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Original Articles

The cost–utility of haemodiafiltration versus haemodialysis in the Convective Transport Study

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Keywords: cost–utility analysis, haemodiafiltration,
haemodialysis

ABSTRACT

Background. Despite the growing interest in haemodiafiltration (HDF), there is no information on the costs and cost-utility of this dialysis modality yet. It was therefore our objective to study the cost–utility of HDF versus haemodialysis (HD).

Methods. A cost–utility analysis was performed using a Markov model. It included data from the Convective Transport Study (CONTRAST), a randomized controlled trial that compared online HDF with low-flux HD. Costs were estimated using a societal perspective. Probabilistic sensitivity analyses were performed to study uncertainty.

Results. Total annual costs for HDF and HD were €88 622 ± 19 272 and €86 086 ± 15 945, respectively (in 2009 euros). When modelled over a 5-year period, the incremental cost per quality-adjusted life year (QALY) of HDF versus HD was €287 679. Sensitivity analyses revealed that this amount will not fall below €140 000, even under the most favourable assumptions like a high-convection volume (>20.3 L).

Conclusions. Based on accepted societal willingness-to-pay thresholds, HDF cannot be considered a cost-effective treatment for patients with end-stage renal disease at present. Apparently, minor additional costs of HDF are not counterbalanced by a relevant QALY gain.

INTRODUCTION

In-centre haemodialysis (HD) is one of the most expensive chronic health care interventions. Indeed, the costs per quality-adjusted life year (QALY, a hypothetical year in optimal health) of HD have been recognized as a kind of benchmark for society's willingness to pay for medical technologies [1]. Both survival and quality of life are strongly impaired in patients with end-stage renal disease (ESRD) [2, 3]. Their quality of life is, for instance, lower than in patients with respiratory or coronary disease, arthritis or metastatic colorectal cancer [4].

Dialysis therapies like peritoneal dialysis and home (nocturnal) HD are cost-effective compared with in-centre HD [5–9]. A kidney transplantation is the most cost-effective treatment for patients with ESRD, but not all patients are able to undergo transplantation, and treatment availability is low due to a shortage in donor kidneys [9]. Furthermore, not all patients are able to undergo transplantation [9]. Online haemodiafiltration (HDF) might be a cost-effective alternative to HD [10]. HDF combines diffusion with convection to enhance the clearance of middle molecules. Recently, however, large randomized controlled trials revealed that there is no significant benefit in terms of survival associated with HDF [11, 12]. Possibly, a positive effect in patient reported outcomes such as quality of life could tip the balance favourably. Conversely, the costs of HDF are also unclear. Accordingly, there is a strong need for an economical evaluation. We therefore aimed to assess the cost-effectiveness of HDF when compared with HD.

MATERIALS AND METHODS

Clinical trial

The present study was conducted in parallel with the Convective Transport Study (CONTRAST) [11, 13]. CONTRAST is a randomized controlled trial (NCT00205556) that compared online post-dilution HDF with low-flux HD on all-cause mortality. Between June 2004 and December 2009, it included 714 patients aged 18 years or above with ESRD undergoing chronic intermittent HD in 29 dialysis centres located in the Netherlands ($n = 26$), Canada ($n = 2$) and Norway ($n = 1$). Follow-up was uniformly stopped in December 2010. CONTRAST was approximately halfway completed when the cost-utility analysis started. This means that prospective data on both costs and quality of life were available in 409 of the 714 patients. Written informed consent was obtained from all patients prior to randomization. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by central and local medical ethics review boards. Detailed information on study design and conduct can be found elsewhere [11, 13].

Cost-utility analysis

Cost analysis. The cost analysis was performed from a societal perspective. Costs were calculated per 3 months in 2009 euros [1 euro = 1.43 US dollars (2009 exchange rate)]. If

necessary, cost estimates were indexed to 2009 with the Dutch consumer price indices (<http://statline.cbs.nl>).

To arrive at our final cost estimates, we combined bottom-up measurements (i.e. registration of the use of resources at the level of participating patients) with top-down estimates for those cost categories that were thought to be similar for all patients, e.g. costs of disposables used during dialysis. The cost analysis included direct healthcare costs as well as direct and indirect non-healthcare costs. Direct healthcare costs comprised dialysis and other medical staff, material (water installation, dialysis machines and disposables), vascular access, routine diagnostics of patients and dialysis water quality, meals during dialysis, hospitalization, medication and overhead. Direct non-healthcare costs comprised travel expenses and indirect non-healthcare costs included productivity losses. Productivity losses cover productivity loss with and without the absence of paid work and substitution of unpaid, domestic work either by family or by home care. Dialysis staff involvement in relation to the number of patients was estimated with a cross-sectional analysis in 24 Dutch dialysis centres. A reference price per full-time equivalent for different job levels was obtained from the Dutch guideline for costing research [14]. Reference prices were also available for the visits to the outpatient department, general practitioner, paramedic, psychologist and complementary medicine. The number of patient visits to these healthcare workers was assessed prospectively with a 3-monthly patient questionnaire. Material costs were provided by a categorical (Dianet) and two university hospitals (University Medical Centre Utrecht and VU Medical Centre). The costs of vascular access were calculated as a weighted average of the costs for an arteriovenous fistula, graft or catheter using the data from Wijnen *et al.* [15] and Manns *et al.* [16]. The frequency of microbiological and endotoxin testing of (ultra)pure water for dialysis is based on the guideline of the Dutch Nephrology Federation [17]. Prices were provided by the pharmacology department of the VU Medical Centre. The frequency of the laboratory diagnostics is based on the guideline of the Dutch Nephrology Federation [18]; the frequency of other diagnostic procedures (chest X-rays and electrocardiograms) on a protocol from the University Medical Centre Utrecht. Prices for these diagnostic procedures were obtained from the Dutch Diagnostic Compass issued by the Health Care Insurance Board [19]. The cost for meals during dialysis were estimated to be 200 euros per 3 months, based on 5 euros per meal and 3 dialysis sessions per week. The price of hospitalization is based on reference prices from the Dutch guideline for costing research, where 1 day of hospitalization for a patient in the Netherlands was calculated to cost €457 on average [14]. Hospitalization and medication use were measured in CONTRAST patients and analysed per age category. Medication use included anaemia drugs, anticoagulants and antiplatelets, antihypertensive drugs, cinacalcet, phosphate binders, resonium, statins and vitamin D3. Prices were based on the Dutch Pharmacotherapeutical Compass from the Health Care Insurance Board (<http://www.fk.cvz.nl/>). The Pharmacotherapeutical Compass delivers prices per unit or per time period of standard use. As recommended by the Dutch guideline for costing research, overhead costs were

calculated as a percentage (35.5%) of direct healthcare costs that did not yet include overhead [14]. Travel expenses were based on 3-weekly visits to a dialysis centre, using the average distance to a Dutch hospital and reference prices per km of taxi use as available from the costing guideline [14]. Productivity loss was assessed with a modified version of the Short-Form Health and Labour Questionnaire and valued using the friction cost approach [20, 21].

Quality-adjusted life years. QALY's were calculated by multiplying survival with utility. Survival data were provided by the main trial as described elsewhere [11]. To obtain QALY's, survival was adjusted for quality of life with an adjustment factor called 'utility'. This utility weight has a score from 0 to 1 (i.e. the worst to best imaginable state of health). Utility was assessed every 3 months with the Euroqol 5D (EQ-5D). This questionnaire offers the transfer of the quality of life scores of patients to societal utilities for patients' health states using the Dutch data [22, 23]. The validated EQ-5D is one of the most widely used instruments to measure health utility and is preferred by National Institute for Health and Clinical Excellence [24, 25]. Missing EQ-5D is imputed by mean values as only 7% of QOL data were missing in our trial.

Statistical analysis

The cost-utility of HDF versus HD was analysed using a Markov model. Cost-utility was determined for three age categories: 18–44 years, 45–64 and 65 and older. The model included two health states, 'ESRD' and 'Death', with treatment-dependent and -independent parameters for costs, utilities and transition probabilities. Probabilistic sensitivity analyses were performed to include parameter uncertainty. A total of 1000 bootstrap replicates were obtained using Microsoft Office Excel 2003. The cycle duration was 3 months as follow-up data were available from the CONTRAST trial for these intervals. The time horizon of the model was 5 years, and a sensitivity analysis was performed with a time horizon up to 10 years. In compliance with Dutch guidelines, a discount rate of 4% was applied for costs and 1.5% for outcome [14]. A second sensitivity analysis was performed to evaluate a uniform discount rate, namely 3% for both costs and outcome. As CONTRAST data suggested that HDF had a beneficial effect on survival if a high convection volume (>20.3 L) was provided [11], a third sensitivity analysis was performed using utility and transition probability measures of HDF patients with the high convection volume. A final sensitivity analysis was performed to explore the influence of excluding standard dialysis costs in life years gained. As pointed out by Grima *et al.* [26], life-extending interventions in dialysis may never be cost-effective as a result of high background costs of dialysis itself, often already exceeding threshold values for cost-effectiveness. In this sensitivity analysis, costs due to life years gained by HDF were excluded by using the survival of HD patients for the HDF population, implying that health benefits of HDF were solely related to the quality of life differences between therapies in this sensitivity analysis.

To evaluate whether HDF and HD patients who participated in the cost-utility analysis were comparable at baseline,

the independent *t*-test, Mann-Whitney test or Fisher's exact test was applied if appropriate. These analyses were performed with SPSS 18 (SPSS Inc., Chicago, IL, USA). Results were considered statistically significant with $P < 0.05$ (two-tailed comparison).

RESULTS

Study patients

Patients participating in the cost-utility data collection were equal at baseline, except for a small but significant difference in spKt/V urea (HDF: 1.45 ± 0.25 ; HD: 1.39 ± 0.20 ; $P = 0.01$).

Cost analysis

Table 1 depicts the costs of HDF and HD per 3 months in 2009 euros. A detailed description of the different cost units can be found in Supplementary material Tables S1–S12. Total annual costs for HDF and HD were €88 622 \pm 19 272 and €86 086 \pm 15 945, respectively, based on measured costs per quarter. Overall, the higher costs for HDF when compared with HD could mainly be attributed to higher expenses for disposables and a more frequent control of water purity.

Utility

Table 2 shows the utility of ESRD per age category while on HDF or HD, as well as the transition probabilities from ESRD to death per 3 months. Overall utility in patients on HDF was slightly higher when compared with HD, and mortality was slightly lower.

Cost-utility ratios

Table 3 shows the cost-utility of HDF and HD for a patient aged 45–65 years, when modelled over a period of 5 years. Over this period, the incremental costs per QALY of HDF versus HD were €287 679, and the incremental costs per life year gained were €206 057. The uncertainty associated with these figures is depicted in Figure 1: the cost-effectiveness plane of HDF versus HD. Figure 2 shows the cost-effectiveness acceptability curve (CEAC). It displays the probability of cost-effectiveness of HDF versus HD for different ceiling ratios, i.e. different thresholds society would be willing to pay for an additional QALY. Results show that, only at ceiling ratios over €300 000 per QALY, the probability that HDF is more cost-effective compared with HD surpasses 50%. Based on the small difference in incremental effect, HDF would be cost-effective if its incremental annual cost was lower than €294 or €960, respectively, based on the usual or upper limit of Dutch society's willingness to pay (i.e. €24 500 or €80 000 per QALY) [27].

In patients younger than 45, the 5-year incremental costs of HDF versus HD were €21 637 (95% confidence interval: –17 652–72 458) for 0.12 (–0.52–0.81) additional QALYs. In this group, only at ceiling ratios of €220 000 and higher, HDF had a higher probability than HD to be cost-effective. In patients aged 65 and older, the incremental costs of HDF versus HD were €15 165 (–19 214–51 022) for 0.03 (–0.27–0.35)

Table 1: The costs of HDF and HD per 3 months in 2009 euros

	Haemodiafiltration	Haemodialysis
Direct healthcare costs		
Staff		
Dialysis	7621	7621
Other medical ^a	347 ± 297	353 ± 312
Material		
Water installation	107	107
Dialysis machine	231	231
Disposables	2552	1895
Vascular access ^b	362	362
Routine diagnostics		
Purified water for dialysis	77	24
Dialysis patient ^c	284	284
Meals		
	200	200
Hospitalization		
Overall	1566 ± 4332	1533 ± 3536
Age <45	1181 ± 6416	481 ± 1806
Age 45–64	1560 ± 4702	1552 ± 3706
Age ≥65	1648 ± 3538	1721 ± 3632
Medication		
Overall	3681 ± 1428	3696 ± 1462
Age <45	3871 ± 1715	3731 ± 1041
Age 45–64	3847 ± 1478	4017 ± 1732
Age ≥65	3544 ± 1322	3446 ± 1259
Overhead ^d	4059	3807
Direct non-healthcare costs		
Travel expenses	1365	1365
Indirect non-healthcare costs		
Productivity loss ^e	225 ± 1140	270 ± 1064
Total		
Per 3 months	22 155 ± 4818	21 521 ± 3986
Per year	88 622 ± 19 272	86 086 ± 15 945
<p>Costs are depicted as mean ± standard deviation if available. Most distributions were left-skewed. 1 euro = 1.43 US dollars (2009 exchange rate).</p> <p>^aVisits to the medical specialist, general practitioner, paramedic, psychologist and alternative healers.</p> <p>^bBased on a weighted average of the costs for an arteriovenous fistula, graft or catheter[15, 16].</p> <p>^cLaboratory analyses, electrocardiogram and chest X-ray.</p> <p>^dCalculated as a percentage (35.5%) of direct healthcare costs that did not yet include overhead.</p> <p>^eProductivity loss with and without the absence of paid work and substitution of unpaid, domestic work by family or home care.</p>		

additional QALYs. In these patients, the probability of HDF being cost-effective compared with HD is unlikely, even at ceiling ratios as high as €300 000.

Sensitivity analyses. For patients aged 45–65, three sensitivity analyses were performed. First, if a time horizon of 10 instead of 5 years was applied, the incremental cost for HDF

versus HD was €25 443 (15 208–35 377) with 0.14 (–0.08–0.35) additional QALYs. The probability that HDF would be cost-effective compared with HD surpassed 50% at ceiling ratios above €190 000 per QALY.

Secondly, a uniform discount rate of 3% for both costs and outcome, resulted in an incremental cost of €16 928 (2866–30 425) while on HDF for 0.07 (–0.09–0.21) additional QALYs. Even with ceiling ratios of €250 000 per QALY, HDF did not become more cost-effective than HD.

Thirdly, if only HDF utilities and transition probabilities for patients with the high convection volume (>20.3 L) were applied [overall utility: 0.75 ± 0.02 (\pm standard error of the mean, SE) and overall mortality probability: 0.0217 ± 0.0039 (\pm SE)], the additional costs of HDF resulted in 0.29 ± 0.16 (–0.02–0.61) additional QALYs. In this scenario analysis, at a ceiling ratio starting from €140 000 per QALY, HDF is expected to be more cost-effective than HD.

Fourthly, if costs due to life years gained by HDF were excluded by using the survival of HD patients for the HDF population, the incremental cost for HDF versus HD was €10 349 (–€17 792–37 536) for 0.01 (–0.26–0.27) additional QALYs. The probability that HDF would be cost-effective compared

with HD did not surpass 50%, even at ceiling ratios of €250 000 per QALY.

DISCUSSION

This study showed that, even though the additional costs of HDF seem minor when compared with HD, they are not outweighed by the limited QALY gain. Elaborate sensitivity analyses revealed that society should be willing to pay €140 000–300 000 per additional QALY for HDF to become cost-effective compared with HD. These figures by far exceed currently accepted thresholds. In the Netherlands, the average willingness to pay is €24 500 per QALY with a suggested upper limit of €80 000 [27]. In the UK, this threshold is £20 000–30 000 per QALY and in the USA, \$50 000–\$100 000 [28]. Thus, HDF exceeds society's willingness to pay for health, even more so because the cost-effectiveness is assessed by comparison with (i.e. investments on the top of) a treatment that already is considered to be of borderline cost-effectiveness [1].

The relatively small additional costs of HDF could mainly be attributed to higher expenses for disposables and a more frequent control of dialysis water purity. In our study, all dialysis centres already used ultrapure dialysis fluids for both HDF and HD as recommended, so no additional investments in water purification were required to commence with online HDF. The price of disposables is often open for negotiations with suppliers/manufacturers. Bearing this in mind, HDF could become within currently accepted standards for cost-effectiveness when its incremental costs compared with HD would be below €294–960. A relatively frequent control of ultrapure water is prescribed in the Netherlands [17]. A less strict regime as recommended by the International Organization for Standardization (ISO) [29] does, however, not lower HDF costs significantly: €66 per 3 months instead of €77 for the control of purified water. Hence, this would hardly influence the unfavourable incremental cost-effectiveness of HDF compared with HD.

To our knowledge, this study is the first to evaluate the cost-utility of HDF. We furthermore provide an update on the current costs of HD from a societal perspective. The last detailed cost analysis of HD in the Netherlands was published in 1997 by de Wit *et al.* [6]. Converted to 2009 euros, their estimate of prevalent HD cost per year was €85 031, which is comparable with our results (€86 992). This indicates that there

Table 2: Utility and transition probability for death on HDF and HD

	Haemodiafiltration	Haemodialysis
Utility		
Overall	0.74 ± 0.01	0.73 ± 0.02
Age <45	0.81 ± 0.04	0.77 ± 0.06
Age 45–64	0.76 ± 0.02	0.73 ± 0.02
Age ≥ 65	0.72 ± 0.02	0.72 ± 0.02
Transition probability for death per 3 months		
Overall	0.0297 ± 0.0026	0.0315 ± 0.0027
Age <45	0.0044 ± 0.0025	0.0019 ± 0.0019
Age 45–64	0.0192 ± 0.0035	0.0221 ± 0.0035
Age ≥ 65	0.0456 ± 0.0047	0.0479 ± 0.0050
Depicted are mean \pm standard error.		

Table 3: HDF and HD: modelled costs, QALYs and survival over 5 years

	Haemodiafiltration	Haemodialysis	Haemodiafiltration versus haemodialysis
Costs (€)	283 931 (264 500–303 187)	267 543 (248 294–286 157)	16 388 (–10 242–43 010)
QALYs	2.40 (2.22–2.59)	2.34 (2.17–2.53)	0.06 (–0.19–0.32)
Life years	3.43 (3.21–3.65)	3.35 (3.12–3.56)	0.08 (–0.22–0.39)
Depicted are means with 95% confidence intervals based on a patient aged 45–65. The third column shows the incremental cost and effectiveness of HDF versus HD. QALY: quality-adjusted life year.			

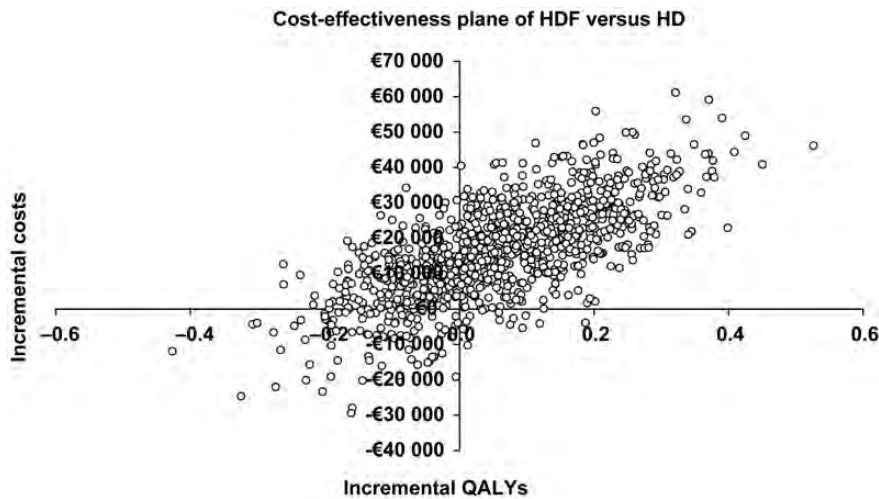


FIGURE 1: Cost-effectiveness plane of HDF versus HD. This figure shows the cost–utility of HDF versus HD as modelled with 1000 bootstrap replicates for 1000 patients aged 45–65 over a 5 year time period. Each dot represents the average for 1000 patients. Whereas sometimes HDF is both cheaper and less effective than HD (the dots in the left lower quadrant), most often HDF is more expensive and more effective (the dots in the right upper quadrant). HDF: haemodiafiltration; HD: haemodialysis; QALY: quality-adjusted life year.

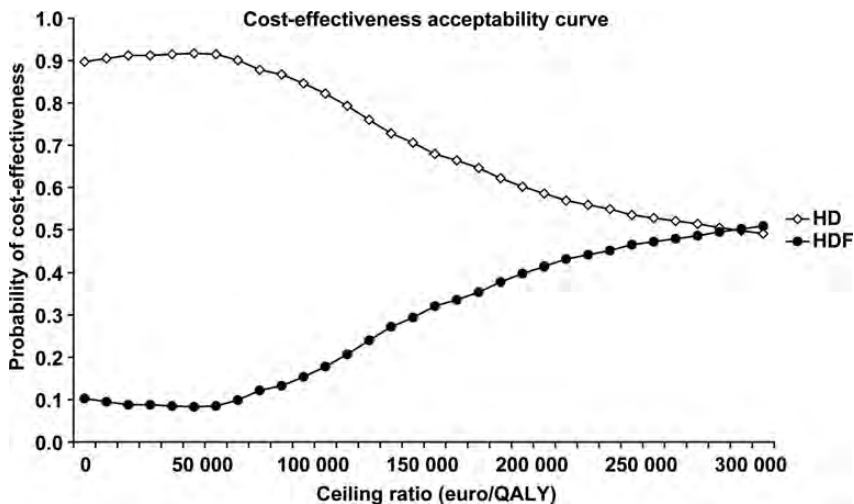


FIGURE 2: CEAC of HDF versus HD. This figure shows the probability that HDF or HD is the most cost-effective treatment for different ceiling ratios in patients aged 45–64. A ceiling ratio is the price society that is willing to pay for a QALY. Overall HDF is more costly and more effective than HD, which means that if the ceiling ratio increases, the probability that HDF becomes the most effective treatment increases. HDF: haemodiafiltration; HD: haemodialysis; QALY: quality-adjusted life year.

were no relevant changes in HD costs between 1997 and 2009. To provide an international reference with regard to the recent cost estimates on HD, Table 4 presents the cost data of five recent international cost analyses. Table 5 furthermore provides a reference with regard to international cost–utility estimates of HD. Unfortunately, a strict comparison is hampered due to different viewpoints and cost allocation methods.

Our model has limitations. First, due to selection criteria and repeated measurements, patients in a randomized clinical trial might be healthier and subjected to a higher level of care when compared with patients in general. Whereas this might influence the generalizability of data, it is unlikely to influence the cost–utility of HDF versus HD. Secondly, as explained in the Materials and Methods section, the prospective analysis of

costs and utility started when the main trial, CONTRAST, was approximately halfway. Participating HDF and HD patients may therefore not be viewed as a random sample as they already survived up until that time. However, there was only a small difference between HDF and HD participants, namely in Kt/V. As the HEMO study did not find a clear effect of Kt/V on quality of life or survival [30, 31], it can be excluded as a potential confounder. The comparison therefore remains valid. Finally, patients and health care professionals could not be blinded for the allocation of treatment, which might induce a placebo effect. If any, this might have a positive effect on utility measures in HDF patients.

In conclusion, HDF is not a more cost-effective option to treat ESRD patients than HD. Although the additional costs of

Table 4: The cost of HD in the recent international literature

Study	Viewpoint	Country	Price reference year	Cost per year	Cost in 2009 euros	
					Exchange rate	Power parity [32]
Baboolal <i>et al.</i> [33]	Service provider	UK	2008	£35 023	€37 211	€46 868
Villa <i>et al.</i> [34]	Public administration	Spain	2010	€37 968	€37 491 ^b	€43 709
Haller <i>et al.</i> [9]	Healthcare?	Austria	2008	€40 600 ^a	€41 087 ^b	€40 773
USRDS [2]	Healthcare	USA	2008	\$77 506	€56 352	€66 328
Mazairac <i>et al.</i> [3]	Society	The Netherlands	2009	€86 086		
Harris <i>et al.</i> [35]	Society	Australia	2008	\$AU 202 124 ^c	€100 893	€116 947
				\$AU 215 354 ^d	€107 496	€124 601

USRDS: United States Renal Data System.
^aCosts for HD beyond 25 months.
^bOnly adjusted for difference in the pricing year using the consumer price index (<http://statline.cbs.nl/statweb/>).
^cPatients with a late start of dialysis: estimated glomerular filtration rate of 5–7 mL/min/1.73 m².
^dPatients with an early start of dialysis: estimated glomerular filtration rate of 10–14 mL/min/1.73 m².

Table 5: The cost–utility of HD in international literature

Study	Viewpoint	Country	Price reference year	Cost per QALY	Cost in 2009 euros	
					Exchange rate	Power parity [32]
McFarlane <i>et al.</i> [7]	Healthcare	Canada	2000–01	\$CAN 125 845	€105 183 ^a	€109 789 ^a
Mazairac <i>et al.</i> [3]	Society	The Netherlands	2009	€114 335		
Gonzalez-Perez <i>et al.</i> [8]	Healthcare	UK	2001–02	£65 817 ^b	€115 566 ^c	€105 988 ^c
Lee <i>et al.</i> [1]	Healthcare	USA	1996–2003	\$129 090	€118 484 ^d	€131 367 ^d
Harris <i>et al.</i> [35]	Society	Australia	2008	\$AU 405 224 ^e	€202 272	€234 458
				\$AU 453 665 ^f	€226 452	€262 485

QALY: quality-adjusted life year.
^aWhen the year 2001 is regarded as the price reference year.
^bBased on £22 246 per year for 1.69 QALYs during 5 years of follow-up.
^cWhen the year 2002 is regarded as the price reference year.
^dWhen the year 2003 is regarded as the price reference year.
^ePatients with a late start of dialysis: estimated glomerular filtration rate of 5–7 mL/min/1.73 m². Based on \$AU 202 124 per year for 2.07 QALYs during 4.15 years of follow-up.
^fPatients with an early start of dialysis: estimated glomerular filtration rate of 10–14 mL/min/1.73 m². Based on \$AU 215 354 per year for 1.97 QALYs during 4.15 years of follow-up.

HDF were limited, they were not compensated for by its marginal positive effect on utility. HDF could become cost-effective when its incremental costs, compared with HD, will be lowered to a maximum of €960.

SUPPLEMENTARY DATA

Supplementary data are available online at <http://ndt.oxfordjournals.org>.

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CONFLICT OF INTEREST STATEMENT

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(See related article by McBrien and Manns. Haemodiafiltration: not effective or cost-effective compared with haemodialysis. *Nephrol Dial Transplant* 2013; 28: 1630–1633.)

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