Improving the outcome of dialysis—opinion vs scientific evidence


Ingrid Ledebo1, on behalf of Norbert Lameire2, Bernard Charra3, Francesco Locatelli4, Menno Kooistra5, Michele Kessler6 and Claude Jacobs7

1Gambro Research, Lund, Sweden, 2Universitair Ziekenhuis, Gent, Belgium, 3Centre de Rein Artificiel de Tassin, Tassin, France, 4Lecco Hospital, Lecco, Italy, 5Stichting Dianet Dialysis Centres, Utrecht, The Netherlands, 6Centre Hospitalier Universitaire, Hôpitaux de Brabois, Nancy, France, 7Groupe Hospitalier Pitie-Salpêtrière, Paris, France

Keywords: biocompatible membranes; daily dialysis; dialysis dose; high-flux membranes; home dialysis; self-care dialysis; treatment time

Introduction

Over one million patients are currently maintained on dialysis, a therapy that has been in clinical practice for 30–40 years. Still we cannot say with confidence that we know which treatment-related factors affect the outcome of dialysis. The only parameter so far shown to have a significant impact on survival, and that only up to a certain level, is the clearance index for small solutes, Kt/V [1].

The possible influence of different treatment-related factors on the outcome of dialysis was the topic for the Dialysis Opinion survey in 1998. In connection with the two major nephrology congresses during that year, the ERA–EDTA Congress held in Rimini in June, and the Annual Meeting of the ASN held in Philadelphia in October, a questionnaire was distributed to the participants asking for their opinion on how the outcome of dialysis is affected by dose, time, membrane, frequency, and self-care. The opinion poll collected 4567 responses in total, with 2836 coming from doctors (Table 1). The result was presented at the Dialysis Opinion Symposium held during the ERA–EDTA Congress in Madrid, where a group of leading nephrologists chaired by E. Ritz gave their personal comments to the issues covered by the survey and discussed the responses from their colleagues around the world.

Table 1. Nationalities of doctors responding to the Dialysis Opinion poll during the ERA–EDTA Congress and the ASN Meeting in 1998

<table>
<thead>
<tr>
<th>Country</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BeNeLux, Austria, Switzerland, United Kingdom, Ireland</td>
<td>147</td>
<td>5</td>
</tr>
<tr>
<td>Czechia, Slovakia, Hungary, Poland</td>
<td>348</td>
<td>12</td>
</tr>
<tr>
<td>France</td>
<td>137</td>
<td>5</td>
</tr>
<tr>
<td>Germany</td>
<td>119</td>
<td>4</td>
</tr>
<tr>
<td>Italy</td>
<td>455</td>
<td>16</td>
</tr>
<tr>
<td>Scandinavia</td>
<td>106</td>
<td>4</td>
</tr>
<tr>
<td>Spain, Portugal</td>
<td>154</td>
<td>5</td>
</tr>
<tr>
<td>Rest of Europe</td>
<td>382</td>
<td>14</td>
</tr>
<tr>
<td>North America</td>
<td>432</td>
<td>15</td>
</tr>
<tr>
<td>Rest of World</td>
<td>556</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>2836</td>
<td>100</td>
</tr>
</tbody>
</table>

The dose of haemodialysis

Question: The dose of haemodialysis (HD) is usually measured in terms of Kt/V for urea. A minimum dose necessary to achieve adequate treatment is recommended by the DOQI guidelines (spKt/V = 1.2). If the dose of dialysis could be increased by 50% above the DOQI minimum level for all HD patients, which impact do you think this would have on the global outcome?

Answer: An overwhelming majority of dialysis professionals, over 90% of the responding nephrologists, expressed the opinion that a major increase of the dose of HD would have a positive effect on patient survival (Figure 1a), with the majority believing that this effect would be significant. This opinion was shared by Europeans and Americans alike, but the majority for
Improving the outcome of dialysis—opinion vs scientific evidence

Fig. 1. Responses from 2836 doctors at the 1998 ERA-EDTA Congress and ASN Meeting to questions about the possible influence of different treatment-related parameters on the outcome of dialysis: (a) the dose of haemodialysis, (b) the treatment time, (c) high-flux, biocompatible membranes, (d) daily dialysis, (e) home/self-care dialysis, and (f) the most important of the parameters above.

1a. The dose of hemodialysis
If the dose of dialysis could be increased by 50% above the DOQI minimum level for all HD patients, which impact would this have on the global outcome?

1b. The treatment time
If it were possible to extend the treatment time by 50% for all HD patients, which impact would this have on the global outcome?

1c. High-flux, biocompatible membranes
If all dialyzers were of the high-flux, biocompatible type, which impact would this have on the global outcome?

1d. Daily dialysis
If daily dialysis were practised for all HD patients, with no change of the total treatment time/week, which impact would this have on the global outcome?

1e. Home/self-care dialysis
If 50% of all new dialysis patients were trained for home/self-care dialysis, with equal numbers on HD and PD, which impact would this have on the global outcome?

1f. What is most important?
Which single factor do you think could have the greatest positive impact on the global outcome?

A significant effect was especially strong (>60%) among German, French and Scandinavian nephrologists.

Comments by N. Lameire

The major scientific effort to elucidate the impact of the dialysis dose on outcome is still the National Cooperative Dialysis Study (NCDS), although now 20 years old. When the result of this study was analysed by Gotch and Sargent [1], a quantification of the dialysis dose was introduced and the well-known step function of morbidity in relation to dose was presented. It showed that dialysis morbidity changed dramatically at Kt/V = 0.8. At lower dialysis doses morbidity was very high, while at dialysis doses above this value morbidity was low and constant. The conclusion was that as long as the dose is above a critical value, which was later set at Kt/V = 1.0, there should be no need to increase it further. The data from the NCDS was later reanalysed by Keshaviah [2], who could show that there is indeed a continuous relationship between morbidity and dose, which indicates that increasing the dose should continue to lead to improvements in
morbidity. Further support for this concept has come from the USRDS, reporting similar improvements in mortality with increased dose of dialysis, expressed as \( \text{Kt/V} \) or urea reduction ratio \([3]\). The dose above which no further improvement could be seen could not be defined in this report, as it appears to exceed the doses currently used in the US.

All reports referred to above used single-pool \( \text{Kt/V} \) values to quantify the dose and therefore did not consider the effect of rebound. When Gotch \textit{et al.} transformed the doses from single-pool to double-pool \( \text{Kt/V} \), i.e. equilibrated \( \text{Kt/V} \) (e\( \text{Kt/V} \)), using patient data in two large US databases, they found that the relative risk of mortality showed a steep decline when the dialysis dose was increased up to \( \text{eKt/V} = 1.05 \) \([4]\). Above this dose there was no further improvement in mortality. Their conclusion was that as long as a thrice-weekly dose of \( \text{eKt/V} = 1.0 \text{–} 1.1 \) is delivered, there is no further benefit to be gained by increasing the dose.

However, there is evidence from Europe that survival can be significantly improved when a large dose of dialysis is delivered. The clinic in Tassin, France, has the best-documented survival of their HD patients in the world and their dialysis is characterized by a high \( \text{Kt/V} \), but also by long treatment times \([5]\). As shown by Gotch \textit{et al.}, in an interesting analysis, the wide distribution of \( \text{Kt/V} \) values around the mean for the Tassin patients makes it difficult to relate the impact on survival to the \( \text{Kt/V} \) \([4]\). This indicates the influence of another factor, perhaps more homogeneously applied in Tassin, namely the treatment time.

My personal response is therefore that if the dose is increased without manipulating the time, there is little evidence that this could have an effect on mortality. Still, I am not surprised by the result of the opinion poll, as most people have the general feeling that more is better. Finally, I can only emphasize that we need studies to find where the limits are.

The treatment time

\textbf{Question:} The treatment time in HD is sometimes claimed to be even more important than the dose. If it were possible to extend the treatment time by 50% for all HD patients, which impact do you think this would have on the global outcome?

\textbf{Answer:} Increasing the treatment time would lead to increased survival according to an overwhelming majority of respondents in the survey, close to 90% (Figure 1b). Over 50% of the responding nephrologists felt that this effect would be significant. The significance of extending the time was most strongly expressed by Scandinavian and German nephrologists (> 70%), while in North America it was chosen by only 48%.

\textbf{Comments by B. Charra}

Having only 5 min to show that longer dialysis duration is better leaves no time for theory, so let me go directly to facts. If we look at the evolution of dialysis session duration, the gold standard of \( 3 \times 10 \) h/week with a 1-m\(^2\) Kil dialyser had been already set during the first decade of HD. The middle molecule hypothesis showed that solutes are cleared differently according to their size and the session could be shortened by increasing the membrane area. This resulted in reducing the treatment time to \( 3 \times 5 \) h in most units. Based on the result of the NCDS Gotch and Sargent \([1]\) suggested a stepwise relationship between clinical outcome and dose expressed as \( \text{Kt/V} \). A consequence of this was that the session time was further reduced to \( 3 \times 3 \) h. However, in 1989 the Dallas conference showed that the mortality of dialysis patients in the US was increasing and that this was developing in parallel with decreases in time and dose \([6]\). Since then the dose as well as the time have increased and mortality has come down in the US \([3]\). Today we see renewed interest in longer and more frequent sessions. The goal of HD for the coming millennium is optimal dialysis and to achieve this we need the combination of at least five factors: sufficient removal of (i) small and (ii) middle molecules, (iii) adequate nutrition for proteins and calories, (iv) satisfactory extracellular volume (ECV) control, and (v) blood pressure (BP) control. Each of these conditions is mandatory, and if only one of them fails to be fulfilled, a poor outcome results. The common denominator for all of them is \textit{TIME}. Only one of them, small molecule removal, can be achieved within a short treatment time. The next two, middle molecule dose and good nutrition, require more time, and the last two, ECV and BP control, are the most time-dependent. The result of reduced treatment times is that today a majority of HD patients are hypertensive and die of uncontrolled cardiovascular disease. At the same time, mortality from these same diseases is reduced by 30% in the general population according to the Framingham study \([7]\). In addition to providing the necessary dose, nutrition, and blood pressure control, an increased treatment time has the benefit of reducing the unphysiological and the intradialytic morbidity and increasing the operational safety of the HD delivery. Altogether a longer or more frequent dialysis is more adapted to the increasingly fragile population we have to treat.

My response to the question is therefore that if everybody could increase the treatment time, it would have a significant and an important positive effect on outcome. I am obviously pleased to see that the majority of nephrologists consider time and dose to be the most important parameters. However, dose in this particular question refers to \( \text{Kt/V} \), which is mainly small solute removal, and for me the removal of phosphate and larger solutes is also important. This is mainly affected by increased time and therefore treatment time remains the most important factor.

High-flux, biocompatible membranes

\textbf{Question:} High-flux, biocompatible dialysis membranes are increasingly used. Still, only about one-third of all
HD patients world-wide are currently dialysed with these membranes. If all dialysers were of the high-flux, biocompatible type and no other parameter of the treatment were changed, which impact do you think this would have on the global outcome? 

**Answer:** In total 75% of the respondents said that the use of high-flux, biocompatible membranes would have a positive impact on survival, but the majority felt that it would only be a trend (Figure 1c).

**Comments by F. Locatelli**

In addition to the dialysis dose, the choice of dialysis membrane is increasingly considered to be essential for improving morbidity and mortality of haemodialysis patients, because the use of so-called bioincompatible membranes can lead to a large number of side-effects. However, the biocompatibility of dialysis also depends on factors other than the membrane, such as the dialysate, dialyser geometry, the distribution of blood in the dialyser, and the sterilizing agent and materials used in reprocessing. Highly permeable synthetic membranes differ from conventional cellulose membranes insofar as they have minimal inflammatory-type contact reactions with blood, and because their large pores allow better convective transport, leading to the removal of medium-sized and large molecules. Epidemiological studies suggest that semi-synthetic and synthetic membranes and/or high-flux may reduce morbidity and mortality in dialysis patients [8]. The results of a historical, prospective study performed using data from the USRDS showed that the relative risk of mortality in patients dialysed with modified cellulose or synthetic membranes was at least 20% less than that of patients treated with unsubstituted cellulose membranes [9]. However, since most synthetic and (to a much lesser extent) modified cellulose membranes have a higher clearance of medium-sized molecules, this could also contribute to the result.

Several groups have found significantly reduced risks of mortality when dialysis with high-flux membranes was compared with standard HD (reviewed in [10]). However, Locatelli et al. did not find any difference in mortality and morbidity among 380 patients randomized to low-flux haemodialysis with biocompatible and bioincompatible membranes and high-flux haemodialysis and haemodiafiltration [11]. This trial, however, was not designed to evaluate the possible difference in morbidity and mortality (also considering that the number of events was rather small), and the observation period of 24 months did not permit any significant evaluation of a possible difference in long-term morbidity and mortality. On the other hand, in a study of 6440 patients treated in Lombardy between 1983 and 1995 the relative risk for mortality was found to be lower when convective treatments were used (~10%) although this difference was not statistically significant [12]. Significantly reduced morbidity, expressed as carpal-tunnel syndrome surgery, has also been reported from some of these studies [12,13].

In conclusion, the use of semi-synthetic and synthetic membranes and high flux seem to reduce morbidity and mortality in dialysis patients. However, the real impact of the biological superiority of synthetic membranes on clinical status and the clinical importance of high-flux treatments still need to be completely clarified [10]. Indeed, the results of published prospective, randomized, controlled trials are conflicting, while on the other hand, in several non-randomized retrospective studies, it is difficult to ascribe the positive effects entirely to the different modalities, because of the many confounders. Only the results of prospective trials with a long follow-up will better clarify the effect of different treatment modalities on the morbidity and mortality of patients on renal replacement therapy [14,15].

**Daily dialysis**

**Question:** The intermittency of HD, as it is organized today, is often cited as the cause of many dialysis-related problems. If daily dialysis (6 days per week) were practised instead for all HD patients, with no change in the total treatment time per week, which impact do you think this would have on the global outcome?

**Answer:** Distributing the weekly treatment time of HD over 6 rather than 3 days is believed to influence survival positively (Figure 1d). One-third of the respondents said such an effect would be significant, while another one-third felt it would be a trend.

**Comments by M. Kooistra**

Most nephrologists agree that maintenance of homeostasis is a prerequisite for health. A continuous and adequate renal function is important for the regulation of a constant and normal biochemical composition and volume of the body fluids. However, the same physicians, while treating HD patients, seem to be satisfied with a very unphysiological therapy that combines inadequacy with infrequency. Many HD patients are overhydrated and dehydrated three times a week, hypertensive and hypotensive three times a week, acidotic and alkalotic three times a week, hyperkalaemic and hypokalaemic three times a week. In fact, most HD patients are still exposed to the so-called ‘unphysiology’ of dialysis, described almost 25 years ago, even when their dialysis is referred to as adequate [16].

Theoretically, when a daily dialysis schedule is compared to a conventional three times per week schedule, both resulting in a similar weekly Kt/V, two major differences can be observed. The urea concentration has lower peaks and is reduced less during daily dialysis, resulting in fewer fluctuations and perhaps less morbidity. The body water content is affected similarly, which may be even more important for clinical practice. The increased frequency results in less
fluctuation between overhydration and dehydration, and greater haemodynamic stability.

It has been shown mathematically that for a given time-average concentration of urea, a lower dialysis dose is required when frequency is higher [17]. In other words: a given weekly Kt/V is worth more when delivered at a higher frequency. This means that the weekly Kt/V of an intermittent treatment cannot be compared with a similar Kt/V delivered in a continuous treatment, which is obvious for everybody working with CAPD patients. When the ‘equivalent renal clearance’ of different treatment schedules is calculated and compared, it shows that increasing the number of dialysis sessions per week is often more effective than increasing the dialysis dose of a session applied three times weekly [18].

What about the clinical relevance of more frequent dialysis? Many workers during the last decades showed a marked improvement of several clinical items, including erythropoiesis, metabolic control, volume and blood pressure regulation, cardiac function, brain function, working capacity, and quality of life when patients were treated on a short daily basis [19]. Unfortunately, these studies were not controlled and when switching to a daily schedule the dialysis dose was often increased. In the special form of daily dialysis referred to as nocturnal dialysis long dialysis sessions are combined with increased frequency and the result is very high Kt/V values and outstanding metabolic and haemodynamic control [20].

To investigate the clinical significance of the mathematical idea that a given weekly Kt/V is worth more when delivered on a more frequent basis, we performed daily (six times per week) home HD without increasing total weekly Kt/V [21]. This resulted in some improvement of metabolic control, a marked improvement of blood pressure and haemodynamic control, and a better quality of life, all achieved at a cost that is similar to in-hospital HD thrice weekly.

In conclusion, I feel that both a theoretical basis and clinical evidence are available for the statement that daily HD improves the outcome of the treatment. Increasing dialysis frequency is a powerful tool that can be used when the dialysis treatment is insufficient. It is reassuring to see that so many colleagues appreciate the importance of increasing the frequency of dialysis, although so few have had the possibility to practise it yet. Personally, I would say that combining an increase of time, dose, and frequency with a biocompatible membrane and doing all this at home would give the best result. That is what is practised in the nocturnal dialysis programme in Toronto [20].

Home/self-care dialysis

Question: Home/self-care dialysis is known to result in better outcomes than dialysis at an institution, but the reasons for this are not clear, because patient selection makes valid comparisons difficult. If 50% of all new dialysis patients were trained for home/self-care dialysis, with equal numbers on HD and PD, which impact do you think this would have on the global outcome?

Answer: Over half of the respondents expressed the opinion that extended use of home/self-care dialysis would improve the survival among dialysis patients, although this would be seen mainly as a trend (Figure 1e). The largest support for home/self-care was found among the respondents from North America, where >70% said it would improve survival.

Comments by M. Kessler

An adequate answer to this question requires an adequate definition of home and self-care dialysis. Home HD is performed at home after several weeks of training for the patient and the assistant, usually the spouse. True self-care HD is performed near the home in a non-medical unit, a home substitute. Patients are trained similarly to home HD and have a personal machine. A nurse is present throughout the session in order to help the patients if necessary. This modality is quite different from the so-called self-care HD in France, which is a disguised form of in-centre HD, justified by the lack of hospital HD facilities.

There are relatively few data comparing clinical outcome of home/self-care HD with hospital HD and PD, and the reports include patients dialysed prior to 1990. Using the Cox proportional hazards model Woods et al. [22] demonstrated that the relative risk of death in 70 home HD patients compared to 3103 centre HD patients in the US was 0.58, when adjusted for comorbidity, age, sex, race, and diabetes. Prescribed dialysis dose and serum albumin were similar in both groups of HD patients. Long-term survival in home/self-care HD is not unusual if patients do not undergo renal transplantation, and the survival rate in 417 patients treated with home and self-care HD was 77% at 10 years and 45% at 20 years [23]. In a study of 859 patients undergoing dialysis or transplantation, Evans et al. [24] showed that among the patients treated by dialysis, those undergoing treatment at home had the highest quality of life. All differences were found to persist even after the patient case mix had been controlled statistically. A recent study also showed that patients trained for self-care HD experienced better subjective quality of life than in-centre patients [25].

In conclusion, haemodialysis at home or in self-care HD units with training provides better survival and quality of life than in-centre HD, and probably than long-term PD, even after adjustment for patient characteristics and comorbidity. These results are supported only by epidemiological studies which show associations but which cannot prove causation. Explanations for the difference are probably multiple. There is undoubtedly a substantial selection of home/self-care HD patients. Comorbidity was found to be as frequent in home HD compared with hospital HD but severity of comorbid conditions might be lower. Patients at
home or in self-care units with training have personal machines and finally independence. Better motivation could lead to more patient involvement.

I find it interesting that the majority of the respondents say that time and dose are the most important parameters for improved outcome. However, under present conditions the only realistic way to increase the time and the dose is to perform dialysis at home. So we should view increased use of home/self-care dialysis as an important component for improved outcome.

**What is most important?**

**Question:** Of the five possible changes discussed above, regarding the dose, time, membrane, frequency, and patient involvement, which single factor do you think could have the greatest positive impact on the global outcome?

**Answer:** One-third of the doctors responding to the survey chose an increased dose of dialysis as the most important factor for improved outcome (Figure 1f). Extending the time was considered slightly less important. The importance of time was especially emphasized by the Germans, while dose was strongly preferred by nephrologists from North America.

**Comments by C. Jacobs**

If we consider the primary end-point of any mode of dialysis therapy to be patient survival, the starting point for attempting to answer the above question is to investigate the causes of death in dialysis patients. All the data collected over the years in large national and international registries concur in ranking cardiovascular diseases as the leading cause of death in dialysis patients, regardless of age, underlying renal disease, or specific mode of treatment. For example, cardiac causes account for 40–50% of all the deaths reported from the USRDS during 1994–1996 for dialysis patients aged 20–65+ years [26]. Altogether, mortality from cardiovascular causes in the ESRD population is about 30 times the risk in the general population [27]. A prolific literature based on retrospective and prospective clinical studies has over the years highlighted some key factors that have an unequivocal impact for reducing the mortality rate in dialysis patients, the most prominent being: (i) adequate control of blood pressure, (ii) adequate prescription and delivery of dialysis dose, (iii) efficacious preventive measures against infections, (iv) early detection and prevention/treatment of malnutrition.

**The issue now reads:** ‘Can a single component of a dialysis/filtration method or strategy optimize all of the above requirements?’ The response to this reformulated question is of course negative, and it can easily be supported by returning to basic facts: The human kidney is a highly sophisticated multifunctional regulatory organ, operating continuously for 10 000 min/week, with a weekly filtration capacity for small molecular weight substances of about 1200 litres. Compare this to the currently available extracorporeal dialysis systems which are exclusively filtration devices, deprived of any reabsorptive or endocrine regulatory function, operating for 700–1500 min/week with a small-molecule filtration capacity no greater than 150–200 l/week, which is at best 15% of that of the healthy human kidney. Indeed, the true miracle is that these very primitive devices are able to provide several decades of survival time for the patients.

If it can be postulated that optimal extracorporeal renal replacement therapies should provide de purative functions closest to that achieved by the human kidney, which of the currently available modes of therapy are best approaching this goal? Haemodiafiltration, by combining diffusive and convective mechanisms of fluid and solute removal, simultaneously enhances the dialysis dose, enlarges the spectrum of removed uraemic toxins, and is performed with the currently best biocompatible components. In spite of these advantages, the patient mortality was not found to be significantly different in a study where one form of haemodiafiltration was compared with conventional dialysis methods [11]. Long nightly haemodialysis is another approach for optimizing the overall performances of an extracorporeal dialysis system insofar as it combines the delivery of a high dialysis dose with a prolonged dialysis time and the benefits from a home-performed treatment, three of the factors specifically proposed above. Long-term results of nocturnal haemodialysis according to the strategy developed in recent years by the group in Toronto are not yet available [20]. However, the results achieved in the well-documented Tassin experience with a long, slow HD technique generate very encouraging expectations with a 6–7 nights/week dialysis strategy [5].

Screening the huge body of literature published over the past 30 years on the results of dialysis therapies one can actually find a positive effect on the outcome for each of the factors listed in the above questionnaire. As for the challenge consisting in selecting one single factor among all others, it is the conviction of the undersigned that we are still awaiting an unequivocal, evidence-based ‘landmark paper’ providing a response to the question. Will and can such a study ever be performed and published? ‘That is another story’ (R. Kipling). Anyhow, stay tuned, since some advance in this field can perhaps come out from the HEMO study currently under way in the USA, results of which are expected in the early years of this new millennium [14].

**References**

2. Keshaviah P. Urea kinetic and middle molecule approaches to assessing the adequacy of hemodialysis and CAPD. *Kidney Int* 1993; 43[Suppl 40]: S28–38


17. Depner T. Benefits of more frequent dialysis: lower TAC at the same Kt/V. *Nephrol Dial Transplant* 1998; 13 [Suppl 6]: 20–24


