Clinical Evaluation and Experience in Treatment Modalities

Treatment modalities in comparison: when do clinical differences emerge?

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Abstract Background. Despite technological advances in dialysis equipment and modalities, the survival, morbidity and quality of life of uraemic patients undergoing regular haemodialysis treatment are still severely affected by acute intradialysis and long-term complications, possibly related to the treatment itself. Convective treatment modalities, such as haemodiafiltration and haemofiltration, are thought to be further improvements over standard diffusive haemodialysis. Moreover, several of the pathways activated in patients during dialysis have the potential to produce many side-effects. These occur three times a week, and are particularly intense in patients dialysed with so-called ‘bio-incompatible’ membranes. Thus the biocompatibility of dialysis membranes is increasingly recognized as one of the main factors in the improvement of dialysis treatment.

Methods. The main clinical studies to date are reviewed to highlight the clinical effects of different treatment modalities and membranes on the most important acute and long-term haemodialysis-related complications.

Results. Epidemiological studies suggest that semisynthetic and synthetic membranes may reduce morbidity and mortality in dialysis patients. Despite the proven biological superiority of biocompatible membranes, we lack definitive evidence that thrice-weekly complement and cell activation over a period of years is detrimental to patients, because the results of prospective randomized studies are conflicting. However, it is important to remember that factors other than the dialysis membrane could influence the ‘biocompatibility’ of dialysis, including the dialysate, dialyser geometry, the distribution of blood in the dialyser, reuse, the sterilizant and materials used in reprocessing.

Conclusions. Further large-scale prospective and randomized trials with a long follow-up are needed in order to better clarify the clinical effect of different treatment modalities on the morbidity and mortality of patients on chronic renal replacement therapy. In particular, it must be clarified whether the possible clinical differences in treatment modalities are based on differences in the clearance of middle molecules or on biocompatibility, or, more generally, on the increasingly recognized clinical importance of high-flux treatments, and the possible interaction between membrane flux and biocompatibility.

Introduction

In recent years, technological innovations in dialysis equipment and new modalities have improved the quality of dialysis treatment. However, a number of acute complications or symptoms, such as intradialysis hypotension, muscle cramps, headache, nausea, pruritus, fatigue and postdialysis lack of energy have been attributed not only to the intermittent and/or insufficient depuration and to the dialysate composition (water and solutes), but also to the type of modality (diffusive treatments) and the type of dialysis membrane used (so-called bio-incompatibles).

In fact, several of the pathways activated in patients during dialysis have the potential to produce many side-effects. It is important to remember that complement and cell activation occurs three times a week over a period of years, and is particularly intense in patients dialysed using ‘bio-incompatible’ membranes.

Thus survival, morbidity and the quality of life of uraemic patients undergoing regular haemodialysis treatment are still severely affected by acute intradialysis and long-term complications, possibly related to the treatment itself.

Cardiovascular instability is certainly the most important acute haemodialysis-related complication (and is possibly also, at least partly, responsible for the deterioration in residual renal function) and malnutrition (possibly cause or consequence of infections), β₂-microglobulin deposition (with consequent dialysis-associated amyloidosis [1]), accelerated atherosclerosis and alterations in immunodefence (with consequent infections and cancers) are possibly the most important long-term complications. Therefore, convective treatments and the biocompatibility of dialysis membranes are increasingly recognized as the main factors in the improvement of dialysis treatment [2,3].
However, it is important to remember that factors other than the dialysis membrane could influence the biocompatibility of dialysis, including the dialysate, dialyser geometry, the distribution of blood in the dialyser, reuse, and the sterilants and materials used in reprocessing.

Moreover it must be clarified whether these improvements are based only on the biocompatibility of the membranes used normally in these convective treatments, or on differences in the clearance of middle molecules, or more generally on the increasingly recognized clinical importance of high-flux treatments, and the possible interaction between biocompatibility and membrane flux.

Although the problem is clinically very important, few prospective, randomized, controlled and adequately sized trials have addressed the clinical effects of different dialysis membranes and technologies on the morbidity and mortality of patients on substitutive treatment, to verify in vivo the short- and long-term benefit reported in vitro.

In the few studies comparing two different modalities or membranes, many technical aspects (the prescribed and delivered dialysis dosage, dialysis time, dialysis machine with or without automatically controlled ultrafiltration, water quality, realized electrolyte and acid–base balances, thermal balance, convection/diffusion ratio), drugs employed (erythropoietin, antihypertension therapy) and many confounders difficult to evaluate, such as patient expectation of the new method, and also the motivation and the belief of the team (physicians and nurses) regarding a new treatment strategy, were either different or not evaluated. Thus, we should be very careful when evaluating the results of uncontrolled retrospective studies.

In order to evaluate the potential benefits of the flux (convective treatments: high-flux dialysis, haemodiafiltration, haemofiltration) and/or the biocompatibility of membranes, overall in terms of morbidity and mortality, we have to take into account acute effects on the cardiovascular stability, the preservation of residual renal function, nutritional aspects, infection, anaemia and the long-term effect on β₂-microglobulin accumulation and deposition and subsequent amyloidosis. The potential ‘renoprotective’ effect of biocompatibility possibly improving acute renal failure recovery and, along with the reduction of infection (fatal sepsis), possibly affecting the survival of patients with acute renal failure, is beyond the scope of this study. This topic has been discussed thoroughly in a recent review [4] from which one should conclude that, to date, an unequivocal detrimental effect of bio-incompatible membranes on the course and outcome of acute renal failure remains controversial.

**Cardiovascular stability**

Cardiovascular instability during haemodialysis treatment is an important clinical problem that still affects a large percentage of uraemic patients undergoing extracorporeal substitution programmes, despite technological advances (monitors with ultrafiltration control, supplied bicarbonate dialysate) and convective strategies. Although its pathogenesis is multifactorial, growing importance is ascribed to the progressive increase in the median age of patients beginning haemodialysis therapy, the prolonged survival of haemodialysis patients and the consequent increase in dialysis median age and cardiovascular risk factors [5]. Another important factor is the tendency to shorten dialysis treatment time by means of increased blood flow rate, larger dialyser surface and greater ultrafiltration rate in order to reach adequate solute and fluid removal. The importance of adequate sodium removal in improving intradialysis cardiovascular stability is well known. The introduction of highly permeable synthetic membranes into routine clinical practice has made the whole issue even more complex. They differ from conventional cellulose membranes because of their minimal inflammatory-type contact reactions with blood and also because they have large pores, which provide better convective transport and the removal of mid-sized and large molecules. As a consequence, the treatment strategies in which these types of membrane are used, such as high-flux haemodialysis, haemodiafiltration and haemofiltration, are considered to be more biocompatible than haemodialysis.

The lower intradialysis hypotension rates reported for haemofiltration and haemodiafiltration may be due, at least in part, to the fact that they generally remove less sodium than haemodialysis (at least given the present use of dialysate and reinfusate sodium concentration), or to their different effects on peripheral resistance compared with haemodialysis, or to the fact that these treatments are usually performed using biocompatible membranes. In contrast, there is the possibility that the recognized superiority of biocompatible membranes on blood–membrane interaction may be counterbalanced by blood–membrane–dialysate interactions. In fact, highly permeable membranes have large pores, therefore a high quality of dialysate is needed in order to prevent pyrogen back-transport affecting cardiovascular stability.

The main prospective clinical studies on the effect of different membranes on intradialysis cardiovascular stability are summarized in Table 1.

Chanard et al. [6] reported that the incidence of hypotension, vomiting, cramps and headaches was less for patients dialysed using the AN69 membrane. However, there was a lack of randomization and patients in the control group (cellulose membrane) did not use machines with automatically controlled ultrafiltration.

Skoedter et al. [7] performed a prospective, randomized, cross-over study on 23 patients, undergoing 12 different bicarbonate haemodialysis sessions using cuprophane, hemophan or polyamide membranes for short (2 h) and long (4 h) treatments, with small or large membrane areas. Subjective and objective symptoms were registered during haemodialysis and 12 and 36 h thereafter. The authors did not find the
bio-incompatibility of the membrane to be a significant cause of subjective or objective symptoms during haemodialysis.

The ‘Bergamo Collaborative Dialysis Group’ [8] carried out a large multicentre trial designed to clarify the intradialysis well-being of the patients. The study was homogeneous with regard to clinical conditions. Patients were dialysed using membranes with a surface area of 1 m² and were randomly assigned to use either cuprophane or polysulfone membranes. No differences were found in the intradialysis symptoms between the two dialysis membranes.

Collins et al. [9] performed a randomized prospective, cross-over study to assess whether patients dialysed with polyacrylonitrile (PAN or AN69) have fewer intradialysis hypotensions and acute symptoms than patients dialysed with a cuprophone membrane. The authors did not find any significant difference concerning intradialysis hypotension during the short follow-up (3 months with each membrane). The authors stressed the inadequate statistical power of the study results. The sample size was estimated on the basis of the expected difference in dialysis treatment tolerance (an 18% reduction in symptomatic treatment, calculated as 30% of the dialysis session) only for the two groups treated with cuprophone and low-flux polysulfone bicarbonate dialysis. For a type I (α) error of <0.05 and a power (1−β) of 0.80 and assuming a drop-out rate of 30%, 115 patients needed to be enrolled into each group. A total of 380 patients were enrolled and followed up for 24 months. Treatment tolerance, evaluated as the sum of the monthly number of dialysis sessions with hypotension, was 1.9 ± 2.8 sessions/month for the cuprophone group and 2.61 ± 3.47 for the low-flux polysulfone group during the run-in phase (P=n.s.). The behaviour of this endpoint during the 24-month follow-up was not significantly different between bicarbonate dialysis with cuprophone (132 patients) or with low-flux polysulfone (147 patients) or among the four dialysis methods under evaluation. Thus, the incidence of intradialysis hypotension in the population as a whole was less than expected, possibly because of a selection bias and/or good medical care. Therefore, the authors did not find that convection and/or membrane biocompatibility was important in improving cardiovascular stability during dialysis, mainly because it is very difficult to find any differences in the percentage incidence of intradialysis hypotension between membranes and treatment modalities if the incidence is low.

Altieri et al. [11] performed a prospective non-randomized study in 23 patients comparing on-line predilution bicarbonate haemofiltration with ultrapure high-flux dialysis using a polyamide membrane. The adequacy of treatment was equilibrated Kt/V values of 1.41 for HD and 1.08 for HF. The number of hypertensive episodes was 1.78 ± 2.8 per patient per month during HD vs 1.17 ± 3.1 during HF (P=0.003) and the number of hypertensive episodes was 1.28 ± 2.8 during HD vs 0.42 ± 0.8 during HF (P=0.04). The incidences of arrhythmia, muscular cramps and headache were significantly less frequent during HF.

Taken together, the results of these studies do not support the hypothesis that membrane biocom-

### Table 1. Prospective clinical studies on the effect of different membranes on intradialysis cardiovascular stability

<table>
<thead>
<tr>
<th>Author</th>
<th>Ref.</th>
<th>Year</th>
<th>Design</th>
<th>Patients*</th>
<th>Membranes*</th>
<th>Effect of synthetic membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chanard</td>
<td>6</td>
<td>1982</td>
<td>Parallel</td>
<td>140</td>
<td>PAN/Cu</td>
<td>Improved</td>
</tr>
<tr>
<td>Skroeder</td>
<td>7</td>
<td>1990</td>
<td>Cross-over</td>
<td>23</td>
<td>PA/Hem/Cu</td>
<td>n.s.</td>
</tr>
<tr>
<td>Bergamo CDG</td>
<td>8</td>
<td>1991</td>
<td>Parallel</td>
<td>328</td>
<td>lf-PS/Cu</td>
<td>n.s.</td>
</tr>
<tr>
<td>Collins</td>
<td>9</td>
<td>1993</td>
<td>Cross-over</td>
<td>35</td>
<td>PAN/Cu</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*In cross-over studies the number of patients must be doubled to compare them with the number of patients of parallel studies (with two groups).

*Cu, cuprophan; PAN, polyacrylonitrile; PA, polyamide; lf-PS, low-flux polysulfone; hf-PS, high-flux polysulfone.
Patibility and/or convection lead to a decrease in acute intradialysis clinical symptoms, at least in the uraemic population selected for these studies. We suggest that future trials should involve a sicker patient population with a higher prevalence of intradialysis hypotension in order to achieve statistical power.

**Residual renal function**

Patients with residual renal function may have lower dietary restriction and shorter dialysis treatment times. Preservation of residual renal function may also contribute significantly to the removal of β₂-microglobulin, thus reducing the risk of β₂-microglobulin-related amyloidosis and possibly reducing the loss of production of calcitriol and erythropoietin. The suggested relationship between the use of different dialysis membranes and the rate of decline in renal function [12] has not yet been confirmed.

Caramelo et al. [13] did not find any difference between cuprophane and polysulfone or polycrylonitrile membranes. However, the number of patients enrolled in this study was rather small (13 and nine respectively) and the follow-up was for only 9 months.

Hakim et al. [14], analysing the effect on plasma β₂-microglobulin, found that the use of biocompatible membranes (low-flux polymethylmethacrylate) was associated with no significant difference in residual renal function during the 18-month follow-up period compared with the use of bio-incompatible membrane.

Schiff et al. [15] reported the results of a prospective, randomized, small trial involving 20 normotensive patients. After 1 year of observation the residual renal function, estimated on the basis of creatinine clearance and daily urine volume, was twice as high in patients treated with high-flux polysulfone than in those treated with cellulosic membranes (P < 0.05).

McCarthy et al. [16] performed a retrospective study using polysulfone and cellulose acetate membranes, comparing 50 consecutive patients with residual renal function and found that patients with parenchimal renal disease (glomerulonephritis or nephrosclerosis) showed markedly better retention of residual renal function with the polysulfone than with the cellulose acetate membrane.

**Nutritional aspects**

It is well known that protein and calorie intake is related to the survival of patients on substitutive treatment.

Gutierrez et al. [17] found that sham dialysis with a cellulose membrane on healthy volunteers was related to the loss of amino acids, thus indicating protein catabolism. Protein catabolism was less detectable using synthetic membranes, such as AN69, polysulfone or cellulose acetate. However, these findings have not been confirmed in uraemic patients [18].

Moreover, it has been suggested, although using data with major methodological drawbacks, that the protein intake increases when the patient changes from a cellulose (cuprophane) to a synthetic membrane (AN69) [19]. One possible explanation could be the removal of higher molecular mass uraemic toxins, thus increasing the well-being of the patients and, consequently, their appetite; the increased protein and calorie intake could increase the serum albumin level, thus possibly decreasing morbidity and mortality. Moreover, dialysis with cellulose membranes promotes or exacerbates a chronic catabolic state, leading to protein wasting and malnutrition.

Parker et al. [20] designed a trial to evaluate, in 143 patients, the relationship between prescribed dialysis dosage, protein catabolic rate, morbidity and mortality, and biocompatibility of the dialysis. The authors found an increase in estimated body weight (~4 kg) and an increase in albumin plasma concentration (~0.35 mg/dl) in patients treated for 18 months with a low-flux polymethylmethacrylate membrane. It is important to stress that these results have been obtained in spite the fact that Kt/V for the biocompatible membrane was 1.24, significantly less than the Kt/V of the bio-incompatible membrane group of 1.37. However, baseline plasma albumin levels of the patients involved in this study (all at the start of renal replacement therapy) were quite low (3.5 g/dl) and the presence of smouldering overhydration in patients treated with biocompatible membranes cannot be excluded. Moreover, the very high number of dropouts (due to treatment inadequacy) in the group of patients on the biocompatible membrane (72%) compared with those on the bio-incompatible membrane (46%) should be taken into account in evaluating the results of Parker et al.’s study.

Locatelli et al. [10] did not find a correlation between Kt/V and protein catabolic rate and this did not depend on the different membrane biocompatibility or fluxes used. One possible reason for this lack of correlation may be the high levels of Kt/V recorded in the study: given the curvilinear relationship between PCR and Kt/V, the studied patients probably fall into the plateau region where the correlation between efficiency and nutrition is lost. One of the inclusion criteria in this study was a protein catabolic rate of no less than 1g/kg/day, moreover the plasma albumin was well preserved in the population as a whole at baseline (4.2 ± 0.4 g/dl) particularly when we consider that the mean dialysis age of the patients of this study was 58 months.

The clinical impact of membranes on the lipid profile of dialysis patients is still debatable; in this respect, the role of the underlying disease, diet, dialysate buffer and heparins should also be taken into account.

In conclusion, our previous considerations concerning cardiovascular stability also apply to the nutritional aspect; thus future trials should be designed to involve a sicker patient population with a high prevalence of malnutrition in order to provide statistical power.
Comparison of treatment modalities

Infections

Vanholder et al. [21] found a reduction in the incidence of sepsis in patients treated with a polysulfone membrane vs patients treated with a cuprophane membrane. However, this is a very provocative paper involving only 16 patients with a very short follow-up (20 weeks). Locatelli et al. [10] were unable to confirm this observation. However, the possibility of a lower mortality rate due to infection being achieved with the use of semisynthetic or synthetic membranes has recently been reported in a USRDS case-mix adequacy study analysis by Bloembergen et al. [22].

Anaemia

Kobayashi et al. [23] found that only highly permeable biocompatible membranes are able to remove high-molecular-mass substances that inhibit erythropoiesis, thus stressing the importance of permeability.

In a prospective randomized study of 135 patients, Ifudu et al. [24] reported that increasing the intensity of dialysis in patients receiving inadequate dialysis led to a significant increase in the response to erythropoietin. However, the increase in dialysis dose was obtained by using more permeable and biocompatible membranes (high-flux polysulfone), which at least suggests a possibly additive effect of biocompatibility and/or permeability on the correction of anaemia.

A prospective randomized controlled trial by Locatelli et al. aimed at assessing the role of the flux of membrane on response to erythropoietin is ongoing.

β₂-Microglobulin removal

The aspect of β₂-microglobulin dialysis-related amyloidosis is very important and it should be stressed that the prevalence of clinical signs of β₂-microglobulin amyloidosis is very low in comparison with the pathological prevalence. Thus the clinical symptoms of β₂-microglobulin amyloidosis should be considered to be the tip of the iceberg of dialysis-related amyloidosis.

In a prospective post-mortem study [1] the prevalence of clinical signs of β₂-microglobulin amyloidosis was 2–4% respectively, compared with a histological prevalence of 48% after a mean period on haemodialysis of 47 months, which reached 100% after more than 13 years on haemodialysis. It is worth noting that a much higher prevalence of amyloidotic β₂-microglobulin deposits in the periosteum of the iliac crest have been found in chronic haemodialysed patients with femoral neck fractures [25], further supporting the clinical relevance of the problem.

It is well known that no relationship between pre-dialysis plasma β₂-microglobulin levels and dialysis-related amyloidosis has been found [26]. However, it is difficult to find other parameters suitable for large clinical trials.

Van Ypersele de Strihou et al. [27], retrospectively analysed patients treated with different membranes, and found a lower incidence of cystic bone lesions in those treated with a synthetic membrane (AN69) than in those treated with a cuprophane membrane. One of the most interesting findings of this study was the important role of age in increasing the incidence of cystic bone lesions in both treatments.

Bonomini et al. [28] retrospectively analysed 122 patients divided into two groups on the basis of the dialysis membrane used (cellulose or synthetic), and did not find any difference between the membranes in terms of survival and general or β₂-microglobulin-related morbidity.

Kuchle et al. [29, 30] conducted a trial involving 20 patients who had been treated previously with low-flux cuprophane HD membranes and who were randomised to continue the same haemodialysis regimen or to receive haemodialysis treatment with high-flux polysulfone membranes. After a 6-year follow up [29], no clinical signs of dialysis-associated amyloidosis were found in any of the 10 patients dialysed using polysulfone membranes, whereas eight of the patients dialysed with cuprophane membranes had carpal tunnel syndrome and/or osteoarticular lesions. After 8 years of follow-up [30] clinical signs of dialysis-associated amyloidosis were found in two of the patients dialysed using polysulfone membranes. Moreover, the serum levels of β₂-microglobulin were significantly reduced in the patients treated with high-flux polysulfone membranes.

Hakim et al. [14] found that the use of biocompatible membranes over a period of 18 months, even in the low-flux configuration (low-flux polymethylmetacrylate), was associated with a significantly slower increase in plasma β₂-microglobulin. However, the authors themselves underlined the fact that there were no significant differences in the actual level of β₂-microglobulin (and residual renal function) between the two groups during the follow-up period.

Locatelli et al. [10] found a significant decrease in pre-dialysis plasma β₂-microglobulin levels in high-flux dialysis and haemodiafiltration (both using a high-flux polysulfone membrane) compared with cuprophan and low-flux polysulfone membranes.

It is well known that carpal tunnel syndrome and β₂-microglobulin dialysis-associated amyloidotic arthropathy are present in a very large percentage of, especially, older patients on long-term regular dialysis treatment and that this greatly affects their quality of life [31]. Using data from the Lombardy Registry, Locatelli et al. [32] carried out a historical prospective study of 6440 patients who had started renal replacement therapy between 1983 and 1995. The authors found that the relative risk for carpal tunnel syndrome surgery (evaluated as a parameter of morbidity) was 44% lower in the patients treated with haemodiafiltration or haemofiltration (RR = 0.56; 95% CI: 0.34–0.92; P = 0.02) than in those treated with standard haemodialysis, thus supporting the importance of...
convective treatment in reducing morbidity from $\beta_2$-microglobulin deposition.

Morbidity and mortality

Chanard et al. [6] reported that, compared with cuprophan, the use of a biocompatible membrane (PAN) was related to positive effects on rehabilitation, the hospitalization index and the number of days in hospital. Although the incidence of hypotension, vomiting, cramps and headaches was notably less for the patients dialysed using the AN69 membrane, there was no real difference in mortality between the two groups.

Churchill et al. [33] performed a randomized, prospective, double-blind, cross-over study on 21 patients comparing low-flux cellulose acetate and high-flux cellulose diacetate membranes to verify the effect of high-flux haemodialysis on cardiac structure and function. The modest improvements in estimates of systolic function during the 4-month follow-up with each membrane suggest a cardiac advantage in high-flux dialysis, the clinical impact of which requires further study.

Hornberger et al. [34] performed a retrospective study comparing 146 patients on standard haemodialysis treatment with 107 patients on high-flux haemodialysis. The relative risk of mortality on high-flux haemodialysis was 0.24 (95% CI: 0.12-0.49), deriving from 69 deaths in the standard dialysis group vs 11 among the patients on high-flux haemodialysis.

Locatelli et al. [10] did not find any difference in mortality and morbidity among the four randomized patient groups during the 24-month follow-up, but the trial was not designed to evaluate the possible difference in morbidity and mortality. Thus the observation period did not allow any evaluation of a possible difference in long-term morbidity and mortality.

In a retrospective analysis of 715 patients, Woods [35] identified two groups: 252 patients treated exclusively with low-flux polysulfone and 463 patients treated for at least 3 months, and up to 5 years, with high-flux polysulfone. The patients treated with high-flux polysulfone experienced lower mortality (21 vs 36 per 1000 years; $P<0.01$) and had a better probability of survival at 5 years (90 vs 60%; $P=0.029$). In a Cox proportional hazards model, high-flux dialysis was associated with a 70% reduction in death risk when compared with low-flux dialysis. The author suggests that the higher clearance of larger molecular species of putative uraemic toxins achieved with high-flux dialysis confers a survival advantage that is independent of any membrane biocompatibility effect.

Hakim et al. [36] performed a historical prospective study using data from the United States Renal Data System (2410 patients) and a Cox proportional hazards model to estimate the relative risk of mortality. The results of the study suggest that, after adjusting for dialysis dose and the presence of comorbid factors, 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. However, the authors themselves stressed that more definitive studies are needed before a cause and effect relationship can be proven. Since synthetic and (to a much lesser extent) modified cellulose membranes have a higher clearance of middle molecules, it must be explained whether the effect may be due to differences in the clearance of such solutes.

Locatelli et al. [32], in a study of 6440 patients treated in Lombardy between 1983 and 1995, found that the relative risk for mortality was not significantly lower in convective treatments ($RR=0.90$).

Conclusion

It is very difficult to ascribe the positive effects found in several non-randomized retrospective studies entirely to the different modalities because of the many confounders (i.e. biocompatibility of the membranes and permeability), although some very sophisticated statistical methods have been used in some studies. It is important to stress that, when there is no difference between treatment groups, one does not accept the null hypothesis but rather fails to reject it. In other words, if the data do not show any between-treatment difference, this does not imply equivalence but rather that there is not enough evidence to conclude that one treatment is better than the others. Therefore, future trials should involve a sicker patient population in order to achieve statistical power.

Epidemiological studies suggest that semisynthetic and synthetic membranes and flux seem to reduce morbidity and mortality in dialysis patients.

The results of the published prospective, randomized, controlled trials are conflicting [37], and only the results of other trials with a long follow-up (for example the HEMO study [38,39]) can better clarify the effect of different treatment modalities on the morbidity and mortality of patients on chronic renal replacement therapy. In particular, it must be explained whether the effect is based only on the biocompatibility of the membrane per se or on differences in the clearance of medium-sized molecules, or more generally on the flux of the membrane. However, these trials are very difficult to conduct because of the need for randomization and the high drop-out rate of patients.


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