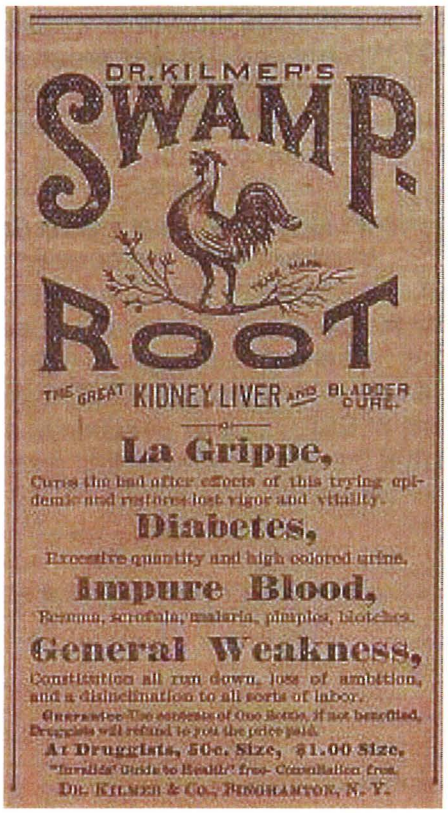
Apocalypse Aversion: Preparing for the Public Health Crisis of End-stage Renal Disease



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This is to acknowledge that Dr. Middleton has not disclosed any financial interests or other relationships with commercial concerns related directly to this program. Dr. Middleton will be discussing off-label uses for medications in his presentation.

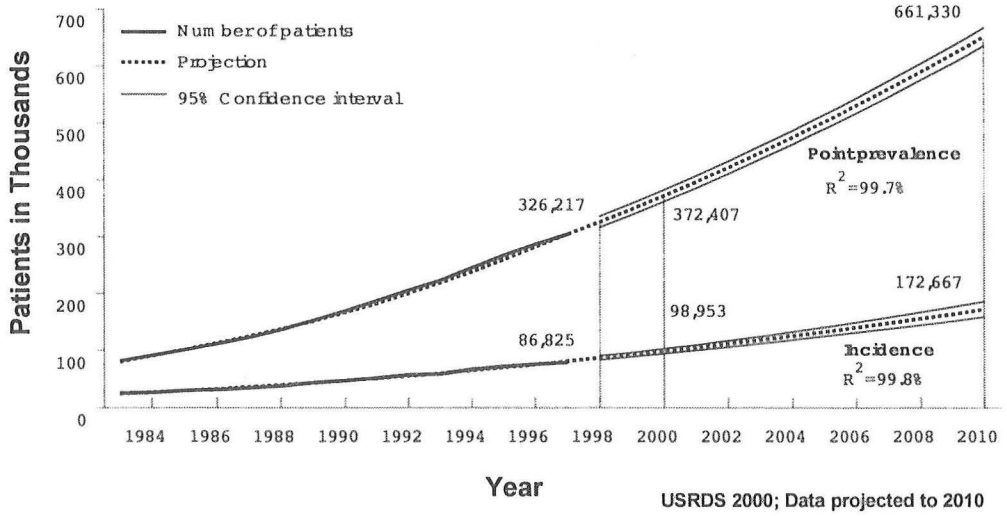
The problem

The extent of the problem for the public in the United States

The practice for Nephrologists in the US is changing dramatically. The most ominous indication of this change is the size of the end-stage renal disease population (Stage 5 chronic kidney disease, or ESRD). In 1991 there were 54,172 new cases of ESRD and the prevalent ESRD population was 199,951 [104]. In 2000, the most recent year that data are available, these numbers ballooned to 96,192 incident and 378,862 prevalent patients, a 77.8% and 89.5% increase, respectively [104]. By comparison, in 2000 an estimated 41,113 new cases and ~340,000 persons were living in the US with HIV/AIDS (Center for Disease Control, MMWR 51:592, 2002).

If ESRD trends persist, the population of prevalent ESRD patients is projected to exceed 660,000 by the year 2010 [103]. In other words, the number of people living in the US in 2010 with ESRD, either with a functioning kidney transplant or on dialysis, will approximate the present-day population of Oklahoma County, OK or Wake Co, NC (data from US Census Bureau, Department of Commerce, 2002). Beyond these staggering numbers, consider that the costs associated with ESRD care is expected to increase from the 1998 Medicare costs of ESRD of $16.74 billion to approximately $30 billion in 2010 [101,103]. It is essential that the components of this problem are addressed to avert a public health crisis.

Figure 1: Past and future incidence and prevalence of ESRD in the United States



By far, the greatest numbers of patients who have ESRD in the world are kept alive in the United States. The United States Renal Data Systems acquired data from 23 countries in 2002 to examine other experiences. The ESRD prevalence rates varied, from as great as 1300-1600/million population in Taiwan and Japan to as low as 50-66/million population reported in Russia, Bangladesh and the Philippines [104]. The incidence of ESRD is also increasing dramatically in Japan and Europe, but in 1999

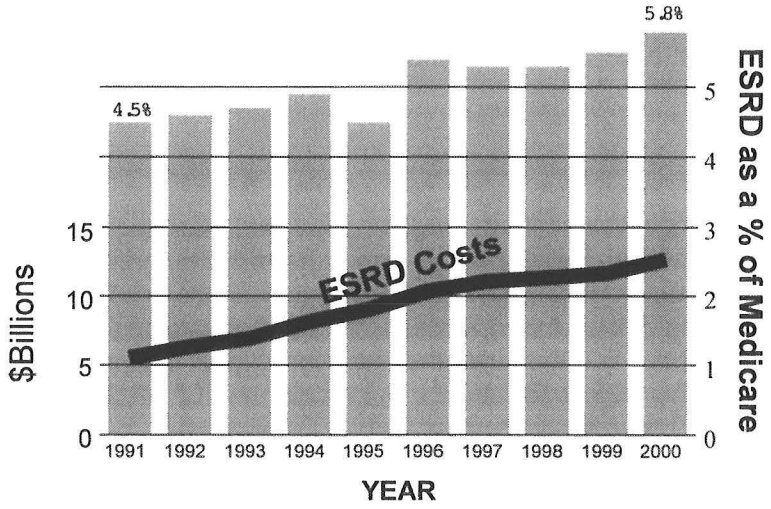
more than 45% of all patients in the world who were treated for ESRD resided in the United States [15,66,104]. Therefore, the most meaningful information will likely be obtained from the US.

Dominant contributors to the problem

Failure to recognize early stages of CKD

An important premise to a strategy of renoprotection is that early stages of renal failure are easily and reliably recognized. Several observations suggest that many patients with renal insufficiency in the US are not aware of their disease. In the general population the awareness of incipient renal disease is poor. The NHANES III phase 2 study included serum creatinine measurements in a cohort of the normal population [21]. In elderly African American patients, more than 15% had creatinine values that were over 1.7 mg/dl, convincing evidence of advanced renal disease [21]. In a parallel but unrelated government study, questionnaires were given to a large population of US residents to explore self-knowledge of individuals' illnesses (data from the US Center for Vital Statistics, 2000). In elderly African American men, the same demographic group with high prevalence of azotemia, only 2% of subjects were aware of any renal disease (or "kidney trouble") in their history. Even more disturbing, a follow-up analysis of the NHANES III database suggested that 75% of patients with elevated creatinine and hypertension were receiving medication therapy, but only 11% had their blood pressure controlled below 130/85 [22]. The National Kidney Foundation (NKF) estimates that nearly 30 million US residents have some degree of CKD [53].

Figure 2: ESRD Costs in the US



Derived from USRDS 2002 ADR

In an effort to enhance public awareness and understanding of kidney disease, the NKF recently simplified a classification of renal diseases [53]. These guidelines emphasize distinct levels of disease, from CKD Class 1 to CKD Class 5. Inherent in this scheme is knowledge of and emphasis on the existing level of glomerular filtration rate (GFR). The NKF guidelines recognize that a true GFR assay (such as urinary clearance of

iothalamate) is often not feasible [1,53,60,106]. Controversy arises about the ideal equation to use, but several GFR equations can estimate GFR based on easily-attainable parameters [53].

Epidemic of diabetes mellitus and lack of early recognition

Diabetic nephropathy is the single most common cause of renal failure leading to enrollment in the US Medicare End-Stage Renal Disease Program, and accounts for 40% of the prevalent US dialysis population [104]. Type 2 diabetes accounts for the majority of patients with diabetes and end-stage renal disease. Thus it is not surprising that the growth rate of the ESRD population has been paralleled by a dramatic increase in the prevalence of diabetes in the general population [4,6]. Nearly 135 million people in the world are known to have diabetes, and that figure will grow to nearly 300 million by the year 2025 [11,42]. Based on observations in the NHANES cohort of individuals over 40 years of age, type 2 diabetes is probably underdiagnosed approximately 30% [4,6,21]. Particularly sobering is the evidence that nearly 50% of the patients with newly-diagnosed type 2 diabetes already display evidence of diabetic tissue damage [6]. It stands to reason that better outcomes will result in nephropathy if the diagnosis of diabetes is made at an earlier stage.

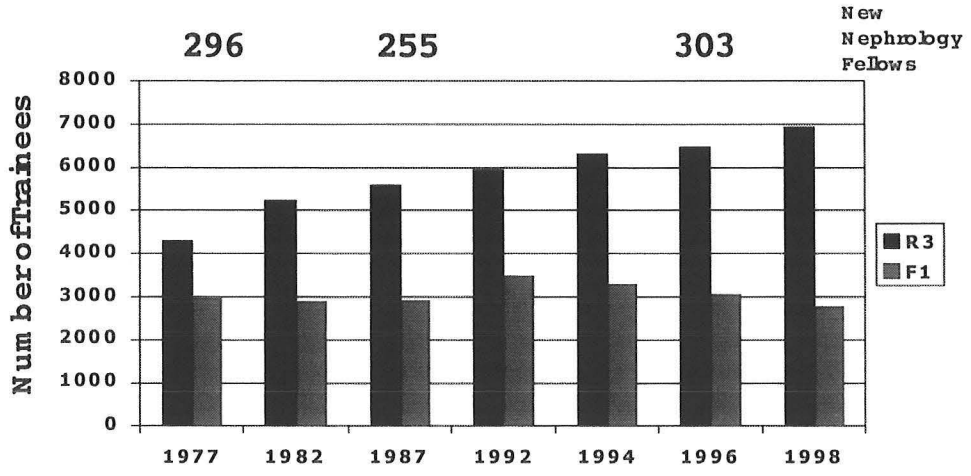
Failure to recognize and effectively treat hypertension

Although awareness, treatment, and control of hypertension increased from the NHANES II (1976–1980) to the NHANES III phase 1 survey (1988–1991), there has been no convincing evidence of further improvement in follow-up analyses [52]. Less than 75% of patients with hypertension in the US are aware of their condition, and only a fourth of individuals have optimal blood pressure control [21,22]. Even though a recent survey in an urban African American population suggested that hypertension awareness is improving, the identification and control of elevated blood pressure remains a tremendous challenge [48].

Manpower deficit

If the supply of resources was limitless, organization and planning could accommodate the ESRD population boom. But the system does have limits, and the most pressing limit will likely be the supply of Nephrology specialists. There are currently 4500-5000 nephrologists practicing in the United States, and each physician works over 1000hrs/yr caring for ESRD patients [72]. Obviously the need for Nephrologists will vary depending on the growth rate of the ESRD population, the incidence of ESRD, survival on dialysis, availability of organs, Nephrologist participation in Primary care, and the rate of new trainees [72]. However, conservative estimates project that fellowship programs will need to augment the number of Fellows by 200 trainees per year (in addition to the current ~250-300/year number) in order to meet the expected 2010 demands (**Figure 3**) [72]. The American Society of Nephrology states an overall goal of attaining 11,000 practicing nephrologists by 2010 [72].

Figure 3: Projected Nephrology manpower in the US is static

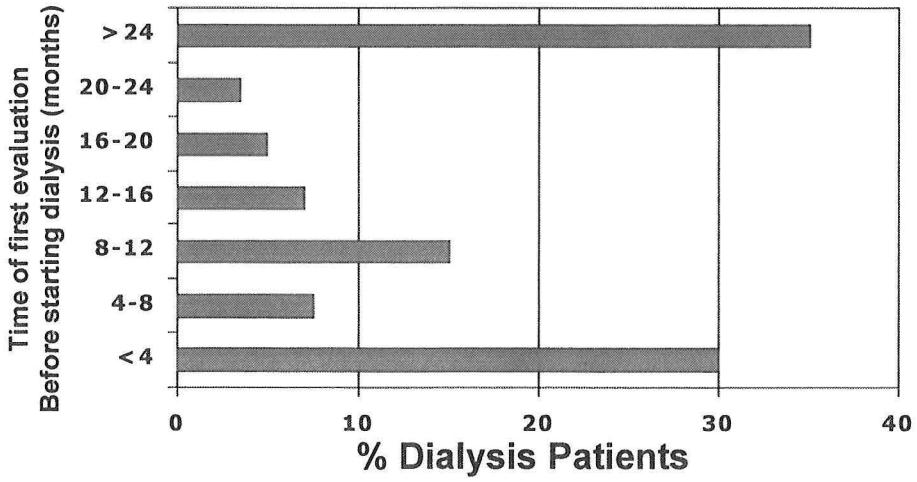


ABIM Tracking System, 1997

Early Referral

Timely referral of a CKD patient to a Nephrologist, as self-serving as it sounds, is needed to optimize clinical outcomes. Many patients on dialysis (either hemo- or peritoneal dialysis) had been evaluated by a Nephrologist within a year of initiating on dialysis, but frequently the referral happens quite a bit later. As part of the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study, investigators studied more than 800 patients in 81 dialysis units in the United States [57]. **Figure 4** shows that 30% of these patients first saw a Nephrologist less than four months before starting dialysis.

Figure 4: Timing of first Nephrologist evaluation in ESRD patients



CHOICE Study, *Annals Int Med* 137: 479, 2002

Black, uninsured, male, medically complicated patients are more likely than their counterparts to have late specialist evaluation [57]. Furthermore, several independent reports suggest that survival of patients referred late to a Nephrology specialist is worse [15,57,88]. Current recommendations include Nephrology referral at a serum creatinine concentration >1.5 mg/dl in women and 2.0 mg/dl in men [15].

"Selling" appropriate therapies to physicans and patients

As difficult as it may be to acknowledge, many observations implicate poor physician performance as a contributor to this problem. With regard to blood pressure treatment, clinicians often fail to increase doses or add new antihypertensive medications despite elevated recorded blood pressures [10]. This "clinical inertia" appears to contribute to worse blood pressure-related outcomes [82]. Physician inaction may also affect outcomes in patients with diabetes. In one analysis, diabetic therapy was unlikely to be intensified even after patients had documented poor metabolic control [82]. In a more recent VA-based study, even though diabetic patients were more likely to have elevated clinic blood pressures, they were less likely to receive intensive blood pressure therapy than their non-diabetic hypertensive peers [11].

Even when physicians do respond to start or change therapies in hypertension, the actions may be incorrect. In one analysis in 1994, angiotensin-converting enzyme inhibitors (ACEis) and calcium-channel blockers accounted for 69% of therapies, but nearly two-thirds of these patients lacked a recognized indication for their use [18]. In 1999, nearly half of all treated hypertensive patients were prescribed medications that were not in-line with published recommendations [18]. Therefore, prescribing practices often differ from public recommendations of panels such as JNC VI [52].

As practicing clinicians we should pay heed to the patient's perspective and to the dramatic influence progressive kidney disease can have on an individual. If we succeed in identifying a particular therapy, our patients will need to identify with and value the same recommendations and goals. A recent study gave some reason for optimism. In a survey of patients with different stages of "pre-dialysis" CKD, more than 75% of patients expressed willingness to stay on a restrictive diet, take six extra medications, and make as many as six additional office visits to avoid even a few weeks of dialysis treatment [101]. These observations might serve to motivate us to try harder to apply aggressive protocols to reduce progression of renal disease.

Strategies for the battle

Limiting progression of CKD

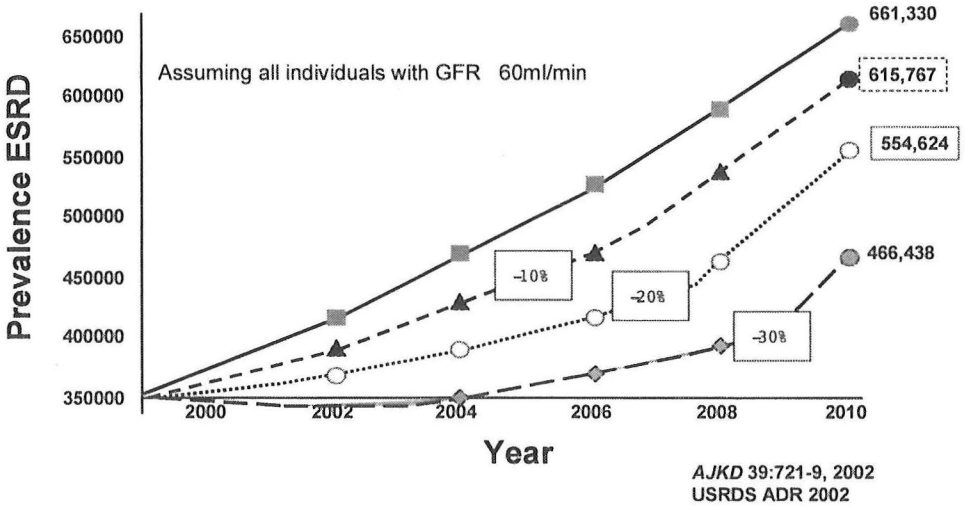
One of the tenets of clinical practice in Nephrology has been that chronic kidney failure will progressively worsen with the passage of time. More than five decades of observations suggest that the progressive deterioration of renal function results from glomerular hemodynamic changes following a renal insult [31,90,91]. A number of experimental models of progressive renal failure suggest that increased glomerular capillary pressure, elevated systemic arterial pressure, and proteinuria are important progression factors [90,91]. Consistent with these observations was evidence in humans with nephropathy that disease progressed more quickly when systemic blood pressure was elevated and proteinuria was more severe [90,91]. Most efforts to protect renal

function in patients with CKD have been designed to interrupt the processes that drive renal progression: systemic hypertension, glomerular hyperperfusion, and proteinuria.

What "renoprotection" can mean to the public health system and to an individual patient

Effective lowering of the rate of deterioration of GFR in patients with established CKD would have a massive effect on the future size of the ESRD population and on the expenditures in the US Medicare programs. The overall effect would, of course, be larger if patients are identified and treated early in the course of CKD progression. A recent analysis projects the magnitude of possible benefit from successful interventions of this type. Using the Medicare and USRDS databases and a series of assumptions, these authors explored how various decreases in the rate of progression would influence the size of the ESRD population and the dollars spent by the year 2010 (**Figure 5**) [101]. Trivedi and colleagues assumed a basal rate of GFR progression in CKD to be 7.56ml/min/yr, based on what was employed in the Modification of Diet in Renal Disease (MDRD) Study [60]. They also assumed that patients initiated ESRD care (dialysis or transplant) with a GFR 8.1ml/min/1.73m^2 [104]. This model predicted that a ΔGFR slope of 10, 20, or 30% would decrease the size of the prevalent ESRD population from the projected 661,330 to 615,767, 554,624, or 466,438 persons, respectively, in the year 2010 [101]. Furthermore, these authors projected that a 30% reduction in GFR slope in all patients with an initial GFR of ≤60ml/min/1.73m^2 would result in as much as $60 billion cumulative savings by 2010. For an individual patient with a GFR ≤60ml/min/1.73m^2, an intervention that would slow the rate of progression 30% would mean nearly three years of life free from the need for dialysis [101].

Figure 5: Potential effects of decreasing rate of GFR progression, US



What do recent RCTs tell us about the hope of reducing progression of renal disease in diabetic nephropathy?

Diabetic patients with microalbuminuria (30-299mg albumin/24hrs) who develop more than 300mg/24hr albuminuria are likely to progress to Stage 5 CKD after several years [6,7,68]. Although medication intervention and tight metabolic control may be important in diabetic patients with microalbuminuria, no prospective trials demonstrate that these interventions will reduce the risk of ESRD (discussed below). But once diabetic nephropathy is well-established (macroalbuminuria, or greater than 300mg/24hrs), recent observations support that interventions can successfully reduce the risk of ESRD.

The United Kingdom Prospective Diabetes Study (UKPDS) and other recent trials support the well-established contention that effective antihypertensive treatment is the best inhibitor of progressive renal disease [7,90,91,105]. This has particular bearing on patients with type 2 diabetes, since nearly all will have elevated blood pressure as a harbinger of nephropathy [4,5,6]. In UKPDS, patients with type 2 diabetes who were also hypertensive were treated with either an ACEi captopril or a β blocker [105]. The results suggested that lowering the blood pressure to a mean 144/82 reduced strokes, deaths, CHF, and microvascular complications compared to "less tight" control (mean BP 154/87). Even though overt nephropathy was uncommon in the UKPDS population, the study did not demonstrate a clear benefit of either antihypertensive class on the onset or progression of proteinuria. Based on the benefits of lower blood pressures, however, the American Diabetes Association recommends a blood pressure goal of 130/80 [5].

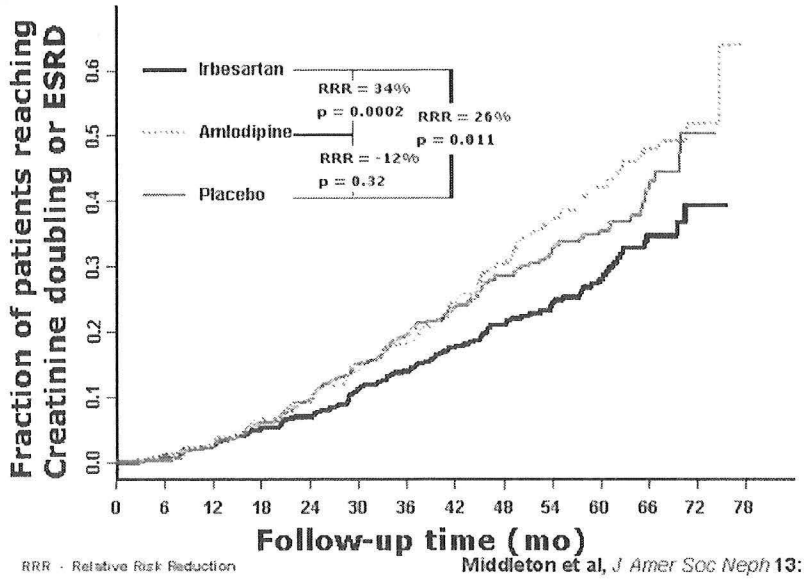
In 1993 the Collaborative Study Group convincingly demonstrated a benefit with the ACEi captopril compared to non-ACEi-based treatment in patients with established nephropathy due to type 1 diabetes [61]. Despite the recommendations at the time, it was not clear if ACEi-based therapy would also benefit patients with nephropathy from type 2 diabetes mellitus. Although patients with type 2 diabetes follow a time course similar to that seen in patients with type 1 diabetes, the date of onset of type 2 diabetes is often unknown and usually precedes the clinical diagnosis by several years [6,7,96]. Perhaps some of these differences explain why ACEi have not been shown to have a consistent benefit in type 2 diabetes compared to non-ACEi-based antihypertensive treatment [85,86,105].

Two large-scale prospective studies, the Irbesartan in Diabetic Nephropathy Trial (IDNT) and the Reduction of End Points in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) studies examined the potential benefits of blood pressure treatment with an angiotensin receptor blockade (ARB) in patients with established nephropathy due to type 2 diabetes [13,62,96]. Both of these trials showed that the ARBs (either irbesartan or losartan) reduced the risk of progressive renal disease independent of the reduction in blood pressure. The results are summarized in **Table 1.**

Table 1: IDNT and RENAAL Comparison

	RRR (%)			
	RENAAL	**IDNT**		
	Losartan vs control	Irbesartan vs control	Irbesartan vs amlodipine	Amlodipine vs control
Doubling of Creat, ESRD, or death	16 (*P*=0.02)	20 (*P*=0.02)	23 (*P*=0.006)	-4 (*P*=0.69)
Doubling of Creat	25 (*P*=0.006)	33 (*P*=0.003)	37 (*P*<0.001)	-6 (*P*=0.60)
ESRD	28 (*P*=0.002)	23 (*P*=0.07)	23 (*P*=0.07)	0 (*P*=0.99)
Death	-2 (*P*=0.88)	8 (*P*=0.57)	-4 (*P*=0.8)	12 (*P*=0.4)
CV Morbidity Mortality	10 (P=0.26)	9 (P=0.4)	-3 (P=0.79)	12 (P=0.29)

Figure 6: IDNT Results: Time to doubling creatinine or ESRD



RRR - Relative Risk Reduction

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Identifying high-risk patients:

The risk of a renal event (doubling of serum creatinine or ESRD) in the IDNT among patients assigned to irbesartan treatment compared to the risk among participants assigned to amlodipine or placebo treatment was reduced by 34% and 26% respectively

(**Table 1**) [62]. Despite this striking result, renal function continued to decline progressively in a significant proportion of the participants. We recently examined the database from the IDNT to determine if certain baseline characteristics were important predictors for progressive loss of renal function. Univariate analysis suggested that a host of baseline factors were associated with a poor renal outcome, and these included younger age, non-Caucasian race, family history of renal disease, retinopathy, history of gastroparesis, elevated pulse rate, and LDL cholesterol [68]. Interestingly, neither fasting glucose nor hemoglobin A_1C was associated with increased renal risk. In multivariate analysis, the baseline factors associated with poor renal outcomes in the IDNT were serum albumin concentration, inverse serum creatinine concentration, hemoglobin concentration and seated diastolic blood pressure [68]. It is conceivable, but certainly not confirmed by this analysis, that patients with CKD from type 2 diabetes who have these factors should be prescribed more intensive therapy at the outset.

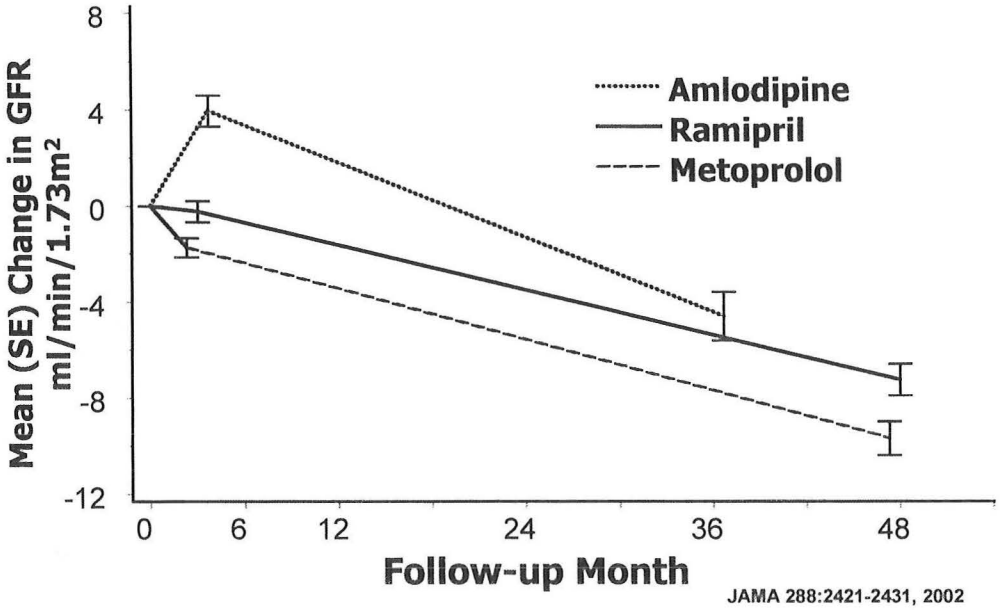
What do recent RCTs tell us about the hope of reducing progression of renal disease in hypertensive nephrosclerosis?

It has only been over the last two decades that "non-malignant" hypertension has been consistently recognized as a distinct cause of ESRD, especially in African Americans. Probably because of this relatively recent recognition, few clinical trials have been designed to determine if specific interventions would preserve kidney function. This is despite the fact that ESRD due to hypertension is now acknowledged to be the second most common cause of ESRD in the US [104].

We recently completed the interventional component of the African American Study of Kidney Disease and Hypertension (AASK) [1,106]. In AASK, 1,094 African Americans with a clinical diagnosis of hypertensive renal disease and a GFR 20-65 ml/min/1.73m^2 were randomly assigned to "usual" mean arterial pressure (MAP) goal (102-107 mmHg) or low MAP goal (<92 mmHg); subjects were also assigned to initial treatment with either a β blocker metoprolol, an ACEi ramipril, or a dihydropyridine calcium channel blocker amlodipine. Other agents were added to achieve the respective BP goals. The primary analysis in AASK was changes in GFR as measured by iothalamate clearance. The most important pre-specified clinical outcome was a composite GFR event (50% decrement or 25ml/min decrease), death, or attainment of ESRD.

The primary analysis in AASK demonstrated the following: First, for the blood pressure intervention, the mean BP decreased from 152/96 to 127/77 mmHg (low group) and from 149/95 to 140/85 mmHg ("usual" group) and was extremely well-maintained over the course of the study [1,106]. However, mean rates of decline in total GFR slope and time to clinical events were similar between the intervention groups. Second, for the analysis of the different medication assignments in AASK, ramipril as compared to metoprolol appeared to slow renal disease progression independent of protein level, while ramipril and metoprolol slowed progression as compared to amlodipine in patients with baseline proteinuria greater than 300mg/day [1,100]. However, none of the drug group comparisons showed consistent significant differences in the GFR slope largely due a large confounding effect of amlodipine. As shown in **Figure 7**, patients exposed to amlodipine had a transient increase followed by progressive decline in GFR.

Figure 7: Change in GFR from Baseline in AASK medication treatment groups



JAMA 288:2421-2431, 2002

We recently re-examined the results from AASK, with particular emphasis on the "hard" clinical outcomes of death and ESRD. The results from this analysis were surprising, and appeared to contradict the GFR responses. Compared to amlodipine, AASK patients in the ramipril group and the metoprolol group had significant risk reduction (49% and 42% respectively) for starting dialysis or dying [67]. Despite the apparent benefit in GFR with amlodipine, the risk reduction for ESRD alone was 59% for the ACEi or β-blocker compared to the calcium channel blocker. (**Figure 8**). Therefore, progression of GFR may not be a fruitful surrogate marker for ESRD in clinical trials of hypertensive nephrosclerosis. From a public health perspective, this analysis also suggests that the transient increase in GFR in some patients treated with amlodipine may actually increase risk of ESRD compared to either ramipril or metoprolol. This is particularly important since dihydropyridine calcium channel blockers are among the most common pharmacologic interventions for hypertension and that they are often recommended for use even as stand-alone medications in hypertensive African Americans [52].

Figure 8A: Time to ESRD in AASK: Amlodipine vs Ramipril

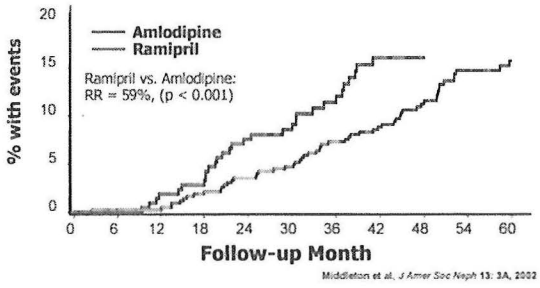


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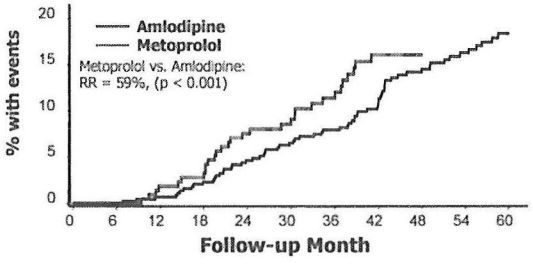
Figure 8B: Time to ESRD in AASK: Amlodipine vs Metoprolol



Why RCTs will have limited application in the ESRD crisis.

On one hand, we can congratulate ourselves on early signs of progress. The rate of growth of ESRD from other diseases (mostly glomerulonephritis) has remained consistent, but the growth rate in diabetes and hypertension ESRD may have slowed recently [104]. These trends have resulted in a slight decrease in growth rate of incident patients with ESRD over the last 5 yrs, with the rate from 1999-2000 being 2.8% [104]. Regardless, the number of prevalent patients with ESRD in 2000 is almost precisely what was predicted two years prior, and the trend continues toward a population of 650,000 ESRD patients in 2010.

Randomized controlled trials in Nephrology will certainly continue to be useful, but their application to the public health problem of ESRD creates a dilemma. These sorts of studies will have limited application for the following reasons:

- They consume money.
- They consume time. The system may be facing a break-point in the next decade. Since well-designed large-scale RCTs take many years to be completed, the system may be broken before we learn what a solution might have been.
- They are expected to show benefits on "hard" clinical endpoints such as death and requirement for dialysis
- They suffer from a shortage of suitable surrogate indicators for ESRD.
- With the trend away from placebo-controlled trials, they will be required to improve outcomes of many standard-of-care interventions, and diminishing increments of improvements can be anticipated.
- Patient selection often creates study populations that are markedly different from the existing CKD population.

Perhaps because of these limitations, one estimate suggests that less than 20% of clinical policies are based on randomized clinical trials (RCTs) [46].

Use of alternative sources to infer new strategies

We can still use medical evidence to make decisions about managing the problem of progressive CKD and the growing ESRD population. We can infer new strategies from sources such as clinical databases, case-control studies, or clinical trials that use surrogate (possible "softer") markers as study endpoints. These sources of information incorporate more bias than the "gold standard"-type of RCT, but information will be available from these sources in a time-frame that will hold promise for the impending ESRD.

The example of early intervention in diabetes.

In the example of diabetic nephropathy, it is impractical to expect to design and complete clinical trials of early intervention if that trial is to use the hard clinical endpoint of ESRD. The problem is that most patients with type 2 diabetes and microalbuminuria do not progress to ESRD, and furthermore the time until ESRD is manifest will likely be more than 10 years [4,5,6,42]. An intervention being tested, even if it proved to be useful,

would need to be applied to a large study population, and most of the treated subjects would not develop progressive renal disease anyway.

Regardless, we can derive recommendations for clinical guidelines from experiences with early intervention in diabetes. One aspect of the UKPDS trials included tight metabolic control in type 2 diabetes [105]. A large group of newly-diagnosed patients with type 2 diabetes mellitus were randomly assigned to intensive therapy compared to conventional care. The study was designed to assess differences in hard endpoints such as deaths and myocardial infarctions (among others), and it was not powered to determine an effect of the intervention on ESRD. The UKPDS data demonstrated that over ten years, the intensive treatment was effective in lowering HbA_1C to 7.0% compared to 7.9% in the conventional group. Compared with the conventional group, the risk in the intensive group was 12% lower for any diabetes-related endpoint; 10% lower for any diabetes-related death; and 6% lower for all-cause mortality [105]. Patients in the intensive therapy arm had a reduced rate of progression of albuminuria, a reduced risk for doubling of creatinine, and a reduced risk for doubling of their plasma urea concentration [105]. There are no firm conclusions about ESRD prevention in UKPDS, but the risk of the intervention is low enough to justify a recommendation for tight metabolic control in type 2 diabetes to avoid significant renal decline [4,24,25,105].

Similarly, many observations suggest that early treatment in diabetic patients with microalbuminuria will restrict the development of more advanced renal disease. Specifically, early interruption of the renin-angiotensin-aldosterone pathway with either ACEi or ARB treatment has been explored in several clinical trials in diabetes [77,85,86]. Most of these trials report that the pharmacologic intervention will diminish the amount of amount of proteinuria. However, there are limitations of a widespread recommendation of this approach, particularly in type 2 diabetes. In contrast to patients with type 1 diabetes, microalbuminuria is not a strong predictor of overt nephropathy in patients with type 2 diabetes [6]. Without specific intervention, ~80% of microalbuminuric type 1 patients but only 20-40% of microalbuminuric type 2 patients will proceed to develop overt nephropathy [5,6]. In other words, 60-80% of patients with type 2 diabetes and microalbuminuria will need to be treated with a medication to avoid a disease that they will not get anyway. In the case of ACEi where a substantial number of patients will not tolerate the medication, the question becomes moot. However, ARBs have much lower frequency of angioedema and cough than ACEi, and therefore the risk of exposing patients to the medication appears to be lower [14,19,91]. Recent reports also suggest that ARBs have exaggerated cardiovascular benefits compared to β blockers in diabetic patients with LVH, and these are the types of patients considered to be early interventions in type 2 diabetes [63].

Experimental therapies to limit progression of disease

Even with successful implementation of the new insights from these clinical trials, we need to acknowledge that we may not avoid the crush of ESRD patients. For example, despite "ideal" management of hypertension in the AASK program, nearly 30% of subjects with hypertensive nephrosclerosis reached the combined clinical endpoint of death, GFR event, or ESRD (described above). We should therefore consider newer interventions, even if they are at this time incompletely tested and may involve higher risk.

The human response to risk-taking

An interesting paradox in decision-making was described several years ago, and the quandary emphasizes how we tend to make decisions when we are working with a knowledge deficit. The so-called "Ellsberg paradox" was applied to the US involvement in the Vietnam War, but it may also apply to our decisions regarding the ESRD impasse [30].

The paradox arises from a series of games involving colored balls in urns. Suppose that we are told that there are two urns, each of which contains a hundred balls, which are either red or black. One urn contains fifty red balls and fifty black balls. The proportion of red and black in the other urn is unknown. Suppose further that we are told that we can draw one ball from one of the urns, without looking, and that if we draw a red ball we win a hundred dollars. Which urn will we choose? In practice, nearly all people will choose the known entity of the half-and-half urn [30]. However, suppose that we are then offered another hundred dollars to draw a black ball. Which urn would we choose now? More than 75% of the time individuals will choose the "fifty-fifty" urn again. This decision is made despite the preceding hunch that the other urn had more black balls in it. Therefore, this example highlights that we so strongly strive to avoid ambiguity that we make choices consistent neither with the laws of probability nor with themselves [30].

Perhaps clinic blood pressure is misleading.

For example, the relationship between blood pressure and renal complications may be missed if we rely solely on office blood pressure readings [96]. In patients with type 1 diabetes, for example, the development of microalbuminuria is heralded by an increase in systolic blood pressure that occurs during sleep [50]. In a similar manner, in an ACE/ARB study in IgA nephropathy (described below), the mean ambulatory BP but not the office blood pressure reading was significantly correlated with a beneficial effect on proteinuria [92]. Recent data from our AASK cohort of nearly 500 patients with hypertensive nephrosclerosis suggests a unique 24-hour blood pressure profile in African Americans with CKD. In these patients, the mean daytime blood pressures were 137 ± 14.3/81.8 ± 10.1mm Hg and the mean night recordings were 133.6 ± 11.1/76.7 ± 8.5 mmHg (R. Phillips, personal communication). However, there seem to be distinct patterns of blood pressure responses in this cohort. It has been well-documented that many African Americans do not exhibit a decreased blood pressure at night, especially compared to Caucasians, and are thus classified as "non-dippers" [50]. In the AASK patients, not only did many patients fail to decrease blood pressure, but 40% of the subjects actually increased nocturnal pressures. In 10% of the AASK patients, the nocturnal BPs were more than 10% greater than the daytime values (R. Phillips). It is conceivable that the end-organ damage in these and other high-risk demographic groups occurs due to unrecognized elevation in blood pressure.

Combination of renin/angiotensin 2/aldosterone antagonists.

In several examples discussed above, a renal-sparing effect of ACEi or ARBs can result, and the benefits of the medications appear to extend beyond the blood-pressure lowering effects. The unique aspects of these pharmacologic intervention is assumed to involve processes such as reducing sclerosis, inhibiting fibrosis, decreasing proteinuria, and/or ameliorating renal hemodynamic responses [14,91,96]. Despite the fact that the classes of ACEis and ARBs act in related manners, the renal sparing effects of these

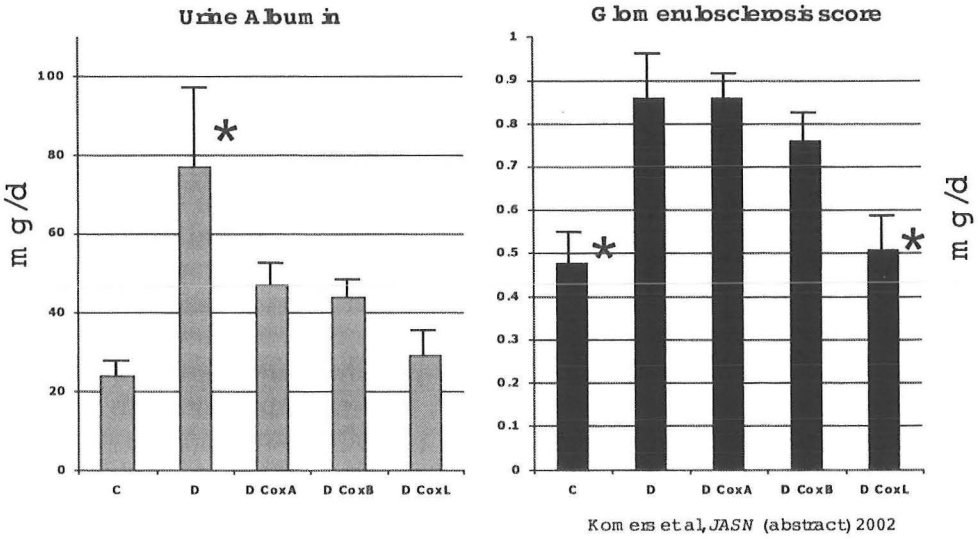
medications may be distinct. Long-term exposure to ACEis reduces but does not completely remove angiotensin II levels [14]. Bradykinin accumulation in ACEi-treated patients does not occur in ARB-treated individuals [14,91]. The currently-available ARBs are only active at the type 1 receptors and do not antagonize other potential angiotensin II binding sites [14].

These characterizations have supported a few efforts to treat pre-existing renal diseases with combinations of ACEi and ARB. In IgA nephropathy, a small prospective randomized trial was reported where patients were exposed to a combination ACEi and ARB [92]. In order to avoid any confounding blood pressure effect, patients with IgA nephropathy were recruited who had proteinuria (mean 1.5g/24hr) but who lacked clinical hypertension or significant renal failure [92]. In the trial, the combination of ACEi/ARB reduced proteinuria an average 73% greater compared to either agent alone. Interestingly, these same patients did not have a discernible change in proteinuria when the ACEi (enalapril 10mg to 20mg/d) or ARB (losartan 50mg to 100mg) doses were doubled. Perhaps more germane to the public health problem, similar results were recently published in type 2 diabetic nephropathy, in the Candesartan and Lisinopril Microalbuminuria (CALM) trial [92]. In this study, nearly 200 patients with type 2 diabetes mellitus and microalbuminuria were treated for 3 months with either the ARB or the ACEi then for 3 months with both medications. The reduction in proteinuria during the combination phase was greater (50% reduction) than for either agent alone (candesartan 24%; lisinopril 39% reduction). However, since the apparent beneficial effects on proteinuria were associated with simultaneous lowering of blood pressure, the interpretation of these findings is complex. Other similar trials have been reported [89]. Since the combination of ARB, ACEi, and β blocker was associated with increased mortality in a post hoc analysis of a heart failure trial, the risk of combination therapy in all patients may not be equivalent [19].

Cyclooxygenase inhibition.

The development of overt diabetic nephropathy is associated with enhanced renal production of prostaniods, and renal prostaglandin metabolism may create renal hemodynamic changes that promote progression of nephropathy [16,79]. Renal prostaglandin production is dependent upon the activity of two enzymes: cyclooxygenase (COX) and prostaglandin synthases. Two distinct isoenzymes of COX have been identified, COX-1 and -2 [16]. COX-2 inhibitors are now routinely available for human use, and have limited gastrointestinal side effects compared to non-selective COX inhibitors [23]. Using animal models of diabetic nephropathy, several studies have demonstrated that COX-2 expression in the kidney (primarily at the macula densa, thick ascending limb and medullary interstitial cells) is increased compared to normal animals and that selective COX-2 inhibitors are associated with functional and/or histologic evidence for renoprotection [44,58,71]. In one recent study, diabetic uninephrectomized rats were treated for 16 weeks with two doses of a selective COX-2 inhibitor [16]. There were salutary functional effects of the medication at either dose used, but the most dramatic responses were seen when the medication was started later in the course of diabetes (**Figure 9**).

Figure 9: COX-2 Inhibition Ameliorates Manifestations of Diabetic Nephropathy in Rats



The prospects of using COX-2 inhibitors in established diabetic nephropathy should be kept in perspective. Even though most of the adverse events are not serious (e.g., edema or transient increase in blood pressure), the rate of renal-related complications can approach 30%, and medication-related adverse events can include acute renal failure [23,79]. To determine if the intervention offers an acceptable risk: benefit relationship, we are currently initiating an NIH-sponsored pilot study of the COX-2 inhibitor celecoxib in patients with established diabetic nephropathy.

Protein kinase C inhibition.

In diabetes, each of the pathophysiologic factors of hyperglycemia, hypertension and angiotensin II is capable of activating the intracellular signaling family of enzymes, protein kinases C (PKC). The intracellular PKCs function as serine-threonine kinases to enable cell growth and differentiation [49]. In diabetes, activation of PKC has been implicated in a variety of end-organ damage, including diabetic nephropathy [8,49]. Of the many isoforms of PKC, PKCß is preferentially activated in endothelial cells in diabetic animals [8,100]. The PKCß isoform also causes physiological abnormalities *in vivo* in experimental animal manipulations, and these responses include increased GFR and elevated albumin excretion [51]. Thus, PKCß may be an important participant in the progression of diabetic nephropathy.

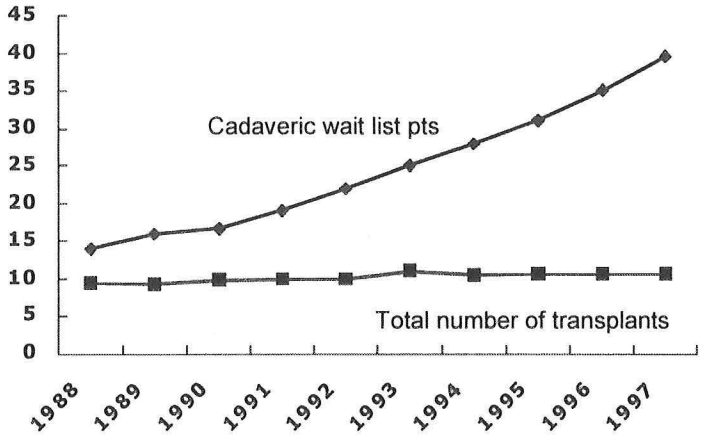
Several experimental models of diabetic nephropathy have tested the responses to pharmacologic inhibition of PKC isoforms. In studies of the STZ (mRen-2)27 rat, a transgenic rodent that has the entire mouse renin gene (Ren-2) inserted into its genome and develops a phenotype similar to human diabetic nephropathy, treatment with the PKCβ inhibitor LY333531 attenuates proteinuria, glomerulosclerosis and tubulointerstitial fibrosis [8]. The same drug has been used in clinical trials. In a randomized, double-blind, placebo-controlled, crossover trial, healthy subjects were

treated with the PKCß inhibitor, LY333531, or matching placebo once a day for a week, then forearm blood flow was measured [8]. Subjects treated with LY333531 exhibited less hyperglycemia-induced hemodynamic changes than the placebo group [8]. It would appear that PKC-active agents such as LY333531 have promise to prevent the glomerular hyperfiltration that occurs early in diabetic nephropathy [49].

Transplantation as an alternative to renoprotection

The evidence, then, that renoprotective interventions will avert an ESRD crisis encourages hope and worry. In order to shift the burden away from dialysis systems, an alternative approach is transplantation. It is notable that it takes ~60% less effort by a Nephrologist to care for a patient with a functioning allograft than one on dialysis [72,75,84]. Native kidney protection and allograft preservation share many strategies. For example, contemporary immunosuppression protocols decrease the risk of acute cellular rejection but increase the significance of chronic allograft nephropathy compared to older practices [73]. It is likely that the interventions discussed above such as blood pressure control, ACEi or ARBs, lipid management, and control of hyperglycemia have bearing on the process of chronic allograft dysfunction [78]. Outcomes with renal allografts, similar to those of native CKD, are also affected by comorbid conditions, especially those that increase cardiovascular risk. A graphic reminder of this is that more than 40% of transplanted patients die from cardiovascular causes with functioning allografts [84,104].

Figure 10: Increasing gap between US waiting list and kidney allografts



Hou et al, *Kidney International 58:1820*, 2000

The gap continues to widen between the number of patients on the waiting list for kidney transplantation and the number of transplants performed (**Figure 10**). From 1988 to 1997, the number of people waiting for kidneys in the United States almost tripled, while the number of transplants (including kidney-pancreas transplants) increased by only 36% [47,73]. The number of white and black patients waiting for transplants increased 116% and 198%, respectively [104]. Several strategies are proposed to address the deficit in transplantable organs.

Redistributing the available cadaveric organs

The United Network of Organ Sharing (UNOS) employs an algorithm to determine priority for organ distribution for cadaveric kidneys. Even though the UNOS algorithm was designed with equal access and efficiency in mind, several investigators argue that neither goal is achieved. A potential recipient gains "points" with the algorithm with time on the list and the degree of HLA matching to the particular kidney donor, but emphasis is also placed on pediatric recipients and on presence of high panel-reactive antibody (a measure of prior immune activation, typically prior transplants) [80,84,87]. The latter group of potential recipients will often be eliminated by a positive cross-match, but the system is weighted to offer an organ to recipients with a high risk of allograft loss [80]. An additional concern has been that Blacks in the US typically have the longest waiting times on the transplant list in the current system, an effect attributed to low likelihood of living donation, incompatible blood types, likelihood of sensitization, and the priority of HLA matching in the UNOS algorithm [27]. Efforts to resolve allocation problems include applying correlates of future survival [107], adding priority to minority recipients [27,35,87,107], weighting priority based on geographic density of ESRD [27], and increasing importance of regional and HLA matching [94]. UNOS initiated a pilot study to examine if they could change the criteria for HLA matching in cadaveric kidney distribution, using broader classifications called cross-reactive groups (CREGs). The results of this study showed an advantage of this system, but the cost saving was estimated to be only 2% per transplant and the average graft survival was estimated to improve only 0.6% [45]. Despite several different approaches, none of these alternatives for distribution of cadaveric organs will release the burden of patients with ESRD on the kidney wait-list [17].

Increasing the pool of potential kidney donors: Living unrelated donors.

As the number of available cadaveric organs has stabilized, kidney donation by living relatives has become an increasingly important source of transplantation [39,65,95,104]. Unrelated donors, particularly spouses, have also become more prevalent in the past two decades [97]. The public already accepts living donors who were not considered 15 years ago. [56]. In a large phone survey, more than three-fourths of the respondents said they would consider donating a kidney to a close friend, but only 25% would do so with a stranger [98]. In 1987, spouses accounted for 2% of the living donors but by 1997, they accounted for almost 10% [55]. The success rate for living unrelated donor kidneys is significantly better than that for cadaveric kidneys, despite the improved outcome for the recipients of cadaveric kidneys who receive calcineurin inhibitors [84] . The 3-year, 10-year, and 15-year allograft survival rates are estimated to be 85%, 54%, and 43%, respectively [84,95]. These rates approximate the outcomes for haploidentical kidneys [95]. Interestingly, husband-to-wife donations are common but have been demonstrated to have better outcomes than wife-to-husband and non-spousal donations [55].

Increasing the pool of potential kidney donors: Expanded cadaveric donor criteria.

An altruistic or perhaps a "feel-good" solution would be to attempt to increase the pool of cadaveric organs in our present-day donation system. Without widespread support of political mandates (such as assumed consent), this effort is not likely to have a measurable effect on the US problem [17]. Therefore, alternative criteria for donor selection have been proposed to increase the number of available kidneys for transplant.

Criteria that would increase the number of cadaveric organs that would be considered for transplantation are listed in the **Table 2.**

Table 2: Alternative criteria to traditional cadaveric donor selection [84]
Accepting older and non–heart-beating donors
Donors with longstanding hypertension
Donors with renal dysfunction, diabetes, or anatomic anomalies
Use of bilateral renal allografts from donors with impaired renal function
Exchange of living donor kidneys
Use of laparoscopic nephrectomy
Selective use of hepatitis C–positive donors

The goal of these criteria would be to expand the pool of donor organs [(84)]. Obviously, each of these alternatives includes specific risks to the graft and to the recipient that must be considered individually. Compared to clinical outcomes from transplants with optimal donors, the results from transplants with "marginal" donors suggest that recipients of marginal kidney transplants will live up to five years longer than transplant candidates who remain on dialysis [(75)]. This is promising, but typically recipients of transplants from better donors will live at least ten years longer than patients on the waiting list [(75)]. Interestingly, patients with ESRD due to diabetes may have the greatest benefit from receiving the marginal allograft [(75)]. Regardless of the criteria used to select potential kidney donors, the resource is probably too limited to resolve the predicted ESRD burden. A 1992 assessment estimated that in the US 7-11,000 deaths occur in potential donors, and that organ procurement was typically only about ~50% efficient [(33)]. Even if procurement efforts could reach 100% consent and success rate, the supply of kidneys will not meet the need.

Hope of genetically modified kidneys

If transplantation is going to have a substantial impact on the future care, it seems unlikely that any change in allocation or improvement in the organ supply will substantially reduce the burden of the expected ESRD population. This rationale has compelled the pursuit of xenotransplantation as a solution. Xenotransplantation is defined as the use of animal organs or tissue for transplantation [(83)]. Since kidneys will need to be available in large numbers, the source will need to be bred easily, the animals will need to be raised free of pathogens, and the tools for genetic manipulation must be available in the species used [(83)]. Most of these criteria are met by the source of most of the investigations, the porcine model.

The main obstacles to xenotransplantation are the immunological reaction of the recipient against the organ, the functional limitations of the organ in the recipient, and the concern about transferring infectious organisms. Xenografts between distantly related species, such as human and pig, are subject to immediate graft loss from "hyperacute" rejection, or vascular rejection [(74)]. For example, the Galα 1-3Gal is a saccharide that is expressed on vascular endothelium of pigs and other lower mammals that is the primary target of the human antibodies that mediate immediate graft loss [(74)]. Approaches to avoid hyperacute rejection include removal of the recipient antibody, altering expression of the Galα 1-3Gal, or introduction of genes in the animal for human complement regulatory proteins. A related approach has been to genetically manipulate

secondary immune processes that contribute to loss of xenografts. For example, human decay accelerating factor is an endogenous regulator of complement activation that has been expressed in transgenic pigs to avoid hyperacute rejection [74].

This field has seen remarkable progress, fueled in large measure by input from pharmaceutical sponsors who forecast huge commercial opportunities in the sale of pig organs. However, industry support has diminished over the last few years due to worries over the effect of potential transfer of pathogens such as porcine endogenous retrovirus (PERV), a virus that is present in the genome of all pigs, that may be transferred to human recipients [20]. The National Heart Lung and Blood Institute recently issued a statement supporting more investigation in the area of xenotransplantation [83]. Interestingly, a National Kidney Foundation survey from 1998 suggested that nearly all people polled in the US were aware of the serious organ shortage, and more than 60% accepted the notion of animal-to-human transplantation as a possible solution (National Kidney Foundation Newsletter, January 21, 1998).

Conclusions

In order to reach conclusions and recommendations for the growth of ESRD in this country, certain assumptions must be made. In the US, ESRD care (dialysis and transplantation) will likely remain as a treatment option for any patient who desires it. Nephrologists will continue to manage the renal problems in patients with stage 5 CKD, or ESRD. Even if Nephrologists limit practices to their subspecialty, expected increases in the size of the workforce will not be sufficient to manage the expected increase in ESRD patients. It seems that we are losing the battle with ESRD because of problems with many groups of individuals: "healthy" Americans, recognized patients, and physicians.

Recommendations

The Nephrology community needs to implore funding agencies to increase research in this area. We have a recognized knowledge deficit, and we need to aggressively work to disseminate information to patients and physicians about what we know. We also need to acknowledge things we do not know. We must be willing to carefully apply what we think we know, especially to high-risk patients. "Fringe" therapies must be identified from less-than-perfect sources such as small clinical trials and established databases, and interventions that are known to be low risk should be advanced.

In the end, to manage the problem we need to establish and publicize the circumstances and cadence of progressive kidney disease. We need to organize our resources and place them in a new arrangement. If the collusion is well-conceived and lucky, we will be able to limit the growth and still deliver the best possible care to this burgeoning segment of the US population.

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