REVIEW ARTICLE

MEDICAL PROGRESS

Hemodialysis

Jonathan Himmelfarb, M.D., and T. Alp Ikizler, M.D.

From the Kidney Research Institute, Department of Medicine, Division of Nephrology, University of Washington, Seattle (J.H.); and the Department of Medicine, Division of Nephrology, Vanderbilt University Medical Center, Nashville (T.A.I.). Address reprint requests to Dr. Himmelfarb at the Kidney Research Institute, Box 359606, 325 9th Ave., Seattle, WA 98104, or at himmej@u.washington.edu.

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Fifty years ago, Belding Scribner and his colleagues at the University of Washington developed a blood-access device using Teflon-coated plastic tubes, which facilitated the use of repeated hemodialysis as a life-sustaining treatment for patients with uremia.[1,2] The introduction of the Scribner shunt, as it became known, soon led to the development of a variety of surgical techniques for the creation of arteriovenous fistulas and grafts. Consequently, hemodialysis has made survival possible for more than a million people throughout the world who have end-stage renal disease (ESRD) with limited or no kidney function. The expansion of dialysis into a form of long-term renal-replacement therapy transformed the field of nephrology and also created a new area of medical science, which has been called the physiology of the artificial kidney. This review describes the medical, social, and economic evolution of hemodialysis therapy.

Goals of Hemodialysis

Dialysis is defined as the diffusion of molecules in solution across a semipermeable membrane along an electrochemical concentration gradient.[3] The primary goal of hemodialysis is to restore the intracellular and extracellular fluid environment that is characteristic of normal kidney function. This is accomplished by the transport of solutes such as urea from the blood into the dialysate and by the transport of solutes such as bicarbonate from the dialysate into the blood (Fig. 1A). Solute concentration and molecular weight are the primary determinants of diffusion rates. Small molecules, such as urea, diffuse quickly, whereas compartmentalized and larger molecules, such as phosphate, β_2-microglobulin, and albumin, and protein-bound solutes, such as p-cresol, diffuse much more slowly (Fig. 1B and 1C). In addition to diffusion, solutes may pass through pores in the membrane by means of a convective process driven by hydrostatic or osmotic pressure gradients — a process called ultrafiltration.[4] During ultrafiltration, there is no change in solute concentrations; its primary purpose is the removal of excess total body water.

For each dialysis session, the patient's physiological status should be assessed so that the dialysis prescription can be aligned with the goals for the session. This is accomplished by integrating the separate but related components of the dialysis prescription to achieve the desired rates and total amount of solute and fluid removal (Table 1). By replacing kidney excretory function, dialysis is intended to eliminate the symptom complex known as the uremic syndrome, although ascribing particular cellular or organ dysfunction to the accumulation of specific solutes in uremia has proved to be difficult.[5]

Quantifying the Dose and Adequacy of Dialysis

Measuring the clearance of solutes that accumulate in patients with uremia has become the mainstay for calculating the dose of dialysis and determining its adequa-

cy as delivered. Precise standards and goals of dialysis adequacy are based on the clearance of urea, a byproduct of protein catabolism, which can be readily and accurately measured. The volume of distribution of urea, which is neither lipophilic nor highly protein-bound, reflects total body water; consequently, urea is an attractive molecule for quantifying dialysis adequacy through mathematical modeling based on changing blood concentrations.[3,6] Urea kinetic modeling predicts morbidity and mortality better than kinetic modeling of any other known solute. The amount of urea to be removed is usually calculated according to the patient's body size with the use of the following dimensionless construct, which relates the clearance of urea to its volume of distribution in the patient: Kt/V_{urea}, where K is the urea clearance of the dialyzer, t is the duration of dialysis, and V_{urea} is the patient's volume of urea distribution. This construct has been readily adopted by the nephrology community to calculate the dialysis dose.[6] Some investigators have suggested that adjusting the amount of solute clearance according to the volume of distribution rather than according to the patient's body-surface area may result in underdosing in small patients and women.[7-9] Although alternative means of adjusting clearance for body size have been proposed, none currently constitute the standard of care.

The importance of clearance of middle-molecular-weight solutes (500 to 30,000 daltons) with respect to clinical outcomes has long been debated.[10] Current high-flux hemodialysis membranes have larger pores than did earlier-generation membranes, and they permit the passage of larger uremic toxins. Since the β_2-microglobulin concentration is easy to measure, it is frequently used as a marker solute for middle-molecular-weight solutes. Several retrospective, observational studies have suggested an association between the use of high-flux hemodialysis membranes and reduced mortality.[11-14] However, increased clearance of middle-molecular-weight solutes has not been conclusively shown to be an important factor in a well-powered, prospective, randomized trial.

TREATMENT TIME

An important component of the dialysis prescription is treatment time, which can influence the ability to safely remove solutes and accumulated excess fluid. In the 1980s, shortening the treatment time to cut costs while maintaining an adequate level of urea clearance became common practice in the United States. However, subsequent studies revealed that outcomes were adversely affected by shorter treatment times.[15] Advocates for longer treatment times pointed to the better outcomes in Europe and Asia, where treatment times are prolonged.[16,17] Patients who gain more weight with dialysis are at increased risk for death,[18] and a longer treatment time is often required for such patients to help maintain fluid balance. However, to date, little effort has been made to evaluate different fluid-removal strategies in controlled studies.

Reports from individual centers that have used extended dialysis sessions (8 to 12 hours per treatment, often provided overnight) are receiving more attention. Extended treatment times clearly improve blood-pressure control and phosphate removal while having a modest effect on overall solute clearance.[19,20] Excellent outcomes have been reported from these centers, although, again, not in the context of randomized clinical trials.[21,22] It is unclear whether extended treatments provided at night are practical and would be accepted by most patients undergoing dialysis.

FREQUENCY OF DIALYSIS

For more than four decades, the standard schedule for hemodialysis has continued to be three sessions a week, largely owing to logistic and cost concerns. Although several centers have treated a small number of patients with more frequent hemodialysis, a systematic study of outcomes after such therapy is only now being undertaken. Most available reports are from case–control studies or uncontrolled interventional studies.[23] A majority of such studies have shown reductions in blood-pressure levels and in the need for antihypertensive medications, with variable effects on regression of left ventricular hypertrophy, a frequent occurrence among patients receiving long-term hemodialysis. Health-related quality-of-life measures appear to improve with more frequent dialysis treatments, whereas mixed results are reported for measures of anemia control and calcium phosphate metabolism.[24] A recent randomized, controlled pilot trial compared daily nocturnal hemodialysis with conventional thrice-weekly hemodialysis.[25] In the primary analysis, there was a significant reduction in left ventricular mass in the group treated with daily dialysis, as compared with the conventionally

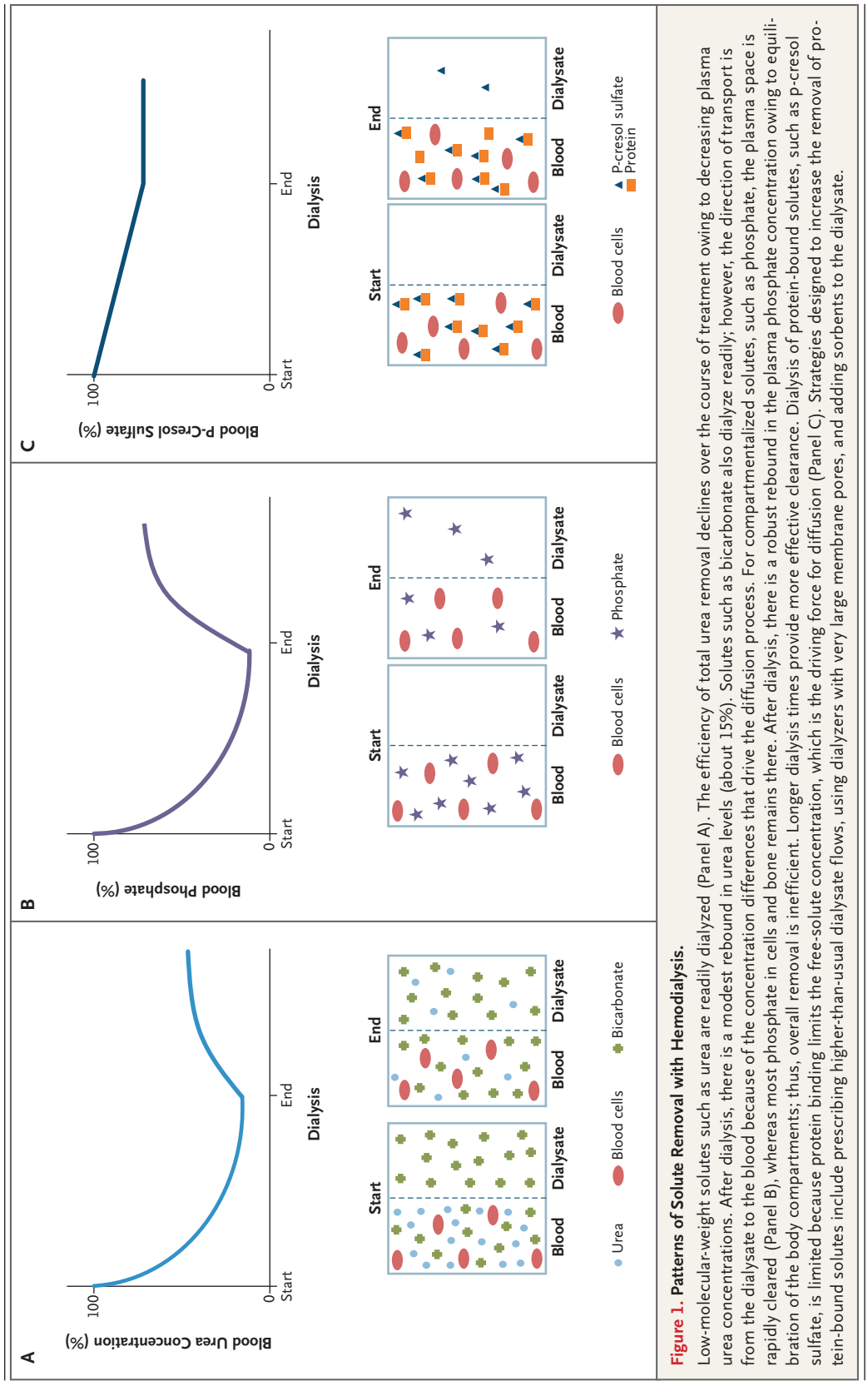

Figure 1. Patterns of Solute Removal with Hemodialysis.

Low-molecular-weight solutes such as urea are readily dialyzed (Panel A). The efficiency of total urea removal declines over the course of treatment owing to decreasing plasma urea concentrations. After dialysis, there is a modest rebound in urea levels (about 15%). Solutes such as bicarbonate also dialyze readily; however, the direction of transport is from the dialysate to the blood because of the concentration differences that drive the diffusion process. For compartmentalized solutes, such as phosphate, the plasma space is rapidly cleared (Panel B), whereas most phosphate in cells and bone remains there. After dialysis, there is a robust rebound in the plasma phosphate concentration owing to equilibration of the body compartments; thus, overall removal is inefficient. Longer dialysis times provide more effective clearance. Dialysis of protein-bound solutes, such as p-cresol sulfate, is limited because protein binding limits the free-solute concentration, which is the driving force for diffusion (Panel C). Strategies designed to increase the removal of protein-bound solutes include prescribing higher-than-usual dialysate flows, using dialyzers with very large membrane pores, and adding sorbents to the dialysate.

Table 1. Key Components of the Hemodialysis Prescription.

Component	Comments
Dialyzer	
Configuration	Hollow-fiber dialyzers are preferred owing to improved safety.
Membrane biomaterials	Synthetic membranes are used more frequently than cellulose membranes owing to fewer blood–membrane interactions.
Membrane permeability	High-flux membranes are constructed with larger pores, which allow greater removal of higher-molecular-weight solutes, with similar removal of lower-molecular-weight solutes as compared with low-flux membranes.
Treatment time	Usual treatment time is about 4 hours. Longer treatment times allow more fluid removal with less risk of intradialytic hypotension, and the removal of compartmentalized solutes such as phosphate is increased; nevertheless, increased dialysis time has limited effects on removal of many solutes because of decreasing plasma concentrations.
Treatment frequency	Usual frequency is 3 times per week. Increasing the frequency of dialysis to >3 times per week improves solute clearance and fluid removal; effects on clinical outcomes and quality of life are being evaluated in randomized trials.
Blood flow rate	Usual prescription is 200 to 400 ml per minute. Achievable blood flow depends on the type and quality of vascular access. Increasing blood flow increases solute removal; however, increased flow resistance will eventually limit the augmented clearance.
Dialysate flow rate	Usual rate is twice the achieved blood flow rate in order to attain near-maximal solute clearance.
Ultrafiltration rate	Should be less than 10 ml per kilogram of body weight per hour to reduce the risk of intradialytic hypotension.
Dialysate composition	
Sodium	Between 130 and 145 mmol per liter. Higher sodium concentrations decrease the risk of intradialytic hypotension but increase thirst and interdialytic weight gain.
Potassium	Generally 2 to 3 mmol per liter. Lower levels of dialysate potassium are associated with sudden cardiac death; intradialytic potassium removal is highly variable, and plasma potassium levels rebound about 30% after dialysis.
Calcium	Generally 1.25 to 1.75 mmol per liter. Only non–protein-bound calcium is removed; higher levels of dialysate calcium increase intradialytic blood pressure.
Magnesium	Generally 0.5 mmol per liter. The optimal level of magnesium is unresolved, and magnesium flux is difficult to predict.
Alkaline buffers	Commonly 30 to 40 mmol per liter. Predominantly bicarbonate with a small amount of acetate; bicarbonate concentration can be adjusted to correct metabolic acidosis.
Chloride	Defined by prescribed cations and alkaline buffers in dialysate.
Glucose	Commonly 100 to 200 mg per deciliter. Higher levels of glucose promote hypertriglyceridemia.
Intradialytic medications	Erythropoietin, iron, vitamin D analogues, antibiotics.
Anticoagulation	Heparin or other agents.

treated group. Improvements in blood-pressure control, serum calcium–phosphorus product, and selected quality-of-life measures were also observed. The Frequent Hemodialysis Network, sponsored by the National Institutes of Health, is currently conducting two studies: in one, daily in-center dialysis involving short treatment times is being compared with conventional thrice-weekly dialysis, and in the other, daily nocturnal dialysis involving longer treatment times is being compared with conventional thrice-weekly dialysis.[26] Outcomes will include survival, change in left ventricular mass, and quality of life.

EVOLUTION OF HEMODIALYSIS IN THE UNITED STATES

Long-term dialysis was initially available only for patients who were enrolled in a handful of programs (Fig. 2). In 1972, President Richard Nixon

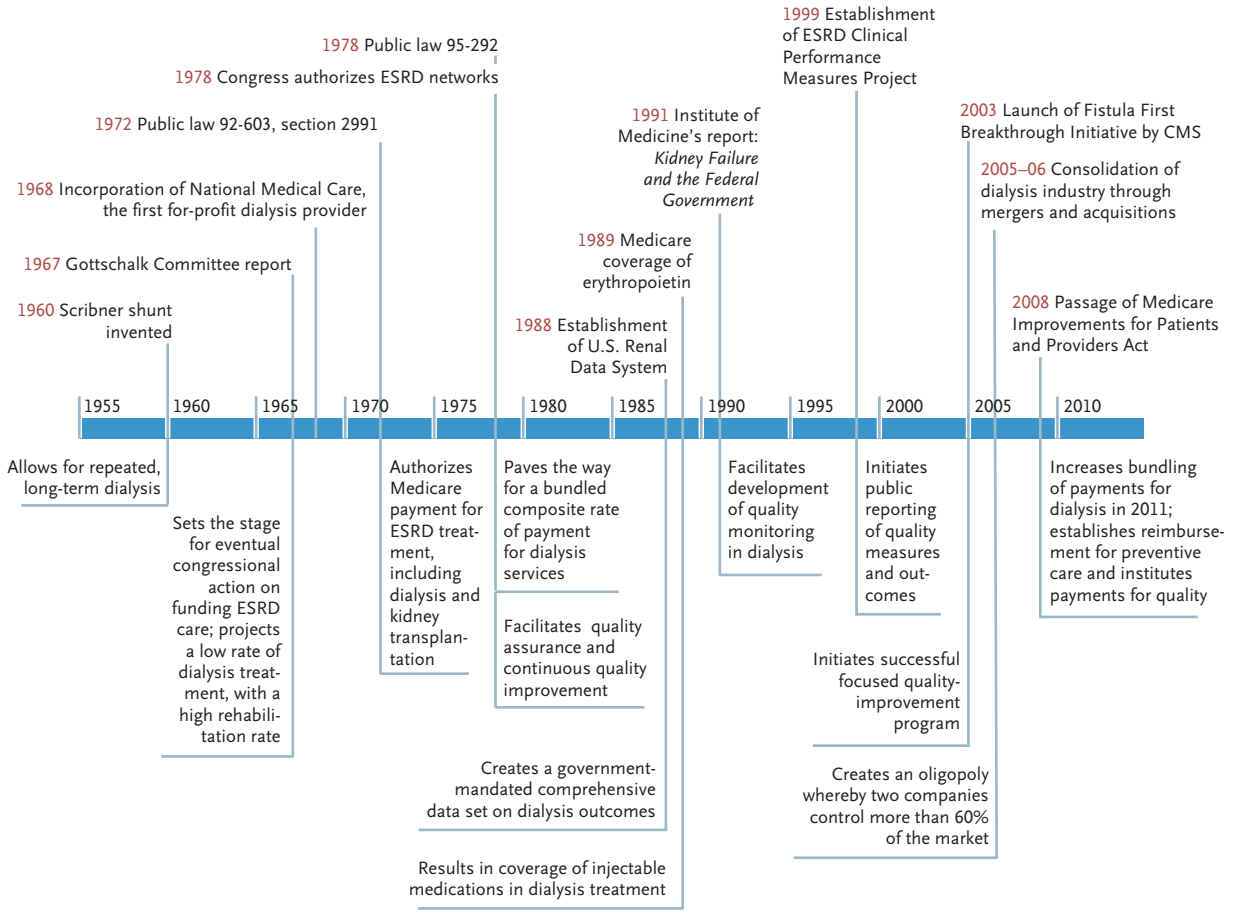

Figure 2. Timeline for the Evolution of Hemodialysis.

The widespread implementation of dialysis therapy over the past 50 years has been accompanied by considerable medical, social, economic, and regulatory changes in the U.S. End-Stage Renal Disease (ESRD) Program. Fueled by concerns about increasing costs for the program, associated high morbidity and mortality, and incomplete rehabilitation for patients undergoing dialysis, developments in the evolution of the ESRD Program provided an early window into trends that have subsequently affected the U.S. health care system as a whole. The ESRD Program has served as an incubator for efforts to develop robust vehicles to collect data, measure quality and determine performance indicators, and initiate quality-improvement projects. Legislative changes are under way to institute payments for the delivery of high-quality care and to increase the bundling of payments for ESRD services. CMS denotes Centers for Medicare and Medicaid Services.

signed legislation authorizing Medicare coverage for the costs of ESRD treatments, including dialysis and kidney transplantation, for all eligible Americans.[27] With little public or congressional debate, the passage of this legislation heralded an era of nearly universal entitlement for ESRD care, in marked contrast to other organ failure–related disease states such as end-stage heart disease or liver disease. Legislators approved the law with the understanding that dialysis would provide high-level rehabilitation and social benefit to a relatively small number of people at low cost.[28] Since 1972, a geometric increase in the number of patients receiving dialysis has expanded the scope of the Medicare ESRD Program enormously. From an economic and societal perspective, salient changes during the evolution of this program have included steadily increasing aggregate costs to Medicare, diminished per-treatment reimbursement in inflation-adjusted dollars, a dramatic increase in costs associated with medications given during dialysis, a steady decline in the use of home

dialysis (including peritoneal dialysis), and the rise and consolidation of a for-profit dialysis-provider industry.[29,30]

The demographics of the dialysis population have also changed dramatically over time. Less stringent selection of patients has led to treatment of an increasing proportion of elderly patients, patients with diabetes, and patients who are frail and have complex coexisting conditions. The initiation of dialysis in patients with higher levels of residual kidney function has occurred concomitantly, particularly among patients older than 75 years of age.[31] Among elderly nursing-home residents, the initiation of dialysis is associated with a substantial decline in functional status and high mortality.[32] The factors driving these clinical practices, and their societal implications, are only beginning to be studied but may well lead to increased consideration of conservative management and palliative-care options for some patients.[30,33-35]

The Medicare Improvements for Patients and Providers Act (MIPPA) of 2008 contains provisions that are likely to change the Medicare ESRD Program substantially. Currently, dialysis facilities receive a bundled payment for each dialysis session they provide, which includes funds to cover supplies, staffing, and selected ESRD-related laboratory tests; the costs of intravenous medications are billed separately. MIPPA mandates an expansion of the bundled-payment system to include funds for all ESRD-related medications and laboratory tests, beginning in 2011. Including medication reimbursement along with these bundled payments to dialysis providers should remove any possible financial incentive to overprescribe medications during treatment, but simultaneously, it may create incentives for providers to underuse medications or choose to treat patients on the basis of characteristics that may translate into reduced medication expenditures. MIPPA relies on adjustments for case mix to prevent providers from deselecting or cherry-picking patients and also mandates the development of a payment system for quality indicators by 2012.

MEASURING AND IMPROVING QUALITY IN DIALYSIS CARE

The ability to evaluate outcomes among patients with ESRD increased dramatically after 1988, when the United States Renal Data System (USRDS) was established to record and issue reports that would track mortality and morbidity and determine factors affecting clinical outcomes. Perhaps the most robust disease-specific data sets available within the entire Medicare population, these USRDS reports have greatly facilitated the development of quality goals and metrics, at the same time as evidence-based clinical practice guidelines, such as those issued by the Kidney Disease Outcomes Quality Initiative and the Kidney Disease: Improving Global Outcomes program, have been developed.[36-38] In 2003 the Centers for Medicare and Medicaid Services (CMS) and other key stakeholders jointly developed a national quality-improvement effort to increase the use of arteriovenous fistulas as the preferred choice for vascular access — a choice that had historically lagged behind other indicators of high-quality care. This collaborative initiative, known as Fistula First, led to a dramatic increase in the use of fistulas.[39] In an effort to facilitate patient choice and promote quality improvement, the CMS developed Dialysis Facility Compare, a Web site that allows consumers to compare the mandatory reported performance of dialysis facilities.[40]

PATIENT SAFETY AND TECHNICAL ADVANCES

Hemodialysis is now substantially safer than it was initially, and deaths directly related to the dialysis procedure are rare. Improved dialysate delivery systems, more reliable monitoring devices, and automated safety mechanisms have reduced the risk of complications. Other technical improvements include the standard use of the more physiologic bicarbonate-based dialysate, better water-quality standards, volumetric ultrafiltration controls, and computer-controlled sodium and potassium modeling.[41] Several in-line devices now allow dynamic monitoring of the rate of blood flow through the vascular access,[42] changes in the hematocrit (to measure vascular refilling during ultrafiltration), and changes in the electrical conductivity of the dialysate (to estimate the amount of solute being removed).[43]

Thus, dialysis machines with feedback-control systems currently allow for computer-controlled, real-time adjustments in the critical components of dialysis, such as the ultrafiltration rate.[44] Automated control of dialysate temperature helps maintain a constant body temperature during di-

alysis, which may reduce the incidence of intradialytic hypotension.[45] Although studies in small groups of patients have suggested possible benefits from in-line monitoring or feedback-control systems, evidence of improved outcomes in large, rigorously controlled trials is lacking.[46]

TRENDS IN OUTCOMES IN THE UNITED STATES

The steady improvement in procedure-focused and process-related measures of quality has led to a noticeable improvement in survival over the past two decades.[36] Nevertheless, the death rate among U.S. patients undergoing dialysis continues to exceed 20% per year during the first 2 years after maintenance dialysis is begun. Unfortunately, hospitalization rates have remained nearly constant, averaging almost 13 hospital days and two admissions per patient-year.[47] The exclusive reliance on dialysis-focused quality measures (e.g., adequacy of dialysis, presence or absence of anemia, and mineral metabolism) has previously been questioned, since such measures may account for only 15% of the variations in mortality and morbidity.[48] It has been suggested that quality measures also include an assessment of risk factors for cardiovascular disease and infection, which constitute the major causes of hospitalization and death in the population receiving dialysis. Practice patterns also vary greatly, such as variations in the placement and use of fistulas, the rate of coronary revascularization, and the rate of pneumococcal vaccination. Practice-pattern variations in achieving quality-of-care goals, including predialysis care with timely fistula placement, represent a potential area for the improvement of outcomes.

Clinical care of the patient undergoing dialysis is highly complex, given the insidious but protean manifestations of uremia (Table 2).[37,38,49-62] Although symptoms of uremia are often nonspecific, virtually every organ system in the body is affected by the disruption in metabolic homeostasis associated with ESRD. Physicians who treat patients receiving dialysis must be cognizant of the numerous complications that can result from the loss of kidney function and of the complex relationships between uremia and dialysis treatment. For example, uremia-induced alterations in gastrointestinal tract function can alter nutrient intake and result in poor nutritional status, which in turn increases the risks of cardiovascular disease and infection, particularly when dialysis involves tunneled catheters. Given the problems associated with ESRD, physicians who care for patients receiving hemodialysis face unique and difficult challenges.[63] Caring for such patients is particularly difficult because of the lack of high-level evidence in support of target ranges for many of the important components of dialysis care, such as optimal concentrations of parathyroid hormone and low-density lipoprotein (LDL) cholesterol or blood-pressure levels (Table 2).

INTERNATIONAL COMPARISONS

Many investigators have noted that crude mortality rates are consistently higher in the United States than in Europe or Japan. Probably the best available comparative data come from the Dialysis Outcomes and Practice Patterns Study (DOPPS), which uses a prospective design and attempts to harmonize data collection across several countries and continents.[64] The DOPPS reported that crude 1-year mortality rates from 1996 to 2002 were 6.6% in Japan, 15.6% in Europe, and 21.7% in the United States.[65] Although dramatic differences in demographic characteristics, clinical factors, completeness of data ascertainment, and access to kidney transplantation can limit the validity of these transnational comparisons, the relative risk of death after adjustments have been made for age and multiple coexisting disorders is still higher in the United States than in Japan or Europe.[66] Features of practice patterns in the United States that differ from those in the other two countries may account in part for the observed differences in the risk of death. Such features include shorter treatment times, less frequent use of fistulas, and staffing of dialysis units with patient care technicians rather than nurses.[67]

One trend of concern in the United States is the increasing proportion of patients who begin dialysis with a tunneled catheter rather than with a more permanent type of vascular access. The use of such catheters is strongly associated with increases in the rate of hospitalization, the risk of death, and the cost of care, owing in large part to the risk of catheter-related bacteremia.[55] Although the preponderance of available data suggests worse outcomes in the United States, not all investigators agree that differences in practice patterns account for the differences in outcomes. Alternatively, results of a study that used the World Health

Table 2. Clinical Care of Patients Receiving Hemodialysis.*

Variable	Goals and Targets
Dialysis dose	Monitor urea kinetic modeling; target single-pool Kt/V_{UREA} >1.4.†
Fluid management and estimated body weight	Carry out individualized management and assessment; interdialytic weight gain should ideally be less than 5% of total body weight.
Dialysate quality	Monitor endotoxin and bacteria concentrations in water used for dialysate; the use of ultrapure dialysate may reduce inflammation.[49]
Anemia	Try to attain a hemoglobin level of 10 to 12 g per deciliter (although current recommendations may change on the basis of results from clinical trials involving patients with chronic kidney disease[50-53]); avoid high-dose erythropoietin; evaluate patients with erythropoietin resistance for inflammation and iron deficiency; monitor iron levels and treat iron deficiency; the long-term safety and efficacy of iron administration in patients with high ferritin levels have not been well established.[54]†‡
Vascular access	Implement strategies to increase the placement and use of fistulas and eliminate catheter use whenever feasible[55]; monitor to detect possible access dysfunction.†§
Bone and mineral disorders	Aim for a serum calcium level of 8.4 to 9.5 mg per deciliter and a serum phosphate level of 3.5 to 5.5 mg per deciliter; monitor serum levels of intact PTH; although the optimal target PTH level has not been well defined, maintain PTH level at >2 times the upper limit of the normal range to minimize risk of low bone turnover; suppress rising PTH levels with vitamin D analogues, calcimimetics, and phosphate binders.¶
Nutrition	Aim for serum albumin level >4.0 g per deciliter; consider enteral supplementation for progressive signs of protein energy wasting; refer patient to dietitian for nutritional counseling; restrict phosphorus, sodium, and potassium intake, as guided by laboratory studies.†
Blood pressure	Optimal targets and management strategies have not been well defined.[57]
LDL cholesterol	Aim for LDL cholesterol level of <100 mg per deciliter; the relationship between LDL cholesterol and cardiovascular risk is confounded by inflammation; statins are without proven benefit.[58-60]
Diabetes management	Balance benefits of tighter glycemic control, which carries an increased risk of hypoglycemia, by means of individualized therapy; glycated hemoglobin targets have not been well defined[61]; manage other aspects of diabetes, such as peripheral vascular disease, intestinal dysmotility, and eye problems.
Transplantation referral	Provide education about transplantation and timely referrals for suitable candidates; monitor status of wait-listed patients.§
Quality-of-life and psychosocial evaluation	The evaluation, conducted by a social worker with the support of a multidisciplinary team, should be aimed at optimizing adjustment to kidney failure and its treatment; the Kidney Disease Quality of Life (KDQOL-36) instrument is often used for the evaluation.[62]§

* LDL denotes low-density lipoprotein, and PTH parathyroid hormone.
† This recommendation is supported by the Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines.[38]
‡ This recommendation is compatible with those of the Food and Drug Administration and the European Medicines Agency.
§ This recommendation is mandated by the Centers for Medicare and Medicaid Services Conditions of Coverage for end-stage renal disease facilities.[56]
¶ This recommendation is supported by the Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines.[37]

Organization mortality database suggest that much of the international variation in mortality is attributable to differences in the risk of death that are related to cardiovascular disease in the respective general populations.[68]

CONTROLLED TRIALS OF DIALYSIS THERAPY

Several randomized, controlled clinical trials with sufficient power to detect changes in mortality or hospitalization rates have evaluated the adequacy of dialysis therapy. The National Cooperative Dialysis Study (NCDS), performed during the 1970s, was designed to determine whether altering the time-averaged concentration of urea or the treatment time — each of which is considered an important determinant of the adequacy of hemodialysis — would affect hospitalization rates.[69] The results of the NCDS indicated that a high urea concentration was significantly associated with increased hospitalizations. On the basis of the NCDS results, a minimum delivered dialysis dose equivalent to a single-pool Kt/V_{urea} value of 1.2 was initially established as a standard, which was incorporated into clinical practice guidelines and performance measures. The NCDS was not powered to evaluate mortality as an outcome. Al-

though the NCDS was an exemplary early randomized, controlled trial of the adequacy of dialysis, the delivered dose in the low-dose treatment group was well below that routinely delivered today, and the patient population was not representative of current dialysis recipients.

In the 1990s, several large, observational studies suggested that doses of dialysis that were higher than standard doses and the use of dialysis membranes with higher-permeability characteristics (or flux) were associated with lower mortality.[11-13,70-72] The Hemodialysis (HEMO) Study, funded by the National Institutes of Health, subsequently compared the effects of a standard dialysis dose (a single-pool Kt/V_{urea} value of 1.25) with a higher dose for urea clearance and also compared the effects of high versus low membrane flux on morbidity and mortality. A total of 1846 subjects were followed for 7 years, and the study had reasonably high power to detect a reduction in mortality. The results of the HEMO study showed no significant differences in all-cause mortality or in seven other prespecified outcomes among any of the treatment groups.[73] Another well-conducted, randomized trial, the Adequacy of Peritoneal Dialysis in Mexico (ADEMEX) trial, also showed no relationship between dialysis dose and outcomes among patients receiving peritoneal dialysis.[74] Taken collectively, the results of these important trials suggest that there is a threshold–plateau relationship between the dose of dialysis and outcomes and that increasing the dose to greater than the currently recommended target of a single-pool Kt/V_{urea} value of 1.4 (in order to ensure an achieved dose of at least 1.2) does not improve important outcomes. These studies also illustrate the limitations of what is achievable with current dialysis practice and underscore the need for more innovative approaches.

CONTROLLED TRIALS TO EVALUATE CARDIOVASCULAR RISK

Many randomized, controlled trials have focused on mitigating cardiovascular events and mortality in patients undergoing hemodialysis, but results have been disappointing. Notably, two investigations evaluating the use of atorvastatin and rosuvastatin showed no improvement in major outcomes, despite being well powered because of the high cardiovascular event rate in each treatment group.[58,59] Trials evaluating homocysteine-lowering drugs,[75] non–calcium-containing phosphorus binders,[76] and erythropoietin at doses that target higher hemoglobin concentrations[77] have all supported the null hypothesis or even suggested harm. In interpreting such trial results, it is important to consider that many metabolic and structural contributors to cardiovascular risk among patients undergoing dialysis may differ from those among patients without kidney disease (Fig. 3). Furthermore, in cross-sectional studies, conventional cardiovascular risk factors, such as elevated serum cholesterol levels and blood pressure or a high degree of adiposity, have been found to be less predictive of risk among patients receiving dialysis than among persons with preserved kidney function.

Uremic cardiovascular disease is characterized by a high prevalence of medial vascular calcification, arterial stiffness, and altered left ventricular geometry.[78-80] The development of aggressive intimal hyperplasia is common after either coronary angioplasty or the establishment of arteriovenous access.[81] Cardiac arrest and congestive heart failure are more prominent causes of cardiovascular death than is acute myocardial infarction in patients with uremia.[82] Metabolically, ESRD is strongly associated with acute inflammation, oxidative stress, endothelial dysfunction, insulin resistance, and excess sympathetic tone.[83-91] A number of uremic toxins that are highly protein-bound or sequestered within cells or bone, such as p-cresol sulfate, indoxyl sulfate, and phosphate, may contribute directly to cardiovascular risk and are not sufficiently removed by means of conventional dialysis (Fig. 1).[5,10] Further research is needed to understand more precisely how uremic toxins contribute to cardiovascular risk and to evaluate novel approaches to reducing this risk. Innovative experimental approaches to dialysis have been advocated, such as wearable artificial kidneys and the use of nanotechnology for more rational membrane design.[92-94] However, the large-scale implementation of any of these novel experimental approaches is not likely to occur in the near future.[95]

CONCLUSIONS

Over the past half century, the widespread use of dialysis to prolong life for people without kidney function has been a remarkable achievement. As a result of its growth and evolution, the U.S. ESRD Program has often provided an early window into

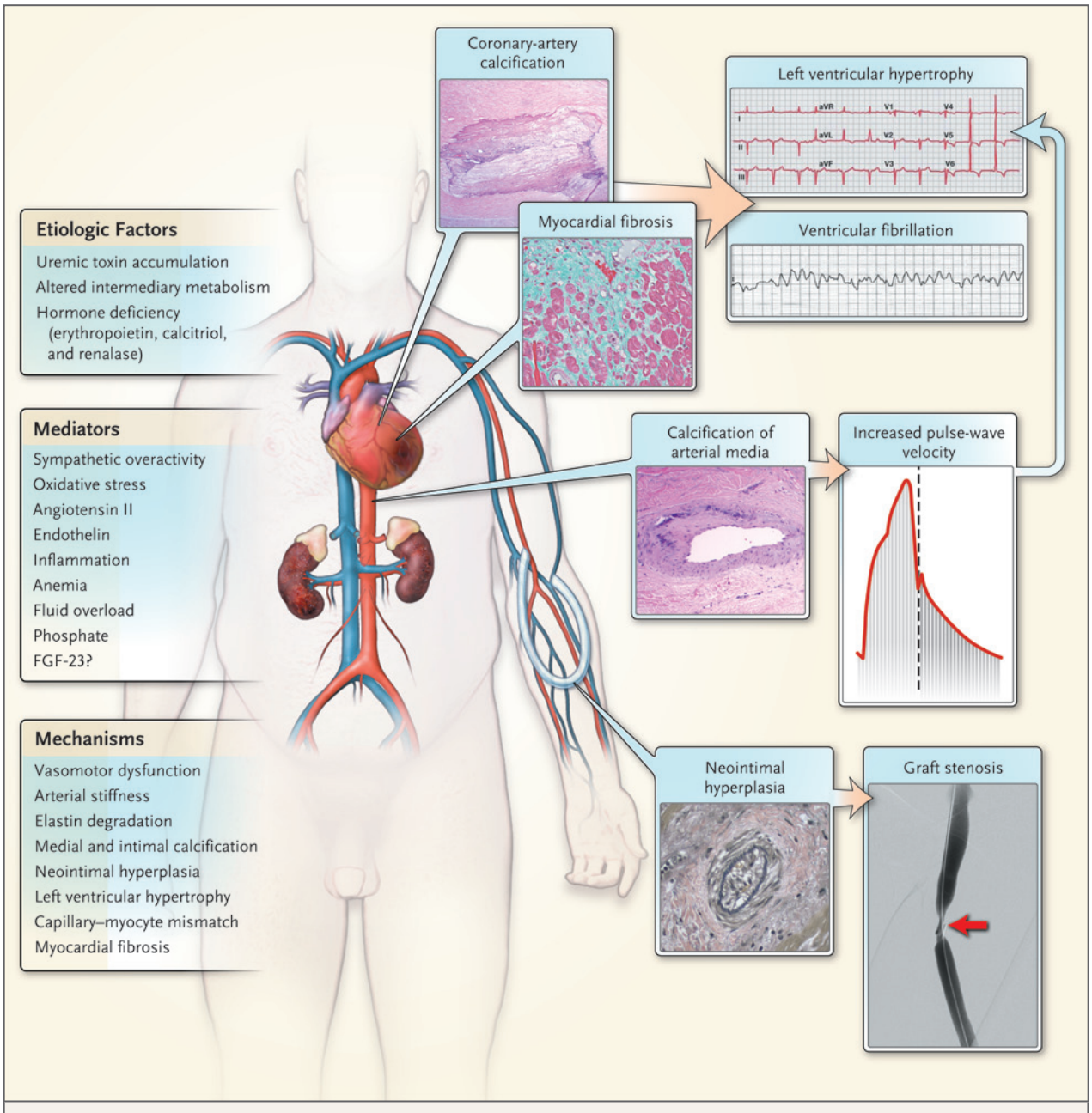

Figure 3. Pathobiology of Increased Cardiovascular Risk in End-Stage Renal Disease (ESRD).

The factors leading to an increased risk of cardiovascular disease among patients with ESRD are multifaceted and in many cases incompletely understood. Although patients who undergo dialysis often have conventional cardiovascular risk factors, the presence of such factors does not appear to fully explain the high level of risk. In patients with uremia, multiple mediators related to the metabolic changes resulting from the loss of kidney function appear to contribute to this increased risk by causing multiple functional and structural changes in the heart and blood vessels. These mediators include increased inflammation, greater sympathetic-nerve activity, oxidative stress, disturbed mineral balance, and profound endothelial dysfunction. Concurrent medical problems, such as anemia, hypertension, and hypervolemia, also contribute to structural cardiac and vascular alterations, frequently resulting in heart failure. Excessive vascular calcification, increased myocardial fibrosis, and increased intimal hyperplasia are common findings. In addition to ischemic cardiovascular events, the incidence of sudden death is excessively high in patients receiving hemodialysis. FGF-23 denotes fibroblast growth factor 23. The histologic photomicrographs are courtesy of Dr. Michael Laflamme and the angiographic image is courtesy of Dr. Thomas S. Hatsukami.

social, political, and economic developments in health care, and these changes have later been reflected throughout the U.S. health care system. Despite such successes, the use of dialysis in the treatment of ESRD is problematic in some respects. The number of patients treated, especially in the United States, has escalated and is far beyond early estimates. Aggregate dialysis-associated costs have increased accordingly, and morbidity and mortality among treated patients remain high despite considerable technical and scientific improvements. Our knowledge of which uremic toxins confer injury and of how they can be optimally removed during dialysis therapy remains incomplete. The limited number of clinical trials that have attempted to improve outcomes have had disappointing results, so more well-designed and adequately powered clinical trials are needed.

Ongoing studies are assessing whether longer or more frequent dialysis treatments, or both, can improve outcomes and whether these changes would be acceptable to most patients. However, substantive improvements for patients receiving dialysis will probably require major technological breakthroughs that will be predicated on an improved understanding of uremic toxins and uremic complications.

Dr. Himmelfarb reports serving on the Shire Pharmaceuticals scientific advisory board on Outcomes Studies in Hemodialysis Patients and the CytoPherx (formerly Nephrion) medical advisory board and receiving consulting fees from KAI Pharmaceuticals, as well as receipt by his former institution, the Maine Medical Center Research Institute, of research support from Fresenius Medical Services of North America (now Fresenius Medical Care North America). All payments for board membership and consulting were donated to the Kidney Research Institute at the University of Washington. Dr. Ikizler reports serving on the boards of the American Board of Internal Medicine and Satellite Healthcare, receiving consulting fees from Amgen, Abbott Renal Care, Novo Nordisk, Renal Advantage, Eli Lilly, and Fresenius Medical Care North America, royalties from Wolter Kluwer, as well as receipt by his institution, the Vanderbilt University Medical Center, of research support from Medical Nutrition USA and Fresenius Medical Care North America. Dr. Ikizler reports having been the medical director of the Vanderbilt Dialysis Unit, which is owned by Vanderbilt University Medical Center and managed by Fresenius Medical Care North America, until June 2010. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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