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REVIEW

The renal replacement therapy landscape in 2030: reducing the global cardiovascular burden in dialysis patients

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ABSTRACT

Despite the significant progress made in understanding chronic kidney disease and uraemic pathophysiology, use of advanced technology and implementation of new strategies in renal replacement therapy, the clinical outcomes of chronic kidney disease 5 dialysis patients remain suboptimal. Considering residual suboptimal medical needs of short intermittent dialysis, it is our medical duty to revisit standards of dialysis practice and propose new therapeutic options for improving the overall effectiveness of dialysis sessions and reduce the burden of stress induced by the therapy. Several themes arise to address the modifiable components of the therapy that are aimed at mitigating some of the cardiovascular risks in patients with end-stage kidney disease. Among them, five are of utmost importance and include: (i) enhancement of treatment efficiency and continuous monitoring of dialysis performances; (ii) prevention of dialysis-induced stress; (iii) precise handling of sodium and fluid balance; (iv) moving towards heparin-free dialysis; and (v) customizing electrolyte prescriptions. In summary, haemodialysis treatment in 2030 will be substantially more personalized to the patient, with a clear focus on cardioprotection, volume management, arrhythmia surveillance, avoidance of anticoagulation and the development of more dynamic systems to align the fluid and electrolyte needs of the patient on the day of the treatment to their particular circumstances.

Keywords: advancing outcome, dialysis, renal replacement therapy, Stage 5 chronic kidney disease dialysis, technology support

INTRODUCTION

Setting the scene

Despite the significant progress made in understanding chronic kidney disease (CKD) and uraemic pathophysiology including premature ageing [1–3], use of advanced technology [4] and implementation of new strategies in renal replacement therapy [5], the clinical outcomes of chronic kidney disease 5 dialysis patients remain suboptimal [6]. Annual crude mortality ranges between 14 and 16% in the western world [7], being similar to colon cancer [8], while hospitalization rates are 3–5 times higher, accounting for 7–9 days/patient/year compared with the non-CKD patient [9]. Cardiovascular events are the leading causes of this mortality, accounting for 50–60% of death causes [10]. Patient experience remains a challenge, and quality of life is reduced and disease burden is of major importance when compared with age-matched general populations [11–13]. These challenges for patients, physicians, care givers and health authorities require continual analysis to improve the societal and economic burden of end-stage kidney disease (ESKD) management. These concerns were recently highlighted with a strong call for moving away from a 'one-size-fits-all' approach to dialysis and providing more personalized care that incorporates patient goals and preferences while still incorporating best practices of quality and safe therapy [14].

Renal replacement therapy represents the overall management of ESKD patients with three layers as shown in Figure 1: the first layer is the blood purification that consists of repetitive dialysis sessions as the basic element integrated in to a treatment schedule; the second layer is the dialysis patient management from a long-term perspective, supported by a medical strategy and defined targets; the third layer is the disease management to provide optimal care to the majority of patients. We believe renal replacement therapy may be optimized to improve a patient's outcome with a focus on cardiovascular protection in the context of personalizing the therapeutic prescription. Due to space limitation, while recognizing the value of peritoneal dialysis (PD), in this review we concentrate on future progress of extracorporeal therapies [e.g. haemodialysis and haemodiafiltration (HDF)] to reduce cardiac burden. The advances in and future of PD will be treated in another chapter. In the same perspective, some interesting features and future development of haemodialysis (e.g. home haemodialysis, daily dialysis and green dialysis) will not be treated here.

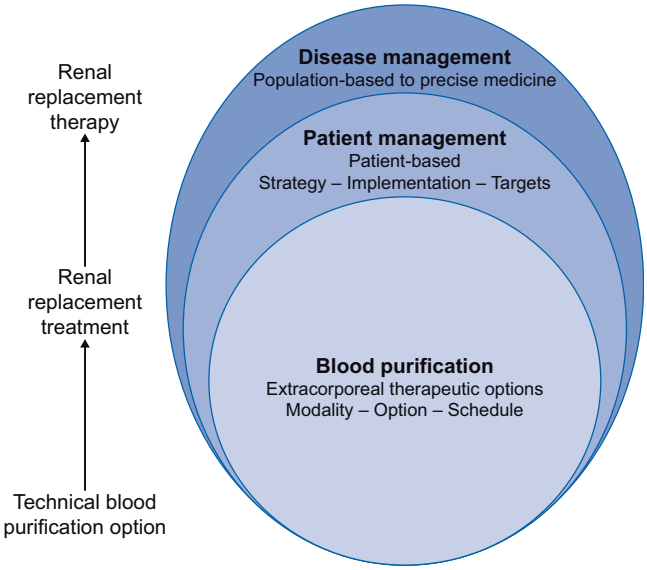

FIGURE 1: Renal replacement therapy integrated and patient centred approach concept.

Individualized patient profiles yield a specific risk that can be estimated from various perspectives [15]. Factors implicated in this risk stratification assessment include clinical parameters (e.g. age, gender, anthropometry, past history and comorbidities), cardiac biomarkers (e.g. left ventricular hypertrophy, vascular stiffness, Troponin and B-type natriuretic peptide) as well as life-style [16]. Renal replacement includes various methodology options classified either by solute flux (haemodialysis low-, high-flux and HDF), by treatment time and frequency or by facility location (incentre, self-care and home therapy). Each bears specific risks that may affect patient outcomes [17]. Individual practice patterns and disease management are strongly associated with outcomes in haemodialysis patients [7].

Treatment modality and future options

Haemodialysis delivering 12 h of treatment per week on a thrice-weekly basis is currently considered the standard of care for ESKD patients in Western countries [7]. However, short treatment schedules are not optimal [18, 19] despite being popularized in earlier decades as a compromise between treatment efficacy, patient tolerance, acceptance and economic sustainability [20]. Several experts have highlighted pitfalls and limitations of short treatment schedules and made a causal link with poor outcomes [21–23]. In line with these clinical facts, it has been postulated that dialysis-related pathology (e.g. cardiovascular disease, vascular calcification, β2-microglobulin (β2M) amyloidosis and protein–energy malnutrition) observed in long-term treated patients might be reflecting a so-called 'residual syndrome' due to the incomplete restoration of the internal milieu homeostasis [24, 25].

From a medical perspective, it is interesting to note that research activity exploring causes of this morbidity and mortality has focused mainly on the accumulation and identification of 'organic uraemic toxins', while inorganic compounds more easily accessible to corrective action such as electrolytes (e.g. sodium, potassium and proton) or inorganic phosphates were neglected for many years [26–30].

As an aggravating factor or a disease modifier, it has recently been shown that haemodialysis sessions were associated with severe haemodynamic stress leading to repetitive ischaemic insults, resulting in various organ damage [e.g. cardiac stunning, leucoaraiosis (a pathological appearance of the brain white matter on MRI, which is likely caused by repetitive hypoperfusion of the deep brain structures), gut ischaemia], probably contributing to the poor outcomes of dialysis patients [31]. In the 'unphysiological context' of intermittent renal replacement therapy, haemodialysis is a cause of additional stress. The first stress is a 'biologic or cytokine storm' that results from blood interaction with a dialyser membrane and its extracorporeal circuit, a so-called haemoincompatibility, consisting of activation of protein and cell systems in cascade with the release of various proinflammatory mediators. The second stress is a 'biochemical stress' that reflects rapid biochemical changes occurring as a consequence of solute, water and osmotic fluxes (e.g. disequilibrium syndrome) with an intensity that is directly related to plasma–dialysate gradient and operating conditions (e.g. blood and dialysate flow) during the treatment.

Considering the residual suboptimal medical needs of short intermittent dialysis, it is our medical duty to revisit standards of dialysis practice and propose new therapeutic options for improving the overall effectiveness of dialysis sessions and reduce the burden of stress induced by the therapy.

MODIFIABLE COMPONENTS OF RENAL REPLACEMENT THERAPY

Five themes arise to address the modifiable components of the therapy, which are aimed at mitigating some of the cardiovascular risks in patients with ESKD. They are schematically summarized in Figure 2.

Enhancement of treatment efficiency and continuous monitoring of dialysis performances

Enhancing global treatment efficiency beyond K_t/V urea while expanding the scope of dialysis dose concepts to include middle and large molecular weight compounds is currently the main target to improve outcomes [1]. In this context, β2M is an interesting compound that deserves to be routinely monitored and incorporated into dialysis adequacy targets [32–35]. β2M has a double meaning, both reflecting dialysis efficacy in terms of solute mass removal, patient bioactivity and inflammation, and also being a proxy for residual kidney function [36–38]. β2M is an excellent surrogate for middle molecules (11.8 kDa) associated with a strong and independent outcome risk in CKD dialysis patients [39, 40]. Post-dilution HDF offers today the most advanced and efficient renal replacement therapy option to target the removal of middle and large molecular weight toxins [41]. Furthermore, recent interventional studies have evidenced clinical beneficial effects of HDF when adequate convective dosing (>23 L/1.73 m^2) in post-dilution mode is administered, reducing the relative risk of all-cause mortality by 14% and cardiac by 23% [42]. In its last update, the National Institute for Health and Care Excellence guideline recommends

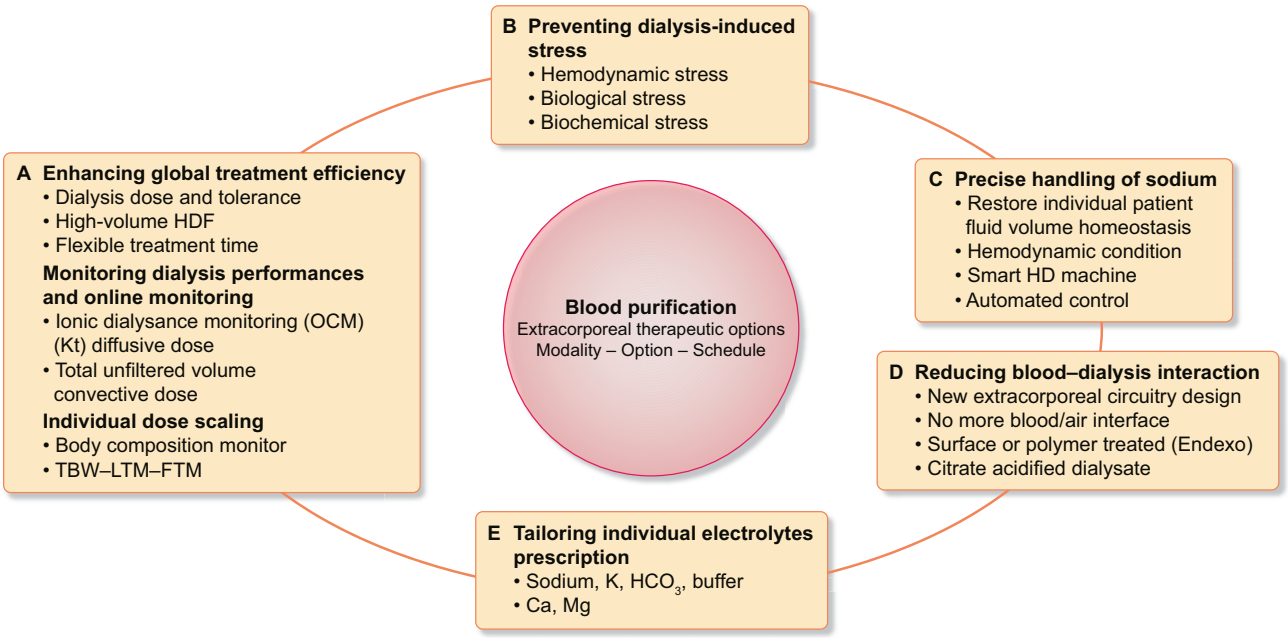

FIGURE 2: Advances in blood purification by extracorporeal therapy with a patient-centric approach. TBW, total body weight; LTM, lean tissue mass; FTM, fat tissue mass; HD, haemodialysis; OCM, online clearance measurement.

the use of HDF as first-line therapy for in in-centre patients [43]. Furthermore, the Kidney Health Initiative consortium resulting from the Food and Drug Administration and American Society of Nephrology alliance recently launched to foster renal care innovation has chosen HDF [44] to address the unmet medical needs of ESKD patients in USA [45]. The HDF acceptance rate is increasing in Europe and Japan with a current share of ∼30% of renal replacement modalities [46]. New dialysis modalities, combining use of medium cut-off membranes and internal filtration to enhance clearance of middle and large molecular compounds, are currently being explored to evaluate their position among the current renal replacement therapy options [47].

Increasing treatment time and/or frequency can enhance efficiency and improve haemodynamic tolerance. In addition, all recent studies (observational and interventional) with primary target focusing on weekly treatment time have confirmed that longer treatment time was associated with beneficial clinical outcomes [48–50].

Monitoring dialysis performances and dose delivery on a regular basis, session-by-session using an embedded tool [ionic online clearance measurement (OCM)] embedded in the haemodialysis machine provides an unmatched quality control opportunity (e.g. vascular dysfunction and dialyser clotting). In a recent and large cohort study aiming to improve care practices, Maduell *et al.* have shown that continuous monitoring of dialysis performances by means of OCM while achieving or exceeding the target recommended dose on a regular basis had a significant positive impact on the life expectancy and hospitalization hazard of dialysis patients [51]. In the quest for personalized dialysis, scaling urea clearance delivered to body surface area appears metabolically more appropriate. The current paradigm to prescribe haemodialysis to achieve a urea clearance adjusted to total body water volume is misleading. Resting energy expenditure is proportionally greater for women and smaller people. Scaling dialysis for body surface area seems more appropriate since urea generation and protein-derived uraemic toxins depend upon resting energy expenditure. Conventional prescription of haemodialysis efficiency based on current K_t/V urea targets leads to less treatment delivered to women, partly explaining their poorer outcome [52]. In the same practical approach, while recognizing the importance of the HDF convective dose on patient outcome, it is crucial to ensure that the optimal convective target dose scaled to body surface area is also effectively and regularly delivered to the patient [53–55].

In brief, advanced technologies embedded on the dialysis machine are designed to improve patient care, to optimize treatment delivery and to reduce care variations, all factors known to affect patient outcomes.

Reducing or preventing dialysis-induced stresses

These are of crucial importance in the quest for cardioprotection during dialysis. A dialysis session is haemodynamic and biochemical stress for patients. We will briefly address these issues and explore several approaches designed to prevent or minimize their impact.

Functional imaging techniques (e.g. echocardiography, cardiac MRI) and cardiac biomarkers kinetics (e.g. Troponin I) have shown that cardiocirculatory stress starts quite early after extracorporeal launch and worsens over the course of the treatment [56, 57]. Several factors contribute to this cardiac stress (e.g. modality, time, fluid management and electrolytes); however, it is recognized that ultrafiltration rate is the most prominent [58, 59]. Briefly, ultrafiltration tends to contract volume, which is compensated by vascular refilling from fluid stored in

the extravascular space. Vascular refilling processes rely mainly on the increase of circulating proteins and oncotic pressure, a condition that favours fluid moving back into the circulatory system. In other words, hypovolaemia results from the imbalance of ultrafiltration and refilling rates, with poor outcomes [60]. From a mechanistic view, preservation of haemodynamic status during dialysis in response to fluid removal and hypovolaemia results from a synergistic increase of cardiac output (e.g. increase of stroke volume, ejection fraction, strength and heart rate), and peripheral vascular resistance and venous tone [61]. From a pathophysiologic view, haemodynamic response to fluid removal in dialysis is more complex and involves others factors such as thermal balance, dialysate electrolytes fluxes (e.g. sodium, calcium, magnesium and potassium), patient condition (e.g. cardiac failure, vascular system and sympathetic tone activity), dialysis condition (e.g. lying or seating, removal of vasoactive substances) and neurohormonal stress response [62]. Furthermore, this response may be mitigated by various factors (e.g. age, comorbidity and medication), which may explain individual or temporal variations in haemodynamic adaptation [63].

Considering the complexity of haemodynamic response to fluid depletion in dialysis, it is easy to see that any active intervention focusing only on one specific component may not be successful. The multifactorial character of haemodynamic adaptation may also explain why interventional studies focusing exclusively on one component (e.g. volume control) using a sensor assessing relative blood volume changes are incompletely addressing the physiology [64]. Sensors measuring relative blood volume changes during dialysis sessions are useful tools to support physicians and caregivers to detect critical volaemic states or to estimate the amount of remaining fluid in the extravascular space [65]. Expert systems developed to ensure a feedback control loop of ultrafiltration based on blood volume changes (e.g. ultrafiltration control) have been shown to improve haemodynamic stability and to reduce incidence in some studies, but not to improve outcome [66–68].

Several tools are currently available to facilitate haemodynamic management but none of them has been shown to be individually able to ensure haemodynamic stability. It is expected that the use of combined tools, supported by advanced analytics and artificial intelligence, will address adequately this challenge by 2030.

Uraemia is characterized by various biologic disorders that include accumulation of organic waste products, so-called 'uraemic toxins', water and electrolytes imbalance (e.g. salt and water retention, acidosis and hyperkalaemia), biochemical modification of circulating or tissular compounds (e.g. oxidative and chlorine stress, carbamylation process) and other metabolic disorders (e.g. vitamin deficiencies, hyperparathyroidism and erythropoietin deficiency). The uraemic syndrome, which expresses clinical intensity of these disorders, is partially or totally reversed by dialysis when adequately designed renal replacement therapy is delivered. This unphysiological and unprecedented condition created by the dialysis/patient interaction is referred to as the 'disequilibrium syndrome', which contributes to dialysis intolerance and intradialytic morbidity (e.g. fatigue, wash out syndrome and headache) [69]. We postulate that such intradialytic hazard first may be quantified by solute dialysate–patient (e.g. solute transfer from dialysate to patient) or patient–dialysate (e.g. solute transfer from patient to dialysate) 'gradients' as surrogate markers of 'solute fluxes' intensity, and second that it may be tackled by changing operating procedures during the dialysis session. In other words, by adjusting the dialysis prescription either manually or automatically, it is postulated that prescribers will be able to reduce biological stress while keeping the same overall treatment efficacy for their patients.

Handling sodium and water to restore patient sodium and fluid volume homoeostasis

Restoring salt and water homeostasis by dialysis while not harming the patient is still an unmet medical need [70]. Salt and water management in a dialysis patient is usually summarized by the 'dry weight' approach [71]. Although this clinical approach has been associated with undisputed benefits on cardiovascular outcome, it is now challenged by studies showing potential organ damage that such an isolated approach may result in as a long-term outcome [72–74]. 'Dry weight' policy is necessary from a clinical perspective, but it is not sufficient from a pathophysiologic perspective to ensure a fully cardioprotective action in dialysis patients. Regarding recent new findings related to sodium toxicity sitting in various pools under different forms (e.g. sodium osmotically active and sodium tissue storage), a more precise and sodium-focused approach is required for dialysis patients [75]. Salt and fluid management must be integrated into a holistic approach combining both dialysis prescription and global patient management. In the context of dialysis, it has been shown recently that the use of calibrated conductivity meters placed on dialysis paths supported by specific algorithms were able to determine the precise contribution of sodium salt among the bulk of electrolytes. In addition, the disposition of sensors on the dialysate path offers a means to ensure a precise mass balance due to a closed-circuit configuration, while use of an advanced analytic embedded in the central processor unit provides a way to ensure direct handling of sodium and water an according to targeted prescription and patient baselines [76, 77]. Advances in the application of dialysis machine technology are yielding tools that will be standard in the next decade for handling directly sodium and water during a haemodialysis session in a precise and personalized way. This advanced technology has the potential for improving cardiovascular outcomes [78].

Reducing blood–extracorporeal circuit interaction

This is of tremendous importance in the quest for improving haemocompatibility while minimizing thrombosis risk in a so-called 'heparin-free dialysis' approach. Although major progress has been already achieved with less reactive biomaterial including synthetic polymer haemodialysers, less bioreactive tubing material and improvement in circuitry geometry, further progress is expected. In this field, four axes of research are currently in progress: the first is the suppression of blood–air interface in the extracorporeal circuit by combining a very short

circuit and introduction of a blood cassette that permits suppression of venous bubble trap; the second is the incorporation within the core polymer of an antithrombotic agent; the third is the use of citric acidified bicarbonate dialysate as an adjunct to the use of the antithrombotic polymer; and the fourth is to prevent microbubble formation within the extracorporeal circuit. By combining these different approaches, the bioreactivity of the extracorporeal circuit will be significantly reduced, the thrombotic risk minimized and heparin-free dialysis will be possible.

Tailoring the electrolyte prescription to the patient's current condition

Tailoring the electrolyte prescription and dialysate composition to the patient's current condition is a further aim for improving dialysis by 2030. The clinical relevance of customized prescriptions is even more important when efficient dialysis sessions are delivered (e.g. high-volume HDF, nocturnal or daily dialysis and home haemodialysis), implicating higher ionic fluxes and more stringent mass balance but also considering the higher risk population being treated (e.g. cardiac patients and elderly). Therefore, further efforts are being developed to support physicians in fine-tuning the prescription of electrolytes in dialysis patients. In addition, dialysate is a recognized source of amino acid losses during dialysis and an additional source of protein–energy wasting that needs to be addressed. Mitigating these losses will enhance the ability to personalize the dialysis prescription for the 2030 patient needing renal replacement therapy.

TAKE HOME MESSAGE

In summary, haemodialysis treatment in 2030 will be substantially more personalized to the patient with a clear focus on cardioprotection, volume management, arrhythmia surveillance, avoidance of anticoagulation and the development of more dynamic systems to align the fluid and electrolyte needs of the patient on the day of the treatment to their particular circumstances. In addition, the need for more highly refined methods of creating a more quickly accessible permanent vascular access and the opportunity to develop assistance in cannulation and removal of needles will enhance the reliability of the dialysis procedure. It is anticipated that certain cardiac rhythms will be monitored and that connected health platforms will provide both human and artificially intelligent monitoring of numerous aspects of the care being delivered. The opportunity to begin to see dialysis treatment incorporate materials that are biologic in nature will decrease more generalized inflammation and improve the compatibility of the systems to the patient's individual needs. The ability to miniaturize components of dialysis treatment will enable more choice by patients on the type and cadence of their therapy and the degree to which that therapy provides them mobility and freedom to participate in their life outside of renal replacement. Within systems of care there will not only be support for the individual treatment, but expectations that patients will be able to participate in their care and have a higher quality of life beyond the lifesaving treatment. Patients in this environment will expect that their care is quite personalized to their life and the needs that they have to control symptoms, participate in life-enabling activities within their family or community, and to have close involvement and contact from a holistic care team that is looking at success in therapy from the viewpoint of living a successful life with kidney failure, as opposed to simply avoiding death from kidney failure.

CONFLICT OF INTEREST STATEMENT

B.C., A.C. and F.M. are employees (part or full-time) of FMC and may hold stock in the company.

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