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Cardiovascular Disease in End Stage Renal Disease Patients

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1. Introduction

Cardiovascular disease is the primary cause of preventable death in industrialized countries (1). It is on a steady rise in many other countries where it had not been traditionally recognized as a major disease burden. There has been a lot of attempts to define the risk factors associated with cardiovascular disease. Similar efforts have been made in defining the treatment and the secondary prevention of cardiovascular diseases.

End Stage Renal Disease (ESRD) patients form a vulnerable sub-group of general population. In 2007, the adjusted annual mortality of dialysis patients in the United States was 19 % (USRDS 2008 Annual Data Report) (2). Cardiovascular and infection related complications are the major cause of morbidity and mortality in this group (3). ESRD patients have a high prevalence of cardiovascular risk factors leading to a phenomenally high cardiovascular morbidity and mortality. In fact it remains the single most important cause of death in ESRD patients. In 2005-2007 it accounted for 45 % of all deaths in ESRD patients (4). Cardiac arrest was responsible for almost half of these deaths (5). This apparently disproportionate burden of cardiovascular disease in ESRD patients is likely due to the many traditional risk factors that both these diseases share. In addition, we are learning more about other non-conventional risk factors unique to ESRD patients that promote and accelerate the atherosclerotic process that underlies most cardiovascular diseases.

In this chapter we will discuss the significant risk factors of cardiovascular diseases in ESRD patients. We will also discuss the treatment and intervention aspects of cardiovascular disease, especially in reference to hemodialysis patients.

2. Risk factors

2.1 Diabetes

Prevalence of diabetes in ESRD patients is about 50% (6). Both macrovascular and microvascular benefits of good glycemic control have been established for both type 1 and type 2 diabetes. Various prospective trials have tried to define a range of glycemic control (target hemoglobin A1c) with maximal cardiovascular and mortality benefit. It appears, at least in general population, that the benefits of better glycemic control follow a J shaped curve with worse outcomes for hemoglobin A1c both above and below the optimal range. Two large randomized trials failed to show any benefit in the reduction of major macrovascular disease in type 2 diabetic patients with intensive glycemic control.

In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial, there was no difference between the incidence of major cardiovascular event, cardiovascular mortality or all cause mortality between the intensive control group with median HbA1c 6.5 % and the standard group with median HbA1c 7.3%. Interestingly benefit was seen in the combined incidence of macrovascular and microvascular complications (HR 0.9, CI 0.82-0.98, P=0.01). (7) This was attributed to the reduction of nephropathy, a microvascular complication, in the intensive group.

In the ACCORD trial, which was another large prospective randomized study, 10,251 patients with a median HbA1c of 8.1 % was assigned to receive intensive therapy (target of 6% and below) or standard therapy (target of 7-7.9%). The primary outcome of interest was a composite of nonfatal MI, nonfatal stroke or death from cardiovascular cause. Though there was no significant difference in the primary outcome, the intensive-therapy group had an increased rate of death; the differences in mortality appeared within 1 to 2 years and persisted during the follow-up period. For ethical reasons, the intensive glycemic treatment was discontinued 17 months before the scheduled end of the study and the patients were switched to the standard glycemic regimen. (8)

Both of these studies did not include dialysis patients and it is not certain whether the conclusions can be directly applied to dialysis patients. Aggressive blood sugar control using multiple drug classes is not recommended. A target HbA1c of 7 % may be appropriate, more along the treatment line of the standard regimen in the ACCORD trial.

2.2 Hyperlipidemia

There is a wealth of data on the benefits of lowering of lipids especially with use of statins in both the primary and secondary prevention of cardiovascular disease. There have been multiple randomized studies which have shown reduced risk of cardiovascular events in patients with normal renal function and varying degrees of chronic kidney disease. Given these studies and other observational studies on dialysis patients, it was generally assumed hemodialysis patients would benefit from lipid lowering too. However, two recent randomized prospective trials (AURORA and 4D) studies did not conform to this notion. The studies failed to show any benefits in reaching the primary end points of cardiovascular death, non-fatal myocardial infarction and stroke in hemodialysis patients, with the use of statins and significant reduction in total and LDL cholesterol.

In the 4D(die deutsche diabetes dialyse) study; a multicenter randomized double-blind and prospective study, 1255 patients with type 2 diabetes who were on maintenance hemodialysis, were randomly assigned to receive either 20 mg of atorvastatin or placebo. The primary outcome measured was the composite of cardiovascular death, non-fatal myocardial infarction and stroke. After four weeks, atorvastatin successfully lowered LDL cholesterol (121 to 72 mg/dl) versus no change with the placebo (125 to 120 mg/dl). During a median follow-up of four years, 469 patients (37%) reached the primary end point; 226 assigned to atorvastatin and 243 assigned to placebo (RR, 0.92; 95% CI,0.77 to 1.1; *P=0.37*). Atorvastatin did not change the incidence of any single components of the primary end point with the exception of fatal stroke for which RR was 2.03, (95% CI,1.05 to 3.93; *P=0.04*). There was however a significant reduction in the combined cardiac events (RR,0.82;95% CI,0.81 to 1.55; *P=0.49*), but there was no reduction in the total mortality (RR,0.93; 95% CI,0.79 to 1.08; *P=0.33*). (9)

ESRD patients with diabetes have an average annual rate of incidence of myocardial infarction or death from coronary artery disease of about 8%, which is higher than any other cohorts included in prospective statin trials. Despite this high incidence and the significant lipid lowering effect with the atorvastatin, there was no reduction in the composite of cardiovascular death, non-fatal MI and non-fatal stroke in the 4D study. Though patients with LDL cholesterol over 190 mg/dl were excluded, subgroup analysis did not reveal any difference in the composite outcome for any level of LDL or for patients with prior history of coronary artery disease. Even more interesting was the increased occurrence of fatal stroke in the atorvastatin group compared to the placebo group (11). This is in contrast to the Collaborative Atorvastatin in Diabetes Study (CARDS) which reported that people with type 2 diabetes who received atorvastatin had a RR for stroke of 0.52 (95% CI, 0.31 to 0.89) compared with the placebo group (12).

The 4D study was the first large scale randomized study which did not show overall benefit from potent dose of statin and significant reduction in the LDL cholesterol, challenging the general assumption about the log-linear relation of level of LDL cholesterol and the risk of cardiovascular disease. The result is in accordance with observational data in patients on hemodialysis therapy that has not linked dyslipidemia with reduced survival; opposite trends have been noted in some. But 4D results are in contrast to an observational retrospective analysis of hemodialysis patients in the US Renal Data System (USRDS) Morbidity and Mortality Study, Wave 2, which indicated that the risk of cardiovascular death decreases by 36% in statin users compared with non-users (13). This finding demonstrates the difficulty associated with basing treatment decisions on uncontrolled observational studies.

Another study that had similar conclusions was the AURORA study (Rosuvastatin and Cardiovascular events in patients undergoing Hemodialysis). It was a well designed, large randomized prospective trial. It involved 2776 patients, 50 to 80 years of age on maintenance hemodialysis, who were randomly assigned to either rosuvastatin 10 mg daily or placebo. The combined primary end point was death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke. Secondary end points included death from all causes and individual cardiac and vascular events. During a median follow-up period of 3.8 years, 396 patients in the rosuvastatin group and 408 patients in the placebo group reached the primary end point (9.2 and 9.5 events per 1000 patient-years, respectively; hazard ratio for the combined end point in the rosuvastatin group vs. the placebo group, 0.96; 95% CI, 0.84 to 1.11; *P=0.59*). Rosuvastatin had no effect on individual components of the primary end point. There was also no significant effect on all-cause mortality (13.5 vs. 14.0 events per 100 patient-years; hazard ratio, 0.96; 95% CI, 0.86 to 1.07; *P=0.51*). This study further corroborated the lack of benefit with statin therapy in ESRD patients shown earlier by the 4D study. However there was no significant effect of statin in the incidence of stroke as seen in 4D study, but there was a marginal increase in the incidence of hemorrhagic stroke in pts with diabetes who were being treated with rosuvastatin (12 events vs. 2, P=0.03). (14)

This lack of benefit may be due to the underlying difference in the pathogenesis and outcome of cardiovascular events in ESRD patients from that in non-dialysis population. (15) More than 50% of cardiac mortality in ESRD patients is due to arrhythmias and sudden cardiac death. The gradual build up of atherosclerotic burden that lipid lowering prevents, might not be as important in the prevention of cardiovascular mortality in this vulnerable population. Similarly the plethora of recognized and unrecognized risk factors for cardiovascular disease in ESRD likely undermines the effect of modification of single risk factor.

In the light of available evidence the National Kidney Foundation recommends against routinely initiating statins for dyslipidemia in ESRD patients (16). However, there is no consensus on continuing or withdrawing statin therapy in dialysis patients already being treated. Both these studies did not specifically address this question. Similarly diabetic patients with severe dyslipidemia with LDL-C>190 mg/dl (who were not included in these studies) may have some benefits of lipid lowering and should not be precluded from statin treatment. (17)

2.3 Hypertension

2.3.1 Prevalence and association with cardiovascular morbidity and mortality

A large number (50-80%) of dialysis patients have hypertension. The relationship between HTN and cardiovascular disease is a complicated one. ESRD patients have a host of co-morbid conditions and risk factors for cardiovascular disease which makes defining the role of one risk factor difficult. It is especially true for risk factor like HTN the effect of which in the progression of cardiovascular disease is slow, insidious and requires a prolonged period of time.

While severe uncontrolled HTN is clearly associated with increased left ventricular mass, LV stiffness and pulse velocity all linked to increased cardiovascular morbidity and mortality (18) (19); the optimal BP target, the preferred agent and the role of dry weight reduction have not been well established.

Udayaraj et al examined the association of BP and mortality among 2770 patients who were on PD in U.K between 1997 and 2004. They looked at the relationship of BP to all-cause mortality using time-stratified models. The median follow up was 3.7 years within which 1104 deaths were observed. In fully adjusted analyses, greater BP (SBP, DBP, MAP and PP) was associated with lower mortality for follow up less than a year but increased mortality for follow up more than six years. However in the subgroup of patients placed on the transplant waitlist (TWL) within six months of starting renal replacement therapy, higher BP was not associated with decreased mortality in the first year. Higher BP was associated with increased mortality at year four or five; earlier for those not enlisted in the transplant list. The TWL patients likely represented relatively healthy and homogenous population who did not need extensive investigation to assess fitness for transplantation. This relatively healthy sub-group likely benefit from better BP control (20).

Similarly Mazuchi et al studied the relationship of pre-dialysis systolic and diastolic BP to all-cause mortality in 450 hemodialysis patients who had survived at least two years on HD. The observation period was initiated at the beginning of the third year. Mortality was analyzed during the first two years of follow-up (years 3 and 4 of HD; early mortality) and after the second year of follow-up (>5 years of HD; late mortality). In the multivariate analysis which included, pre-dialysis BP, demographic features and co-morbid conditions as independent variables, SBP and DBP were significantly associated with death. The adjusted total mortalities were U shaped. When early mortality was analyzed, low BP (DBP<74.5 mm Hg) was significantly associated with mortality. When late mortality was analyzed, only high BP (SBP>160 mmHg) was significantly associated with mortality (21).

While these observational studies suggest this reverse association of HTN and cardiovascular events one should draw conclusions only after careful statistical analyses. Low BP could be a surrogate marker for severe co-morbid conditions like heart failure independently contributing to cardiovascular death; similarly competing risk factors, chronic inflammation, malnutrition and survival bias can confound the effects of BP in uncontrolled retrospective studies. (22)

2.3.2 Management of HTN

There is still a significant element of uncertainty in the management of HTN in dialysis patients. While lowering BP may have benefits in reducing the cardiovascular morbidity and mortality in dialysis patients, certain epidemiological studies have shown increased mortality in the short term with lower BP. It is also not clear what BP targets should be achieved.

There is a growing indication that home BP monitoring may have a better role in therapeutic decision making than the pre-dialysis BP that is often used. In a recent open-labeled randomized control trial by Silva et al. the patients who were treated on the basis of home BP achieved better BP control than those who were treated on the basis of pre-dialysis BP at 6 months. However, there was no difference noted in the LV mass index , a surrogate for cardiovascular outcome in between the two groups (23).

2.3.3 Role of antihypertensives

There are two recent meta-analyses published on the role of antihypertensives in HD patients. The authors specifically were interested in the question whether the published randomized studies supported the observation about the increase in mortality seen with lowering of BP in some epidemiological studies. Both meta-analyses concluded that use of antihypertensives was not associated with increased mortality and there were benefits in cardiovascular outcomes (24).

The first meta-analysis by Agrawal et al (Cardiovascular protection with antihypertensive drugs in dialysis patients, *Hypertension.* 2009; 53:860) included five published randomized studies and one unpublished randomized study. The authors found that there was an overall benefit of antihypertensive therapy compared with the control (or placebo) group; the combined hazard ratio for cardiovascular events was reduced by 31% using a fixed-effects model and by 38% using a random-effects model. The hypertensive group had a pooled hazard ratio of 0.49 (95% CI: 0.35 to 0.67) inferring a greater benefit than the normotensive group, the pooled hazard ratio being 0.86 (95% CI: 0.67 to 1.12). Heterogeneity between normotensive and hypertensive group was significant *(P=0.006).* Of note, there was no increase in the all-cause mortality (25).

A limitation of this meta-analysis, as admitted by the authors, was the presence of publication bias. Low precision studies with effect estimates that did not show benefit, were missing. The trial discussed in this review did not specifically target a lower BP and whether the outcome benefits observed in this meta-analysis were attributable to blood pressure lowering or some non-hemodynamic effects of these drugs is unclear.

The second meta-analysis by Heerspink et al included eight randomized control trials and provided data for 1679 patients and 495 cardiovascular events. Weighted mean systolic blood pressure was 4.5 mm Hg lower and diastolic blood pressure 2.3 mm Hg lower in actively treated patients than in the controls. Blood pressure lowering treatment was associated with lower risks of cardiovascular events (RR 0.71, 95% CI 0.55-0.92; p=0.009), all-cause mortality (RR 0.80, 0.66-0.96; p=0.014) and cardiovascular mortality (RR 0.71, 0.50-0.99; p=0.044) than control regimens. The effects seem to be consistent across a range of patient groups included in the studies (26).

2.3.4 Choice of antihypertensives

ACEI/ARBs Vs Other Anti-Hypertensive agents: In the non-ESRD population, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) lead to reduction in LV mass, a validated surrogate endpoint for improved cardiovascular survival.

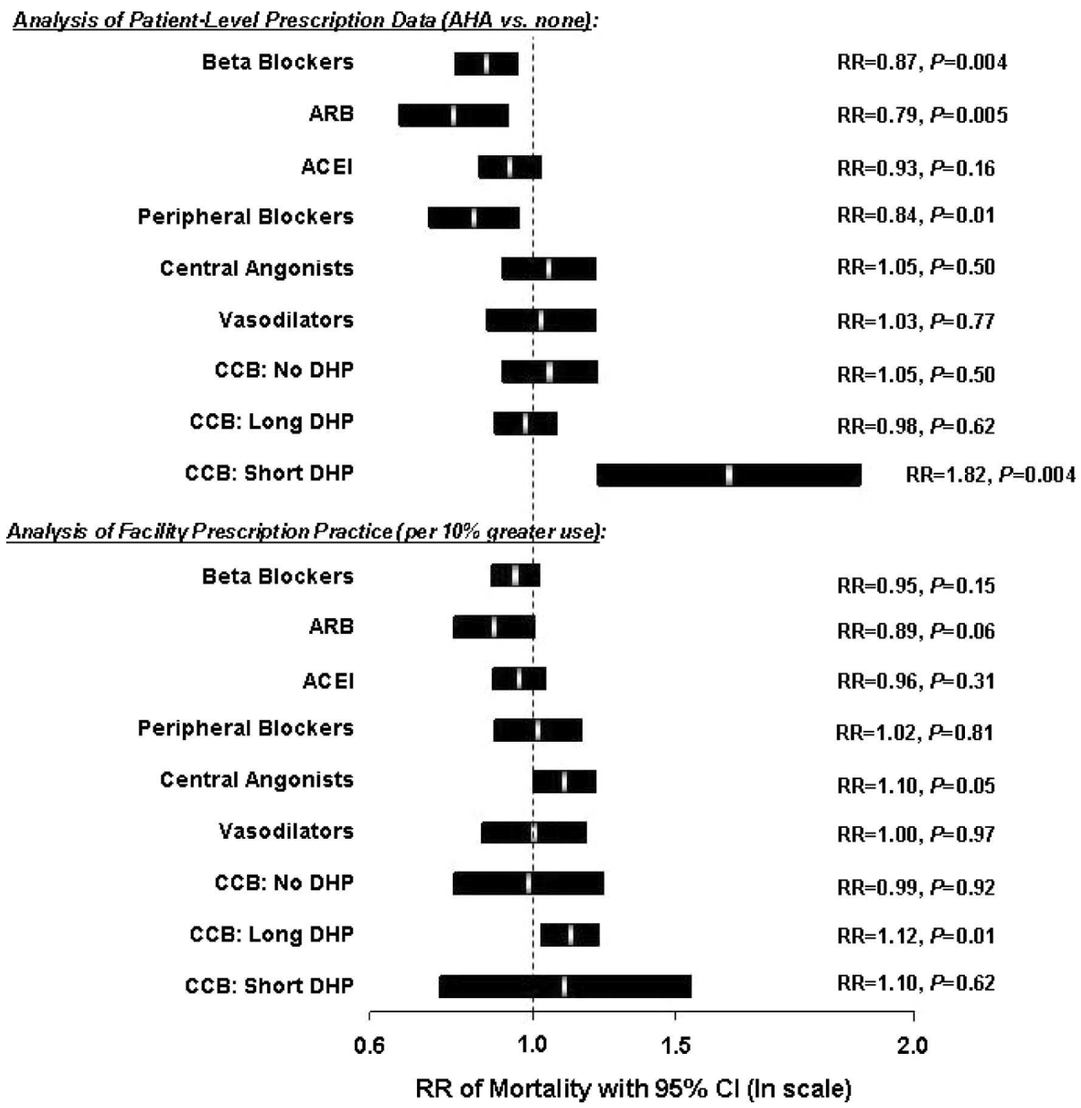

Fig. 1. Mortality Benefits with various Antihypertensive agents as seen in Dialysis Outcomes and Practice Pattern Study (DOPPS)
Prescription of antihypertensive agents to hemodialysis patients: time trends and associations with patient characteristics, country and survival in the DOPPS. Lopes AA, Young EW et al. Nephrol Dial Transplant 2009; 24(9):2809-16

LV hypertrophy is fairly common in ESRD patients and is probably multi-factorial contributed by chronic hypertension, volume overload, anemia and upregulation of renin-angiotensin system (27). Observational studies in dialysis patients have suggested blockade of RAS can lead to reduction in LV mass over and beyond the BP lowering effect (28). Though this LV mass reduction is known to translate as improved cardiovascular outcomes in general population, it remains to be proven whether such is the case in dialysis patients.
A recent meta-analysis by Tai DJ et al looked into the evidence for cardio-protective effects of ACEI/ARBs in dialysis patients. The primary outcome of interest was the composite of fatal and nonfatal CV events. The secondary outcomes were change in LV mass index,

change in systolic BP and change in LV ejection fraction. The authors pooled data from 8 randomized controlled trials which compared ACE/ARB to placebo or calcium channel blockers (22 out of 487 controls). There was no statistically significant reduction in the risk of fatal and non-fatal cardiovascular events (RR of 0.66, 95% CI 0.35-1.25; *P=0.2*), however there was a significant reduction in LV mass, with a weighted mean difference of 15.4 gm/m2 (95% CI 7.4-23.3;*P <0.001*) (29).

Dialysis Outcomes and Practice Pattern study (DOPPS) is a prospective observational study of practice patterns of prescription of antihypertensive agent associated with survival in twelve countries. The authors analyzed the usage of different class of antihypertensive among a total of 28, 513 hemodialysis patients enrolled in this study. There was a significant variation in the use of antihypertensive drug class in different countries. Facilities that treated 10% more patients with ARBs had, on average, 7% lower all-cause mortality, independent of patient characteristics and the prescription patterns of other antihypertensive medications (*P*=0.05). In the analysis of patient-level prescription data, the all-cause mortality was significantly ($P < 0.05$) lower for patients prescribed BBs, peripheral vasodilators and long-acting dihydropyridine CCBs and marginally significantly lower ($P = 0.06$) for patients prescribed ARBs. In contrast, the mortality risk was significantly higher for patients' prescribed short-acting dihydropyridine CCBs. Similar trends were observed for cardiovascular mortality. Beta-blockers (RR = 0.87, $P = 0.004$), ARBs (RR = 0.79, $P = 0.005$) and peripheral Vasodialtors (RR = 0.84, $P = 0.01$) were found to be significantly associated with lower risk of cardiovascular death in the analysis of patient level prescription. The risk of cardiovascular death was significantly higher for patients prescribed a short-acting dihydropyridine, a finding consistent with that for all-cause mortality (30).

2.3.5 BP control via lowering of dry weight

Challenging the dry weight to new targets has been an effective strategy to better control blood pressure in many chronic hemodialysis patients. PD patients with adequate volume control and daily or nocturnal hemodialysis patients typically have better BP control and require less antihypertensive treatment than conventional hemodialysis.

Kayikcioglu et al compared the benefit of non-pharmacologic therapy for control of LV mass among HD patients. In this cross-sectional study patients who were treated with salt and water restriction and dry weight reduction at one center were compared with patients who were primarily treated with antihypertensive treatment at another center. Despite similar systolic and diastolic BP, interdialytic weight gain and LV mass were lesser in the non-pharmacological group (31).

Similarly volume overloaded state has been linked to increased mortality in some observational studies. In a study cohort of 269 HD patients, volume overload defined as more than 15 % excess extracellular water (about 2.5 liters) as measured by body composition analyzer, was associated with increased mortality in a multivariate analysis (HR 2.1, *P=0.003*) (32).

However there is a subset of patients who develop significant intradialytic hypotension, cramps and lightheadedness or even paradoxical hypertension with more aggressive UF. In these patients reducing the dry weight would not be a favored approach as it would diminish compliance and even precipitate acute cardiovascular events. Identifying who would respond better to challenging dry weight and who would do better with antihypertensive agent alone would help the nephrologists in tailoring HD prescription to individual patient.

2.3.6 Relative plasma volume (RPV)

RPV can be a used as a marker of dry weight. It can be measured by continuously monitoring hematocrit during dialysis with commercially available equipment. Since it gives a real-time data on change in intravascular volume during hemodialysis it can be a valuable tool to adjust the rate and the amount of ultrafiltration. It would not only give a more objective assessment of dry weight but also the rate at which it can be achieved.

In a recent study by Sinha AD et al, 100 dialysis patients had their dry weight probed using continuous RPV monitoring during HD and were compared to 50 patients who served as time controls, over an 8 week period. RPV slopes were defined as flat when they were less than the median (1.33% per hour) at the baseline visit. The study found that flat RPV slopes suggest a volume-overloaded state for the following reasons: (1) probing dry weight in these patients led to steeper slopes; (2) those with flatter slopes at baseline had greater weight loss; (3) both baseline RPV slopes and the intensity of weight loss were found to be important for subsequent change in RPV slopes; and, most importantly, (4) RPV slopes predicted the subsequent reduction in interdialytic ambulatory systolic blood pressure. Those with the flattest slopes had the greatest decline in blood pressure on probing dry weight. Both baseline RPV slopes and the change in RPV slopes were important for subsequent changes in ambulatory blood pressure (33).

3. Hyperphosphatemia

Mineral bone disorder has been a focus of intense research in the last two decades and new evidence is unfolding linking this universal phenomenon in advanced CKD and ESRD to increased all cause and cardiovascular mortality. Most of the research has focused on increase in phosphorus as a risk factor for worse outcomes but there is increasing evidence that other mediators like calcium, PTH and vitamin D may contribute too.

An observational study by Ganesh SK et al. looked at the pooled data from two large random samples of prevalent hemodialysis patients in the early 1990s (n=12,833) and hyperphosphatemia was associated with increased risk of cardiac death. During a follow up period of 2 years after adjustments for patient demographics and non-cardiovascular co-morbid conditions, elevated phosphorus(>6.5mg/dl) was significantly associated with increased death from CAD (RR 1.41; $P < 0.0005$), sudden death (RR 1.2; $P < 0.01$), infection (RR 1.2; $P< 0.05$) and unknown causes (RR 1.25; $P < 0.05$) The RR of sudden death was also strongly associated with elevated Ca x PO4 product (RR 1.07 per 10 mg(2)/dl(2); $P < 0.005$) and serum parathyroid hormone levels greater than 495 pg/ml (RR 1.25; $P < 0.05$). (34)

In another observational study by Block et al, the authors looked at the relationship of serum calcium, phosphorus and PTH level with mortality and morbidity among 40,538 hemodialyis patients who had at least one measurement of calcium and phosphorus during the last 3 months of 1997. The sample was taken from Fresenius Medical Care North America Patient Statistical Profile system and the follow up time was 12-18 months. Several confounding variables were included in the analysis. Age, gender, race or ethnicity, diabetes and vintage (time since initiation of dialysis) were considered to represent "case mix". Multivariable adjustment included case mix plus body weight, URR (Urea Reduction Ratio), serum albumin, creatinine, predialysis BUN , bicarbonate, cholesterol, hemoglobin, ferritin and aluminium. After adjustment for case mix and laboratory variables, serum phosphorus concentrations > 5.0 mg/dl were associated with an increased relative risk of death.

(p< 0.001). Higher adjusted serum calcium concentrations were also associated with an increased risk of death, even when examined within narrow ranges of serum phosphorus. Moderate to severe hyperparathyroidism (PTH concentrations above _600 pg/ml) was associated with an increase in the relative risk of death, whereas more modest increases in PTH were not. (35)

Both these observational studies made adjustments for many confounding variables but given the complexity and interactions of multiple risk factors a definitive relationship between mineral metabolism disorder and cardiovascular or all-cause mortality in hemodialysis patients is difficult to establish. For example, hyperphosphatemia is often associated with non-compliant behavior and nutritional status (increased serum phosphate with higher dietary intake and with higher lean body mass) of the patient, both of which can affect patient morbidity and mortality.

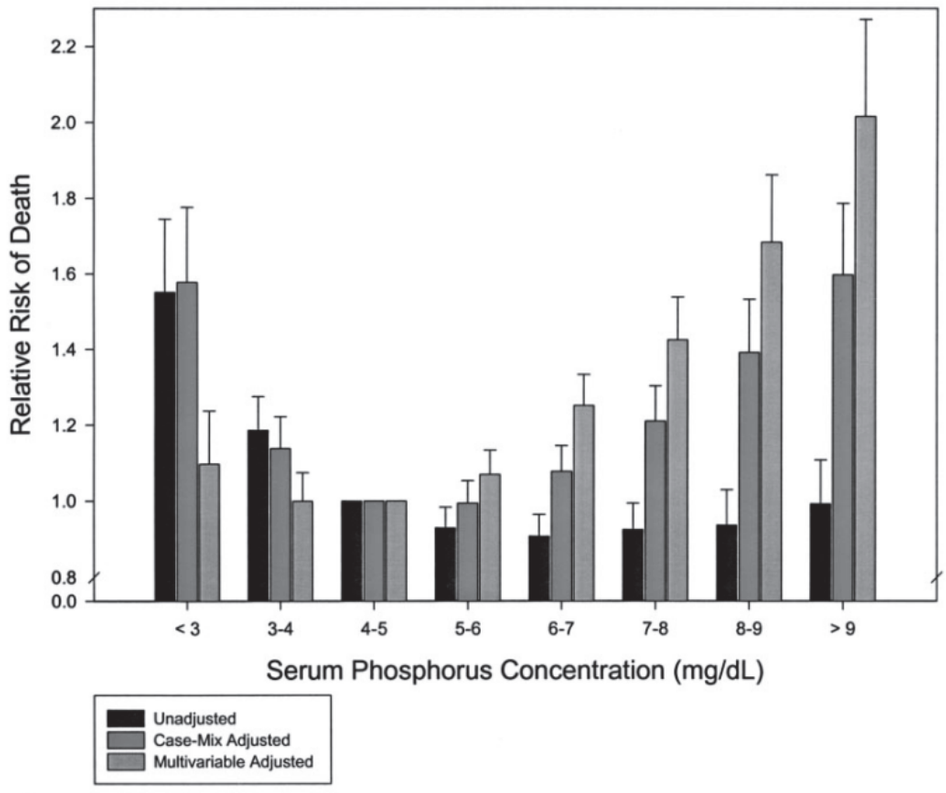

Fig. 2. Mortality Risks with Hyperphosphatemia in Hemodialysis patients.
Mineral Metabolism, Mortality, and Morbidity in Maintenance Hemodialysis. Block GA, Chertow GM et al. J Am Soc Nephrol 15: 2208–2218, 2004 (adopted)

3.1 Role in the pathogenesis of cardiovascular disease

Studies of various in vivo animal models and in vitro in tissues from patients, hyperphosphatemia have been shown to promote osteoblastic transformation of vascular smoothe muscles and matrix calcification in blood vessel wall. Similar process probably results in the vascular calcification seen in CKD and ESRD patients. However there is controversy as to whether vascular calcification itself is the cause for vascular dysfunction or

whether it is an epiphenomenon to another common underlying process leading to vascular dysfunction.

Mc Cullough et al. in his recent paper proposed that vascular medial calcification seen in advanced CKD patients starts as intimal atherosclerotic lesion with cholesterol deposition. Based on pathological evidence and existing studies he believed Monckeberg sclerosis to be a manifestation of accelerated atherosclerosis in patients with CKD and a variant of advanced, calcified atherosclerosis with little inflammation and no clear evidence of independent, non-atherogenic process. High phosphate would promote osteoblastic transformation of vascular smooth muscle cells that already contained lipid deposits and enhanced deposition of calcium-hydroxyapatite crystals at the atherosclerotic plaque or in the lipid deposits in the vessel wall. In this model phosphate would promote medial calcification as part of an accelerated atherosclerotic process. (36)

In direct contrast, Drueke in his paper argued that medial calcification is a distinct disease entity unrelated to atherosclerosis. He believed medial calcification to be directly related to pathophysiological disturbance in mineral metabolism rather than to the conventional risk factors associated with atherosclerotic disease. He suggested that medial calcification can be induced experimentally in animals that are fairly resistant to atherosclerosis (such as wild type strains of rats and mice) by creating chronic renal failure and feeding vitamin D or its derivatives. Medial calcification can occur in the absence of intimal calcification in some experimental animal models. Whether this applies for humans is not known. Next, he cited a study by London et al, which showed using intravascular ultrasonography that hemodialysis patients with intimal atherosclerotic calcification have a higher risk of mortality than those with predominantly medial calcification. Based on these and other observations he concluded that medial calcification is different in origin and has different clinical implications than intimal calcification of atherosclerosis. (37)

Despite the controversy about the origin of medial calcification, there is a consensus on the role of hyperphosphatemia in promoting this accelerated calcification. Hyperphosphatemia leads to increased calcification and vascular stiffness. The resultant increase in aortic stiffness, aortic pulse wave velocity and left ventricular hypertrophy contributes to the high rate of cardiovascular morbidity and mortality in these patients.

4. Cardiovascular morbidity and mortality

Dialysis patients have a very high rate of mortality. In 2007, the adjusted annual mortality of dialysis patients in the United States was 19%. Bulk of this mortality is attributable to cardiovascular causes which contributes to about 40-45% of all deaths (38). Among cardiovascular causes, Sudden Cardiac Death (SCD) is the most common. It alone was responsible for 62 % of total cardiovascular deaths and 27 % of all cause deaths (39).

4.1 Sudden Cardiac Death (SCD)

4.1.1 Pathogenesis

We do not have a complete understanding of why SCD is such a disproportionate contributor to cardiovascular mortality in dialysis patients. The most common immediate cause for SCD is a ventricular tachyarrhythmia. In general population, these arrhythmias are often triggered by critical ischemia in a previously injured and often scarred myocardium. The wide prevalence of Left ventricular hypertrophy, anemia, the rapid fluid and electrolyte

shifts during hemodialysis, endothelial dysfunction, myocardial interstitial fibrosis and low myocardial tolerance to ischemia possibly contribute to the high frequency of these arrhythmogenic events in dialysis patients (40).

Like in general population, obstructive coronary artery disease is likely a substrate for SCD in dialysis patients. It alone however is not a sufficient reason for the high incidence of SCD. This is supported by the observation that revascularization (both surgical and percutaneous) does not significantly reduce SCDs in the initial years. Data from USRDS Cardiovascular Special Studies Center show a rather unexpectedly high mortality after both CABG (2 year mortality of 43% for CABG using internal mammary graft) and PCI (2 year mortality of 48 % for bare metal stent) in the initial years. The annual mortality attributed to arrhythmias was 8.5% and 7 % for CABG and PCI respectively (41).

In general population, ventricular arrhythmia is the predominant fatal rhythm leading to SCD. Sustained monomorphic ventricular tachycardia and ventricular fibrillation are the most common ventricular arrhythmias in these terminal events. Myocardial scar or fibrotic tissue due to prior ischemic injuries and diminished LV function are the substrates while acute myocardial ischemia is the triggering event for these malignant arrhythmias (42). While this pathogenic mechanism is likely shared by hemodialysis patients there are probably additional mechanisms in play, like those mentioned earlier.

4.1.2 Incidence

The incidence of sudden cardiac death is not uniform over time. The risk increases with patient age and duration of dialysis. Data from USRDS study of all incident US dialysis patients (1995-1999), the rate of cardiac arrest progressively increased from 93 events per 1000 patients-years at 2 yrs after dialysis initiation to 164 events per 1000 patient-years 5 year after dialysis initiation (43). Interestingly, the rate of cardiac arrest in hemodialysis patients when compared to that of PD patients is significantly higher in the first 3 months (HR of 1.5), but rates are similar at 2 years and lower after 3 years (44). There is a temporal trend linking certain days of the week with more SCDs among dialysis patients than others. On Sunday preceding the dialysis on Monday (after a weekend without dialysis) the risk of SCD is three times the average risk. Mondays for patients who dialyze on Tuesdays hold similar risk. (45)

4.1.3 Prevention of SCD

4.1.3.1 B-Blockers

B-Blockers have been shown to be an effective drug for the primary prevention of SCD in non-dialysis patients and improve outcomes in patients with congestive heart failure. The USRDS Wave 3 and 4 studies showed decreased risk of death in patients who were on B-Blockers. Similarly in a randomized study in dialysis patients with dilated cardiomyopathy, there was a 68 % reduction in cardiovascular mortality ($P<0.0001$) and a trend towards reduction in the incidence of sudden death (HR 0.76, $P=0.12$) (46). There is however no randomized prospective study on the use of B-blockers for prevention of SCD in HD patients with preserved left ventricular function.

4.1.3.2 ACEI/ARBs

ACE inhibitors and ARBs have been shown to reverse ventricular hypertrophy, help with ventricular remodeling and have favorable effect on cardiovascular mortality over and

beyond BP control in multiple prospective studies in non-dialysis patients. As previously discussed some observational studies have suggested survival benefits with the use of ACEI and ARBs compared to other antihypertensives. But there is no large prospective study on the benefits of ACE inhibitor or ARBs on cardiovascular mortality and in particular, on the incidence of SCDs in dialysis patients.

4.1.3.3 Implantable defibrillators

Role in primary prevention

There is a significant benefit in the primary prevention of Sudden Cardiac Death with the use of Implanted Cardioverter Defibrillator (ICD) in both ischemic and non-ischemic heart failure with low ejection fraction (EF<35%) (47) (48). The trials (MADIT1, MADIT 2, DEFINITE, MUST) that established this benefit however either excluded patients who were on dialysis or did not provide data on renal function of the subjects. While prospective randomized study on the benefits of ICDs in ESRD patients is lacking, the reduction in mortality seen with ICD use in non-dialysis patients is compellingly high (in the range of 30 % over a period of 20 months) and hence ICD should not be withheld on HD patients with low ejection fraction. However it is likely to be beneficial only if the patient is estimated to survive beyond a year and has a reasonable quality of life.

Impaired LV function with low ejection fraction (EF) increases the risk of SCD but many HD patients with relatively preserved LV function suffer SCDs. These patients clearly did not meet the requirement for ICD placement for SCD primary prevention. A retrospective study showed that 71 % of dialysis patients who died of sudden cardiac death had either normal left ventricular function or mild-moderate dysfunction (49). This reinforces the idea that there might not be one single predominant risk factor for sudden cardiac death in hemodialysis patients and interventions to reduce SCD have to be made at multiple levels.

Role in secondary prevention

Patients who survive sudden cardiac death or have had life-threatening ventricular arrhythmias are strongly recommended to have ICD implantation. ICD implantation has been found to be significantly superior to antiarrhythmic drug treatment and non-dialysis patients routinely get ICD implantation after such an event. However, ICD placement seems to be under-utilized in dialysis patients. In a retrospective study by Herzog et al, among ESRD patients who were hospitalized from 1996 to 2001 for cardiac arrest/ventricular fibrillation only 7.6 % of dialysis patients had ICD implantation. ICD implantation was independently associated with a 42% reduction in death risk [relative risk 0.58 (95% CI 0.5-0.66) (50).

Overall benefit and complications of ICD placement

In a meta-analysis by Sakhuja et. al, the authors investigated the mortality outcome of ICD placement in relation to renal function; particularly, the exposure of interest was dialysis. After initial screening, the study analyzed 6 retrospective cohort and 1 case-control studies (January 1999 to July 2008). Patients on dialysis had a 2.7 higher risk of mortality than patients not on dialysis despite the presence of ICDs. The authors suggested that despite the high risk of SCD in dialysis patients, there are other significant causes of death in dialysis patients that undermine the survival benefit offered by interventions aimed at reducing SCDs. Surprisingly, 4 out of 27 deaths in dialysis patients with documented cause were due to arrhythmias. This was attributed to inappropriately high defibrillation threshold for the ICD device (51). In another study, Wase et al found that >35% of dialysis patients had elevated defibrillation threshold compared to <10 % of patients without any CKD. (52)

ICD placement in hemodialysis patients is associated with higher rate of immediate (bleeding) and long-term complications (including infection and central venous stenosis/occlusion). This has to be balanced against the survival benefit ICD can potentially offer to dialysis patients. Life expectancy for the hemodialysis patient also needs to be considered when making any intervention decisions. The 2008 guidelines consider primary prevention ICD therapy to be contraindicated in patients who do not have "a reasonable expectation of survival with an acceptable functional status for at least 1 year". In a decision model analysis that weighed the potential risks and benefits, implantation of defibrillator for primary prevention was favored only for dialysis patients who were younger than 65 years of age. (53)

The treatment guidelines at this time are not very clear and based on either observational studies with conflicting conclusions or on randomized studies for non-dialysis patients. The Implantable Cardioverter Defibrillator in Dialysis patients (ICD2) study will be the first randomized prospective trial which will likely define the benefits of ICD in the prevention of Sudden Cardiac Death in Dialysis patients (54). Until we have results from this study or other randomized prospective study, an individualized treatment decision has to be made for each dialysis patient.

4.1.3.4 External cardioverter defibrillators

There are mixed conclusions among available studies about the benefits of having on-site defibrillators in the dialysis units. Majority of sudden cardiac deaths do not occur during delivery of dialysis. For those who have life-threatening arrhythmias during dialysis, defibrillators likely do prevent sudden death. These patients will likely have repeat arrhythmogenic events and unless the primary cause is identified and addressed, the mortality tends to be exceptionally high.

KDOQI guidelines recommend basic life support (cardiopulmonary resuscitation) training for dialysis unit staff and on-site capability for external cardiac defibrillation either with an automated external defibrillator (AED) or standard manual defibrillator (55).

4.2 Ischemic heart disease

4.2.1 Clinical signs and symptoms

Ischemic heart disease is very common in hemodialysis patients. Obstructive coronary artery disease can most commonly present with chest pain and exertional dyspnea similar to that in non-dialysis patients. In addition, the symptoms can be chest pain and hypotension during dialysis. A significant minority of patients can have silent myocardial ischemia and myocardial infarction. Arrhythmias and sudden cardiac death can occur secondary to myocardial ischemia during dialysis or in the interdialytic period. Anemia and left ventricular hypertrophy which are very prevalent among dialysis patients can exaggerate the ischemic effects of obstructive coronary lesion by increasing the myocardial oxygen demand.

4.2.2 Screening

Beyond a complete history and physical examination and a baseline EKG at the initiation of dialysis, the role of screening for coronary artery disease (CAD) in dialysis patients is not established. KDOQI guideline recommends a baseline echocardiogram at the initiation of dialysis and every 3 yrs after (56). The evidence behind this recommendation is rather weak.

4.2.3 Evaluation and diagnosis of ischemic heart disease

Evaluation of atherosclerotic coronary artery disease is done as part of ongoing care for dialysis patients depending on the symptoms and risk stratification. If the patients develop classical angina/ angina equivalent symptoms, recurrent hypotension, CHF unresponsive to dry weight changes or inability to achieve dry weight because of hypotension, significant LV dysfunction with EF< 40 %; evaluation for CAD is recommended (57).

The other groups of dialysis patients who need periodic evaluation for CAD are discussed below (58).

- Patients with history of coronary artery disease with complete coronary surgical revascularization (CABG) are recommended to have initial evaluation for CAD in 3 years and then annually thereafter. Patients with incomplete coronary revascularization are recommended to have this evaluation every year.
- Diabetic patients on transplant list are recommended to have evaluation for CAD annually.
- Patients on transplant list deemed high risk on Framingham risk score (>20 % per 10 yr cardiovascular event rate) are recommended to have annual evaluation for CAD.
- Patients on transplant list not considered high risk are recommended to have evaluation for CAD every three years.
- Patients on transplant list with known CAD (not revascularized or vascularized with PTCA/coronary stent) should have annual evaluation for CAD.

4.2.4 Choice of diagnostic modalities

A variety of non-invasive stress test is available. Part of the choice and usefulness of such test is dependent on the institutional expertise. Stress test however should not be a routine diagnostic test for all dialysis patients. EKG and echocardiogram can be fairly useful and informative in many stable, low risk dialysis patients who do not have a history of previous coronary artery disease. Similarly, in some patients with appropriate risk and prior history of coronary artery disease the pretest probability of a significant coronary artery disease is high enough to warrant a coronary angiogram without a need for non-invasive stress test.

Exercise EKG is not recommended because of poor exercise tolerance and a high prevalence of left ventricular hypertrophy among dialysis patients. Exercise echocardiography has similarly been found not suitable for a majority of dialysis patients (59). There have been concerns about the validity of nuclear scintigraphy on the ground that it could potentially be influenced by the abnormal metabolic milieu in renal failure.

Dobutamine stress echocardiography is a fairly reliable diagnostic test. In a study of 125 dialysis patients, all of them had coronary angiography, dobutamine stress echocardiography, and resting and exercise electrocardiography. Independent predictors of severe coronary artery disease (defined as luminal stenosis >70 percent by visual estimation in at least one epicardial artery) were a positive stress echo result (Odds Ratio of 23, 95% CI 6-88) or an abnormal resting EKG (OR 7, 95% CI 2-34). Overall, the sensitivity and specificity of dobutamine stress echocardiography was approximately 75 percent (60). The additional advantage of this test is that with the pre-test imaging we can get information on left ventricular ejection fraction, valvular disease, pulmonary artery pressure, volume status and any associated pericardial disease. The risk of arrhythmias, typically atrial fibrillation, (2-4 % versus 0.5% in non-dialysis patients) is however higher with this test (61).

Stress test using vasodilator (adenosine, dipyridamole) and imaging with nuclear scintigraphy is another widely used and perhaps equally reliable test. Though available

studies suggest that vasodilator-induced stress nuclear scintigraphy may be less sensitive than dobutamine stress test in detecting obstructive CAD in dialysis patients, it is used in many centers with equally good results. In a recent head to head study comparing dobutamine echocardiography with dipyridamole myocardial perfusion imaging in 102 dialysis patients, the latter test was found to be more specific and accurate for the diagnosis of coronary artery disease. Positive test result of myocardial perfusion imaging was predictive of fatal and non-fatal coronary events. Surprisingly, no association was observed between abnormalities on dobutamine echocardiography and patient outcome (62).
Given the lack of consistent conclusion among available studies, the choice between dobutamine echocardiography and myocardial perfusion imaging should be guided by available resource and institutional expertise.

4.2.5 Acute coronary syndrome

Like in non-dialysis patients acute coronary syndrome is diagnosed with a triad of clinical signs and symptoms, EKG changes and serum biomarkers of myocardial injury. A significant number of acute coronary events can be asymptomatic or present with atypical symptoms which may be overlooked. Dyspnea and pulmonary edema due to acute MI can be overlooked as "volume overload" in a dialysis patient; hypotension due to shock, often during dialysis may be falsely attributed to transient intradialytic hemodynamic change. This may be one of the factors for the dismally poor prognosis of acute myocardial infarction in dialysis patients. The estimated survival is only about 35 % in 2 years.

4.2.5.1 Diagnosis

Dialysis patients have a high prevalence of coronary artery disease. Outcome of an acute coronary event is time dependent and delay in diagnosis can be the biggest impediment in lowering the subsequent mortality. Index of suspicion for acute coronary event should be high among the physicians involved in the care of dialysis patients. The diagnosis as mentioned earlier is based on a triad of clinical symptoms/signs, dynamic EKG changes and elevation of cardiac biomarkers.
The EKG changes of ischemia may be difficult to interpret on a background of a pre-existing ST changes of LV hypertrophy. Similarly cardiac biomarkers may be falsely elevated (false positive) in ESRD patients. Out of the commonly used markers, Troponin I (cTnI) has been found to be a more specific marker of cardiac injury compared to both Troponin T (cTnT) and CK MB. In a prospective study of 817 consecutive patients (including 51 dialysis patients) with possible acute myocardial infarction, cTnI serum level was found to be independent of creatinine clearance while CK-MB and myoglobin correlated with creatinine clearance (63).

4.2.5.2 Treatment

After a diagnosis of acute coronary syndrome has been established, the treatment should be similar to that in non-dialysis patients. Careful attention should be paid when using certain drugs that have altered clearance in renal failure.
Patients with acute ST-segment elevation MI should receive acute reperfusion therapy preferably Percutaneous Coronary Intervention (PCI) with similar time urgency as in non-dialysis patients. When primary PCI is not available, thrombolytics should be used. The risk of significant hemorrhage with thrombolytic therapy is more than in non-dialysis patients.
Aspirin, Clopidogrel, B-Blocker and ACE Inhibitor are recommended both in both acute myocardial infarction and for the secondary prevention of future ACS. There is no

randomized controlled trial to support this recommendation in dialysis patients but these therapies have been found to be effective in retrospective observational studies in all stages of CKD (64,65). Similarly Glycoprotein 2b/3a inhibitor should be considered in dialysis patients like in non-dialysis patients. These antiplatelet agents have been shown to increase survival in high risk NSTEMI and STEMI patients undergoing PCI. These drugs act by inhibiting glycoprotein GP 2b/3a, an integrin in platelet membrane, necessary for platelet aggregation. The risk of bleeding with these drugs is higher in dialysis patients because of the underlying uremic platelet dysfunction. When used, Abciximab and Tirofiban should be considered preferred agents, since no dosing changes are required for Abciximab, and dialysis-specific dosing recommendations are available for Tirofiban. Abciximab is typically used for PCI as clearance of this drug is not affected in dialysis patients.

Hemodialysis is often deferred for patients who are admitted with an acute myocardial infarction. There is no good evidence to support this practice. The timing of dialysis should be individualized after taking into account the patients' volume / electrolyte status. With the use of thrombolytics, heparin and different platelet agents the risk of bleeding from the AV fistula/graft site may be increased. Significant hypotension should be avoided because it can put additional strain on the myocardium and also can increase the risk of stent thrombosis.

4.2.6 Chronic coronary artery disease

The medical management of stable CAD is not different than in the general population. B-Blockers are indicated to reduce afterload and myocardial oxygen demand; ACE Inhibitors to reduce afterload and for their favorable effects on ventricular remodeling; antiplatelet agents to inhibit platelet aggregation in unstable atherosclerotic plaques and statins for LDL lowering and plaque stabilizing effect. All of these drugs have been shown to have strong beneficial effects on progression of CAD and recurrence of acute myocardial infarction in multiple well-designed randomized prospective trials. But dialysis patients have traditionally been excluded from these studies, so while the conventional wisdom probably applies to dialysis patients too, some uncertainties still exist.

4.2.7 Coronary revascularization

4.2.7.1 Percutaneous Coronary Intervention (PCI) Vs Coronary Artery Bypass (CABG)

As mentioned earlier in the chapter, the mortality rate after coronary revascularization is very high (2-year 48 % mortality after bare metal stents and 43 % after coronary artery bypass surgery using internal mammary graft)(38). There have been no prospective randomized studies that have compared CABG and PCI head-to-head. Observational studies have mixed conclusions about the relative benefit of one revascularization procedure over the other. Diabetes patients who undergo CABG using internal mammary graft in general tend to do better than diabetic patients undergoing percutaneous coronary interventions (PCI).

Herzog et.al looked at the USRDS database for the long-term survival of dialysis patients undergoing coronary artery bypass comparing it to dialysis patients (n=10,941) who received drug-eluting stent (DES) in 2004-2006. The authors found DES patients had better survival at 12 months, but after 18 months CABG patients had better outcome. CABG patients receiving internal mammary grafts (68% of CAB pts, n=2356) did significantly better than those without (66). Similarly in a meta-analysis by Nevi F et al. which included 17

retrospective cohort studies from 1977 to 2002, there was no difference in mortality in patients who received CABG compared to PCI. However there was a higher mortality for CABG patients within the first 30 days compared to PCI (67). The authors pointed out that the baseline differences among the patient groups were adjusted for final analysis in only four of the studies. Given the lack of randomized prospective trial and methodological flaws with the available retrospective studies, no definite conclusion can be drawn in regards to preference of one revascularization procedure over the other.

4.2.7.2 Drug Eluting Stent (DES) Vs Bare Metal Stent (BMS)

There is again no randomized prospective trial to establish the superiority of one over the other. Many trials of Drug Eluting Stent have excluded dialysis patients. In a single center study by Ayoma et al in Japan, 88 consecutive HD patients who received sirolimus-eluting stent were compared with 78 patients who received bare-metal stent in the preceding year. There was no difference in the rate of restenosis, the primary endpoint, at 6-8 months (68). But in another single center retrospective study from Japan, there was less late in-stent stenosis and better major cardiovascular event profile with sirolimus-eluting stent. Particularly, all cause mortality and need for revascularization was lower in the DES group (69). It is difficult to draw conclusions based on small single-center non-randomized study and whether Drug eluting stent is really superior to bare-metal stent in dialysis patients is still not settled.

5. Stroke/transient ischemic attack (TIA)

Stroke is the third leading cause of death in the United States and other developed countries. Dialysis patients have a markedly elevated risk of atherosclerotic cerebrovascular disease, the substrate for stroke and transient ischemic attack. Data available for hospitalized ESRD patients show the rate of stroke to be 5-10 fold higher compared to non-ESRD patients (70). However the risk factors for stroke in dialysis patients have not been well studied and the recommendations for prevention and treatment are largely based on studies done on non-dialysis patients.

5.1 Risk factors

Hypertension, age, diabetes, malnutrition and ethnicity have been found to be associated with risk of stroke in available studies. Seigel et al. conducted a retrospective study on data collected by USRDS looking at the relationship of black ethnicity, BP and markers of malnutrition with elevated risk of stroke. Adult ESRD patients without a history of stroke or transient ischemic attack were considered for analysis. The primary outcome was hospitalization or fatal stroke. The rate of incident stroke was 33/1,000 person-years in the study sample. In a Cox proportional hazard model, after adjustment for age and other patient characteristics, three markers of malnutrition were associated with the risk of stroke—serum albumin (per 1 g/dl decrease, hazard ratio [HR] = 1.43), height-adjusted body weight (per 25% decrease, HR = 1.09), and a subjective assessment of undernourishment (HR = 1.27)—as was higher mean BP (per 10 mmHg, HR = 1.11). The association between black race varied by cardiac disease status, with blacks estimated to be at lower risk than whites among individuals with cardiac disease (HR = 0.74), but at higher risk among individuals without cardiac disease (HR = 1.24). In exploratory analysis looking at laboratory parameters and their relation to stroke risk there was no relationship between

baseline cholesterol (per 10 mg/dl increment, HR = 1.00), serum calcium, phosphorous, or parathyroid hormone and incident stroke. Patients with severe anemia with hemoglobin (<9 g/dl) were at a 22% higher risk for stroke (HR = 1.22, 95% CI = 1.00 to 1.49) (71).
While severe anemia has been considered a risk factor in observational studies, there probably is a significant risk associated with attempting to normalize hemoglobin too. In the TREAT study, the incidence of stroke was significantly higher in the treatment group receiving darbopoetin compared to the placebo group(HR 1.92; 95 % CI 1.38-2.68; P< 0.001). The median Hb concentration achieved was 12.5 gm % and 10.6 gm % in the Darbopoetin and the placebo group respectively. The primary end-point (death or non-fatal cardiovascular event) was not different between the two groups. (72)

5.2 Prevention and treatment

In general, the prevention and treatment of stroke should be along the lines of recommendations for general population. Antiplatelet agent is fairly safe and can be used for both primary and secondary prevention of stroke. The risk of stroke and need for anticoagulation with Coumadin can be assessed using the standard CHADS2 score. INR targets should be in accordance with general guidelines. The treating physician should also keep in mind the increased propensity of dialysis patients for bleeding.
The other issue is the safety and efficacy of thrombolytic therapy in acute stroke patients who present within three hours of symptom onset. In non-dialysis stroke patients thrombolytic have been shown to increase resolution of neurological deficit and improve functional outcomes. This has been validated in multiple studies. But in dialysis patients there is no prospective trial to examine the benefit and risk of thrombolytic. In the original NINDS study, the ESRD status and the renal function were not mentioned for the study population (73). While no prospective data is available for ESRD patients, guidelines from AHA do not make distinction between dialysis and non-dialysis patients for thrombolytic indication in acute stroke.

6. Peripheral vascular disease

PVD is very common in both diabetic and non-diabetic dialysis patients. Almost 15% of incident dialysis patients have a clinical diagnosis of PVD (74). The treatment and secondary prevention of PVD follow the recommendations for general population although the evidence behind this approach is weak.

6.1 Diagnosis

All dialysis patients should have a thorough examination looking for evidence of peripheral vascular disease. History of claudication, poor wound healing and weak peripheral pulse or non-healing ischemic ulcers on exam should be the basis of a diagnostic work-up. Further evaluation is done non-invasively with Ankle Brachial Index (Ankle systolic blood pressure divided by brachial systolic blood pressure), Duplex and if indicated with arteriogram. ABI is a useful screening test in most instances but can be falsely elevated due to heavy vascular calcification in dialysis patients.
Prevention begins with risk factor modification like in any other atherosclerotic disease. Smoking cessation, lipid lowering, glycemic control, HTN control and use of antiplatelet agents are important in primary prevention. The relative role of these risk factor modifications on the outcome, after PVD has already set in; is not known.

6.2 Therapy

Revascularization procedures do not have as good an outcome as in non-dialysis patients. Indications for revascularization are similar to general population, those being severe claudication, rest pain and critical leg ischemia with non-healing ulcers.

Angioplasty is preferred for amenable stenotic lesions. In a study by Kumada et al. the immediate results of angioplasty in 118 HD patients and 108 control subjects were equally good. Dialysis patients seem to have more fem-popliteal atherosclerotic lesions than iliac lesions (75). Formal surgical revascularization with bypass grafts is needed for many dialysis patients. The problems with revascularization include high peri-operative and one year mortality, delayed wound healing, loss of limb despite patent graft, prolonged hospitalization and poor rehabilitation (76). Because of all these issues, some experts recommend primary amputation, especially for patients who are non-ambulatory, bedridden and have extensive tissue necrosis and infection. Revascularization with either percutaneous or surgical intervention can be beneficial in selected dialysis patients who are ambulatory or use the affected limb for weight bearing or for transfer purpose.

7. Conclusion

Cardiovascular disease is very common in ESRD patients and is the major cause of morbidity and mortality. While we partly understand the role of traditional risk factors in the pathogenesis of cardiovascular disease, much remains to be defined as to how modification of these would translate into improved survival. Similarly more studies are needed to define the role of other non-traditional risk factors like calcium, phosphorus, anemia. Large randomized controlled trials specifically designed to answer these questions are awaited.

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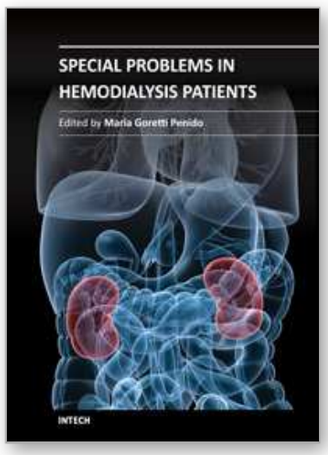

Special Problems in Hemodialysis Patients

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This book provides an overview of special cases in hemodialysis patients. Authors have contributed their most interesting findings in dealing with patients suffering of other diseases simultaneously, such as diabetes, cardiovascular disease and other health problems. Each chapter has been thoroughly revised and updated so the readers are acquainted with the latest data and observations in these complex cases, where several aspects are to be considered. The book is comprehensive and not limited to a partial discussion of hemodialysis. To accomplish this we are pleased to have been able to summarize state of the art knowledge in each chapter of the book.

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