Cardiovascular Outcomes in ESRD: Can We Do Better?

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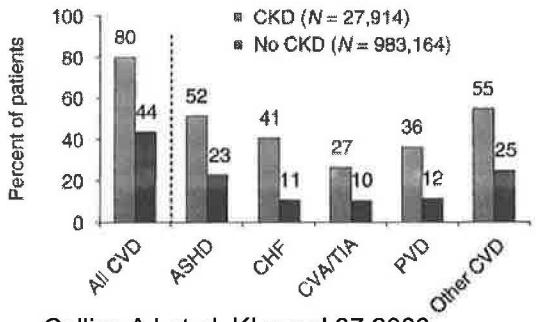
1. Introduction

Approximately 90,000 new end stage renal disease (ESRD) patients are being added yearly to the current 400 thousand patients requiring maintenance therapy or awaiting kidney transplant (1). Cardiovascular death claims 50% of these patients with an average life span of 5 years on maintenance dialysis therapy and morbidity can be significant with limb loss from peripheral vascular disease and marked economic burden (2). While co-morbid burden including the presence of diabetes and hypertension is also significant in this population, other added risk of ESRD associated with poorly controlled volume status, chronic inflammatory state, anemia, poorly controlled mineral metabolism seem to accelerate disease. The magic bullet will be to regenerate new kidneys. Transplant kidneys serve as current surrogates. Donor availability precludes widespread transplantation. Approximately 1 in 50 patients waiting for renal transplant gets transplanted each year. Furthermore, only those who can surgically tolerate transplantation and the burden of chronic immunosuppression post transplant are even listed for transplant. This then underscores the reason to control factors associated with acceleration of disease. In this grand round, the goal will be to understand factors associated with acceleration of cardiovascular disease in the ESRD patient and explore options to improve care.

2. Burden of Disease

A. CKD population

Traditional risk factors for cardiovascular disease including increasing age, diabetes and hypertension are prevalent risk burden in the patient with renal failure and those progressing to ESRD. More than two-thirds of patients starting dialysis have diabetes and hypertension prevalence in ESRD can be as high as 90% depending on the definition (1, 3). Even high normal blood pressure as defined by systolic pressures between 130-139 mmHg systolic with diastolic pressures of 80-89 mmHG predispose to an increased incidence of cardiovascular events in both men and women (3). Cardiovascular disease prevalence in the chronic kidney disease (CKD) population is nearly 2-3 times the general population in each category of cardiac or vascular disease compared with those without CKD amongst Medicare

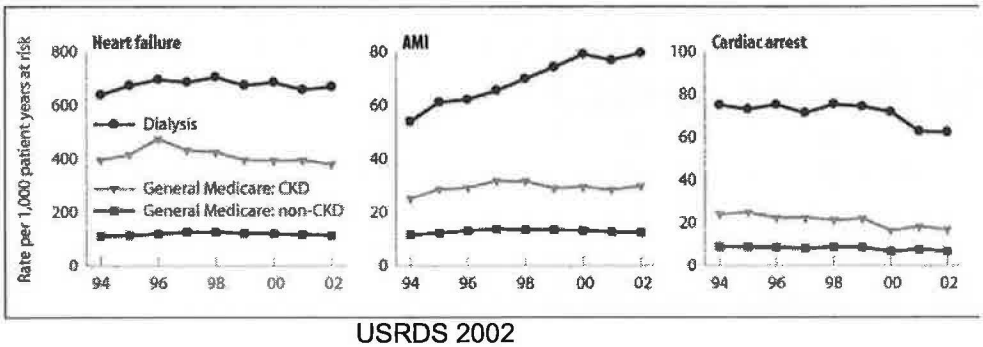


Collins AJ et al. KI suppl 87 2003

patients from 1996-1997 followed to 1998 who survived and did not develop CKD (4). Moreover medicare patients hospitalized for acute myocardial infarction (AMI) or congestive heart failure (CHF) not only demonstrate a high prevalence of CKD but also a greater rate of progression to ESRD (5). Incidence of peripheral vascular disease also increases with loss of renal reserve (6). Furthermore with progressive loss of renal clearance, there seems to already be evidence for an increase in inflammatory risk markers for cardiovascular disease (7). Therefore the burden of disease even prior to reaching ESRD is quite significant and our ability to modify risk factors should begin early in the course of loss of renal function. As generalists and internists then, our immediate goal is meticulous pre-ESRD care of blood pressure, diabetes, lipids and other lifestyle modifiable factors that can prevent progressive loss of renal reserve. As nephrologists, we need to investigate further the nontraditional risk markers associated with cardiovascular disease progression such as homocysteine, oxidized LDL, leptin and other markers of inflammation, as well as markers of abnormal mineral metabolism and vascular calcification carefully in relation to chronic kidney failure.

B. ESRD

With progression to ESRD then, the cardiovascular death rate can increase anywhere from 10 to 100 fold (8) in comparison to the general population depending on age. In fact the rate of events whether it is heart failure, acute myocardial infarction, or cardiac arrest



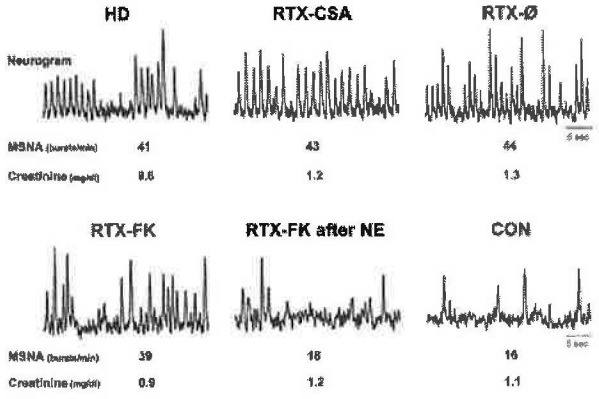
USRDS 2002

is greater in each category for dialysis patients in comparison to CKD patients and non CKD patients, adjusted for age, gender, race, diabetes. Furthermore, peripheral arterial disease in ESRD is 10 times higher than that of non-ESRD patients (9). So the natural question that arises is what is the reason for accelerated disease? Examination of specific factors associated with increased cardiovascular disease in the context of renal failure may provide clues for accelerated disease.

3. Risk Markers and Disease Progression in ESRD

A. ESRD Hypertension

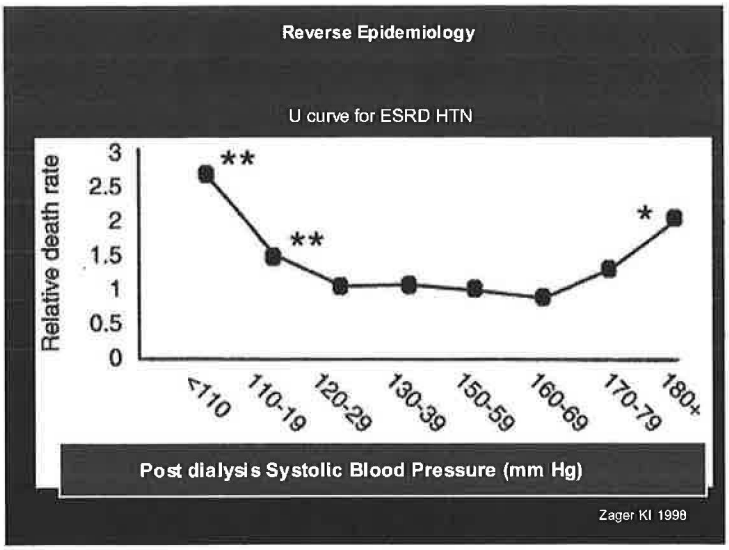
How is this entity different in ESRD than in others with hypertension? Response to changes in tissue perfusion with changes in vascular tone is of critical importance. For this reason various pathways to sense and respond to changes in volume to ensure appropriate vascular response have developed, including baroreceptors, sympathetic response, urinary sodium volume regulation, and hormonal mechanisms such as renin-angiotensin-aldosterone as well as autocrine mechanisms of control such as the nitric oxide, endothelin and prostaglandin mediated vasoregulatory pathways. These regulatory mechanisms in ESRD patients are often found to be dysfunctional (10-12). Angiotensin II levels may be inappropriately increased in relation to volume and exchangeable sodium. ESRD patients are also exhibit a greater vascular sensitivity to endogenous pressors and fail to fully suppress the vasoconstrictor system. The cardiac output is also higher despite an inappropriately elevated peripheral vascular resistance (3, (13). There is evidence for chronic sympathetic hyperactivity with renal failure and ESRD (10). In fact ESRD patients with bilateral nephrectomy have normalization of microneurographic changes detecting sympathetic activity, while those with transplantation do not show improvement whether they are or not on calcineurin inhibitors.



Hausberg M et. al.Circulation. 2002;106(15):1974

With afferent sensory input prevented via dorsal root section of subtotal nephrectomized rats, hypertension is ameliorated (14, 15). These studies indicate then that afferent signals from diseased kidneys through the brain vasomotor center increase blood pressure. Elevated plasma norepinephrine levels have also been associated with mortality and cardiovascular events in ESRD (16). Other factors contributing to poorly controlled blood pressure are decreased nitric oxide levels with increased levels of inhibitors of nitric oxide synthesis such as asymmetric dimethylarginine (ADMA) which accumulate in patients with ESRD and can impair vasodilation as seen in uremia (11).

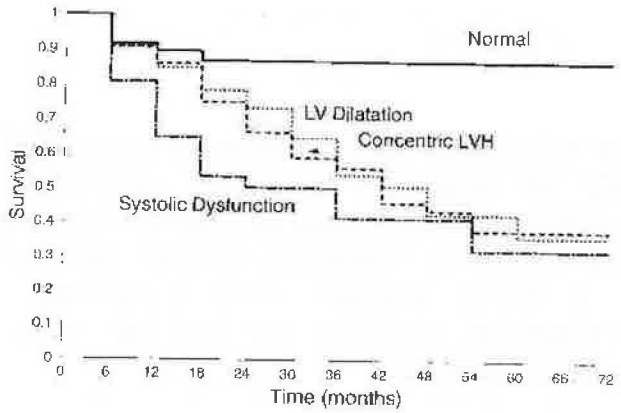
Endothelin-1 levels also are noted to be elevated in hypertensive ESRD patients suggesting the possibility of increased systemic vasoconstriction (17). Furthermore, most ESRD patients are in a state of chronic volume excess with the inability to excrete daily volume to "actual dry weight." Some in relation to blood pressure control in ESRD patients have suggested a "reverse epidemiology". That is mortality is increased not only with increasing blood pressure but also with low blood pressure.



ESRD patients with low blood pressure frequently are found with significant progression of cardiovascular disease, often presenting with heart failure and dilated cardiomyopathy, low ejection fraction. Long standing elevated blood pressure and vascular changes then lead to these impaired cardiac compensatory mechanisms and hypotension (18-20). Control of blood pressure early on in incident dialysis patients may improve survival (21) Therefore controlling elevated blood pressure early on in renal failure and subsequent ESRD becomes imperative.

B. Changes in Cardiac Mass and Function in ESRD

A chronic state of blood pressure elevation and volume excess, a hyper-dynamic state from anemia, sympathetic overactivity, hyperparathyroid state and the presence of an AV fistula have been associated with changes in left ventricular mass and function ((22-25). The ability to estimate total body volume is primarily clinical, based on physical findings of volume excess such as edema or effusions in body cavities, elevated venous pressures or marked blood pressure elevation. In fact left ventricular hypertrophy is an independent risk factor for cardiovascular death in the ESRD population with up to 90% of patients noted to have an increase in left ventricular mass (26-28).



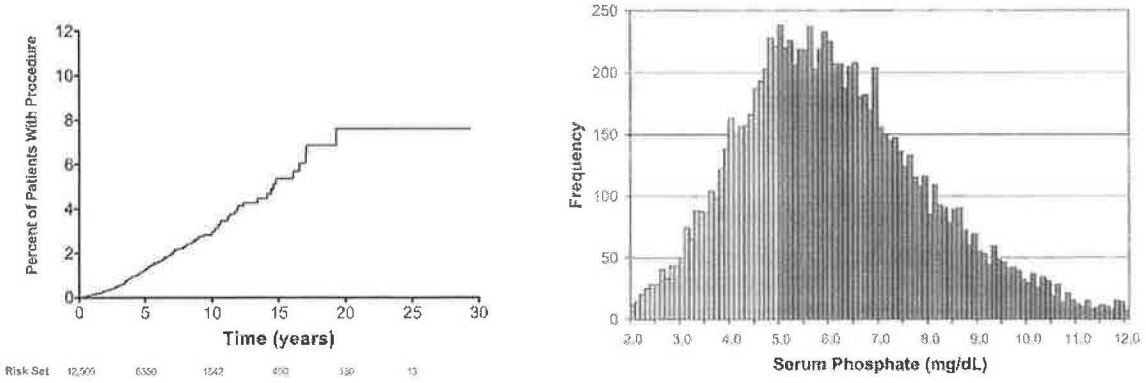
ESRD Patient Survival with Various Ventricular Disorders

Parfrey PS, NDT 1996

In addition, left ventricular dilatation is evident in nearly 30% of patients with systolic dysfunction with subsequent dismal prognosis of a 40% survival at 3 years (27). Cardiovascular events are noted to be minimal in ESRD patients with normal LV mass and function, intermediate in patients with either LVH or systolic dysfunction and maximal in patients with both abnormalities ((29). Furthermore, even a partial regression in left ventricular mass (10% or more) had a favorable impact on both cardiovascular and all cause mortality in ESRD patients (26). Anemia of chronic renal failure contributes to changes in left ventricular mass and dilation that are seen (30). Control of anemia in the hemodialysis population to maintain hemoglobin between 11 to 12 gm/dl is considered the standard of care. Erythropoietin administration in hemodialysis (HD) patients appears to improve parameters of left ventricular geometry including left ventricular septal (IVS) and posterior wall (LVPW) thickness, and LV mass index (LVMI) (31). Increased cardiac sympathetic activity in heart failure is associated with increased premature cardiac death. ESRD patients are noted to have higher sympathetic and lower vagal modulation of heart rate(12, 32, 33). In addition sleep apnea with nocturnal hypoxemia is prevalent in this population and correlates with parasympathetic withdrawl when assessed by heart rate variability and concentric left ventricular hypertrophy (34). Secondary hyperparathyroidism in ESRD may also be associated with a hyperkinetic state and increase cardiac contractility ((24) The presence of an AV fistula is independently associated with progression of LVH in ESRD ((25). Furthermore, sclerotic and calcified mitral or aortic valves are not infrequent in the ESRD patient and on occasion if severe mitral regurgitation or aortic stenosis occurs lead to changes in cardiac structure and function and require replacement (35).

In a cross- sectional study of 205 hemodialysis patients with baseline EBCT, 45% were noted to have a calcified mitral valve, 34% had calcified aortic valve,

and 21% noted to have both in comparison to an expected prevalence of 3-5% in the general population (36). Elevated levels of serum phosphorus have been shown to correlate with increased valvular calcification and need for valve replacement (35).



Rubel JR et. al. AJKD 2003 41:411-421

C. Changes in Vascular Structure in ERSD

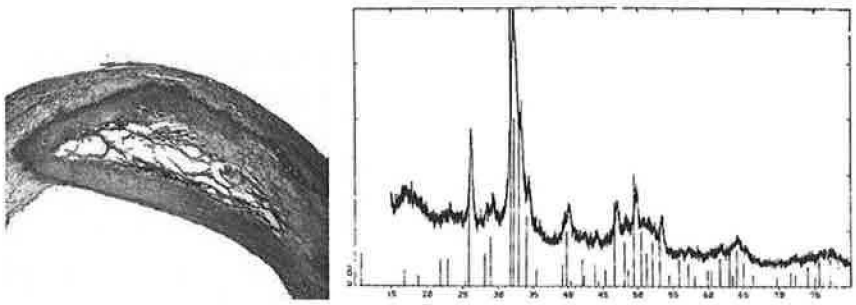
Calcification occurs not only in the cardiac valves but also in the arterial tree at accelerated pace in the ESRD patient. This is evidenced by increased EBCT calcium score 2-5 times in patients with renal disease compared to the general population(37-39).

Clinical Correlates of Coronary Artery Calcification Score

	0	1-400	401-1,000	>1,000	p Value
Previous MI (%)	6%	3%	10%	30%	<0.0001
Angina (%)	9%	10%	19%	41%	<0.0001
Known CAD (%)	3%	17%	26%	60%	<0.0001
Any ASVD	14%	23%	50%	84%	<0.0001
	0	Tertile 1	Tertile 2	Tertile 3	p Value
Claudication (%)	7%	7%	25%	25%	0.001
Aneurysm (%)	0%	0%	6%	5%	0.02

Raggi P et al. JACC 2002;39:695

Furthermore a greater degree of vascular calcification is noted in patients with CKD and DM than in patients with only DM and no kidney disease (40). A controlled postmortem study of coronary arteries from patients with and without end stage renal disease and chronic renal failure show evidence for marked increase in media thickness and calcification with hydroxyapatite isolated by xray diffraction technique (41).



Schwarz U et al. NDT 2000;15:218.

Various factors have been associated with the increased burden of calcification in ESRD. Besides traditional known risk factors of cardiovascular disease such as diabetes, hypertension, dyslipidemia, smoking, and age leading to an increase in intimal atherosclerotic plaque burden other factors including dialysis vintage, altered calcium-phosphate metabolism, fetuin deficiency, oxidative stress, hyperhomocystinemia, and a chronic inflammatory uremic milieu may also be associated with an increased rate of not only intimal vascular calcification but also an increase in medial vascular calcification (42). While the pathophysiology is not completely understood, in vitro studies indicate that vascular calcification is a regulated process similar to that of skeletal osteogenesis with various bone related proteins including osteonectin, osteopontin, parathyroid hormone (PTH), PTH related protein, osteoprotegerin and bone morphogenic proteins identified from vascular atherosclerotic plaques as well as sites of medial arterial calcification. Increased atherosclerotic intimal lesions can impinge upon the arterial lumen to compromise blood flow and increased tissue ischemia. This is evidenced by a higher rate of peripheral vascular disease in the ESRD population (8).

The calcification increases vascular stiffness and reduces vascular compliance. Increased medial calcification is associated with increased arterial stiffness with changes in pulsatile dynamics (43) and may contribute to an increase in ventricular afterload, decreased stoke volume (44), and compromise coronary blood flow during diastole (45). Ultrasonographic determination of common carotid artery distensibility as well as aortic pulse wave velocity (PWV) by Doppler methods indicate decreased distensiblity and increased PWV with increasing degrees of calcification (44).

Arterial structure and function according to calcification score (0 to 4)

Parameters	0	1	2	3	4	ANOVA
CCA diameter (mm)	6±0.82	6.3±0.89	6.3±0.70	6.67±0.97	6.73±0.80	0.001
CCA IMT (μm)	700±95	784±156	800±102	849±80	830±81	0.001

Ao_{root} diameter (mm)	26.4±4	26.3±4	27.8±3.9	27.5±4.1	29.7±4.5	0.01
Ao_{bif} diameter (mm)	16±2.4	16.7±4.4	16.7±1.5	17.8±3.3	18.1±2.6	0.01
CCA distens. ($kPa^{-1}.10^{-3}$)	22.6±9.5	17.5±7.8	18.7±11.9	13.5±6.3	11.5±6.3	0.001
CCA Einc ($kPa.10^{3}$)	0.47±0.24	0.61±0.31	0.62±0.48	0.76±0.37	1.01±0.60	0.001
Aortic PWV (cm/s)	914±180	946±141	1040±268	1270±384	1302±317	0.001

CCA, common carotid artery; Ao, aortic; Ao_{bif}, aortic bifurcation; CCA distens, CCA distensibility; Einc, incremental elastic modulus; PWV, pulse wave velocity.

Guerin AP et al. NDT 2000;15:1014.

Uremic serum has been shown to aggravate vascular calcification (46, 47). High phosphorus and or calcium phosphate product among other factors in uremic serum has been associated with greater degree of cardiovascular mortality (48). Human smooth muscle cells in culture seem to undergo phenotypic transformation when exposed to higher phosphorus level (2 mmol/l or 6.2 mg/dl Pi) to express markers of mineralization including osteocalcin and increase hydroxyapatite formation and collagen in the extracellular matrix. When increased phosphate uptake via the Na-phosphate transporter type 3 was blocked by phosphoformic acid, this transformation was blocked (49). While the leap is far, these basic studies appear to provide the background for possible acceleration of vascular calcification that is clinically seen. Decreased phosphate clearance serves to represent other solutes and toxins that may not be adequately cleared from the ESRD patient leading to possible inflammation and further vascular injury.

D. ESRD Inflammation

Uremia is a state that is difficult to define but has been described by Bouchard as "a complex poisoning to which contribute, in various measures, all the poisons normally acquired or resulting from physiologic processes in the organism (50)" Many solutes have been identified and others are still being investigated. Some of the solutes identified already are also known to be inflammatory markers and are associated with cardiovascular mortality in renal disease.

Table 1. Main known uremic retention solutes

Small water soluble solutes	Protein-bound solutes	Middle molecules
Asymmetric dimethylarginine	3-Deoxyglucosone	Adrenomedullin
Benzylalcohol	CMPF	Atrial natriuretic peptide
β-Guanidinopropionic acid	Fructoselysine	β_2-Microglobulin
β-Lipotropin	Glyoxal	β-Endorphin
Creatinine	Hippuric acid	Cholecystokinin
Cytidine	Homocysteine	Clara cell protein
Guanidine	Hydroquinone	Complement factor D
Guanidinoacetic acid	Indole-3-acetic acid	Cystatin C
Guanidinosuccinic acid	Indoxyl sulfate	Degranulation inhibiting protein I
Hypoxanthine	Kinurenine	Delta-sleep-inducing peptide
Malondialdehyde	Kynurenic acid	Endothelin
Methylguanidine	Methylglyoxal	Hyaluronic acid
Myoinositol	N-carboxymethyllysine	Interleukin 1β
Orotic acid	P-cresol	Interleukin 6
Orotidine	Pentosidine	Kappa-Ig light chain
Oxalate	Phenol	Lambda-Ig light chain
Pseudouridine	P-OHhippuric acid	Leptin
Symmetric dimethylarginine	Quinolinic acid	Methionine-enkepahlin
Urea	Spermidine	Neuropeptide Y
Uric acid	Spermine	Parathyroid hormone
Xanthine		Retinol binding protein
		Tumor necrosis factor alpha
CMPF is carboxy-methyl-propyl-furanpropionic acid.		

Vanholder R et al. KI 2003;84:S6

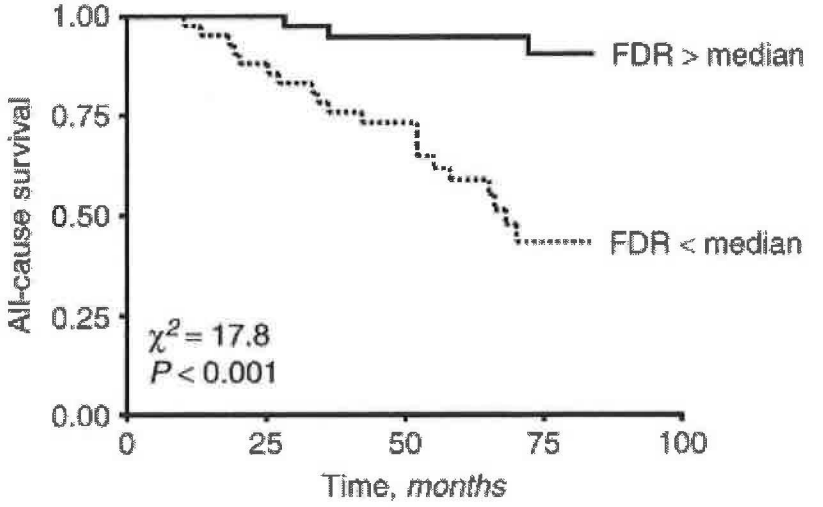
Homocysteine levels in the general population in the mild range of 12-16 umol/l have been associated with increased cardiovascular risk (51). In renal failure, many have homocysteine levels elevated ranging from 16 to 100 umol/l (52). Reasons for this are believed to be due to decreased renal clearance and metabolism in uremia (52). Similarly, elevated plasma concentrations of the inflammatory cytokine interleukin-6 (IL-6) not only predict CV and all-cause mortality, but are associated with rapid progression of underlying atherosclerosis (53, 54). Both IL-6 and CRP are strong predictors of cardiovascular morbidity and mortality in ESRD (55).

Inflammation also signifies increased oxidative stress which can add to endothelial dysfunction. In the early stages of atherosclerosis, endothelial dysfunction can be detected by the presence of enhanced endothelial permeability and expression of adhesion molecules, monocyte adhesion, oxygen

radical formation, and enhanced lipooxygenase activities (56). Blood levels of proinflammatory cytokines including TNF-α, IL-1β are increased and associated with increased levels of receptor for advanced glycation end-products in renal failure and ESRD ((57). One important factor that has been linked to elevated cytokine and CRP levels is elevated levels of advanced glycation end-products. Normally associated with diabetes mellitus, the AGEs are also increased in renal failure patients, irrespective of their blood glucose levels (58). In normal states, the kidney processes the AGEs via glomerular filtration followed by tubular uptake and metabolism (59) However, it is not dialyzed because most AGEs are albumin bound (60)

Increased levels of adhesion molecules and chemokines including ICAM-1, VCAM-1, MCP-1 which are associated with inflammation, dyslipidemia and cardiovascular events are also elevated in hemodialysis patients free of infection or other chronic illness or comorbid condition associated with inflammation or cytokine generation in comparison to healthy controls ((61). The type of dialysis membranes used (cellulose versus polysulphone) did not make a difference in the measurement though post dialysis levels were significantly higher than pre levels. When the HD patient group was divided into those with clinical evidence or history of vascular disease, patient with known history of vascular disease had higher levels of CRP and those patients with higher CRP levels also had higher ICAM-1 levels ((61).

Clinically the effect of inflammation on endothelial function is seen by evaluating flow mediated dilation (FMD) of the brachial artery in men with atherosclerosis where FMD decreases with an increase in common carotid intima-media thickness (62). Decreased flow mediated vasodilation evaluated in ESRD patients was found to be an independent predictor of mortality (63).



London GM et al. KI 2004;65(2):700

In the ESRD patient there is increased opportunity for inflammation both from retention of solutes and sources of external including infection, malnutrition, immune abnormalities (56, 64).

4. Therapeutic Considerations

A. Medical Therapy

Meticulous treatment of traditional cardiovascular risk factors including hypertension, diabetes, smoking, lipids with medications particularly angiotensin converting enzyme inhibitors and angiotensin receptor blockers, insulin and other insulin sensitizing agents, statins, antiplatelet agents in addition to exercise and avoidance of smoking and other nephrotoxins needs to occur for patients at risk early on to prevent progression of both cardiovascular disease and progression of renal disease. Anemia of CKD should also be addressed and treated with erythropoietin if indicated.

A Veterans Administration multicenter randomized double blind trial (HOST Homosysteine Study) evaluating the effect of high dose vitamin B12 and folic acid treatment in chronic renal failure and ESRD patients with homocysteinemia and cardiovascular disease on all cause mortality is currently in progress. This study started on 2001 and will conclude on 2007. The primary objective of this trial tests the hypothesis that lowering homocysteine levels in this population will decrease mortality. The secondary objective evaluates the effect of these vitamins on the incidence of cardiovascular outcome, specifically myocardial infarction, cerebrovascular accident, lower extremity amputation, and vascular access thrombosis. This trial will be important in determining possible medical treatment for a nontraditional risk factor in renal failure, homocysteine.

B. Dialysis Therapy

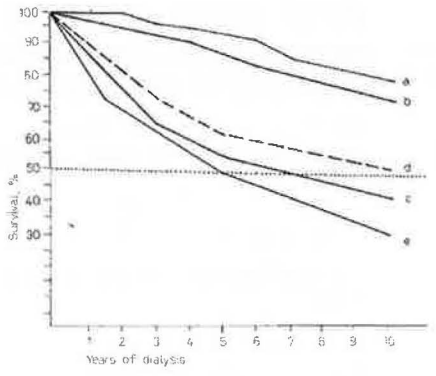
Current dialytic modalities for chronic renal replacement therapy include hemodialysis (HD), a variant hemodialfiltration, and peritoneal dialysis (PD).
For the majority of ESRD patients, hemodialysis thrice weekly with session lengths of 3-4 hours is the standard. Hemodiafiltration combines hemodialysis and hemofiltration with infusion of replacement fluid and is more effective than conventional dialysis in removing large solutes. Hemodialfiltration is not commonly used for chronic renal support in the US but appears to have gained some popularity in a few centers in Europe. Whether this modality of dialysis in combination with increased frequency improves cardiovascular outcome still needs to be investigated. About 10% percent of dialysis patients are on peritoneal dialysis (1). Survival characteristics by observational and cross sectional data are relatively similar for cardiovascular disease and survival for both PD and HD (1). PD patients for the most part receive more daily and continuous dialysis. Electrolyte shifts may be more gradual and allow for improved quality of life for patients on PD. However underlying co morbidites as

well as a greater state of constant volume overload, poorly controlled blood pressure does not appear to change the long term outcome in most patients with loss of residual renal function which is important to maintain adequate clearances for most patients. Given that a more daily and or continuous mode of renal replacement therapy such as PD has not improved survival is there then benefit to increasing the dialysis length or changing the dialysis frequency for hemodialysis?

(i) Long Intermittent Hemodialysis: We know from a recent study evaluating the effect of greater dialysis dose as measured by small solute (urea) and middle molecule (B2 microglobulin) clearance on survival, known as the HEMO study, had little impact on survival. Greater dose was achieved through the use of biocompatible membranes with greater solute diffusivity as well as an increase dialysis time. The average dialysis time was increased up to 4 and ½ hours (65). While all cause mortality was unchanged, there appeared to be a trend toward decreased cardiac mortality of patients who were receiving the higher flux membrane with better solute diffusivity (66). This finding needs to be further evaluated.

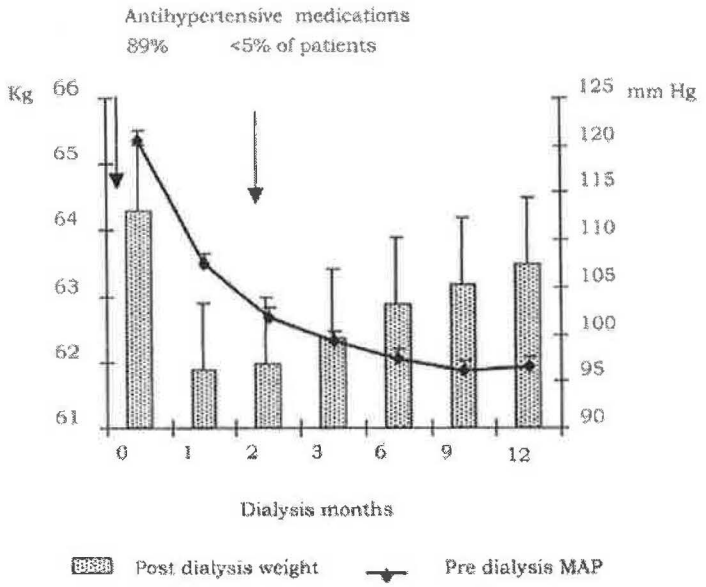
However when dialysis time is doubled to 8 hours as done by Bernard Charra and colleagues from Tassin France there may be a greater mortality benefit.

a: Series of 52 patients, Tassin
b: All Tassin patients
c: EDTA curve, 1978 (age group 15-54)
d: Seattle series, 1960-1965
e: USRDS, 1983 (adjusted for age, race, sex & primary disease)



Adapted from Charra, B., et al, Nephron 33: 96-99 (1983)

Patients in Tassin dialyzed twice the conventional session length (8 hours in comparison to 4 hours standard) on a thrice weekly schedule. Long term observational data from their center note improvement in blood pressure control from a MAP initially of 110 mmHg to 98 mmHG and have attributed the improvement in survival to better control of blood pressure.



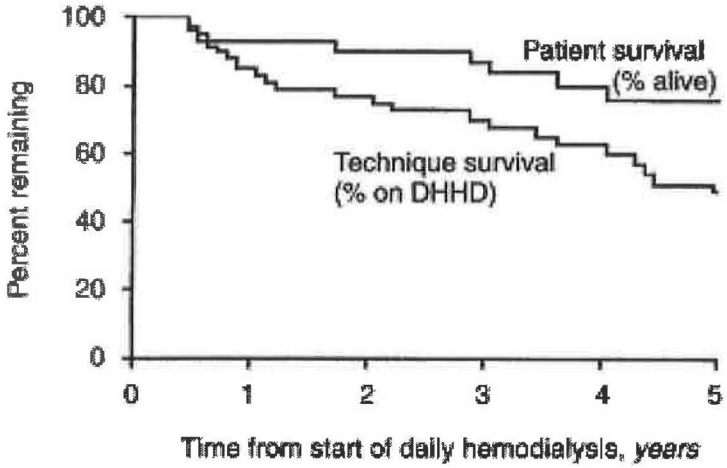
Raj D. et al. Am J Kidney Dis. 1999 Oct;34(4):597-610.

This is not inconsistent with data from general Framingham population studies which suggests that even elevated high normal or normal blood pressure is associated with increased cardiovascular incidence in comparison to an optimal BP of 120/80 or less (3). Data from Tassin suggest then that improving BP by long alternate day dialysis can have long term survival benefit in ESRD patients. Improved blood pressure in this group of patients appears to be the result of improved extracelluar volume and dietary sodium restriction. A small study from Germany evaluated whether the effect of volume loss or length of the dialysis session affected control of blood pressure in dialysis (67). This study randomized 7 to 8 patients to 1 of 3 groups: in group 1 dialysis time was increased an extra 2 hours from standard dialysis treatment from 3-5 hours and EDW gradually decreased, group 2 patients underwent increase in dialysis time of 2 hours but no change in EDW, and group 3 underwent gradual change in EDW without change in treatment time. While the number of blood pressure medications decreased in all groups, the change in blood pressure and pulse pressure decreased significantly in group 2, suggesting that there may be some effect of longer dialysis session length on blood pressure independent of changes in body volume (52).

What about other cardiovascular changes including arterial compliance or inflammation or left ventricular hypertrophy? No published data is currently available on long intermittent dialysis and inflammatory markers or vascular calcification. Left ventricular hypertrophy in patients on long intermittent dialysis when compared with historical cohorts on shorter intermittent dialysis appears unchanged (68, 69). Randomized comparisons between long and standard dialysis sessions need to be done to better evaluate the effect of longer dialysis sessions on myocardial and vascular structure and function. It is possible that alternate day therapies while improving blood pressure still expose the heart to a

higher volume load state that can then lead to changes in cardiac structure. Since LVH is an independent predictor of mortality, therapy for ESRD should also aim to target better volume control.

(ii) Daily Short Dialysis: What better way to assure volume removal then to dialyze daily? Fagugli and colleagues in Italy have shown a significant decrease in left ventricular mass and interventricular septal wall thickness with daily 2-hour dialysis. In a prospective crossover study of 12 hypertensive patients dialyzing 2 hours 6 days per week for 6 months and alternate day thrice weekly dialysis for 6 months both systolic and diastolic improved significantly from 148±19 to 128± 11.6 and 85±12 to 73±5 to 67±8 mmHG respectively ($p<0.01$) while on daily dialysis when compared to standard thrice weekly dialysis. Few patients were noted to require antihypertensive agents while on daily treatment sessions. Mean extracellular water also improved significantly from 53 ±11% to 48±8%, ($p <0.02$), during daily dialysis in these patients and this seemed to correlate with the change in both blood pressure and LVMI which also decreased from 149±60 g/m2 to 120±60 g/m2 ($p=0.01$). Weekly small solute clearance remained unchanged in the two groups as did protein bound solutes (70). All the patients had arteriovenous fistulas for hemoaccess. Furthermore, retrospective data from a collective group of 72 patients dialyzing from 1972 to 1996 were evaluated for changes in blood pressure, nutrition, survival and fistula patency from 9 centers in Europe and showed improvement in each category while in daily short HD versus data from when they were on conventional hemodialysis (71).

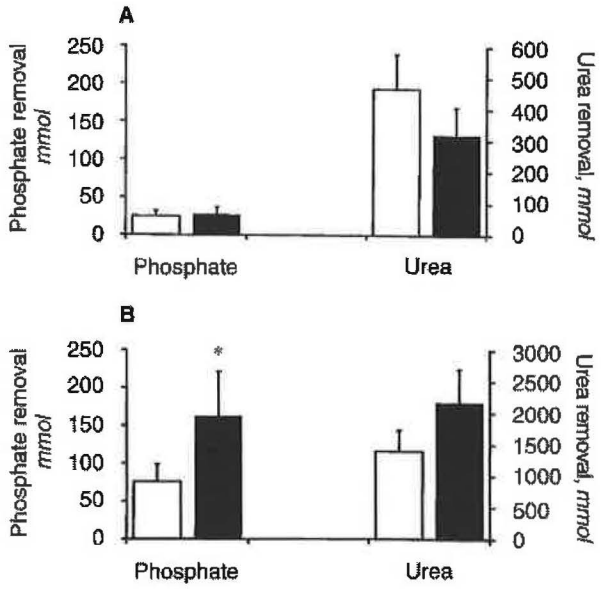


Woods J et al. KI 1999 55:2467

While this suggests that 5 years survival may be good with increased dialysis frequency, only 17 patients were left for analysis at the end. Therefore larger prospective studies evaluating survival with daily short dialysis are important. We do know from previous studies that decreasing dialysis time (3 to 3 ½ hour) on alternate day dialysis treatment schedules can lead to low small molecule solute

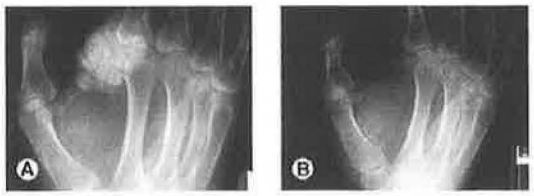
clearance, decreased phosphate clearance and may be associated with greater morbidity (72-74).

(iii) Daily Long Dialysis: Observational studies of combination daily and long dialysis at home for 6 to 8 hours 6-7 nights per week during the night (nocturnal dialysis) has shown significant improvement of ESRD cardiovascular morbidity including blood pressure, left ventricular hypertrophy, CHF, arterial stiffness. In addition, there is marked improvement in toxin clearance such as phosphate which has been shown to be associated with increased mortality in the dialysis population (75).



Mucsi I et al. KI 1998;53:1399

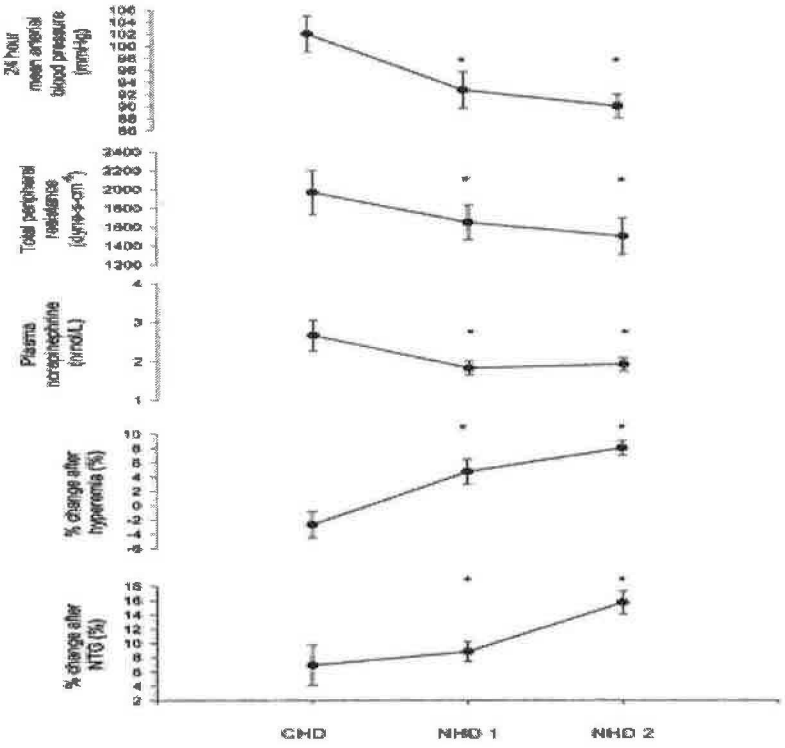
Tumoral calcinosis of the hand in one patient resolved after nocturnal dialysis for 9 months, despite using a higher dialysis calcium bath suggesting the importance of long and daily treatments in the control of mineral deposition in ESRD (76, 77).



Kim SJ et. Al. AJKD 2003;41:E12

Total plasma homocysteine levels were also found to be lower in a cross-sectional study cohort of nocturnal dialysis patients to conventional HD patients (78).

Changes in blood pressure in nocturnal long dialysis is accompanied by improvements in total peripheral resistance as noted by improved brachial artery endothelial dependent and independent vasodilation to both hyperemia and nitroglycerin administration as well as decreased plasma norepinephrine levels.



Chan CT et al, Hypertension 2003;42:925

Concurrent sympathetic nerve activation was not evaluated. Cohort comparison between nocturnal dialysis (NHD) patients and conventional home hemodialysis patients eligible for NHD but not on NHD in the Toronto Nocturnal Hemodialysis program shows that LVMI significantly decreases from 150±56 in the conventional group and 147±42 prior to starting NHD to 114±40 one year after NHD as did end diastolic volume. Hemoglobin did increase by 1 gm however in this study, although erythropoietin dose decreased, which certainly also can affect change in LV mass (31). The investigators noted little change in ECF volume as evaluated by BIA and came to the conclusion that the change in daily ECF oscillations between those on conventional hemodialysis (CHD) and NHD may be also be contributory in lessening the eccentric hypertrophy observed (79). This group also observed a significant difference in ejection fraction %, (EF%). EF% between NHD (n=6) and a CHD cohort was improved in NHD patients in association with a decrease in septal wall thickness. Again there was an increase in hemoglobin which cannot be ruled out as contributing to improved cardiac parameters since improving anemia is associated with improved LV geometry (80). Furthermore, NHD patients show improvement of sleep apnea by polysomnographic studies although abnormalities in nocturnal blood pressure

dipping did not improve. (81). While these data suggest significant benefit in short term cardiovascular morbidity, long term survival data are yet to be generated.

C. Sorbents

While sorbents have been utilized in dialysis for various treatments such as poisonings, their use has not been popularized. Sorbents may be useful to remove larger molecular weight toxins such as B2 microglobulin, leptin, and cytokines (82). However further studies using sorbents in combination with hemodialysis need to be considered treatment to evaluate its effect on cardiovascular outcome.

5. Conclusion

In summary, cardiovascular risk and disease progression is significant with the progression to and the presence of ESRD. Given that GFR loss is a main contributing factor in this progression, our first goal in those that are not yet on renal replacement therapy should be encouraged to aggressively practice lifestyle changes including healthy dietary intake, exercise, discontinuation of smoking, meticulous control of diabetes, hyperlipidemia, avoidance of nephrotoxic medications in addition to treatment of anemia and strict medical compliance of known cardioprotective medications.

These recommendations should continue for patients on renal replacement therapy but added goals to modify renal replacement practices so as to improve blood pressure control, prevent heart failure, and improve treatment and clearance of toxins that may potentiate vascular inflammation, calcification and or endothelial dysfunction need to be considered. Observational cohort comparative studies seem to suggest some benefit for increasing dialysis frequency and session length with respect to cardiovascular and longterm outcome. However controlled randomized trials are necessary to determine optimal renal replacement therapy so as to improve cardiovascular health in ESRD.

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