadily. ESRD patients require active renal replacement therapy (RRT) which consists in either dialysis, in its different forms, or transplantation.

Despite the fact that transplantation represents the best treatment option for most patients, the scarcity of kidney donors remains a challenge and waiting lists in most EU countries continue to grow. In Belgium in 2012, 67.9% (537/791) of patients eligible for a kidney transplant were effectively grafted.² Furthermore, all patients on the waiting list face a possible risk of death. In Belgium, death on the waiting list for kidney transplantation reached 3.6 % in 2012 and was higher in former years (www.eurotransplant.org).

The main population of kidney donors has traditionally been relatively young (often aged below 50), brain death donors (DBD) still heart beating. However, the volume of this donor population has remained stable or even decreased in the last years, (see Table 4) due to better prevention and management of cerebrovascular events and less traffic accidents. As a consequence, three alternative donor populations are being used to better respond to the increasing need for transplantable kidneys. These include living donors but also two types of deceased donors often referred to as “marginal donors”:

1. Expanded criteria donors (ECD). These are defined by the United Network for Organ Sharing (UNOS) as donors aged 60 years or older, or between 50 and 59 years with at least two of the following conditions: hypertension history, serum creatinine > 1.5 mg/dl or death from cerebrovascular accident. In Belgium in 2012, 23% of renal transplants were performed with organs from donors aged 65 or over.³



2. Circulatory death donors (DCD), also called non-heart beating donors (NHBD). The Maastricht classification includes 4 categories of DCDs (see Table 1). In Belgium kidneys transplants from category II, III and IV are authorized⁴ and, according to Eurotransplant, the use of this type of donation has grown by 59%, from 58 in 2010 to 92 in 2012, accounting now for almost 20% of all deceased donor transplants.²

Table 1 – Maastricht Classification – Donation after Cardiocirculatory Death (DCD)

Category	Definition
Category I	Dead on arrival
Category II	Unsuccessful resuscitation
Category III	Cardiac arrest awaited after withdrawal of life support in patients who are not brain dead
Category IV	Cardiac arrest after brain-stem death

Source: Kootstra et al.⁵

Despite their potential to expand the current pool of kidneys, or at least maintain it under the current sub-optimal epidemiological conditions, these types of deceased donors are considered as “risky” because they present more frequent clinical complications^{6,7} such as:

- delayed graft function (DGF): most often defined as a need for at least one dialysis during the first week post-transplant,
- primary non-function (PNF): the graft never works after implantation, resulting in either a return to dialysis or a need for a re-transplant.

The use of machine perfusion (MP) instead of the most commonly used cold storage (CS) for the preservation of kidneys prior to transplantation represents a hopeful alternative, with further developments expected in the near future, which could help to improve clinical outcomes by reducing complications such as DGF or PNF or increasing graft survival. The utilization of MP, not reimbursed by INAMI/RIZIV to this date, varies widely among transplant centres in Belgium (see chapter 5).

1.2 Objective of this study

The objective of this report is to assess the efficacy and cost-effectiveness of MP versus CS for the preservation of transplantable kidneys from various donor types (DBD, ECD, DCD), in order to formulate recommendations for Belgium. This question was submitted to the KCE by the Ministry of Health.

1.3 The Belgian context

The number of patients suffering from ESRD is highly prevalent in Belgium when compared to other EU countries.⁸

Data on incidence and prevalence of ESRD in Belgium have been taken (unless otherwise stated) from the latest report published in common by the two Belgian societies of nephrologists; the Dutch speaking Nephrology Association (NBVN^a) and the French speaking Nephrologists Association (GNFB^b). The report refers to data from the period 2003 to 2009⁹ during which the number of patients requiring Renal Replacement Therapy (RRT) grew at a mean annual rate of approximately 5%, from 9 483 patients in 2003 to 12 424 patients in 2009 (Table 2 – Epidemiology of patients on RRT in Belgium 2003-2009). The overall incidence grew by 22% over the same time period, at a mean annual growth of 4%.

^a <http://www.nbvn.be>

^b <http://www.gnfb.be>

**Table 2 – Epidemiology of patients on RRT in Belgium 2003-2009**

	2003	2004	2005	2006	2007	2008	2009
Prevalence	9 483	10 013	10 468	11 007	11 462	11 920	12 424
Prevalence (pmp)	916	963	1 002	1 047	1 083	1 118	1 155
Incidence	1 751	1 915	1 891	2 008	2 002	2 033	2 128
Incidence (pmp)	169	184	181	191	189	191	198

pmp: per million population

An ageing population and more prevalent diabetes and hypertension are important contributing factors to this growth.

1.4 Renal Replacement Therapy

At present, there are only two alternative forms of RRT: dialysis (haemodialysis or peritoneal dialysis) and transplantation. The latter is globally recognized as the best treatment response to ESRD, yielding better efficacy rates, improved QoL and lower costs when compared to dialysis.¹⁰⁻¹³ According to the most recent common report by NBVN-GNFB⁹ around 42% of patients on RRT in Belgium received a transplant in 2009 against 58% of patients who were on dialysis (of which 65% received centre-based haemodialysis, 25% satellite haemodialysis and 10% peritoneal dialysis).

1.4.1 Transplantation

In Belgium, renal transplantation is regulated by the law of June 13rd, 1986^c, corresponding to an “opting-out” system by which individuals are considered to be potential donors unless they explicitly express opposition over their lifetime.

There are currently seven Belgian renal transplant centres^d, all collaborating with Eurotransplant. The Eurotransplant International Foundation is responsible for the mediation and allocation of organ donation procedures in Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia. Eurotransplant has an allocation system of kidneys based on five factors: HLA matching, frequency of HLA type, waiting time, geographical distance between place of kidney removal and transplantation and balance between the number of kidneys offered and received at the national level. Organs can also be allocated on the basis of medical urgency.

^c Law of 13 June 1986 on the donation and transplantation of organs. B.S./M.B 14/02/1987, operational since 24/02/1987

^d Universitair Ziekenhuis Antwerpen,
Academisch Ziekenhuis der Vrije Universiteit
Hôpital Erasme, Bruxelles
Universitair Ziekenhuis, Gent
Cliniques Universitaires St. Luc, Bruxelles
Centre Hospitalier Universitaire, Liège
Universitair Ziekenhuis Gasthuisberg, Leuven.



The Belgian waiting list for a kidney transplant peaked in 2010, with over 900 patients listed and decreased substantially thereafter (see Table 3). Still, the challenge is likely to remain an important one in the future, particularly as the general population ages, making chronic conditions, such as ESRD more prevalent.

In 2012, the median waiting time between first dialysis and kidney transplantation was 49 months in the area covered by Eurotransplant, with 529 patients dying while waiting for a transplant (29 in Belgium).

Table 3 – Active Kidney transplant (tx.) waiting list 2007-2012.

	2007		2008		2009		2010		2011		2012	
	Active kidney tx. list	Deaths while on waiting list	Active kidney tx. list	Deaths while on waiting list	Active kidney tx. list	Deaths while on waiting list	Active kidney tx. list	Deaths while on waiting list	Active kidney tx. list	Deaths while on waiting list	Active kidney tx. list	Deaths while on waiting list
Belgium	840	NA	813	18	886	27	914	34	883	34	791	29
France	6 490	153	6 881	220	7 594	212	8 459	224	9 064	223	9 835	211
Germany	8 207	NA	8 003	267	8 014	319	7 869	374	7 873	370	7 919	373
Netherlands	937	NA	952	77	926	88	892	92	883	89	855	93
Spain	4 291	NA	4 301	NA	4 552	NA	4 434	NA	4 524	NA	4 293	NA
UK*	6 480	264	6 980	300	7 190	259	7 183	327	6 871	288	6 633	303

Source: BE, DE and NL: Eurotransplant annual reports 2007-2012 (www.eurotransplant.org); FR: Greffe renale - 2007-2011 - Agence de la Biomedecine (www.agence-biomedecine.fr); ES: Memoria Actividad Organizacion Nacional de trasplantes 2007-2012 (www.ont.es); UK: Organ donation and transplantation activity reports - NHS Blood and Transplant (www.organdonation.nhs.uk)

*Data at 31st of March of the relevant year

In Belgium, in 2012 there were, according to Eurotransplant, 43 kidney transplants with organs from deceased donors per million population (pmp). Comparing these figures to those of other European neighbouring countries it can be seen that Belgium ranks second in number of transplants done with organs from deceased donors, coming after Spain and before France, with the remaining countries analysed (*i.e.* Germany, The Netherlands and the UK) displaying lower numbers.

When focusing specifically on transplants performed with organs from DCD Belgium ranks third amongst the selected countries, after the Netherlands and the UK, with 8.3 transplants performed with kidneys coming from donors after cardiac death (DCD) per million population in 2012 (see Table 4 for more details).

Table 4 – Annual kidney transplants by type of donor 2005-2012

	2007	2008	2009	2010	2011	2012
	N	N	N	N	N	N
	(pmp)	(pmp)	(pmp)	(pmp)	(pmp)	(pmp)
Belgium						
Kidney Tx deceased donors	449 (40.7)	442 (40.0)	428 (38.8)	404 (36.6)	474 (42.9)	480 (43.0)
from DBD	384 (34.8)	389 (35.2)	357 (32.3)	346 (31.3)	385 (34.9)	388 (35.1)
from DCD	65 (5.9)	53 (4.8)	71 (6.4)	58 (5.3)	89 (8.1)	92 (8.3)
Kidney Tx living donors	42 (3.8)	45 (4.1)	49 (4.4)	49 (4.4)	40 (3.6)	57 (5.2)
Kidney Tx (all)	491 (44.5)	487 (44.1)	477 (43.2)	453 (41.0)	514 (46.6)	537 (48.6)
France						
Kidney Tx deceased donors	2676 (40.9)	2715 (41.5)	2603 (39.8)	2609 (39.9)	2674 (40.9)	2687 (41.1)

from DBD	2633 (40.3)	2663 (40.7)	2533 (38.7)	2530 (38.7)	2609 (39.9)	2606 (39.8)
from DCD	43 (0.7)	52 (0.8)	70 (1.1)	79 (1.2)	65 (1.0)	81 (1.2)
Kidney Tx living donors	236 (3.6)	222 (3.4)	223 (3.4)	283 (4.3)	302 (4.6)	357 (5.5)
Kidney Tx (all)	2912 (44.5)	2937 (44.9)	2826 (43.2)	2892 (44.2)	2976 (45.5)	3044 (46.5)
Germany						
Kidney Tx deceased donors	2340 (28.6)	2188 (26.7)	2172 (26.5)	2272 (27.8)	2055 (25.1)	1820 (22.2)
from DBD	2340 (28.6)	2188 (26.7)	2172 (26.5)	2272 (27.8)	2055 (25.1)	1820 (22.2)
from DCD	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Kidney Tx living donors	567 (6.9)	565 (6.9)	600 (7.3)	665 (8.1)	795 (9.7)	766 (9.4)
Kidney Tx (all)	2907 (35.5)	2753 (33.6)	2772 (33.9)	2937 (35.9)	2850 (34.8)	2586 (31.6)
Netherlands						
Kidney Tx deceased donors	464 (27.7)	352 (21.0)	397 (23.7)	394 (23.6)	420 (25.1)	476 (28.5)
from DBD	298 (17.8)	218 (13.0)	237 (14.2)	265 (15.8)	218 (13.0)	256 (15.3)
from DCD	166 (9.9)	134 (8.0)	160 (9.6)	129 (7.7)	202 (12.1)	220 (13.1)
Kidney Tx living donors	360 (21.5)	411 (24.6)	417 (24.9)	473 (28.3)	440 (26.3)	485 (29.0)
Kidney Tx (all)	824 (49.3)	763 (45.6)	814 (48.7)	867 (51.8)	860 (51.4)	961 (57.4)

Spain						
Kidney Tx deceased donors	2074 (44.9)	2073 (44.9)	2093 (45.3)	1985 (43.0)	2186 (47.3)	2190 (47.4)
from DBD	1970 (42.6)	1968 (42.6)	1945 (42.1)	1827 (39.5)	2046 (44.3)	1989 (43.1)
from DCD	104 (2.3)	105 (2.3)	148 (3.2)	158 (3.4)	140 (3.0)	201 (4.4)
Kidney Tx living donors	137 (3.0)	156 (3.4)	235 (5.1)	240 (5.2)	312 (6.8)	361 (7.8)
Kidney Tx (all)	2211 (47.9)	2229 (48.3)	2328 (50.4)	2225 (48.2)	2498 (54.1)	2551 (55.2)
UK						
Kidney Tx deceased donors	1440 (22.9)	1453 (23.1)	1570 (24.9)	1657 (26.3)	1667 (26.5)	1792 (28.4)
from DBD	1164 (18.5)	1118 (17.7)	1096 (17.4)	1105 (17.5)	1100 (17.5)	1118 (17.7)
from DCD	276 (4.4)	335 (5.3)	474 (7.5)	552 (8.8)	567 (9.0)	674 (10.7)
Kidney Tx living donors	690 (11.0)	829 (13.2)	927 (14.7)	1037 (16.5)	1020 (16.2)	1009 (16.0)
Kidney Tx (all)	2130 (33.8)	2282 (36.2)	2497 (39.6)	2694 (42.8)	2687 (42.7)	2801 (44.5)

Source: BE, DE and NL: Eurotransplant annual reports 2007-2012 (www.eurotransplant.org); FR: Greffe renale - 2007-2011 - Agence de la Biomedecine (www.agence-biomedecine.fr); ES: Memoria Actividad Organizacion Nacional de trasplantes 2007-2012 (www.ont.es); UK: Organ donation and transplantation activity reports - NHS Blood and Transplant (www.organdonation.nhs.uk)

*Data at 31st of March of the relevant year

Tx: Transplants; DBD: donation after brain death; DCD: donations after cardiac death

2 KIDNEY PRESERVATION

In renal transplantation, long periods of cold ischemia (CIs) are strongly associated with DGF, which in turn is a risk factor for reduced graft survival.¹⁴ MP is thought to mitigate these harmful effects by delivering nutrients and energy substrates while removing toxic waste products during the preservation phase.

There are at present two alternative preservation techniques:

2.1 Cold storage

Cold storage (CS) represents the most common practice not just in Belgium but all over Europe.^{15, 16} CS is based on the effects of cooling, supplemented by the use of special preservation solutions aimed at reducing the inevitable cellular changes that take place in the organs from the moment in which cessation of blood supply occurs.

2.2 Machine Perfusion

MP represents an alternative to CS and consists of continuously pumping cold preservation solutions through the kidneys, via the renal artery.

2.2.1 Machine unit

Although two different devices are currently commercially available in Europe (LifePort[®] Kidney Transporter –by Organ Recovery Systems Inc– and RM3[®] –by Waters Corporation Medical Systems Inc–), only the former is transportable, offering more flexibility and being the preferred option in centres currently using MP technology to perfuse kidneys prior to their transplantation. The LifePort[®] machine allows for the perfusion of only one kidney at a time and thus, two machines are usually required at the time of retrieval. Being transportable, it facilitates the perfusion of kidneys from their extraction to their transplantation.

At least two more transportable machines are entering the European market: Waves, by waters-IGL and Kidney assist by Organ Assist. Given the current lack of clinical and cost data on these two machines no further reference is made specifically to them in this review.



A decision to acquire these machines implies an investment of approximately €14 400 per machine unit (based on purchasing prices quoted in the literature and direct communication with the manufacturer of LifePort®). The machine has a minimum lifetime of five years and its acquisition requires payment of a yearly insurance fee of around €1 960 per transplant centre, independently of the number of machines acquired per centre (based on a direct communication with the manufacturers of LifePort®).

2.2.2 Disposables

Every time a kidney is perfused by means of the only commercially available transportable MP system in Europe up to date (LifePort®), a “perfusion kit” is required. This perfusion kit includes the necessary disposables needed to complete the perfusion process from the harvesting of the kidneys to their eventual transplantation. The kit consists of:

- LifePort® Perfusion Circuit (closed system with in-line filter and pressure sensor),
- SealRing™ 7x20 cannula,
- sterile drape,
- one litre of KPS-1 preservation solution.

In addition to the kit, an extra sterile drape is needed every time a kidney is machine-perfused and the acquisition of a set of extra cannulae is recommended, although these tend to be used in few occasions when the ordinary cannulae size is not appropriate (around 10% of cases according to a communication with experts in the field and the LifePort® manufacturers, ORS, based on their experience).

An all-inclusive “loan” service is currently organized by Organ Recovery Systems Inc in Belgium at an approximate cost of €3 000 per machine-perfused kidney ultimately transplanted (*i.e.* in case of failed transplantation, the service is not charged).

Figure 1 shows the LifePort® machine as well as its various components (disposables and capital equipment).

As it already happens with LifePort®, any other machines entering the market would require specific consumables and preservation solutions. Thus, once hospitals buy a specific machine unit they would need to buy both the consumables and the solution from the same manufacturer.

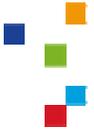


Figure 1 – LifePort® machine and consumables (provided by the manufacturer of LifePort® – Organ Recovery Systems)





3 SYSTEMATIC LITERATURE REVIEW ON CLINICAL EFFECTIVENESS

3.1 Introduction

This chapter presents a review of the evidence on the clinical benefit of MP versus CS. Three recent systematic reviews of the evidence on the comparison of MP versus CS for preserving kidneys prior to transplantation were identified,¹⁷⁻¹⁹ one of which was restricted to DCD donors.¹⁷ There were however important differences in evidence retrieved in the reviews by Lam et al.¹⁸ and by O'Callaghan et al.¹⁹ For instance, O'Callaghan et al. included the studies by Danielewicz et al.²⁰ and Van der Vliet et al.²¹ and excluded the ones by Kwiatkowski et al.²² and Jaffers et al.,²³ while the opposite was observed in the review by Lam et al.¹⁸ Unfortunately, no table of excluded studies with reasons for exclusion was provided in any of these two systematic reviews making it impossible for the reader to decide on which review to rely on in priority. Moreover, these two reviews mixed outcomes from studies on DCD and DBD donors whereas different results might be expected for these different patient populations (see introduction).

For these reasons, we present here a *de novo* systematic review on MP versus CS for preservation of kidneys prior to their transplantation.

3.2 Methods

A systematic search for relevant publications was carried out with the consultation of electronic reference databases up to June 2013. Medline (through OVID), EMBASE, and the Cochrane Library were searched to retrieve primary randomized controlled trials comparing MP with CS and reporting on the following main outcomes: DGF, PNF, quality of life (QoL) and graft loss at one year post-transplantation (Table 5). Secondary outcomes were number of hospital days and number of dialysis sessions post-transplantation. An overview of the search strategy is given in Appendix 1 and inclusion and exclusion criteria are presented in Table 5.

The hits from the three electronic databases were merged in a unique EndNote file and duplicates were removed. We then screened titles and abstracts to identify and exclude articles which did not fulfil the inclusion

criteria. The remaining papers were retrieved and read in full for a final selection of studies to include in the review. No restrictions were imposed for language or publication date. The flow chart of the selection process is presented in Appendix 2.

All studies finally included in our review were critically appraised by using the Cochrane grid for risk of bias.²⁴ Meta-analysis and forest plots were produced in Review Manager 5.2 (RevMan [Computer program], Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) following the Mantel-Haenszel method. As most of the studies had a paired design (one kidney from a same donor was randomized to either MP or CS, and the other one was automatically allocated to the other group), we had planned an analysis based on the generic inverse variance. Unfortunately, most of the studies had not accounted for the paired design in their analysis and moreover did not report risk ratio or odds ratio with confidence interval but mere proportions. Therefore, only the Mantel-Haenszel method was possible. Global heterogeneity and heterogeneity among studies was assessed by a X^2 test or an I^2 test, respectively.²⁴ In case of significant heterogeneity, a random effect model was applied to measure a pooled point estimate of intervention efficacy, following the DerSimonian and Laird method.²⁴

We stratified the results by donor types. As a sensitivity analysis, we compared the results of the pooled analysis to those of the European Machine Perfusion trial (EMPT) for two reasons. First, except the study by Watson et al.,²⁵ other studies were more ancient and surgery procedures and drugs were likely to differ substantially from current practice. Second, although most studies had a paired design, the EMPT was the only one to adjust the result for that paired design and that might have increase the precision of the estimates. However, it should be kept in mind that the sensitivity analysis is done to provide a range of results and that the pooled estimate should be considered in priority, as relying on the results of only one study can bias our judgment of effectiveness.²⁶

The quality of evidence per outcome was graded following the GRADE methodology²⁷ which takes into account the risk of bias in studies, the heterogeneity among studies, the risk of publication bias, the indirectness and the imprecision of results.



Finally, we searched the International Clinical Trials Registry Platform (<http://apps.who.int/trialsearch/>), which covers major clinical trials registry worldwide, to trace on-going trials.

Table 5 – PICO table and selection criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Kidneys from deceased donor	Kidneys from living donors
Intervention	Preservation by machine perfusion	Any other organ preservation method
Comparator	Preservation by static cold storage	Any other organ preservation method
Outcomes	Delayed Graft Function (DGF) Primary Non Function (PNF) Graft Survival after 1 year or longer Quality of life Hospital days Number of dialysis	-
Study design	Randomized controlled trial*	Observational studies Letters, editorials, notes, abstracts

*Unit of randomization could be donors or kidneys



3.3 Results

After screening titles and abstract, 28 of the 643 eligible records were retained, 13 of which were included in the review (Table 7). The list of excluded records is provided in Appendix 3. Of the 13 included records, five related to the EMPT study.²⁸⁻³² The main results of that study on 336 donors (294 DBD and 42 DCD) have been published by Moers et al. in 2009.³¹ The study was extended to recruit more DCD donors, and the results on that specific group of patients are presented in Jochmans et al.²⁹

The analysis in this latter paper included 82 donors, 42 of whom were already part of the main analysis in 2009. The study was also extended to recruit more patients ≥ 65 years and results on 85 donors, 39 of whom were already part of the main 2009 paper, were published by Gallinat et al.²⁸ Finally, Treckmann et al.³² published a subgroup analysis of the main trial to assess outcomes in ECD donors. Graft survival three years after kidney transplantation was analysed in Moers 2012 (same study population as in Moers 2009).³⁰

The main characteristics of included studies are presented in Table 7. The EMPT study was by far the biggest one providing half of the participants included in the meta-analysis.²⁸⁻³² The two perfusion machines most often used were the Lifeport[®] in two studies^{25, 31} and the Waters Mox 100[®] in the majority of others. Donors were primarily DBD in most studies. Outcomes in DCD donors were assessed in three studies,^{21, 25, 29} whereas ECD donors were studied in two sub-group analyses of the EMPT study^{28, 32} and in a third trial carried out in Poland.²² The quality appraisal of these studies is presented in Table 8 (details on the quality appraisal can be found in Appendix 4). All the studies but two^{25, 31} described poorly their methods hampering an accurate quality appraisal.

3.3.1 Delayed Graft Function (DGF)

Overall, MP decreased the risk of DGF (RR=0.78; 95%CI: 0.59; 1.03; p=0.08) in DBD, although not reaching statistical significance (Figure 2). This risk reduction was of similar amplitude in DCD and ECD donors, with no evidence of heterogeneity across donor types.^e Therefore we pooled all studies with the exclusion of the ones by Gallinat²⁸ and Treckman³² because a substantial proportion of their study population was already included in the study by Moers 2009 (Figure 3). The overall relative risk reduction was 22% (95%CI: 8%; 34%; p=0.004). There was no evidence of publication bias by visually appraising the funnel plot (Figure 5). Although the poor reporting of the majority of included studies did not allow an in-depth appraisal, we did not downgrade the quality of evidence because half of the information was provided by the EMPT which was rated high quality and whose results were consistent with those of other studies. There was no downgrading neither for inconsistency, indirectness, or imprecision. Therefore, we rated this evidence as high quality. In the EMPT study, adjusted^f OR were 0.61 (95%CI: 0.37; 1.00), 0.35 (95% CI: 0.16; 0.75) and 0.51 (95%CI: 0.24; 1.09) for DBD, DCD, and ECD respectively, and the authors reported that the effect was not statistically different across patient types.³¹ The overall OR in that study was 0.63 (95%CI: 0.41; 0.97; p=0.035) after adjustment for study design (matching of kidneys on donors) but no adjustment on other factors (personal communication of Cyril Moers).

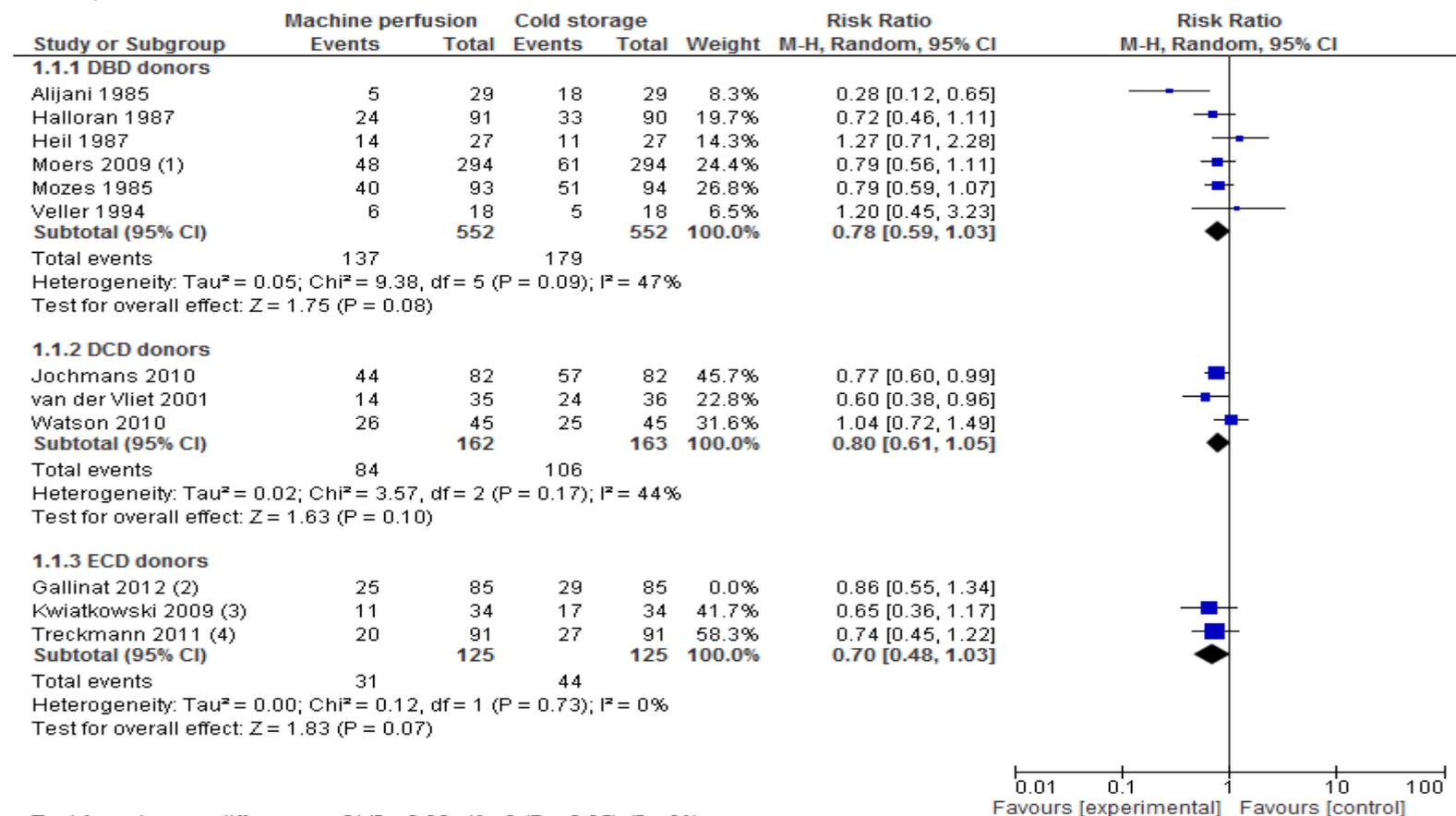
When DGF occurred, its duration tended to be from three³¹ to five days^{33, 34} longer in the CS group compared to the MP group (outcome reported in only three studies). In the EMPT study, the difference of DGF duration was 4 days (p=0.082) in DCD, and no difference was found in ECD.^{28, 32}

^e In the ECD subgroup, the data from Gallinat et al.²⁸ were not integrated in the meta-analysis because their study population (donors ≥ 65 years of the EMPT trial) overlap grossly with the study population of Treckman et al.³², and in this latter study the definition of ECD was standard.

^f Adjustment was made on donor type (DCD vs. DBD and ECD vs. SCD), recipient and donor ages, duration of pre-transplantation dialysis, panel-reactive antibody level, cold ischemic time, HLA mismatches, later transplantation vs. first transplantation.



Figure 2 – Meta-analysis of delayed graft function in machine perfused versus cold stored transplantation kidneys (pooling per subgroup of donors)



Test for subgroup differences: Chi² = 0.33, df = 2 (P = 0.85), I² = 0%

(1) The majority of BDD were SCD (72%)

(2) 46 % (39/85) pairs already analysed in Moers 2009. Not integrated in meta-analysis because overlaps with Treckman 2011 (see text).

(3) 24 of the 37 donors were ECD, 13 were SCD

(4) 53% (48/91) already in analysis by Moers 2009. Not integrated in meta-analysis

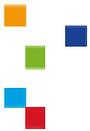
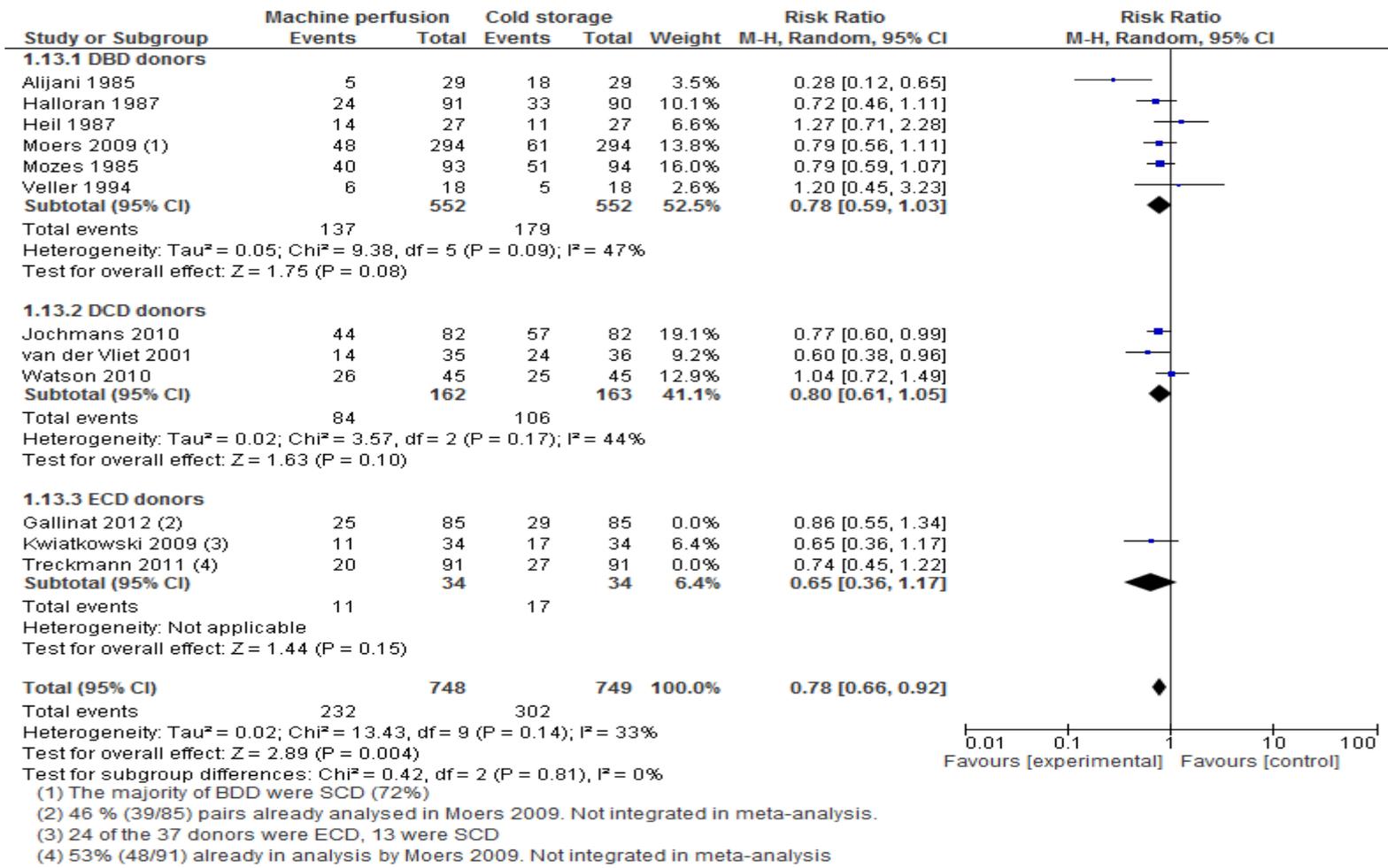


Figure 3 – Meta-analysis of delayed graft function in machine perfused versus cold stored transplantation kidneys (overall pooling)



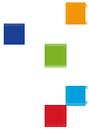
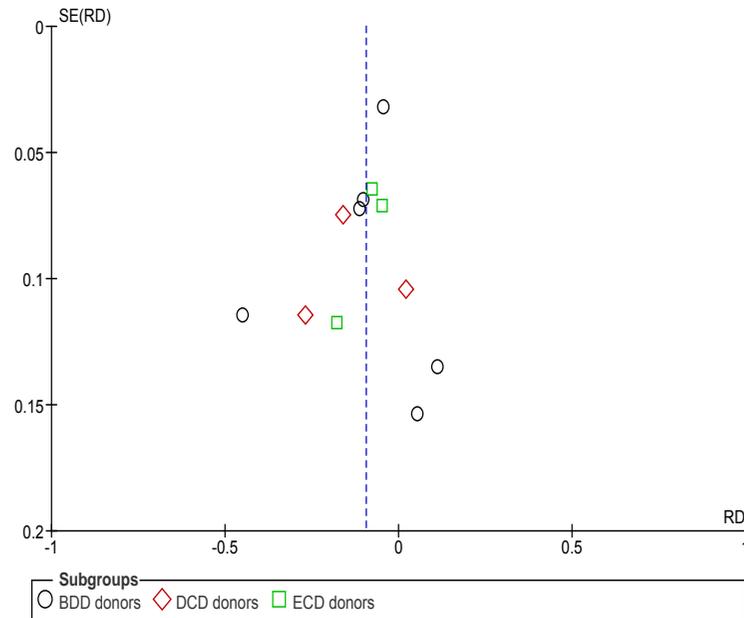


Figure 4 – Funnel plot of the studies comparing machine perfusion versus cold storage with outcome DGF



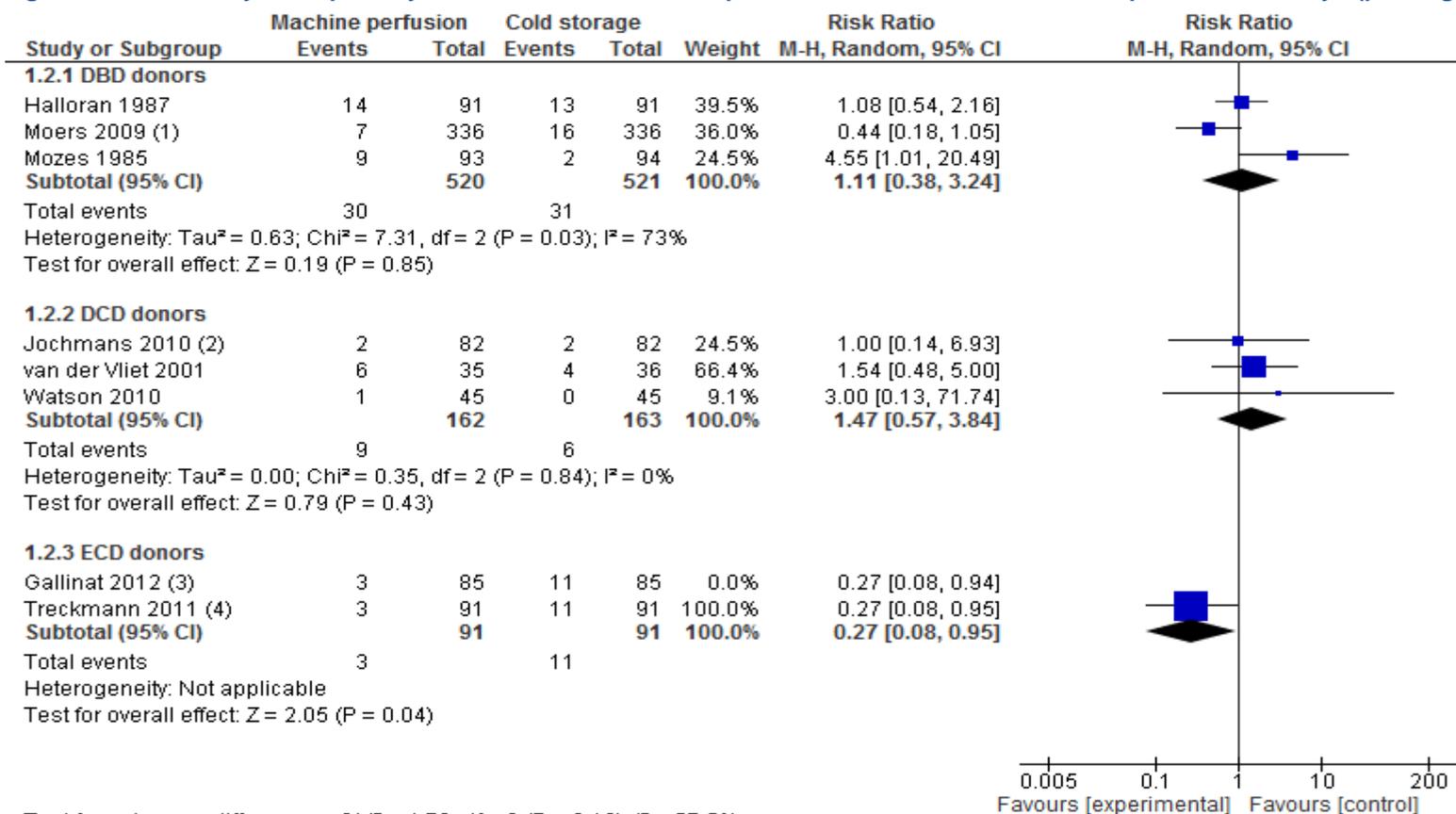
3.3.2 Primary non-function (PNF)

There was no statistical difference in incidence of primary kidney non function between MP and CS in DBD (three studies) or in DCD donors (three studies) (Figure 6). A difference in the incidence of PNF was apparent only in the subgroup of ECD donors of the EMPT study, but this relied on a single study⁹ and numbers were small.³² Because of this heterogeneity, we did not pool results across donor groups. The studies were not powered to assess such a rare event, and even after the pooling by type of donors, the optimal information size was not reached.³⁵ We downgraded the quality of the evidence for imprecision in all sub-group analyses (by -2 for DBD and DCD because the confidence intervals included both strong benefit and strong harm; -2 for ECD because the evidence comes from one single underpowered study). Moreover, there was a clear inconsistency in outcomes among studies of the DBD group and significant heterogeneity and evidence was downgraded one more degree for that reason. Therefore, the quality of evidence was rated very low for DBD and low for DCD and ECD.

⁹ In the ECD subgroup, the data from Gallinat et al. 28 were not integrated in the meta-analysis because their study population (donors ≥ 65 years of the EMPT trial) overlap grossly with the study population of Treckman et al. 32, and in this latter study the definition of ECD was standard.



Figure 5 – Meta-analysis of primary non function in machine perfused versus cold stored transplantation kidneys (pooling per subgroup of donors)



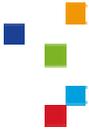
Test for subgroup differences: Chi² = 4.70, df = 2 (P = 0.10), I² = 57.5%

(1) The majority of BDD were SCD (72%; 242/336)

(2) 51% (42/82) donors already part of the analysis by Moers 2009

(3) 46 % (39/85) pairs already analysed in Moers 2009. Not integrated in meta-analysis because overlaps with Treckmann 2011 (see text)

(4) All data were already included in the study by Moers 2009.



3.3.3 Graft failure

There was a trend towards a reduction of graft failure with MP versus CS in DBD (Risk Ratio (RR)=0.89; 95%CI: 0.72; 1.10; p=0.28; 4 studies) (Figure 6). Such effect was not retrieved in DCD donors, in whom a trend towards a negative effect of MP versus CS was observed (three studies). In the subgroup of ECD donors, the risk reduction appeared larger (risk difference=-13%; 95%CI: -21%; -4%; p=0.007), although only 2 underpowered studies contributed to the evidence and the confidence interval around the pooled estimate was large (Figure 6). The evidence was downgraded in every subgroup for imprecision (-1 for DBD and ECD; -2 for DCD because the CI included both strong effects and strong harms), and the evidence was thus of moderate quality for DBD and ECD and of low quality for DCD.

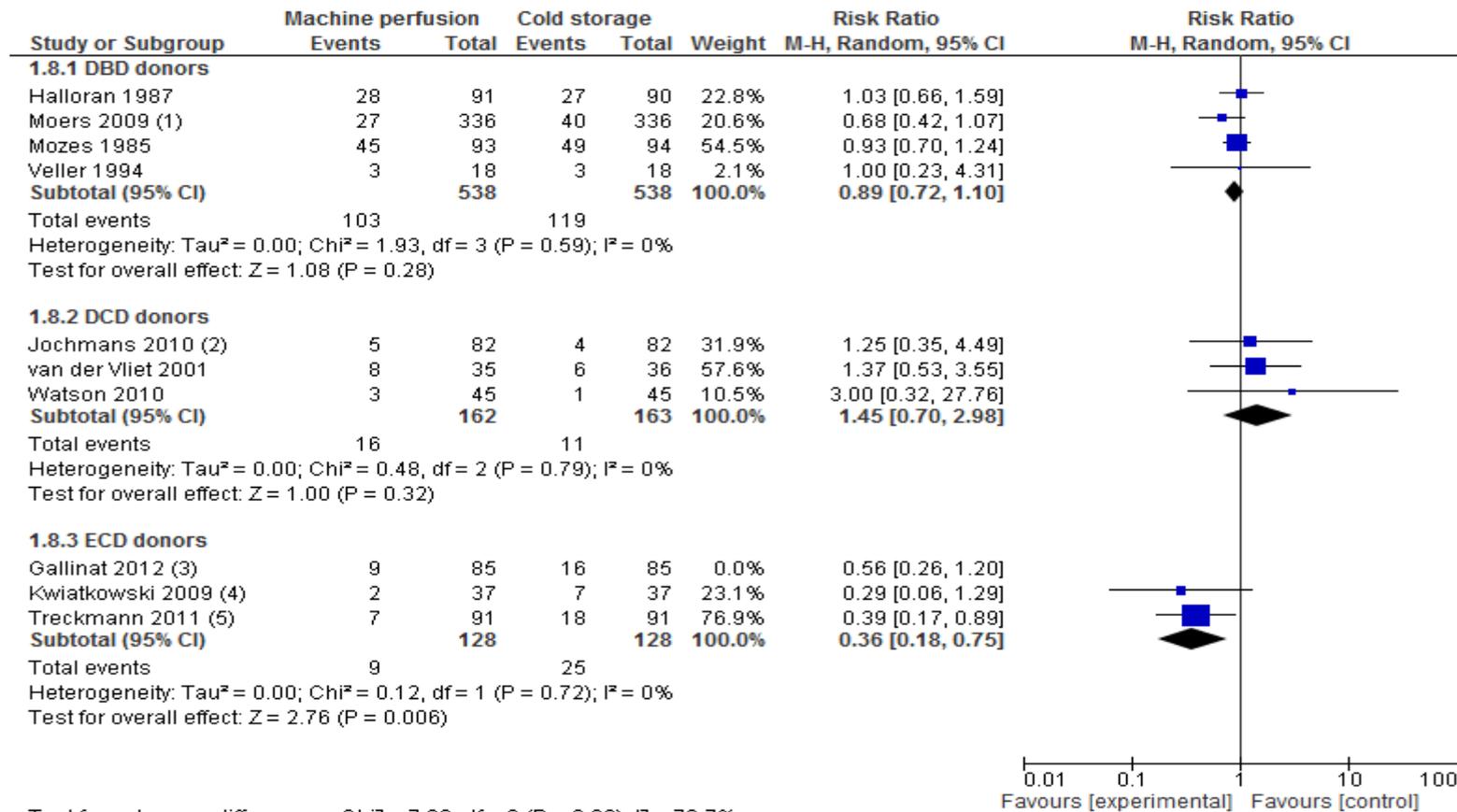
As a comparison, the adjusted^h hazard ratio (HR) of the EMPT study were 0.52 (95%CI: 0.29; 0.93; p=0.03) and 0.35 (95%CI: 0.14; 0.86; p=0.022) for DBD and the subgroup of ECD donors respectively. The confidence intervals overlapped, and more than half of ECD donors were already included in the DBD group. Therefore it is unknown if the effect of MP is greater in ECD than in all DBD, and what the effect of MP in DBD with standard criteria would be. Adjusted HR for DCD was not reported. The overall HR was 0.54 (95%CI: 0.31; 0.96; p=0.035) after adjustment for study design (kidneys matched by donors) but no adjustment for the other parameters (personal communication Cyril Moers).

Participants of the EMPT study were followed up for three years post-transplantation. The RR in DBD donors was 0.63 (95%CI: 0.40; 1.01; p=0.05), 1.14 (95%CI: 0.43; 3.01; p=0.79) in DCD donors and 0.57 (95%CI: 0.30; 1.05; p=0.07) in ECD donors. The authors reported that the respective adjusted HR were 0.54 (95% CI: 0.32; 0.90; p=0.02), 1.16 (95%CI: 0.41; 3.28; p=0.78) and 0.38 (95%CI: 0.18; 0.80; p=0.01).³⁰ The corresponding results when only adjustment for the study design was made were HR=0.57 (95%CI: 0.35; 0.94; p=0.028) for DBD, HR=1.14 (95%CI: 0.41; 3.14; p=0.80) for DCD and HR=0.41 (95%CI: 0.20; 0.83; p=0.013) for ECD and HR=0.64 (95%CI: 0.40; 1.03; p=0.067) over all patient groups (personal communication Cyril Moers). Given the imprecision around the estimates and the fact that results come from a single study, we downgraded the quality by 2 degrees and the evidence was rated low quality. Kwiatkowski et al. reported a RR ten years after transplantation of 0.67 (95%CI: 0.40; 1.10; p=0.11) in 74 kidney pairs which came primarily from ECD donors, and that recipients of kidneys stored in CS prior to transplantation returned to dialysis twice as frequently as patients with MP kidneys (50% versus 25%; p=0.02).²² This evidence was also rated as low quality.

^h Adjustment was made on donor type (DCD vs. DBD and ECD vs. SCD), recipient and donor ages, duration of pre-transplantation dialysis, panel-reactive antibody level, cold ischemic time, HLA mismatches, later transplantation vs. first transplantation.



Figure 6 – Meta-analysis of graft loss at one year in machine perfused versus cold stored transplantation kidneys (pooling per subgroup of donors)



Test for subgroup differences: Chi² = 7.60, df = 2 (P = 0.02), I² = 73.7%

(1) The majority of DBD were SCD (72%; 242/336)

(2) 51% (42/82) donors already part of the analysis by Moers 2009

(3) 46 % (39/85) pairs already analysed in Moers 2009. Not integrated in meta-analysis because overlaps with Treckmann 2011 (see text)

(4) These figures are not in the original paper, but from the review by Lam 2013. 24 donors were ECD, 13 were standards

(5) All data were already included in the study by Moers 2009.



3.3.4 Other outcomes

Evidence was scanty on the impact of MP versus CS in terms of dialysis sessions or hospital days avoided. Two small sized studies reported an average difference of around 0.4 less dialysis per patient in the MP group^{36, 37} whereas there was no difference in the duration of the post-transplantation hospital stay in the EMPT study.³¹

A summary of findings together with a quality grading of evidence per outcome following the GRADE methodology²⁷ is presented in Table 9.

3.3.5 Ongoing trials

We have identified 3 further trials, one of which is still recruiting, and the remainders being completed but results not yet published (Table 6).

Table 6 – Ongoing trials

Patients	Intervention	Main outcome	Completion
120 ECD	Kidney put on LifePort [®] upon arrival in the transplant center vs. cold storage	3 months graft survival	Not before mid-2015 (still recruiting patient and 1-year graft survival is a secondary outcome)
270 DCD	Lifeport [®] vs. cold storage	DGF	Completed on 06/08/2012
200 DBD	Machine perfusion of the kidney before transplantation versus simple cold storage	DGF	Completed on 30/06/2012

3.4 Discussion

Our meta-analysis of 9 randomized controlled trials involving 1 463 kidney transplant recipients showed that MP significantly reduced the incidence of DGF (good quality evidence) in any type of donors. However, MP had no effect on the incidence of PNF of the graft (very low quality evidence for DBD, and low quality evidence for DCD and ECD). A statistically significant reduction in graft loss one year after transplantation was observed only in ECD donors (2 studies; moderate quality evidence), whereas a trend towards such reduction was apparent in DBD donors (moderate quality evidence). No effect on graft survival was observed in DCD, and there could even be a risk of increasing graft failure (low quality evidence).

These results -globally a decrease in DGF but no demonstrated effect on PNF or graft survival, except maybe in ECD- are consistent with those of two previously published systematic reviews,^{18, 19} and also from those of 2 other systematic reviews that focused on DCDs,^{17, 38} one of which was published after the inception of our research.³⁸ Our results are also consistent with observations from routine data in the USA.³⁹⁻⁴¹ Our review however deepens previous knowledge in three important ways: we complied with the recommendations of the PRISMA statement, e.g. the list of excluded studies and reasons for exclusion is provided, the search strategies in the various electronic databases utilized are provided, and judgment on quality appraisal is explained for each study included;⁴² we stratified the pooled estimates by donor types, an approach which allowed to test for effect variation among groups of donors; we graded the quality of evidence per main outcomes following the GRADE methodology.²⁷

DGF was considered the primary outcome in most of the studies on the ground that DGF is an important risk factor of graft loss.¹⁴ However, DGF is a complex manifestation of many different types of tissue injury, not all of which have long-term consequences.⁴³ On the one hand, decreasing the incidence of DGF may result in no differences in graft survival, as illustrated by our systematic review. It should be noted that the included studies had DGF as a main outcome and were thus not powered to assess an improvement in graft survival. An indirect indication that DGF may not matter so much in terms of graft survival comes from observational studies reporting similar graft survival rates in DBD and DCD donors in spite of higher incidence of DGF in DCD donors.^{6, 44, 45}



However, this observation might be true only for DCD. On the other hand, the effect of MP may not be entirely mediated through the avoidance of DGF, as illustrated in the EMPT study where the adjusted HR for graft failure at year 1 was marginally affected by adding DGF as a covariate in the model (0.52 (95%CI: 0.29; 0.92) versus 0.60 (95%CI: 0.34; 1.06)).³¹ It also appeared in the three year follow-up of the EMPT study that MP may decrease the risk of graft failure more particularly in those developing DGF, although the interaction was not formally tested,³⁰ implying that decrease in DGF may not be an appropriate intermediate outcome to assess. It is therefore crucial that further studies do not rely on surrogate endpoints but be powered to assess differences in graft loss, QoL or even recipient mortality.

Another argument often put forward to consider DGF an important outcome, independently of its association with graft failure, is cost savings through a decrease in dialysis and hospital days needed post-transplantation.¹⁸ However, we retrieved very scarce evidence on how MP affects the number of dialysis and hospital days, which tended to indicate no or minimal effect on these parameters. It is unfortunate that these data were not collected in the vast majority of trials.

One important finding of our review was the potential variation of MP effect according to recipient group, with a statistically significant effect on PNF and graft survival at year 1 in ECD donors, with 4% to 21% less occurrence of graft failure, *i.e.* for each 5 to 20 transplantations, one additional graft will still be functional at year 1 if MP is used instead of CS in ECD. This could have dramatic implication on the utilization of such donor pool. Unfortunately, the effect estimate was quite imprecise because of the small number of studies (three among which two overlap greatly) and their small size. There was also a similar trend observed in DBD, although not reaching statistical significance. However, it is unclear how much of the effect observed in DBD was actually attributable to improvement in the subgroup of ECD donors, and what would be the effect size in DBD with standard criteria only. DCD donors are often considered a group of donors in whom MP should be used. In France, for instance, the utilization of MP is compulsory in that group of donors. The evidence shows that indeed the reduction of DGF in that group was similar to the one in the other types of donors, although one of the 3 studies included reported no effect.²⁵ This might have been due to MP being used after a

period of CS, *i.e.* not directly after kidney recovery. However, there was no evidence of improvement in graft survival in that group. Our results are consistent with the review by Deng¹⁷ and Bathini.³⁸ There could even be an increased risk of graft failure with MP. This is a worrying finding, and the risk-benefit balance of MP in that group needs urgent further appraisal.

Finally, MP provides the theoretical opportunity to assess the viability of kidneys. However, the present viability tests are not reliable predictors of transplant outcome. New developments in kidney graft viability assessment are necessary to have a chance of being clinically useful in the future.^{46, 47}

One limitation of our review relates to the suboptimal reporting of most primary studies included. Methods were generally poorly described which rendered the rating of the quality of the evidence very uncertain. In most studies, the matching was not accounted for by authors during the analysis, and in others, crude risk or hazard ratio along with their corresponding standard error which would have allowed a meta-analysis based on the inverse variance approach were not provided. Another limitation was the short time span of the primary studies. Only four studies reported graft survival one year after transplantation,^{25, 31, 34, 37} and one of those also reported graft survival at three years.³⁰ The study by Kwiatkowski et al. reported a risk ratio (RR) ten years after transplantation but given the small sample size and the uncertainties around the study methods, this result should be considered with great caution.²² It is also worth mentioning that in all trials, different preservation solutions were used in the MP and CS groups. If preservation liquids have a different effect on kidney outcomes,⁴⁸ this could have confounded the results positively or negatively to an unknown extent. Finally, our review was based only on published trials. Valuable information could also be drawn from on-going transplantation programs provided that the information is collected in a systematic way and that kidneys preserved with CS vs. MP present as much as possible similar characteristics apart from the preservation methods.

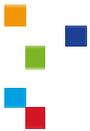
In summary, there is good quality evidence that MP significantly decreases the incidence of DGF but evidence is unclear on the number of additional dialysis sessions and extra hospitalisation days that patients experiencing DGF require in practice. There is also moderate quality of evidence that



MP could substantially decrease the incidence of graft failure one year after transplantation in ECD donors. A similar effect might also be plausible in DBD donors but with a much lower effect size. High-quality trials powered to assess graft survival in the mid-term (several years), are still required to strengthen the current promising but fragile evidence.

Table 7 – Characteristics of included studies

Study	Country	Donor type	Sample size		Perfusate		Machine type	Donor age		Recipient age		CIT (hours)		WIT (min)	
			CS	MP	CS	MP		CS	MP	CS	MP	CS	MP	CS	MP
Halloran 1987 ³⁷	Ontario	NR	90	91	Collins	Plasmanate	Waters MOX-100 ¹	29.7 ±15	38.0 ±16	38.7±16	38.1±16	27.7±12	27.2±10 ²	3.4 ±3	3.8 ±5
Watson 2010 ²⁵	UK	DCD	45	45	ViaSpan	KPS-1	LifePort	45.6±14.6		48.6±13.9	50.3±14.2	13.9	14.3	15	
Alijani 1985 ³⁶	Washington DC	NR	38	38	Collins	Plasmanate	Waters MOX-100	NR		NR	NR	29.6±6	32.5±8	NR	
Van der Vliet 2001 ²¹	The Netherlands	DCD	38	38	UW	Belzer solution	Gambro	36.6±2.7		NR	NR	23.0±1.3	25.0±1.0	28.4±1.6	
Veller 1994 ⁴⁹	South Africa	DBD	18	18	UW	Plasmanate	Waters MOX-100	NR		34	34	19	20	NR	NR
Moers 2009 ³¹ Moers 2012 ³⁰	The Netherlands, Belgium, Germany	294 DBD/42 DCD	336	336	UW or HTK	KPS-1	LifePort	51 (16-81)		53 (11-79)	52 (2-79)	15.0 (3.5-29.7)	15.0 (2.5-29.7)	NR	NR
Treckmann 2011 ³²		ECD ³	91	91											
Jochmans 2010 ²⁹		DCD ⁴	82	82				43 (17-67)		52 (24-77)	49 (24-73)	15.9 (8.6-46.6)	15.0 (4.3-28.9)	16 (6-38)	
Gallinat 2012 ²⁸		DBD ≥65 y ⁵	85	85				70 (65-83)		66 (37-)	66 (39-)	10.5 (3-)	11 (4-24)	NR	NR



									79)	79)	24)			
Kwiatkowski 2009²²	Poland	13 DBD/24 ECD ⁶	37	37	NR	MPS II	Waters MOX-100	36 (5-70)	40±15	37±12	27.5	34.5	NR	N R
Mozes 1985³⁴	Illinois	DBD	94	93	Euro-Collins	Plasmanate	Waters MOX-100	26.5±11.7	NR	NR	34.4±8.6 ⁷	35.9±11.5°	NR	N R
Heil 1987³³	Minesotta	DBD	27	27	Euro-Collins	Plasmanate	Waters MOX-100	NR	NR	NR	NR	NR	NR	N R

1: + 10 kidneys in Gambro machine; 2: plus 3.3±2 hours before perfusion starts;

3: Included in Moers 2009; 4: of the 82 donors of this study, 42 were already analysed in Moers 2009; 5: 39 donors were already included in Moers 2009

6: definition of ECD not provided; 7: in patients developing DGF

UW: solution of the University of Wisconsin; HTK: histidine-tryptophan-ketogluarate; KPS-1: Kidney Preservation Solution-1; MP: Machine perfusion; CS: cold storage; CIT: cold ischemic time; WIT: Warm ischemic time

Table 8 – Risk of bias summary

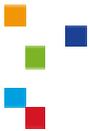
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Mozes 1985 ³⁴	?	?	-	?	+	+	?
Alijani 1985 ³⁶	?	-	?	?	?	+	?
Halloran 1987 ³⁷	?	?	?	?	-	?	-
Heil 1987 ³³	?	?	?	?	?	?	?
Veller 1994 ⁴⁹	?	?	?	?	?	?	?
Van der Vliet 2001 ²¹	?	?	?	?	+	+	?
Kwiatkowski 2009 ²²	?	?	?	?	?	?	?
Moers 2009 ³¹ ; Jochmans 2010 ²⁹ ; Treckman 2011 ³² ; Gallinat 2012 ²⁸	+	+	+	?	?	+	?
Watson 2010 ²⁵	+	?	?	+	+	+	+

-: high risk of bias;?: unclear risk of bias; +: low risk of bias



Table 9 – Summary of findings

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Machine perfusion	Cold storage	Relative (95% CI)	Absolute		
Delayed graft function - all donors												
10	randomised trials	no serious risk of bias ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	232/748 (31%)	302/749 (40.3%)	0.78 [0.66, 0.92]	89 fewer per 1000 (from 32 fewer to 137 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Primary nonfunction - DBD donors												
3	randomised trials	no serious risk of bias	serious ²	no serious indirectness	very serious ³	none	30/520 (5.8%)	31/521 (6%)	1.11 [0.38, 3.24]	7 more per 1000 (from 37 fewer to 133 more)	⊕○○○ VERY LOW	CRITICAL
Primary nonfunction - DCD donors												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ³	none	9/162 (5.6%)	6/163 (3.7%)	1.47 [0.57, 3.84]	17 more per 1000 (from 16 fewer to 105 more)	⊕⊕○○ LOW	CRITICAL
Primary nonfunction - ECD donors												
1 ⁴	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁵	none	6/176 (3.4%)	22/176 (12.5%)	0.27 [0.08, 0.95]	91 fewer per 1000 (from 6 fewer to 115 fewer)	⊕⊕○○ LOW	CRITICAL
Graft loss in the 1st year - DBD donors												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ³	none	103/538 (19.1%)	119/538 (22.1%)	0.89 [0.72, 1.10]	24 fewer per 1000 (from 62 fewer to 22)	⊕⊕⊕○ MODERATE	CRITICAL



										more)		
Graft loss in the 1st year - DCD donors												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁶	none	16/162 (9.9%)	11/163 (6.7%)	1.45 [0.70, 2.98]	30 more per 1000 (from 20 fewer to 134 more)	⊕⊕○○ LOW	CRITICAL
Graft loss in the 1st year - ECD donors												
2 ⁴	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁷	none	9/128 (7%)	25/128 (19.5%)	0.36 [0.18, 0.75]	125 fewer per 1000 (from 49 fewer to 160 fewer)	⊕⊕⊕○ MODERATE	CRITICAL

¹ Many risk of bias cannot be assessed because of poor reporting. However the study by Moers 2009 provides half of the events, is rated high quality, and its results are consistent with those of a meta-analysis excluding it. So we don't downgrade.

² Results by Mozes 1985 and Moers 2009 contradict

³ Very wide interval confidence intervals around the point estimate which include both benefit and harm. Optimal information size not achieved.

⁴ The studies by Treckman 2011 and Gallinat 2012 are both subgroup analysis of the MPT study and their populations overlap greatly. We keep at this level the study by Treckman et al 2011 because it applied a common definition of ECD (whereas Gallinat defined ECD as donors >=65 years)

⁵ The interval confidence around the point estimate is wide. The evidence comes from one single underpowered study.

⁶ Very wide confidence interval around the point estimate which include both strong benefit and strong harm

⁷ Wide confidence interval, although it is unlikely to change the clinical decision as the upper bound is already -25%. Evidence comes from only 2 underpowered studies

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.



4 SYSTEMATIC LITERATURE REVIEW OF ECONOMIC STUDIES

4.1 Introduction

This chapter provides an overview of studies evaluating the use of MP in the storage of kidneys from deceased donors from an economic perspective. The aim is to evaluate the potential cost-effectiveness of this storage method as an alternative to static cold CS in renal transplantation.

4.2 Methods

4.2.1 Search strategy

A systematic search for relevant publications was carried out with the consultation of electronic reference databases up to March 2013.

Medline (through OVID), EMBASE, Econlit (through OVID), NHSEED (CRD) and NHSHTA (CRD) were searched to retrieve primary full economic evaluations (studies comparing at least two competing alternatives in terms of both costs and outcomes) and reviews of economic evaluations (i.e. secondary economic evaluations). An overview of the search strategy is given in Appendix 1.

Furthermore, the websites of Health Technology Assessment (HTA) institutes listed on the INAHTA website (International Network of Agencies for Health Technology Assessment) and NICE (National Institute for Health and Care Excellence) were consulted to capture reports on the use of MP in the storage of kidneys from deceased donors prior to renal transplantation. No restrictions were imposed for language or time period. The search strategy was checked by a second researcher.

4.2.2 Selection procedure

To identify potentially relevant studies for our analysis we first went through all titles and abstracts in order to exclude any obvious studies that did not match our research subject. All articles that appeared to be interesting, or for which there were some doubts, were read in full in order to select those relevant for inclusion in our review.

Reference lists of the selected primary and secondary economic evaluations found via our search were checked for additional references worth adding to our analysis.

Study selection was completed by one researcher but any doubts that came up during the exercise were discussed and solved in collaboration with a second reviewer.

All studies finally included in our review were critically appraised by using an in-house structured data extraction sheet. A summary of the studies, their characteristics and overall results is provided in the appendices in an individual tabular form (Appendix 5).

4.2.3 Selection criteria

All full economic evaluations looking at MP as a potential method for storing kidneys from deceased donors prior to their transplantation were included in our review. Analyses performed on kidneys coming from living donors were excluded from our analysis.

Cost descriptive analyses or cost comparisons not taking into consideration effectiveness were always discarded. Similarly we decided to exclude publications in the form of letters, editorials or notes and abstracts since these would not offer enough information to include them in our analysis and critically appraise their findings. An overview of the inclusion/exclusion criteria is given in Table 10.

**Table 10 – Selection criteria for economic evaluations**

Selection criteria	Inclusion criteria	Exclusion criteria
Population	ESRD patients undergoing renal transplantation in which kidneys from deceased donors are to be used	ESRD patients not suitable for transplantation or those to receive kidneys from living donors
Intervention	Machine Perfusion	Any other organ preservation method
Comparator	Static cold storage	Any other organ preservation method
Design	Full economic evaluations (primary or secondary)	Cost descriptive analysis, cost comparisons
Type of publication	Articles or reviews	Letters, editorials, notes, abstracts

ESRD – End Stage Renal Disease

Our search returned 59 citations, after eliminating duplicates. Of those, 38 did not meet our inclusion criteria based on a review of their title and/or abstract. Of the 21 citations left, 13 were excluded after reading their full text because of the study design (5), publication type (4), population (1), intervention (1) or being a duplicate (2), which left us with 8 relevant studies to be included in our review. Further exploration of the references of the selected articles did not result in the identification of any additional study that could be of interest to our research.

Our literature selection process is illustrated in a flow chart in Appendix 2. Out of the eight full economic evaluations identified, three consisted of HTA reports which included the development of original cost models.

4.3 Overview of economic evaluations

As shown in Table 11 four studies were undertaken in Western Europe, with two of them performed in the UK,^{50, 51} while the two most recent studies were undertaken in Spain⁵² and Belgium, Germany and The Netherlands⁵³. A further study was undertaken in Eastern Europe, more specifically in Poland,⁵⁴ two more in the USA^{55, 56} and one in Canada.⁵⁷

All studies were published after 2002 and all but one,⁵¹ in 2007 or after, reflecting the importance that the topic has gained in recent years. Six studies^{50-53, 56, 57} were model-based (decision-tree and/or Markov models). The study by Groen et al.⁵³ included, in addition to the long-term evaluation done by means of a Markov model, a short-term evaluation built on the EMPT study. The remaining two studies were built on case control studies.^{54, 55}



Table 11 – Overview of economic evaluations of Machine Perfusion in renal transplantation involving organs from deceased donors

Author	Year	Country	Type of analysis	Perspective	Time horizon (in years)	Discount rate; both costs and outcomes (%)
Gómez ⁵²	2012	Spain	Cost-effectiveness	Hospital	Up to patient discharge post-transplantation	NA
Groen ⁵³	2012	Belgium, Germany & Netherlands	Cost-effectiveness and Cost-utility	Hospital	10	4
Bond ⁵⁰	2009	UK	Cost-utility	Third party payer	Lifetime	3,5
Garfield ⁵⁶	2009	USA	Cost-utility	Third party payer	1	NA
Wszola ⁵⁴	2009	Poland	Cost-consequences	Hospital	5-10	NA
Buchanan ⁵⁵	2008	USA	Cost-consequences	Third party payer	3	NA
Costa ⁵⁷	2007	Canada	Cost-effectiveness	Hospital	1	NA
Wight ⁵¹	2003	UK	Cost-utility	Third party payer	10	6 (costs); 1.5 (outcomes)



4.3.1 Type of economic evaluation

Three of the studies performed cost-utility analyses,^{50, 51, 56} two of which^{50, 51} expressed their clinical outcomes in terms of quality-adjusted-life-years (QALYs). Groen et al.⁵³ carried out both cost-utility and cost-effectiveness evaluations with results reported as cost per QALY and cost per life-years saved (LYS).

Gómez et al.,⁵² captured outcomes as cost per DGF and PNF episodes avoided, while Costa et al.⁵⁷ purely looked at the cost per DGF episodes avoided. The remaining two studies^{54, 55} consisted of cost-consequences analyses in which the authors analysed both costs and outcomes but did not attempt to present them in a combined manner. Amongst the outcomes captured in these studies we find DGF and rejection rates as well as hospital length of stay (LOS). In addition to these, Buchanan et al.⁵⁵ also captured mortality.

4.3.2 Time frame of analyses and discounting

Only one cost-utility study included in this analysis looked at costs and outcomes over a patient's lifetime⁵⁰ while the other two used a time horizon of 10 years^{51, 53} and justified it by the relatively old age of ESRD patients coupled with a lack of robust long-term survival data above that time period.

Wszola et al.⁵⁴ followed patients from five to ten years in their cost-consequences study but the remaining of the studies used a time horizon of three years or less^{52, 55-57} with the most recent cost-effectiveness analysis focusing purely on the period going from the transplantation up to hospital discharge.⁵²

Out of the five studies with a time frame of over a year, only three discounted costs and outcomes and gave information on the rates used. Groen et al.⁵³ used 4% for both costs and outcomes in their base case scenario, and justified it as an average of the most commonly used discount rates in economic evaluation (ranging from 3 to 5%). Bond et al.⁵⁰ used 3.5% following the most recent NICE guidelines and Wight et al.⁵¹ referred to discount rates of 6% for the outcomes and 1.5% for costs, reflecting the original UK Treasury recommendation commonly used by NICE prior to 2004, when a new guideline on methods of technology appraisal was published.⁵⁸

4.3.3 Perspective

Four studies were performed from a third party payer perspective,^{50, 51, 55, 56} while the remaining four presented their results purely from a hospital perspective.^{52-54, 57}

All considered for their analyses direct medical costs only, defined as any costs falling within the health care system and paid for by a third party payer and thus, excluded patient co-payments. No study captured productivity losses or family costs.

4.3.4 Population

Five studies identified in our review were model-based,^{50-52, 56, 57} while the evaluation by Groen et al.⁵³ was, for its short-term analysis, performed alongside a multicentre RCT (*i.e.* the European Machine Perfusion Trial – EMPT). This population-based study included 672 recipients overall. The two remaining studies, built on case reviews, presented populations of 5 840⁵⁵ and 415⁵⁴ recipients.

The extent to which donor type could influence the cost-effectiveness of MP remains an interesting question. Donor types included in the analyses varied from one study to another with two evaluations focusing purely on expanded criteria donors (ECD).^{52, 55, 57} Three further studies^{53, 56, 57} included both ECD, and standard criteria donors (SCD). It is important to highlight that although the EMPT on which the studies by Gómez et al.,⁵² Groen et al.⁵³ and Garfield et al.⁵⁶ were based, mainly included SCD (n=242), they also included 94 ECD and subgroup analysis was performed for this population to assess how the results would vary from those obtained for the SCD population.

The involvement of both donations after cardiac death (DCD) and donations after brain death (DBD) was present in four studies.^{50, 51, 53, 57} The two most recent of these studies, covered in the case of DCD, the so called “controlled DCDs”; that is to say Maastricht categories III and or IV, the most commonly used categories in countries where DCD is authorised (see Table 1 on the Maastricht classification). This is important and may explain why the recent Spanish study by Gómez et al.⁵² focused exclusively on ECD and did not evaluate DCD, another interesting pool of donors according to the recent literature,^{29, 51} since in Spain DCD transplants have, up to date, been limited to “uncontrolled” cardiac deaths



(i.e. Maastricht categories I and II) and thus, the results from the EMPT for DCD, primarily based on “controlled” (Maastricht category III and IV) would not fit well with the current legal and clinical national situation in the country. This is also the case in France.⁵⁹

The remaining retrospective case review⁵⁴ considered kidneys coming from DBD only, reflecting the national legal framework in that country, since DCD was not legal in Poland at the time the study was performed. The situation has since then, changed. However, there are still countries such as Germany,⁵⁹ where despite participation of German patients in the EMPT, DCD is still not allowed.

4.3.5 Intervention and comparator

All studies but two^{51, 54} evaluated the cost-effectiveness of LifePort[®]. There are different reasons why this may be the case: 1. Most recent trials, including the EMPT and the UK PPART trials involved the use of the LifePort[®] as opposed to the RM3[®] system; 2. RM3[®] is not portable and thus, cannot be used to transport the organs but to perfuse them at the “recipients” site, which makes LifePort[®] the preferred option, most commonly used around Europe 3. Bond et al.⁵⁰ explicitly mentioned the lack of data on RM3[®] machine costs, as the main reason to model only the costs of LifePort[®].

CS represents the only other option to preserve kidneys prior to transplantation.

4.3.6 Cost and outcome inputs

Costs were derived from the published literature or the hospital’s own finance records. With regard to outcomes all studies but four, the two case reviews^{54, 55} and the two modelling exercises published before 2009^{51, 57} used for their models data obtained from the EMPT as one of their main sources of clinical inputs. The two cost-models published before the results of the EMPT were known based their inputs on the results from their own meta-analyses composed primarily of retrospective case studies, since no good quality, large RCT studying the value of MP was published before that time, while the two case reviews made use of their own hospital records for analysing relevant outcomes.

QoL is an important factor to bear in mind when studying chronic conditions such as ESRD, for which important differences have already been reported in the literature between patients with a functional graft versus those on dialysis.^{10, 11, 13} QoL values for three of the four cost-utility studies here included^{50, 51, 53} were taken from different published sources and while Bond et al.⁵⁰ and Groen et al.⁵³ based their assumptions on UK general population valuations of the different health states and sensitivity-tested assumptions taken from a previously published economic evaluation on ESRD treatment by de Wit et al.,⁶⁰ Wight et al.⁵¹ used a study which employed time-trade-off⁶¹ to calculate the relevant utilities. The remaining cost-utility study by Garfield et al.⁵⁶ made overly simplistic assumptions in which those with a functional graft after a year received a weight of 1, those with PNF received a weight of 0 and those with DGF received a utility score of 0.5.

4.3.7 Modelling

Two studies consisted of Markov models. The most recent used a very simple structure including a cycle length of a year, with three possible states: functioning graft, graft failure and death.⁵³ The other used monthly cycles and nine discrete health states, presenting overall, a more complex structure which was nevertheless, well described⁵⁰ offering additional information in the form of appendices to the main document in order to increase transparency.

The remaining four models were decision-analytic models^{51, 52, 56, 57} the design of which was, overall, kept simple.



4.3.8 Results

4.3.8.1 Incremental costs

Table 12 shows the average costs obtained in the eight studies included in our review. Comparisons between studies are difficult primarily because of the different costs borne in mind but also due to the different time horizons or donor types included in the calculations.

Only one study out of the eight showed a small increment in costs when using MP⁵² in ECD but covered only the period from transplantation to hospital discharge, while a further study⁵⁰ included three separate models, two of them based on data from two RCTs with different clinical results. On the one hand, the UK PPART study²⁵, concluded that MP did not offer any clinical advantage over CS in terms of DGF, graft function (measured by estimated glomerular filtration rate – eGFR) at 3 and 12 months or long-term outcomes (*i.e.* graft or patient survival) at year 1, while on the other hand, the EMPT³¹ showed significant improvements in DGF rates, shorter DGF periods and higher graft survival with MP versus CS at year 1. Costs shown in these two last models mirrored the clinical evidence used, with the model based on the EMPT showing cost savings linked to the use of MP versus CS and the model based on the PPART study showing savings for CS use.

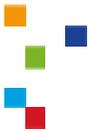
The remaining evaluations (including the third model developed by Bond et al., based on a cohort study in 60 DCD kidney recipients) showed CS to be more expensive overall than MP, despite the higher initial purchasing costs linked to the latter. The main cost components that helped to balance out these high initial purchasing costs appeared to be hospitalisation costs (longer LOS for patients on CS) and dialysis costs.

With regard to unitary machine prices, the literature quotes prices ranging from a high of €14 400⁵³ to a low of US\$6 060 (\cong €4 709)⁵² for LifePort[®]. The unitary prices for the RM3 machine quoted in Wight et al.⁵¹ are higher: GBP25 762 (€30 302), although a direct comparison between these two machines may not be advisable since there are important differences in their use (*e.g.* RM3 is a non-portable machine that allows for the perfusion of one or two kidneys at a time). With regard to the price of the consumables required to perfuse the organs, the literature quotes prices ranging from a low GBP475 (€559)⁵⁰ to a high US\$1 337 (€1 039)⁵² per transplant; while those for the RM3 machine are of GBP732 (€861).⁵¹ It is important to note that the study by Gómez et al.⁵² in which the unitary price of the machine appears to be the lowest is also the one quoting the highest cost of consumables required to perfuse a kidney.



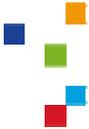
Table 12 – Costs of Machine Perfusion in renal transplantation

Study	Costing year	Time horizon (years)	Costs included	Donor	Clinical data source	Intervention	Mean cost/patient over study period (as reported)
Gómez 2012 Spain	2010	Up to patient discharge post Tx	Labour costs, hospital stay, dialysis, diagnostic test, technical equipment, consumables	ECD	EMPT (MP)	MP (LifePort)+UW solution	US\$10 759
					Own hospital records (CS)	CS (UW solution)	US\$10 254
Groen 2012 Belgium, Germany & Netherlands	2007	Short-term: 1	Hospital stay, dialysis, complications, diagnostic tests, technical equipment, consumables	DBD, DCD, ECD	EMPT	MP (LifePort)+modified UW solution	€6180
		Long-term: 10				CS: assumed 50% UW, 50% HTK solutions	€8053
Bond 2009	2007	Lifetime	Storage solution, capital equipment, post-Tx dialysis (inpatient), explants, ongoing care	DCD	PPART	MP (LifePort)	GBP141 319
						CS (ViaSpan solution)	GBP139 205
				DBD, DCD	EMPT	MP (LifePort)	GBP139 110
						CS (ViaSpan solution)	GBP142 805
				DCD	Cohort data registry	MP (LifePort)	GBP132 953
						CS (Marshall's solution)	GBP144 332
Garfield 2009 USA	NA	1	Material and capital equipment, dialysis, hospitalisation, Tx, ongoing care	SCD, ECD	EMPT	MP (LifePort)	SCD: US\$87 254; ECD: US\$91 871
						CS	SCD: US\$92 035; ECD: US\$95 676



Wszola 2009 Poland	NA	5	MP, post-Tx haemodialysis, hospitalisation and lab tests	DBD	Data registry	MP (MOX-100)+ MPS-II solution	US\$43 787
						CS	US\$46 484
Buchanan 2008 USA	NA	3	Hospitalisation costs related to Tx	ECD	Data registry (OPTN)	MP	US\$137 995
						CS	US\$141 882
Costa 2007 Canada	2006	1	Capital equipment and disposables, in-hospital resource consumption (lab tests, medication, dialysis, etc) associated to DGF	DBD, DCD, ECD	MA of published literature - no RCTs (MP)	MP	Incremental cost of MP vs CS: -CAN\$698
						Own centre data (CS)	NA
Wight 2003 UK	2002	10	Capital equipment and disposables, graft loss, DGF	DBD, DCD	MA of published literature - no RCTs	MP (RM3)	Incremental cost of MP vs CS: in SCD: GBP600; in DCD: GBP1900
						CS	NA

CS= Cold storage; DBD= Donation after brain death; DCD= Donation after cardiac death; DGF= Delayed graft function; ECD= Expanded criteria donors; EMPT= European Machine Perfusion Trial; HTK=Histidine-Typtophan-Ketoglutarate (HTK); MA= Meta analysis; MP= Machine perfusion; NA= Not available; OPTN= Organ Procurement and Transplantation Network; PPART= Pulsatile Perfusion in Asystolic Donor Renal Transplantation; RCT=Randomised controlled trial; Tx= Transplant; UW= University of Wisconsin.



4.3.8.2 Incremental outcomes

Seven⁵¹⁻⁵⁷ out of the eight studies reported positive effects for MP in perfusing kidneys from different types of donors when compared to CS (Table 13). Four of the studies were based on clinical data derived from the same trial (EMPT).

The remaining study by Bond et al.⁵⁰ resulted, once more, in different results depending on the clinical data source used, displaying positive results towards MP, when using EMPT data³¹ or data from the Plata Muñoz et al. cohort study,⁶² but supporting the use of CS when using data from the PPART study,²⁵ although it is important to highlight that both the PPART study and the study by Plata Muñoz et al. included DCD only and presented smaller sample sizes.

Three of the cost-utility studies^{50, 51, 53} included in this review used QALYs as their main outcome measurement. Incremental QALYs from using MP as opposed to CS ranged from a high of 7.79 QALYs in a population with different types of donors (by cause of death: DBD=294 versus DCD=42; by type of donor: SCS=242 versus ECD=94)⁵³ to a low of 0.03 QALYs, in kidneys from DBD, and 0.05, in kidneys from DCD.⁵¹ The cost-utility study by Garfield et al.⁵⁶ incorporated overly simplistic utility weights applied to their main outcome, described as graft function.

The remaining four analyses^{52, 54, 55, 57} focused their evaluations on DGF as their main outcome, with Gómez et al.⁵² using the clinical data from the EMPT. All of these evaluations showed a benefit when using MP as opposed to CS, although the size and significance of the differences varied from one study to another.

The two studies built on case reviews^{54, 55} considered other outcomes in addition to DGF, such as hospital length of stay (LOS) post-transplantation, and graft and patient survival. Wszola et al.⁵⁴ found no statistically significant differences in terms of mortality but did find significant differences in long-term graft survival (68% with MP versus 54% with CS; $p=0.02$) and return to dialysis (20% with MP versus 36% with CS; $p=0.01$). Although the same authors also reported benefits from using MP in short-term outcomes such as hospital LOS post-transplantation, this difference was small.⁵⁴ In contrast, Buchanan et al.⁵⁵ did not find significant differences in either hospital LOS post-transplantation or long-term graft

rejection or survival. The differences in outcomes between these two retrospective case reviews could come partly explained by the study populations, with Wszola et al. focusing in DBD and Buchanan et al. on ECD, or by study time horizons with the former looking at a 5-year period, more appropriate to capture long-term clinical outcomes such as graft or patient survival, versus the latter, covering a 3-year period.

4.3.8.3 Incremental cost-effectiveness ratios (ICERs)

Table 14 shows that with the exception of one of the models developed by Bond et al.⁵⁰ using the clinical data from the PPART study, and the short-horizon study by Gómez et al.,⁵² all other evaluations found MP in renal transplantation to be dominant (*i.e.* more effective and less costly) when compared to CS, while in the case of Gómez et al. the ICER was low (US\$3 369; €2 402).

The consistency of results should, once more, not come as a surprise, given that four out of the six studies which calculated ICERs, used as their clinical basis the results obtained in the EMPT study which showed MP to be significantly more effective in terms of functioning grafts when compared to CS.

According to the studies reviewed, the more frequent need for dialysis and the longer hospital stays in the CS groups were the main factors explaining the lower overall costs of MP compared to CS despite the higher initial acquisition costs linked to the use of the former. However, both Bond et al. and Groen et al.^{50, 53} highlighted in their studies the greatest weight of graft survival on the overall dialysis and hospitalisation costs versus the limited weight of DGF, which may explain in part why results of their EMPT models were unclear for the DCD population in which DGF rates appear to be much higher in the CS group but graft survival does not significantly differ from one group to the other.

Looking at the literature on costs of dialysis versus transplantation we can easily illustrate the importance of graft survival and its weight on overall costs. A recent study by Cleemput et al.⁶³ reported mean yearly expenditures to the hospital for dialysis of approximately €45 715 per patient in Belgium, while a study by Van Biesen et al.⁶⁴ estimated transplantation expenditures to be around €37 166 on the first year, decreasing to around €12 810 from the second year post-transplant (stable



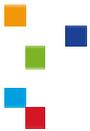
transplant). Based on these data, (updated to 2011 costs by using consumer price indexes by the OECD - www.oecd.org), cost differences between a successfully transplanted patient and a patient on dialysis in Belgium would be of approximately €147 743 in favour of the transplanted patient over a 5-year horizon. The impact of DGF on costs is, on the other hand, not as clear and would largely depend on the length of DGF and the number of extra dialysis sessions (at approximately €313 per hospital session) or extra hospitalisation days required by a patient.

The available evidence for which sensitivity tests were performed concluded that their main findings were robust, with probabilities for MP being dominant of 86% in the case of Groen et al.⁵³ and of 99.10% in the case of Costa et al.⁵⁷ The analysis by Wight et al.⁵¹ showed a probability of MP being dominant of 50-60% if kidneys came from DBD, which increased to 80% when kidneys came from DCD. However, it is important to note that this model was based on a meta-analysis (MA) of clinical studies considered of poor quality and which preceded the development of large RCTs in this area. Finally, Bond et al.⁵⁰ showed robust results when modelling clinical data from the EMPT, with a probability of MP being dominant of 77.7%. This probability went down to 27.4% when the model was based on the PPART clinical data. The model developed by the same authors comparing Marshall's solution CS preservation with LifePort[®] also found robust results favouring MP over CS but the fact that it was based on a non-randomized study coupled with a low sample size made their results less reliable.

With regards to transferability of results to the Belgian case, the EMPT included Belgian patients and, although the authors made use of Dutch costs for their base case calculations, some country specific variations in resource consumption were taken into consideration in their sensitivity analyses to ensure the overall results would not largely change. Thus, for Belgium, the authors included in their calculations an additional ultrasound and biopsy in case of graft failure, as well as weekly biopsies for cases presenting persistent DGF. These additions resulted in procedural costs in case of graft failure €324 higher for the MP arm and €400 higher for the CS arm when compared to the base case populated with Dutch cost data. Thus, the Belgian specific scenario did not change the overall results which remained favourable towards MP use. Table 13 – Outcomes of Machine Perfusion in renal transplantation.



Study	Time horizon (years)	Outcomes considered	Donor	Source of clinical data	Intervention	Results (discounted information is available) if
Gómez 2012 Spain	Up to patient discharge post Tx	Probability of IGF, DGF, PNF	ECD	EMPT (MP)	MP (LifePort)+UW solution	IGF: 0,71; DGF: 0,26; PNF: 0,03
				Own hospital records (CS)	CS (UW solution)	IGF: 0,56; DGF: 0,38; PNF: 0,06
Groen 2012 Belgium, Germany & Netherlands	Short term: 1 Long term: 10	QALYs	DBD, DCD, ECD	EMPT	MP (LifePort) + modified UW solution	Incremental QALYs: 7.79*
					CS: assumed 50% UW, 50% HTK solutions	NA
Bond 2009 UK	Lifetime	QALYs	DCD	PPART	MP (LifePort)	9.13
					CS (ViaSpan solution)	9.19
			DBD, DCD	EMPT	MP (LifePort)	9.79
					CS (ViaSpan solution)	9.58
			DCD	Cohort data registry	MP (LifePort)	9.54
					CS (Marshall's solution)	8.55
Garfield 2009 USA	1	Probability of (utility-weighted) graft function	SCD, ECD	EMPT	MP (LifePort)	SCD:0.94; ECD:0.87
					CS	SCD: 0.88; ECD: 0.84
Wszola 2009 Poland	5	<u>Short-term:</u> DGF, hospital LOS post-Tx; # of HD; <u>Long-term:</u> graft and patient survival; return to dialysis	DBD	Data registry	MP (MOX-100)+ MPS-II solution	<u>Short-term:</u> DGF: no ss difference; LOS(days): 21.24** ; # of HD: 1.47** <u>Long-term:</u> graft survival: 68%** ; return to dialysis: 20%**; patient survival: 83.5%
					CS	<u>Short-term:</u> DGF: no ss difference;



						LOS(days): 22.43** ; # of HD: 2.67** <u>Long-term</u> : graft survival: 54%**; return to dialysis: 36%**; patient survival: 83%
Buchanan 2008 USA	3	Short-term: DGF, DGF duration; LOS post- Tx <u>Long-term</u> : Graft rejection; graft and patient survival	ECD	Data registry (OPTN)	MP	Short term: DGF: 26.9%**; LOS post-Tx (days): 12.2 <u>Long-term</u> : rejection: 9.8%; graft and patient survival: no ss difference.
					CS	<u>Short-term</u> : DGF:38%**; LOS post-Tx (days): 14.1 <u>Long-term</u> : rejection: 9.0%; graft and patient survival: no ss difference.
Costa 2007 Canada	1	DGF events avoided	DBD, DCD, ECD	MA of published literature - no RCTs (MP)	MP	Incremental effects: 0.059
					CS	NA
Wight 2003 UK	10	QALYs	DBD, DCD	MA of published literature - no RCTs	MP	Incremental effects: for MP vs CS in DBD: 0.03; in DCD: 0.05
					CS	NA

* Adjusted, discounted estimations

** statistically significant results (taken from the retrospective reviews).

CS= Cold storage; DBD= Donation after brain death; DCD= Donation after cardiac death; DGF= Delayed graft function; ECD= Expanded criteria donors; EMPT= European Machine Perfusion Trial; HTK=Histidine-Tryptophan-Ketoglutarate; IGF= Immediate graft function; LOS= Length of stay; MA= Meta analysis; MP= Machine perfusion; NA= Not available; OPTN= Organ Procurement and Transplantation Network; PNF= primary non-function; PPART= Pulsatile Perfusion in Asystolic Donor Renal Transplantation; QALYs= Quality adjusted life years; RCT=Randomised controlled trial; ss= statistically significant; Tx= Transplant; UW= University of Wisconsin.



Table 14 – ICERs for Machine perfusion in renal transplantation

Study	Time horizon (years)	Donor	Source of clinical data	Intervention	ICER-definition	ICER (base case)	Prob. Of MP being dominant
Gómez 2012 Spain	Up to patient discharge post Tx	ECD	EMPT	MP (LifePort)+ solution (UW)	Cost/avoided case of PNF or DGF	US\$3369	NA
Groen 2012 Belgium, Germany, Netherlands	10	DBD, DCD, ECD	EMPT	MP (LifePort)+ solution (modified UW)	Cost/QALY	MP dominates	86%
Bond 2009 UK	Lifetime	DCD	PPART	MP (LifePort)	Cost/QALY	CS dominates	27%
		DBD, DCD	EMPT			MP dominates	78%
		DCD	Cohort data registry			MP dominates	87%
Garfield 2009 USA	1	SCS, ECD	EMPT	MP (LifePort)	Cost/functioning graft	MP dominates	NA
Costa 2007 Canada	1	DCD, ECD	Own MA (no RCTs)	MP (LifePort)	Cost/avoided cases of DGF	MP dominates	99%
Wight 2003 UK	10	DBD, DCD	Own MA- (no RCTs)	MP	Cost/QALY	MP dominates	DCD: 80%; DBD: 50-60%

CS= Cold storage; DBD= Donation after brain death; DCD= Donation after cardiac death; DGF= Delayed graft function; ECD= Expanded criteria donors; EMPT= European Machine Perfusion Trial; MA= Meta analysis; MP= Machine perfusion; NA= Not available; PPART= Pulsatile Perfusion in Asystolic Donor Renal Transplantation; RCT=Randomised controlled trial; Tx= Transplant; UW= University of Wisconsin.



4.3.9 Sensitivity analysis

Uncertainty is intrinsic to any economic evaluations and should therefore always be accounted for. Two evaluations built on case reviews^{54, 55} and the most recent cost-effectiveness analysis⁵² did not undertake any kind of sensitivity analysis to assess the robustness of their results, while a further study⁵⁶ undertook a best and worst scenario analysis for the clinical outcomes and talked about a sensitivity analysis but neither did it clearly state what kind of method was used nor did it provide a detailed reporting of its results. The remaining four studies^{50, 51, 53, 57} included probabilistic sensitivity analyses, which in two cases^{53, 57} supported their main findings and in the other two, robustness depended on donor pool⁵¹ (increased probability of MP for being cost-effective in DCD as opposed to DBD where the advantage was not that clear), or source of clinical data⁵⁰ (more robust results when using EMPT data as opposed to UK PPART study, looking purely at DCD).

Probabilistic sensitivity testing showed results to be primarily sensitive to effectiveness parameters (*i.e.* long-term graft survival or DGF), dialysis costs according to Bond et al.⁵⁰ and to important increases (three-fold) in the cost of MP disposables, according to Groen et al.⁵³

4.3.10 Conflict of interest

Three studies^{52, 54, 57} did not include in their manuscripts a declaration of conflict of interest. From the five studies which did, only three^{51, 53, 55} reported no conflict of interest; while the study by Garfield et al.⁵⁶ was sponsored by the industry. The evaluation by Bond et al.⁵⁰ reported an indirect potential conflict of interest since one of their investigators took part in the PPART study. The existence of conflicts of interest may introduce a bias which could affect the validity of the study results, although there is, up to date, no hard evidence on this.

4.3.11 Discussion

Despite the limited evidence coming from randomized controlled trials up to date, there is a high level of consistency indicating that machine perfusion is likely to be cost-effective compared to cold storage in, particular for kidneys coming from expanded criteria donors, a pool of donors which is becoming more common due to large waiting lists for kidney transplantation and insufficient numbers of standard criteria donors

to meet the existing demand in EU countries. However, despite this consistency there is a number of important points worthwhile considering:

Sources of clinical data

The most recent four analyses used clinical data from the same trial: the European Machine Perfusion trial, so consistency in their overall results is expected. Although the choice of the source is justified in that the European Machine Perfusion trial represents the largest multi-country, multicentre randomized controlled trial up to date, its repeated use in a number of recent cost-effectiveness studies may give the wrong impression that there is more evidence than there actually is. Moreover, there are uncertainties on the robustness of results from this clinical study (see clinical review).

Time horizon

One weakness in all models included in our review was the short time horizon used, with only three looking at time periods of ten years or over^{50, 51, 53} while three^{52, 56, 57} covered one year or less, an insufficient time frame to adequately capture any long-term consequences of the intervention of focus.

Effectiveness in brain-dead donors and expanded criteria donors

There was, at the time the studies here included were published, important uncertainties specifically linked to the lack of robust long-term graft survival data. As explained in the clinical chapter, some evidence was published in 2012 reflecting an extension of the European Machine Perfusion trial showing a continuous beneficial effect of machine perfusion over cold storage over a 3-year period.³⁰ This evidence gives more weight to the results obtained in the long-term economic evaluations based on that trial.^{50, 53}

Despite delayed graft function being only a short-term outcome which offers a partial view of the cost-effectiveness of machine perfusion, the higher costs and worse clinical outcomes linked to patients on dialysis compared to those transplanted and with a functioning graft⁶³ make the short-term impact of machine perfusion on delayed graft function, for brain-dead donors and expanded criteria donors still relevant.



Thus, although limited, the available economic evaluations published to date for brain-dead donors, and in particular for expanded criteria donors appear to show a benefit, mainly driven by either higher graft survival or lower delayed graft function rates when kidneys are machine-perfused as opposed to preserved by means of cold storage.

Effectiveness in donation after cardiac death

Similarly to what we saw in the clinical chapter, results regarding the cost-effectiveness of machine perfusion specifically in donation after cardiac death remain unclear. On the one hand, the European Machine Perfusion trial showed lower delayed graft function rates by using machine perfusion versus cold storage but captured a very low number of graft failures for this type of donations which impeded the drawing of clear conclusions on overall graft survival. On the other hand, the results obtained in the Pulsatile Perfusion in Asystolic Donor Renal Transplantation trial concluded that no significant differences exist in either delayed graft function or graft survival for kidneys coming from donors after cardiocirculatory death between machine perfusion and cold storage.

Modelling/assumptions

Some of the studies included assumptions not well backed-up with literature regarding the cost of machine perfusion since this was often calculated by taking into consideration the number of transplants performed per year in which machine perfusion was used/to be used, assuming two machine units per centre and around 30 kidneys perfused per machine unit.

In addition to this and given the limited recent experience with machine perfusion, it is not clear how many machines would truly be required in clinical practice to cover specific numbers of transplants, and although all studies which mentioned this explicitly appear to quote two machines per transplantation unit, this simply reflects the minimum required, given that each (LifePort[®]) machine can only perfuse one kidney at a time and thus, two are needed at the time of procurement. Despite the theoretical basis for such estimates the studies by Bond et al. and Groen et al.^{50, 53} specifically looked at the weight of these factors on the overall results during their sensitivity analyses and concluded that they would not be likely to greatly affect their overall conclusions.

Finally, the main trial used as source of clinical data (the European Machine Perfusion trial) presented a limitation in that there were some missing values with regard to subsequent dialysis which should have followed the first session, in patients experiencing primary non function or late graft failure. In such cases, estimates of the expected number of dialysis according to established clinical practice were used (*i.e.* three sessions/week). Missing values were replaced for a year after primary non function or graft failure (unless death was recorded prior to that time). There were also some missing values regarding hospital admissions which were replaced by “0” values under the assumption that, should a hospitalisation have taken place, it would have been captured by the researchers. Since these factors could have some weight on the overall results, given the importance of dialysis and hospitalisations costs, Groen et al.⁵³ studied the impact that potential variations in such estimates could have on the overall study results and concluded that even if these costs were set to 0, the estimates would still favour machine perfusion over cold storage.

Transferability of results to the Belgian situation

The study by Groen et al.⁵³ is of particular interest not only because the results obtained by the authors appear to be backed up with results previously seen in retrospective case reviews and the recent extension of the trial confirmed the short-term results over a longer 3-year time period, but also because it was carried out alongside an international, multicentre randomized controlled trial which included Belgian patients and an important number of kidneys coming from different types of donors. However, the evidence offered by this trial, is not exempt of weaknesses (see chapter 4 for more details), which coupled with the limitations here discussed make a cautious interpretation of the results necessary.

The authors of this review believe that the potential value of modelling the Belgian situation would be, at present, limited since the best clinical source up to date has already been modelled by Groen et al.,⁵³ incorporating Belgian-specific resource consumption in their sensitivity analysis and so our own model would likely suffer similar drawbacks as those here discussed, linked primarily to the estimations on graft survival (in particular for donation after cardiac death), reflecting existing knowledge gaps.



A crucial factor to bear in mind when transferring the results from Groen et al. to the Belgian situation is the sensitivity to changes in the price of machine perfusion consumables. Three-fold increases would, according to the authors of the study, make the current results (machine perfusion dominance) uncertain, which would put a cap on disposable costs at around €2 000. A similar price ceiling is reached by using the Belgian model considered by these authors in their sensitivity analysis (Table 15).

Table 15 – Impact on mean total costs per patient of changes in the price of consumables in Belgium

Baseline case: consumable cost = €635		
	Machine Perfusion	Cold Storage
Preservation cost	842	167
Mean total cost/patient	6 148	7 403
Sensitivity analysis: consumable cost = €1 270		
Preservation cost	1 477	167
Mean total cost/patient	6 783	7 403
Sensitivity analysis: consumable cost = €1 905		
Preservation cost	2 112	167
Mean total cost/patient	7 418	7 403

Note: Estimations reflecting Belgian resource consumption used in the sensitivity analysis by Groen et al.⁵³ Data provided by the authors of the study.

5 ORGANIZATIONAL AND FINANCIAL ASPECTS LINKED TO MACHINE PERFUSION USE IN BELGIUM AND NEIGHBOURING COUNTRIES

The use of these perfusion machines in renal transplantation has, so far, been limited in Europe, with both organisational and financial barriers hindering their widespread adoption.

This chapter focuses on these issues. Scientific, grey literature as well as contacts with MP manufacturers and experts in the field formed the basis for the content of this chapter.

5.1 Reimbursement and organization of machine perfusion in neighboring EU countries

The main barrier for the use of MP at present in most EU countries is the lack of reimbursement, which makes it necessary for transplant units to absorb the whole cost of their use. This has resulted in a fragmented picture with some centres (2 in Belgium) deciding to use it in certain situations and others not having had any experience with it. This is the case in most EU countries with the exception of France, where a decision was taken to introduce public coverage for the use of these machines in 2012, in an attempt to increase the quality and number of kidney transplants.

In this chapter, we will first introduce the specific case of France to then describe what the situation currently is in Belgium and neighbouring countries.

5.1.1 France

The use of MP in renal transplantation in France has been, up to date, limited and focused on kidneys from DCD. However, this is likely to change, following the recent introduction of specific funding for machine-perfused kidneys from ECD. This makes France the first EU country putting in place financial incentives for expanding the use of these machines in clinical practice.



The decision was made with the aim of better responding to the growing waiting list for kidneys in the country and was primarily based on the findings regarding survival at one and three years reported in the EMPT.³¹ In addition to the clinical evidence considered, a macroeconomic analysis looking at the overall costs of transplantation versus dialysis in ESRD⁶⁵ was also performed to gain an idea of the potential savings to be made if MP helped to expand the current “usable” kidney pool.

The available funding/reimbursement scheme is explained below in some detail. Information was extracted from a report by the *Agence de la Biomédecine* in France (French Biomedicine Agency).⁶⁶ Parts of this funding are being paid from public research sources and data will be captured in the next few years to further clarify the value of MP in renal transplantation.

5.1.1.1 Kidney extraction – professional act

For the professional act “extraction of the kidney/s” a lump sum is paid to the centre where the operation takes place. This is of €7 332.86 if only kidney/s (and not other organs) are harvested. A further lump sum is paid to the centre of affiliation of the surgical team performing the extraction. This is usually €404.74 for the kidney/s, but new 2012 funding arrangements include a lump sum which doubles the regular payment (*i.e.* €404.74) if the two kidneys extracted are placed on a perfusion machine (€808.00). This new lump sum aims at recognizing the additional operating time required to place the kidneys onto the machine.

If the kidneys come from DCD a different, higher, lump sum of €11 257.81, already covering the use of MP, is paid to the centre where the operation takes place. In this case a further payment is also made, as previously described, to the centre of affiliation of the surgical team performing the operation but only the tariff of €404.74 can be charged, since the use of MP is already covered under the first tariff. It is important to explain that at present in France only “uncontrolled” DCD are allowed (Maastricht categories I and II, see Table 1),⁶⁷ although there are discussions to extend this to “controlled” DCD in order to further expand the current pool of donors.⁶⁸

5.1.1.2 Annual transplantation tariff

A new component of the annual transplantation tariff (*Forfait Annuel Greffe*) was also introduced in 2012 to partly cover, the purchasing, maintenance and transportation of the machines, the purchasing of the software to control the parameters of the machine, the perfusion kit and the management and organization linked to the practical use of MP. This tariff is a once-off yearly payment based on the transplant activity of the previous year. More specifically, a new payment of €8 814 can be requested per block of six kidney perfusions, at €1 469 per perfusion. Patients are exempt of any co-payment.

The types of donors in which this machine is currently recommended have been clearly identified by the *Conseil Médical et Scientifique de l'Agence de Biomédecine Française* (Scientific and Medical Council of the French Biomedicine Agency). Thus, all kidneys coming from DCD or those coming from DBD donor categorized as ECD because of their age or co-morbidities should be preserved by means of MP. No reimbursement is granted if MP is used in other donor types. The exclusion from reimbursement of kidneys coming from SCD was decided on the basis of the evidence found via the Eurotransplant study which showed a much larger graft survival benefit when kidneys from ECDs were machine perfused as opposed to kidneys from SCD.³¹

The organizational structure to be put in place for the acquisition of the machines varies. Transplant centres may decide to buy their own machines on an individual basis, in which case three is the recommended number of units to acquire, two to cover a pair of kidneys coming from a donor and the third one to cover for an eventual technical problem. Others may decide to use a central repository, located in an already established transplant centre, serving all units falling within their geographical area. This model has been chosen by the region of Lyon and is believed to offer advantages in terms of both the number of units needed to be acquired, and the negotiating power to buy the disposables.



Direct communication with representatives of the Biomedicine's agency in France revealed that, although procurement from ECD is already high, the uptake of MP is progressive and do not yet have enough data to confirm whether its use is facilitating and encouraging transplants with kidneys that would have otherwise been discarded. The necessary logistics, organisational structures and acquisition costs all play a role in this slow, yet progressive uptake.

Data on outcomes is currently being captured by the different French transplantation centres using the machine with the aim of analysing them in some detail in the near future.

5.1.2 Germany

The Deutsche Stiftung Organtransplantation (DSO, German Organ Transplantation Foundation, www.dso.de) coordinates all steps involved in organ donation procedures and provides a range of services to support hospitals around the clock. These services include the transport of kidneys to the transplant units and ensuring donations can be performed in any German hospital. Similarly to the situation in Belgium, Germany is part of Eurotransplant, organization responsible for the allocation of organs. Transplantations are exclusively performed in approximately 50 transplant units located all over the country. In contrast with the situation in any of the other countries here analysed and based on the German Transplant Actⁱ, DCD is not allowed. This fact, coupled with logistical challenges linked to MP use and the current financial crisis have resulted in a lack of use of these machines. This is the case despite the participation of the federal state of North Rhine-Westphalia in the Eurotransplant trial,³¹ covered in some detail in chapters 3 and 4.

5.1.3 The Netherlands

In the Netherlands there are, at present, five procurement teams overall. Transplant surgeons are responsible for organ harvesting and, when MP is used, for their placement in the machine that is then used to transport the organs to the recipient's site.

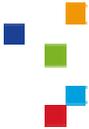
So far, no reimbursement is available to specifically cover the cost of the machines, although negotiations are under way for reimbursing the machine for all kidneys (DBD and DCD) which will stay local (*i.e.* Dutch kidneys for Dutch recipients).

A recent thesis¹⁶ covered the potential organizational structure required in the Netherlands to ensure the appropriate use of these machines and suggested the acquisition of 4-6 machines per procurement region (four in total which would translate into 16-24 machines for the whole of the country). This would correspond approximately to a minimum of two machines per transplantation centre since there are overall eight of these centres according to the Dutch Transplant Foundation (NTS – www.transplantatiestichting.nl). The idea behind having 4-6 machines per procurement region was justified as a way to maintain a regular number of machines within each region which could then be used to respond to the overall demand. The recipient centre would be responsible for cleaning and storing the machine until this is needed for a further transplant. If there is a shortage in one region at a specific point in time the machines could be couriered between two regions to ensure a balance is kept.

5.1.4 Spain

In Spain there are, up to date, no organizational or financial structures set at a national or local level to facilitate the use of MP in renal transplantation, and as a consequence, few transplantation units own and use this type of devices. In those cases in which they are used it is the hospital that pays for the acquisition cost of the device as well as for the disposables required for its use. The few transplant units that use MP at present have two machine units.

ⁱ German Transplantation Act (Transplantationsgesetz, TPG) on organ and tissue donation, removal and transplantation from the 5/11/1987, operational since 1/12/1997.



The indication and use differ slightly from one centre to another but in general, these machines are only used for the preservation of ECD or “uncontrolled” (Maastricht categories I-II- see Table 1) DCD kidneys.

There are no transplant centres per se in Spain. Transplants are performed in hospitals specifically accredited to perform such operations (around 45 overall, of which 37 focus on adult and 7 in paediatric transplantation). In those cases in which the kidney is obtained in a different centre to the one where the transplantation is to take place, and given the fact that only a few centres own the machines, organs are usually machine perfused only once they reach the hospital where the recipient is.

5.1.5 UK

So far, no reimbursement is available in the UK. The use of MP in renal transplantation is organised on a case by case basis and decided by individual transplant units.

At present, it is mainly kidneys from DCDs which are being machine-perfused in some centres. The main reason for this is that DCD kidneys are handled locally, which simplifies the logistics linked to machine use and transportation. The final decision remains surgeon/centre specific.

Kidney retrieval is the responsibility of seven nationally commissioned organ retrieval teams. The system works independently of the type of donor. If one of the 25 renal centres currently in place in the UK decides to put the DCD kidneys on a machine, they would need to transport the machines to the hospital themselves and most frequently, the retrieval team transports kidneys back to the transplant unit by means of CS. Only once the kidneys are within the premises of the transplant unit they are machine-perfused. This model replicates the one used in the PPART UK trial on MP in DCD kidneys,²⁵ covered in more detail in chapters 3 and 4.

The number of machines available per transplant unit largely depends on the funding model. Some centres are provided with machines on a loan basis from Organ Recovery Systems (ORS), the manufacturers of LifePort[®] while others buy their own. Since only those kidneys extracted and transplanted locally (*i.e.* DCD) are usually perfused with these machines, it is very uncommon to require pumping more than two kidneys at a time. Thus, most often the number of machines used or acquired is limited to two.

A full review of this technology was undertaken in 2009 and revised in March 2013 by NICE,⁶⁹ following the publication of the results at one and three years of the Eurotransplant trial.³⁰ These reviews concluded that MP and CS are both recommended options for the storage of kidneys from deceased donors. The specific choice of preservation method should, according to this review, be made by taking into consideration a number of factors such as clinical and logistical factors. Finally, they argue that in those situations where both methods are considered equally appropriate the least costly should be prioritised. Despite recognising in their revision of 2013 the value of the recently published, long-term data captured via the extension of the EMPT, the reviewers decided not to change their original recommendations since MP was already presented as a valuable alternative to CS depending on the clinical situation.

5.2 Belgium – current situation and funding models to consider

Similarly to other EU countries aside from France, the lack of reimbursement in Belgium has resulted in very limited and fragmented use of MP in renal preservation by which, even those Belgian centres using the technology (at present only 2), do so for very specific cases since they have to absorb the costs themselves.

5.2.1 All-inclusive loan model

The current financial and logistical challenges linked to the acquisition of machine units, their transportation and maintenance have resulted in the manufacturers of LifePort[®] (ORS) offering an all-inclusive “loan” service”. In this model, one of the manufacturer’s perfusionists drives the machines (and necessary consumables) to the donor centre, assists in the placing of the kidneys onto the machines, then transports the organs to the recipients centre, once the latter has been confirmed by Eurotransplant, to finally take the machines back to clean and storage them following the completion of the transplant/s.



The current cost of this loan service amounts to approximately €3 000 per perfused kidney. Thus, if transplant numbers remained more or less stable we could assume (based on Eurotransplant figures) an overall target transplant population of 480 per year, which would translate into an all-inclusive yearly investment of approximately € 1 440 000. If the use and reimbursement of MP was limited to kidneys coming from sub-optimal donor populations (*i.e.* DCD and ECD), the yearly investment would instead be of € 676 800, assuming (based on 2012 Eurotransplant figures) that around 19% of all transplants from deceased donors are DCD, and 28% are ECD.

It is important to note that, at present, under this model, the manufacturer only requests payment if the kidney is finally transplanted.

Advantages linked to this model include:

- The relationship between the industry and the surgeon is intensified, while no real ties that could hinder competition exist. This is of particular importance in the current Belgian context in which only one machine is commercialised but there are at least two more currently entering the market. Increasing competition in the market is likely to influence prices, which in turn would influence positively the cost-effectiveness of machine perfusion (see section 4 for more details).
- Know-how directly passed from industry professionals to surgeons avoiding machine-specific learning curves.
- No need for maintenance and no risk of remaining without a machine for a period of time.
- Risk-sharing arrangement in which the manufacturer charges only for those perfused kidneys that are transplanted helps to limit waste.

5.2.2 Purchasing model

The alternative purchasing model would require for each Belgian transplantation centre to acquire a minimum of two machines per centre (one per kidney), or three machines, as per the French model, to ensure coverage for any technical or transportation problem. This would result in an overall investment of around €201 600 or €302 400 purely in machine units (for two or three machines respectively), based on an acquisition cost of €14 400.⁵³ Annualisation of these purchasing costs under a conservative

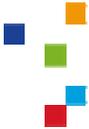
assumption of five years for the lifetime of each machine would result in a yearly investment of € 40 320 or € 60 480 for two or three machines respectively. In addition to this, a yearly insurance fee is required, amounting to approximately € 1 960 per centre, per year, independently of the number of machines bought per centre, that is to say an approximate annual cost of €13 720 in the case of Belgium (€1 960, multiplied by seven centres).

Finally, there would be the necessary investment in disposables, which according to a direct communication with the manufacturer have a commercial purchasing price of approximately €2 560 per perfused kidney. Assuming the same annual target population estimated for the “loan” model of 480 for all deceased donor transplants, it would result in a yearly cost of consumables of € 1 228 800. Thus, under this model, the overall mean yearly investment over a 5-year time horizon would be €1 282 840 or €1 303 000 for two or three machines bought respectively. If MP use was limited to ECD and DCD, the approximate mean yearly investment over the 5-year time horizon would be of € 631 576 or €651 736 for two or three machines (under the same assumptions on yearly transplants with DCD and ECD used for the loan model).

A disadvantage of this model would be that once the machines are bought, and bearing in mind there is at present only one transportable machine commercially available (Lifeport[®]), transplant units will be tied-up to buy the consumables from the manufacturers of this machine over the whole of the machine’s lifetime even if other machines entered the market during that time frame.

Transplantation centres would be responsible for the transportation of the machines to the donor centre and then back to their centre, as well as for their maintenance.

On the other hand, exchanges of machines between centres are likely to be more realistic once each centre owns the same number of machines. If however, not all centres buy the same number of machines, such exchanges would remain a challenge (centres owning the machine are likely to be reluctant to send off their machines to those that do not own one).



5.2.3 Central repository model

An alternative model would be to replicate the loan system currently offered by the manufacturers of LifePort® in Belgium within the premises of an already established centre, which could then act as a central repository for the whole of the Belgian territory. This would follow the example of the region of Lyon in France. A further possibility, although more expensive, would be to set up a completely new laboratory in a convenient, central location. The main advantage of such models would be that, given potential target transplantation figures for MP, likely to be limited, and the extension of the territory to be covered, the need for machine units is likely to be much lower. Under such scenario 6-8 machines (translating into 34 or 25 transplants, per machine, per year) are likely to be sufficient versus the 14-21 needed under the centre-specific purchasing scenario. Under these circumstances the necessary mean annual investment in machine units, over a 5-year time horizon, would amount to €17 280 or €23 040 for 6 or 8 machines respectively. Adding the insurance fee of €1 960 per year the mean annual investment in capital equipment would be of approximately €19 240 or €25 000 per year for 6 or 8 machines respectively, assuming the conditions of the insurance did not change (under this scenario a one-off yearly payment for the central repository centre for four incidences). After adding up the consumable costs, which would be the same detailed in the purchasing model (*i.e.* €1 228 800), the overall mean annual investment required over a 5-year horizon would be of approximately €1 248 040 or €1 253 800 per 6 or 8 machines respectively. Once more, if the use of this technology was limited to kidneys from ECDs or DCDs the mean yearly investment over the same time frame would go down to € 596 776 or € 602 536 per 6 or 8 machines respectively.

Similarly what we saw in the purchasing model, once the capital equipment is bought there would be a tie between the manufacturers or LifePort® and the transplant unit in that consumables would need to be bought from the former. However, considering the lower initial capital investment costs, this tie would be less restrictive than in the purchasing scenario.

This structure may thus, appear to provide a more economical organization method when compared to the purchasing model, while still moving the management of the machines from the hands of the manufacturer to the central repository unit. However, its main disadvantage is that it would require an investment to set up the new and necessary organization and human resources to co-ordinate the transport, storage, 24h/24 on-duty services, cleansing and use of these machines for the whole of the Belgian territory. Although this has not been accounted for in our calculations, it is likely to exceed the small economies expected when compared to the all-inclusive loan model, while a careful comparison with the “purchasing” model, taking into consideration the Belgian context and costs, would be required to confirm which of these last two models may be economically more attractive in the long-term.

In the case of France, the purchasing model was preferred over the central repository system, since the personnel already devoted to CS in each transplantation centre took over the responsibility for MP and so a significant increase in the need for human resources was not noticed, while a noticeable investment in human resources would have been required if wanting to set up a central repository model. In addition to that, the extension of the French territory posed a further challenge for the adoption of a central repository system (personal communication, Benoit Barrou, Groupe hospitalier Pitié – Salpêtrière, Paris). However, given that the extension of the Belgian territory would not pose a similar challenge in the adoption of a centralised model, careful consultation with experts in the field, already using the machine, would be required to truly understand the human resources and organisational implications that would be linked to each of the two last models before clear conclusions can be drawn in this regard.



It is important to clarify that these calculations are an oversimplification. Clearly, not 100% of the kidneys coming from the relevant donor populations (all deceased donors or DCD and ECD, depending on the reimbursement decision made) would be machine-perfused, since, for example any organs coming from abroad would be transported by CS. Furthermore, there is likely to be a learning curve and a natural uptake during the first years of implementation and finally, transplant figures, in particular those with kidneys coming from DCD or ECD may change (likely to increase) from one year to another, but the purpose of these calculations is purely to give an idea of the sort of magnitudes that should be born in mind.

Although for the purpose of these illustrations a conservative approach was taken and commercial prices directly communicated by the manufacturer were used, it is important to remember that the evidence on cost-effectiveness published up to date made use of lower prices and that the overall results showed some sensitivity in particular to the price of the consumables, with a ceiling of around €2 000, after which dominance became more uncertain (see section 4).

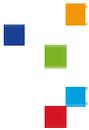
Since the potential clinical benefits would be the same independently of the model pursued, it is interesting to draw attention to more economical approaches or to logistically-easier alternatives that could facilitate the adoption of these machines, should reimbursement be pursued.

6 DISCUSSION AND CONCLUSIONS

Delayed graft function, described as the need for dialysis during the first week post-op is a frequent complication in renal transplantation, detrimental to the longevity of the allograft.¹⁴ In addition to being a risk factor for graft failure, delayed graft function also increases the number of dialysis sessions required and lengthens hospital stay post-transplantation, which in turn affects health care costs.^{70,71}

The current high, and increasing, prevalence rates of end stage renal disease, coupled with large waiting lists for renal transplantation have encouraged the use of new types of donors, *i.e.* donors after cardiocirculatory death and expanded criteria donors (older donors and/or with comorbidities).⁷ However, kidneys coming from these donors are reported up to date, considerably higher incidence rates of delayed graft function and primary non function when compared with those coming from standard criteria donors.⁷² Using machine perfusion instead of cold storage is considered one strategy, among others available, to decrease such complications. Our review of published randomized controlled trials reported that machine perfusion decreases the incidence of delayed graft function (numbers needed to treat=9; 95%: 5; 33) (high quality evidence). However, we found scarce and inconclusive evidence on how this decrease in delayed graft function may translate into lower costs. On primary non function, a less common but clinically more crucial complication, there was low to very low quality evidence that machine perfusion had no effect. As regards to graft survival, there was moderate quality evidence that machine perfusion could decrease graft failure one year post-transplantation in expanded criteria donors, and possibly in brain-dead kidney donors, but not in donors after cardiocirculatory death. There was low quality evidence that this effect was maintained up to three years post- transplantation (one study).³⁰

In summary, machine perfusion decreased the relative risk of delayed graft function by around 20% in all donor types, but had no effect on primary non function, and could potentially decrease the risk of graft failure at one and three year post-transplantation in expanded criteria donors and brain-dead kidney donors.



Variation of the benefit offered by machine perfusion according to donor type is an interesting subject. Donation after cardiac death is of particular relevance because, although kidneys from these donors, contrary to traditional views, appear to yield good overall results,^{6, 44, 45} their utilization is yet to be optimized.⁷² Our analysis has shown that in this specific group, the utilization of machine perfusion affected only the incidence of delayed graft function but not that of graft survival. This said, graft survival was excellent in this group with or without machine perfusion, a fact already highlighted in previously published observational studies.⁴¹

In expanded criteria donors, another relevant pool of donors given current ageing population trends, machine perfusion was effective at decreasing not only the incidence of delayed graft function and primary non function, but also graft failure at one and three years' post-transplantation. Most of the evidence came from a sub-group analysis of the European machine perfusion trial and numbers were small, so such evidence was rated moderate/low-quality.

In donation after brain death there was overall, a trend towards an increase in graft survival, but the results were more fragile.

The economic evidence mirrored the results from the clinical analysis, with published studies including brain-dead donors, and in particular expanded criteria donors, showing that machine perfusion may be dominant (both more effective, and less expensive). This economic dominance should nevertheless, be interpreted with some caution, primarily as a consequence of the uncertainties surrounding graft survival and the need for extrapolating the evidence from the short over to the long-term period, as well as the sensitivity of the overall results to machine-consumable prices.

Despite the clinical and economic evidence for donors after cardiocirculatory death being inconclusive, it should be highlighted that machine perfusion is at present, mainly used in this specific pool of donors, not just in Belgium, but also in other EU countries such as France, the Netherlands or the UK. This field-based interest is probably justified by the higher delayed graft function rates found in this donor pool, although graft survival has the most weight on cost-effectiveness since delayed graft

function represents only a temporary condition, while graft failure implies returning to lengthy, frequent and costly dialysis sessions.

Whether MP may indeed help to increase the current donor pool is still unknown.⁷² Moreover, many other factors influence the outcomes of kidney transplantation, such as the reduction of ischemia time, the prevention of diabetes or hypertension, which could also affect the incidence of renal failure, and thus the demand for transplantable kidneys, or changes in procurement techniques and immunosuppressant therapy.

To conclude, although in principle donors with cardiocirculatory death and expanded criteria donors appear to be the most attractive donor populations in which to use this preservation method given the lower quality of their kidneys and the more frequent complications they present as well as their growing presence in this ever changing area, it is at present difficult to make strong recommendations, in particular for kidneys coming from donors after cardiocirculatory death, based on the available evidence.

Still, the limited evidence published up to date indicates that machine perfusion could be both clinically and economically superior to cold storage, particularly in the case of expanded criteria donors and should thus, be considered as a valuable alternative to cold storage in the preservation of kidneys prior to transplantation.

In order to facilitate the adoption of this preservation method, the authorities could consider the reimbursement of machine perfusion in donors after cardiocirculatory death and expanded criteria donors conditioned to the collection by transplant units of accurate measurements of both costs and outcomes.

Given the relative novelty of the topic and the re-gained interest that surrounds it, in the context of a changing donor environment and technical innovations, the evidence base is likely to evolve rapidly and thus, future updates of this and other reviews may be necessary in 3 to 5 years. Future technical innovations comprises normothermia instead of hypothermia, oxygen persufflation, drug interventions during perfusion. Cold Machine Perfusion is only the start of a multimodality strategy to recover marginal organs.



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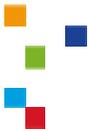
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