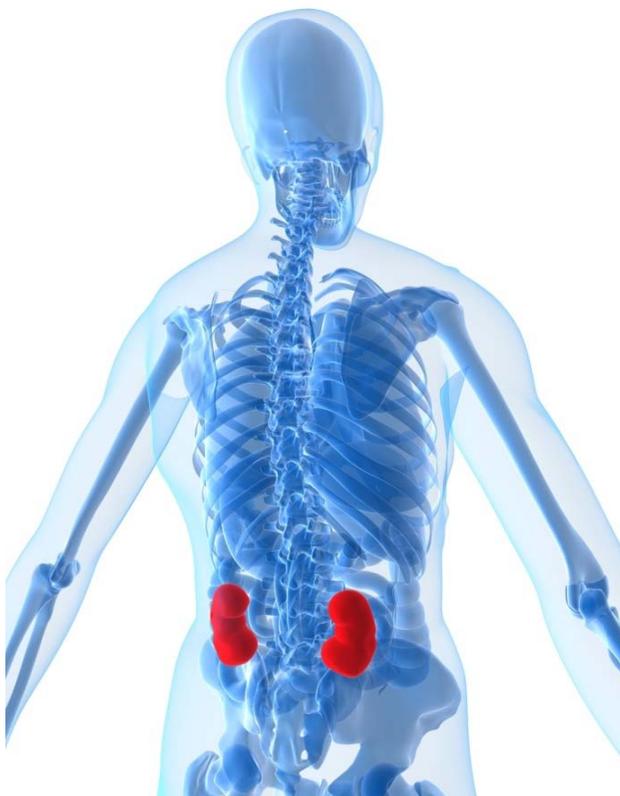


## SYNTHESIS

# MACHINE PERFUSION IN THE PRESERVATION OF KIDNEYS FROM DECEASED DONORS





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## **SYNTHESIS**

# MACHINE PERFUSION IN THE PRESERVATION OF KIDNEYS FROM DECEASED DONORS

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



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and validators have a certain degree of conflict of interest to the main topic of this report.  
Ine Verhulst

Layout:

**Disclaimer:**

**The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**

**Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.**

**Finally, this report has been approved by common assent by the Executive Board.**

**Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

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## ■ FOREWORD

“Kidney transplantation is, in principle, the treatment of choice”, as written in our 2010 report on the organisation of chronic dialysis for end stage renal disease patients (report KCE 124). But straight after that we added “Not all patients are eligible for a kidney transplant, and those who are, need to wait for a compatible kidney to become available”. Thus, in recent years efforts have been made to increase the available pool of deceased donors. In addition to “standard” donors, the use of donors after cardiac death, older donors or donors suffering from co-morbidities has become more common. However, the quality of their kidneys is suboptimal, often requiring longer times to become fully functional or even failing to ever work.

In the chain of causes of this low success rate, kidney damage during transportation is an important factor. As a consequence, a regained interest has emerged in a technique, long-known: “perfusing” kidneys during their transportation, as an alternative to cold storage. Although expensive, this is a promising technique for optimizing the utilization of the available kidneys.

Thus, the Minister of Health asked KCE to examine to what extent this technology responded to those promises, and whether its use could be justified on efficiency terms. We searched for inspiration abroad, either within the geographical limits of Eurotransplant or beyond them, without losing sight of the Belgian context, with its limited number of transplantation centers, relatively short distances and a quasi - monopolistic market situation.

As usual with technologies which are not yet widely used, the scientific literature remains scarce. Nevertheless, we hope to have shed some light on the role that should be granted to this technology. We thank the clinical and research experts in the field of renal transplantation who kindly shared their knowledge with us for the benefit of this study.

Christian LÉONARD  
Deputy general director

Raf MERTENS  
General director



## ■ ABSTRACT

### CONTEXT AND AIMS

The aim of our review was to critically appraise the available evidence for the efficacy/effectiveness and cost-effectiveness of machine perfusion compared to cold storage in the preservation prior to transplantation of kidneys coming from deceased donors.

### METHODS

A systematic search of the published literature up to June 2013 on the effectiveness and cost-effectiveness of machine perfusion versus cold storage was undertaken by consulting electronic databases, including Medline, EMBASE and the Cochrane Library. The clinical evaluation was based on a meta-analysis of randomised controlled trials (RCTs); the economic review included full primary and secondary economic evaluations. Bibliographies of articles found via our original search were also reviewed to identify further relevant studies. No language or time limitations were imposed.

### RESULTS

Machine perfusion resulted in a relative risk reduction of delayed graft function (entailing the need for at least one dialysis during the first week post-transplant) by 22% (95%CI: 8% to 34%;  $p=0.005$ ), in all donor types. It had no effect on primary non-function (i.e. transplantation's failure resulting in either a return to dialysis or a need for a re-transplant). It could substantially increase graft survival at one and three year post-transplantation, except for kidneys from donors after cardiac death, but the scientific evidence is of moderate quality.

The results from the economic evaluations mirrored those from the clinical analysis: in donors after brain death, and in particular in expanded criteria donors (older donors and/or with co-morbidities), machine perfusion may be dominant (both more effective, and less expensive). However, unclear results were reported in donation after cardiac death.



## CONCLUSIONS

Although the available evidence up to date is not exempt of weaknesses and should be interpreted with some caution, our review showed that machine perfusion could represent a valuable alternative to cold storage in clinical practice.



## ■ SYNTHESIS

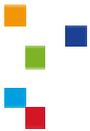
### 1. CONTEXT AND OBJECTIVES

End stage renal disease (ESRD) is a severe life-threatening condition in which kidneys can no longer function properly.<sup>1</sup> Diabetes and hypertension, very common chronic conditions in today's ageing society, are amongst the main causes of this disease.<sup>2</sup>

ESRD patients require active renal replacement therapy which consists of either dialysis or transplantation. But although the latter is globally recognised as the best treatment option for most patients, the scarcity of kidney donors remains a challenge and in most EU countries waiting lists continue to grow. There is, therefore, a need for all potential kidney donor sources to be considered and optimized.

Kidneys may come from deceased or living donors. The main population of kidney donors, also known as standard criteria donors, has traditionally belonged to the first group (i.e. deceased donors) and consisted of relatively young (below 60 years of age) brain-dead donors, still heart-beating. However, the volume of this "optimal" donor population is insufficient to respond to the current demand and appears to show a diminishing trend ([ww.eurotransplant.org](http://ww.eurotransplant.org)), which explains the increased interest in alternative "suboptimal" kidney sources.

There are two types of deceased donors in particular which may have been discarded in the past because of the poorer clinical outcomes compared to standard criteria donors. These are donors after cardiac death (DCD) and expanded criteria donors (ECD) (see Table 1 for definitions). Both are increasingly used worldwide.

**Table 1 – Definitions of different types of donors**

Type of donors	Definition
Donors after brain death (DBD)	Donors with an irreversible cessation of cerebral and brain stem function, but still heart beating <sup>3</sup>
Donors after cardiac death (DCD)	Donors with an irreversible cessation of circulatory and respiratory functions <sup>3</sup> (non-heart beating)
Expanded criteria donor (ECD)	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. <sup>4</sup>

During the period 2003 to 2009<sup>2</sup> the prevalence of end stage renal disease in Belgium grew at a mean annual rate of approximately 5%, from 9 483 patients in 2003 to 12 424 patients in 2009 (1 155 per million population), while the overall incidence grew by 22%, at a mean annual growth of 3.4%, reaching 2 128 new patients in 2009 (198 per million population).

Specifically, the use of donors after cardiac death in renal transplantation experienced a growth of 59%, from 58 transplants performed with this type of donor in 2010 to 92 in 2012. Twenty eight per cent of all kidney donors in Belgium in 2012 categorised as expanded criteria donors ([www.eurotransplant.org](http://www.eurotransplant.org)), a figure likely to continue to rise in the forthcoming years.

Despite their potential to expand the current pool of kidneys, or at least maintain the current sub-optimal supply, donors after cardiac death and expanded criteria donors are considered as “risky” because they are associated with more frequent clinical complications<sup>5, 6</sup> 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.

Machine perfusion represents a promising alternative when compared to cold storage, which could help to improve clinical outcomes by reducing the complications previously listed (*i.e.* delayed graft function, primary non function) or by increasing graft survival.

Our project team performed a systematic search (up to June 2013) of the published literature, consulting databases including Medline, EMBASE, and the Cochrane Library, in order to answer the following questions:

- What is the efficacy/effectiveness of machine perfusion versus cold storage in renal transplantation?
  - What is the added clinical value of machine perfusion in the preservation of kidneys coming from specific donor pools?
- What is the cost-effectiveness of machine perfusion versus cold storage in renal transplantation?
  - Is machine perfusion more cost-effective in the preservation of kidneys coming from specific donor pools?
- How is machine perfusion currently used and paid for in Belgium and its neighbouring countries?



## 2. HOW DOES MACHINE PERFUSION WORK IN THE CONTEXT OF RENAL TRANSPLANTATION?

In renal transplantation, long periods of cold ischemia are strongly associated with delayed graft function, which in turn is a risk factor for reduced graft survival.<sup>7</sup> Machine perfusion is thought to mitigate these harmful effects by delivering nutrients and energy substrates while removing toxic waste products during the preservation phase. It does so by continuously pumping cold preservation solutions through the kidneys, via the renal artery.

However, cold storage (i.e. ice box) is still standard practice in Europe, primarily because of its simplicity and lower capital equipment and consumable costs.

### 2.1. Perfusion Machine unit

Although at least two new machines are currently entering the European market, data is currently available on only two different machine perfusion devices (LifePort<sup>®</sup> Kidney Transporter, by Organ Recovery Systems Inc. and RM3<sup>®</sup>, by Waters Corporation Medical Systems Inc.). However, only the former is transportable, offering more flexibility, making it the preferred option in centres currently using machine perfusion technology. The LifePort<sup>®</sup> 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.

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 confirmed by direct communication with the manufacturer of LifePort<sup>®</sup>). The machine has a minimum lifetime of five years and its acquisition requires payment of a yearly insurance fee (full service coverage) 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<sup>®</sup>).

### 2.2. Disposables

Every time a kidney is perfused by means of LifePort<sup>®</sup>, a “perfusion kit” is required. This perfusion kit includes the necessary disposables for a complete perfusion process from the harvesting of the kidney to its eventual transplantation.

A picture of the LifePort<sup>®</sup> machine unit and consumables is provided in Figure 1.

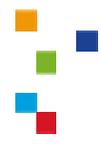
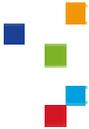


Figure 1 – LifePort® machine and consumables (provided by the manufacturer of LifePort® – Organ Recovery Systems)





### 3. HOW EFFECTIVE IS MACHINE PERFUSION IN RENAL TRANSPLANTATION?

Our analysis, which included a *de novo* meta-analysis of the currently available evidence, showed that overall, machine perfusion resulted in a relative risk reduction of delayed graft function by 22% (95%CI: 8% to 34%;  $p=0.005$ ) with no evidence of heterogeneity across donor types. The NNT (number needed to treat) was 9.1 (95%CI: 5.3 to 33.3) (good quality of evidence).

Despite delayed graft function being only a short-term outcome, the higher costs and worse quality of life linked to patients requiring dialysis compared to those transplanted and with a functioning graft,<sup>8</sup> make it a relevant factor to consider. If a sufficient number of dialysis sessions or hospitalisations could be avoided by using machine perfusion, the necessary investment required for its use could be balanced out. However, evidence was scant on the impact of machine perfusion versus cold storage in terms of number of dialysis sessions or hospital days that could be avoided.<sup>9, 10, 11</sup>

On primary non function, a less common but clinically more crucial complication, there was moderate to low quality evidence that machine perfusion had no effect in donors after brain death and donors after cardiac death, while there was low quality evidence that it could decrease such complication in expanded criteria donors, but this relied on one study only and numbers were small.<sup>12</sup> Because of this heterogeneity, no pooling of results was performed across donor groups.

With regard to graft survival, there was moderate quality evidence that machine perfusion could decrease the risk of graft failure one year post-transplantation in donation after brain death, and particularly in expanded criteria donors where the relative risk reduction was 64% (95%CI: 25% to 82%;  $p=0.006$ ) and the NNT was 7.7 (95%CI: 4.8; 25.0). No effect was observed in donors after cardiac death. There was low quality evidence that this effect was maintained up to three years post-transplantation (one study only).<sup>13</sup>

### 4. HOW COST-EFFECTIVE IS MACHINE PERFUSION IN RENAL TRANSPLANTATION?

The overall picture emerging from the economic literature is that machine perfusion is cost-effective in the preservation of kidneys of deceased donors when compared to cold storage. One exception is donors after cardiac death, where results are, similarly to what our clinical analysis showed, unclear.

The limited available evidence suffered from important weaknesses. More specifically it relied too heavily on a single clinical source: the European Machine Perfusion trial (EMPT).<sup>11</sup> Moreover, the sensitivity analysis carried out by Groen et al.<sup>14</sup> showed the overall results to be highly sensitive to changes in the price of machine perfusion consumables. Finally, the short time horizon used in some of the evaluations, with three studies<sup>15-17</sup> out of eight covering one year or less, an insufficient time frame to adequately capture any long-term consequences of machine perfusion represents an additional weakness.



## 5. HOW IS IT CURRENTLY USED AND PAID FOR IN BELGIUM AND ITS 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. The main barrier for the use of machine perfusion at present in most EU countries is the lack of health insurance coverage, which makes it necessary for transplant units to absorb the whole cost of their use. This has resulted in a fragmented picture with few centres using it in very specific 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, specifically for the perfusion of kidneys coming from “riskier” donors (i.e. donors after cardiac death and expanded criteria donors), in an attempt to increase the quality and number of renal transplants.

### 5.1. Alternative organizational models to be considered for the introduction of machine perfusion in Belgium

#### 5.1.1. 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 recipient centre, once the latter has been confirmed by Eurotransplant, to finally take the machines back to clean and storage them after completion of the transplant/s.

The current cost (year 2013) 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 for 2012, an overall target transplant population of approximately 480 per year, which would translate into an all-inclusive yearly investment

of € 1 440 000. If the use and reimbursement of machine perfusion was limited to kidneys coming from sub-optimal donor populations (i.e. donation after cardiac death and expanded criteria donors), the yearly investment would instead be of around € 680 000, (around 19% of all transplants from deceased donors are from donation after cardiac death, and 28% of donors used for a transplant are expanded criteria donors, based on Eurotransplant figures for 2012).

It is important to note that, at present, under this model, hospitals only pay the fee of LifePort® (ORS) if the kidney is finally transplanted.

The main advantages linked to this model include:

- The know-how of the manufacturer would be available for the surgeon, avoiding machine-specific learning curves,
- No permanent ties that could hinder future competition would exist,
- No need for maintenance at hospital level 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 transplanted, limiting waste.

Potential disadvantages:

- Intransparent price setting.

#### 5.1.2. Purchasing model

The purchasing model would require each of the seven Belgian transplantation centres to acquire a minimum of two machines (one per kidney), or three machines, as per the French model, to ensure coverage for any technical or transportation problem.

Based on 2013 prices and 2012 transplantation figures, the mean annual financial investment, over a 5 year time horizon under this scenario was estimated to range from approximately € 1.280 000 to € 1.300 000 for two and three machines respectively if using the machine in all deceased donor transplants or between € 630 000 and € 650 000 if focusing purely on suboptimal donor populations. The 5 year time horizon reflected a conservative assumption on the lifetime of the machine unit.



An important 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<sup>®</sup>), transplant units will be tied-up to buying the consumables from the manufacturer 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 machine maintenance.

### 5.1.3. Central repository model

A third alternative would be to replicate the loan system currently offered by the manufacturers of LifePort<sup>®</sup> in Belgium within the premises of an already established transplant 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. The main advantage of such a model would be that, given the relatively low potential target transplantation figures for machine perfusion, and the limited size of the territory to be covered, the need for machine units is likely to be lower than in the previous alternative. So in theory, small economies in capital equipment could be made when compared to the purchasing model.

Its main disadvantage is that it would require an investment to set up the necessary organization and human resources to co-ordinate the transport, storage, cleansing and use of these machines for the whole of the Belgian territory. Furthermore, similarly to the purchasing model, once the capital equipment is bought, there would be a tie between the manufacturers of LifePort<sup>®</sup> and the transplant unit, since consumables would need to be bought from the former. Still, given the lower initial investment costs, this tie would be less constraining than under the purchasing scenario.

## 6. 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.<sup>7</sup> 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.<sup>18, 19</sup>

The high, and increasing, prevalence rates of end stage renal disease coupled with long waiting lists for renal transplantation have encouraged the use of new types of donors, *i.e.* donors after cardiac death and expanded criteria donors (older donors and/or with comorbidities).<sup>6</sup> However, kidneys coming from these donors are reported to present considerably higher incidence rates of delayed graft function and primary non function when compared with those coming from standard criteria donors.<sup>20</sup> Using machine perfusion instead of cold storage is considered one strategy, among others available, to decrease the rates of delayed graft function or primary non function. Our review of published randomised controlled trials showed that machine perfusion decreased the 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 donors after brain death.

Variations in the benefit offered by machine perfusion according to donor type are noticeable. Donors after cardiac death is a group of particular interest because, although kidneys from these donors, contrary to traditional views, appear to yield good results,<sup>5, 21, 22</sup> their utilization is yet to be optimized.<sup>20</sup> Our analysis has shown that in this specific group however, the utilization of machine perfusion affected only the incidence of delayed graft function but not that of primary non function or graft survival.



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 at improving graft survival at one and three years' post-transplantation. However, 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 as low-quality. In donors 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 studies published in donors after brain death, and in particular in expanded criteria donors, showing that machine perfusion may be dominant (both more effective, and less expensive), but unclear results in donors after cardiac death.

Against the evidence found, it is necessary to mention that currently machine perfusion is mainly used in donation after cardiac death, not just in Belgium, but also in other EU countries such as France, the Netherlands or the UK.

Given the growing presence in this ever changing area of donors after cardiac death and expanded criteria donors, and the higher frequency of complications in these donors, they would appear to be the most attractive donor pool in which to use machine perfusion, even if improvements in graft survival have not been supported by the current evidence in donors after cardiac death. On the other hand, the potential economic dominance of machine perfusion found in the literature reviewed should be interpreted with caution, primarily as a consequence of the uncertainties surrounding graft survival, the need for extrapolating the evidence from the short over to the long-term period and the sensitivity of the overall results to the price of machine consumables.



## ■ RECOMMENDATIONS<sup>a</sup>

*These recommendations should be part of a comprehensive approach to the management of patients with kidney failure.*

### To the Minister of Public Health and Social Affairs:

- It is reasonable, on the basis of current scientific evidence, to foresee an intervention of the National Institute for Health for the use of machine perfusion in kidneys from sub-optimal donors (*i.e.* expanded criteria donors and donors after cardiac death). This intervention should be conditional to:
  - the collection by the 7 Belgian transplantation centres of harmonised data on donor and recipient characteristics, and outcomes (duration of hospitalisation, number of dialysis sessions post-transplantation, proportion of graft failure and time to failure). Data collection should begin as soon as possible to allow the comparison of outcomes before and after the intervention.
- If a contribution by the health insurance is pursued, the all-inclusive “loan” model, currently used by 2 transplantation centres in Belgium, would offer the most interesting option provided that the current quasi-monopolistic position of the manufacturer is broken and similar services are offered by new companies entering the market. Alternatively, a similar model could be run by a partner, independent from the manufacturer, based on a pool of purchased machines.

### To the Kidney-pancreas Committee of the Belgian Transplantation Society (BTS):

- We recommend organizing/facilitating the data collection described above in the short-term.

### To the research community:

- The potential clinical benefits of machine perfusion in multi-organ transplantation should be investigated.
- Technical innovations to improve the clinical benefits of machine perfusion need to be further explored, e.g. normothermia instead of hypothermia, oxygen persufflation or drug injection in the perfusion.
- Given rapid changes in techniques, epidemiology of renal disease and donor characteristics, an updated review of the scientific evidence is recommended in the mid-term (3 to 5 years).

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<sup>a</sup> The KCE has sole responsibility for the recommendations.



## ■ REFERENCES

1. Greenberg A, Cheung A, Coffman T, Falk R, Jennette J, editors. Primer On Kidney Diseases. National Kidney Foundation 2005.
2. NBVN Ge. Rapport commun du GNFB et du NBVN pour le college de nephrologie et des centres de traitement de l'insuffisance renale chronique. 2008-2009.
3. World Health Organisation (WHO). Global Glossary of Terms and Definitions on Donation and Transplantation [Web page]. Geneva; 2009. Available from: <http://www.who.int/transplantation/activities/GlobalGlossaryonDonationTransplantation.pdf>
4. Policy 3.5.I. Expanded criteria donor definition and point system., 2002.
5. Kokkinos C, Antcliffe D, Nanidis T, Darzi AW, Tekkis P, Papalois V. Outcome of kidney transplantation from nonheart-beating versus heart-beating cadaveric donors. Transplantation. 2007;83(9):1193-9.
6. Moers C, Leuvenink HG, Ploeg RJ. Non-heart beating organ donation: overview and future perspectives. Transpl Int. 2007;20(7):567-75.
7. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. Am J Transplant. 2011;11(11):2279-96.
8. Cleemput I, Beguin C, de la Kethulle Y, Gerkens S, Jadoul M, Verpooten G, et al. Organisation and financing of chronic dialysis in Belgium. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2010 10/02/2010. KCE Reports 124C (D/2010/10.273/13) Available from: [https://kce.fgov.be/sites/default/files/page\\_documents/d20101027313.pdf](https://kce.fgov.be/sites/default/files/page_documents/d20101027313.pdf)
9. Alijani MR, Cutler JA, DeValle CJ, Morres DN, Fawzy A, Pechan BW, et al. Single-donor cold storage versus machine perfusion in cadaver kidney preservation. Transplantation. 1985;40(6):659-61.
10. Halloran P, Aprile M. A randomized prospective trial of cold storage versus pulsatile perfusion for cadaver kidney preservation. Transplantation. 1987;43(6):827-32.



11. Moers C, Smits JM, Maathuis MH, Treckmann J, van Gelder F, Napieralski BP, et al. Machine perfusion or cold storage in deceased-donor kidney transplantation. *N Engl J Med*. 2009;360(1):7-19.
12. Treckmann J, Moers C, Smits JM, Gallinat A, Maathuis MH, van Kasterop-Kutz M, et al. Machine perfusion versus cold storage for preservation of kidneys from expanded criteria donors after brain death. *Transpl Int*. 2011;24(6):548-54.
13. Moers C, Pirenne J, Paul A, Ploeg RJ. Machine perfusion or cold storage in deceased-donor kidney transplantation. *N Engl J Med*. 2012;366(8):770-1.
14. Groen H, Moers C, Smits JM, Treckmann J, Monbaliu D, Rahmel A, et al. Cost-effectiveness of hypothermic machine preservation versus static cold storage in renal transplantation. *American Journal of Transplantation*. 2012;12(7):1824-30.
15. Costa V, Brophy J, McGregor M. Pulsatile machine perfusion compared to cold storage in kidney preservation. Report. Montreal: Technology Assessment Unit of the McGill University Health Centre (MUHC); 2007. Available from: [http://www.mcgill.ca/files/tau/machine\\_perfusion\\_May\\_10.pdf](http://www.mcgill.ca/files/tau/machine_perfusion_May_10.pdf)
16. Garfield SS, Poret AW, Evans RW. The Cost-Effectiveness of Organ Preservation Methods in Renal Transplantation: US Projections Based on the Machine Preservation Trial. *Transplantation Proceedings*. 2009;41(9):3531-6.
17. Gomez V, Galeano C, Diez V, Bueno C, Diaz F, Burgos FJ. Economic impact of the introduction of machine perfusion preservation in a kidney transplantation program in the expanded donor era: Cost-effectiveness assessment. *Transplantation Proceedings*. 2012;44(9):2521-4.
18. Hagenmeyer EG, Haussler B, Hempel E, Grannas G, Kalo Z, Kilburg A, et al. Resource use and treatment costs after kidney transplantation: impact of demographic factors, comorbidities, and complications. *Transplantation*. 2004;77(10):1545-50.
19. Rosenthal JT, Danovitch GM, Wilkinson A, Ettenger RB. The high cost of delayed graft function in cadaveric renal transplantation. *Transplantation*. 1991;51(5):1115-8.
20. Jochmans I, Darius T, Kuypers D, Monbaliu D, Goffin E, Mourad M, et al. Kidney donation after circulatory death in a country with a high number of brain dead donors: 10-year experience in Belgium. *Transpl Int*. 2012;25(8):857-66.
21. Nicholson ML, Metcalfe MS, White SA, Waller JR, Doughman TM, Horsburgh T, et al. A comparison of the results of renal transplantation from non-heart-beating, conventional cadaveric, and living donors. *Kidney Int*. 2000;58(6):2585-91.
22. Weber M, Dindo D, Demartines N, Ambuhl PM, Clavien PA. Kidney transplantation from donors without a heartbeat. *N Engl J Med*. 2002;347(4):248-55.



