Management of Cardiovascular Risk Factors in Dialysis-Dependent End Stage Kidney Disease

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INTRODUCTION

Over nineteen million patients face progressive chronic kidney disease (CKD) in the United States.[1] The preferred treatment with proven clinical outcomes for end stage kidney disease (ESKD) patients remains kidney transplantation. Unfortunately, the number of kidney transplants has reached a plateau in recent years with a simultaneous increase in the number of patients awaiting transplantation and the length of time they wait.[2] For the majority of these patients, renal replacement therapy is the initial treatment while they await transplantation, during which time they face many barriers. One medical barrier is cardiovascular disease (CVD), which is reported to be 20 times higher than the general population, accounting for 40% of deaths of US dialysis patients.[3] By comparison, a 30-year-old dialysis patient bears nearly the same risk as an 80-year-old non-dialysis patient for CVD-related death.[4] The complete etiology of the increased risk of CVD is not fully understood and is likely a combination of both traditional and novel risks factors. The traditional risk factors include non-modifiable (age and sex) and modifiable (dyslipidemia, diabetes, smoking, and hypertension) components. This review will discuss ways to address the latter modifiable risk factors.

Identification of high risk individuals with the use of assessment tools such the Framingham Risk Score (FRS-CVD) and the ASCVD (American Heart Association (AHA)/ American College of Cardiology (ACC) 2013) have been validated in the general population, provide guidance on optimal therapy for primary prevention using lifestyle modifications and pharmacological interventions.[5] While proposals are ongoing for the addition of renal function to current scores or developing new scores, the current use of these tools in CKD and ESKD patients has limited applicability.[6–9] The Pan American Health Organization/World Health Organization (PAHO/WHO) has developed a calculator that includes glomerular filtration rate (GFR) but further studies are needed to assess its applicability.[10] Even without the use of these tools, evidence has established that decreasing GFR increases CVD and mortality.[11–14] Proposed novel risk factors that may be contributing to this higher incidence of mortality and CVD unique to CKD and ESKD population include anemia, volume status, mineral metabolism, electrolyte disarray, albuminuria, uremia and inflammation.[15–17]

DYSLIPIDEMIA

Dyslipidemia in the general population is characterized by elevated low density lipoprotein (LDL) which is oxidized to form atherosclerotic plaques. In contrast, ESKD patients also develop hypertriglyceridemia, a decrease in high density lipoprotein cholesterol (HDL-C), an accumulation of apolipoprotein B (Apo B) containing lipoproteins, and increased concentrations of lipoprotein(a) particles.[18,19] All lipid classes are affected. One hypothesis is that as CKD progresses, so does uremia and oxidative stress. This causes post-translation protein modification of both LDL and HDL through glycation, oxidation and carbamylation, resulting in both a decrease in the quantity and quality of their function.[20–22] This hypothesis may explain why statins have not been beneficial in this population.

The mainstay of guideline therapy has been the use of statins to reduce LDL levels in the general population and in CKD patients.[23] Unfortunately these guidelines do not include ESKD patients due to lack of robust evidence. The SHARP study showed a 17% proportional reduction in major atherosclerotic events in 3,023 patients on dialysis who were randomized to receive simvastatin plus ezetimibe vs placebo during a 4.9 year follow-up period.[24] The 4-D trial and the AURORA did not reflect the same outcome, and showed there was no significant difference in either the placebo or intervention group. The current Kidney Disease Improving Global Outcomes (KDIGO) and ACC/AHA guidelines do not support the initiation of statins in ESKD. KDIGO recommends statins for all patients with CKD not on RRT and who are at least 50 years old. For adults 18 to 49 years old who have CKD, statins are recommended if there is a history of coronary artery disease, diabetes mellitus, stroke, or an ASCVD risk > 10%. Statins when initiated prior to dialysis can be continued, as there are no recommendations on discontinuation.[25] Extrapolating from hemodialysis patients, International Society for Peritoneal Dialysis (ISPD) guidelines refers to KDIGO for dyslipidemia management in peritoneal dialysis patients (PD).[26,27]

While statins have become the cornerstone, the latest discovery for dyslipidemia treatment is monoclonal antibodies. Currently, evolocumab and alirocumab are the available proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors. PCSK-9 binds to hepatocyte receptors and promotes increased LDL levels.[28] Inhibition of this protein by evolocumab has shown reduction of LDL levels by 59% and a reduction in cardiovascular events.[28] Unfortunately there is limited data on safety and efficacy in CKD patients and ESKD patients have been excluded from trials so there is a paucity of guidance for use in this patient population.[29–31]

Eicosapentaenoic acid (EPA) or omega-3 fatty acids decrease pro-inflammatory cytokines, interleukin-6 and leukotriene B4 by inhibiting the activation of their gene production.[32] The ACC/AHA guidelines do include recommendations for fish intake twice a week and use of omega-3 fatty acids in hypertriglyceridemia. In ESKD patients, omega-3 fatty acids have been studied for an effect on arterio-venous fistula patency with unfortunately no clear benefit established.[25] However, in a small study by Lok, 99 out of 196 ESKD patients who were randomized to receive the supplement demonstrated superior cardiovascular event-free survival in the fish oil group (HR 0.43 [95% CI, 0.19 to 0.96], p = 0.035) and a 7.74 point reduction in systolic BP.[33] Fish oil is generally well tolerated with the major side effects being gastrointestinal from belching or flatulence, and taste perversion. Nevertheless, use in ESKD patients should be individualized.[34]

ASPIRIN

There has been a change in the use of aspirin as primary prevention in the general population as new data has shown less benefit. Recent guidelines recommend patients with high calculated CVD risk scores based on traditional factors to initiate therapy.[35]

Unfortunately, this may not be applicable to ESKD patients since there is limited data on mortality benefit. Analysis of hemodialysis patients receiving aspirin prescriptions in the DOPPS study demonstrated that an aspirin prescription was associated with an increase in myocardial infarction and any cardiac event. [36] In a meta-analysis evaluating CKD and use of anti-platelet therapy, there was no clear effect of antiplatelet therapy on the risk of cardiovascular death (OR, 0.91; 95% CI, 0.67–1.13; I^2 = 0%) or all-cause death (OR, 0.87; 95% CI, 0.71–1.01; I^2 = 0.8%) compared with placebo or usual-care control groups in 27,773 participants from 50 trials.[36] They did show that for every 1,000 people with CKD treated, 23 patients would avoid major cardiovascular events but 9 patients would have a major bleeding episode and 35 would have minor bleeding episodes. At this time there is no recommendation to initiate aspirin therapy for primary prevention in ESKD patients.

SMOKING CESSATION

Smoking continues to challenge both the general and kidney disease populations. It remains the leading cause of preventable death in the United States. While specific data in dialysis patients is lacking, cessation is likely to reduce cardiovascular disease and mortality. Similar strategies involving nicotine replacement therapy can be utilized as well as drug therapy such bupropion and varenicline, with varenicline requiring renal dosing. [35]

DIABETES MANAGEMENT

Glycemic control involving dietary modifications, exercise, metformin, SGLT-2 inhibitors and GLP-1R agonists with a target hemoglobin A1C (HbA1C) of < 7% has shown CVD and mortality benefit in type 2 diabetic patients in the general population.[37] KDIGO recommends all type 2 diabetic patients with GFR greater than 30 (CKD stages 1-3) be treated with metformin, sodium–glucose cotransporter-2 (SGLT-2) inhibitors with the addition of lifestyle modifications (physical activity, nutrition and weight loss) to reach a target HbA1c of less than 6.5% or 7%.[38] Unfortunately the accuracy of HbA1c measurements in dialysis patients is unclear but without an alternative and wide use in clinical trials, it remains the marker of choice.[39] After initiation of first-line treatments, additional oral agents will require dose adjustment based on renal function and individualized to the patient.[39] The lack of data for HbA1c targets in dialysis patients poses an exceptional challenge for management in dialysis dependent diabetic patients.[39] As all cause mortality and CVD outcomes are worse in patients with poor glycemic and these patients are to be evaluated for transplantation, it is reasonable to provide targeted glycemic control based on observational data. [37,40–43]

HYPERTENSION

Deciphering the various definitions and recommendations for hypertension between guidelines from different societies can add to the complexity of treating this patient population. While all seem to agree that elevated blood pressure increases CVD and mortality, blood pressure thresholds and targets for different groups remains an area of debate.[44–46] Blood pressure readings can be taken in office, at home and continuously with an ambulatory pressure monitoring (ABPM) device. The 2017 ACC/AHA guidelines defines hypertension as an office systolic blood pressure greater than 130 mmHg or diastolic blood pressure of greater than 80 mmHg, while the 2018 ESC/ESH guidelines uses an office systolic blood pressure of greater than 140 mmHg and/or diastolic blood pressure of greater than 90 mmHg.[47–49] In the ground breaking SPRINT trial, diagnosis of hypertension was based on automated cuff readings in an office setting.[50] The National Institutes of Health and Care Excellence

(NICE) recommends confirming an elevated office reading with an ABPM daytime average or home blood pressure average of 135/85 mmHg or higher while the European Society of Cardiology/European Society of Hypertension (ESC/ESH) accepts an average ABPM of greater than 130/80 mmHg to be hypertensive.[47,48]

Once the hurdle of diagnosis has been achieved, the complexity continues in target goals and recommendations on the initial pharmacological regimen. Counseling on lifestyle modifications such as smoking, diet and exercise is recommended by the majority of the guidelines at initiation of treatment.[44,45,47–49] In both the diabetic and non-diabetic adult CKD population, KDIGO stratifies blood pressure targets based on albuminuria. When urine albumin excretion is less than 30mg/24hours the suggested targets are: systolic blood pressure of less than 140 mmHg and diastolic blood pressure of less than 90 mmHg. When albumin excretion is greater than 30mg/ 24hours, the recommended targets are: systolic blood pressure of less than 130 mmHg and diastolic blood pressure of less than 80 mmHg.[51] Angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers and diuretics are effective in the treatment of hypertension. Initial choice of medication should be individualized. In patients with diabetes, CKD, and albuminuria, ACEis and ARBs should be considered first as renin angiotensin aldosterone system (RAAS) blockade has shown benefit in reducing albuminuria and preventing CVD events.[52,53] Additional therapy should be individualized based on side effects, patient characteristics and co-morbidities.

Unique to dialysis patients is that blood pressure readings can vary when taken pre-, inter- and post-dialysis treatments in addition to in-dialysis unit, office and home locations.[54,55] The relation between the various readings has shown a stronger association of home or out of center BP readings with CVD and mortality.[56,57] The European Renal and Cardiovascular Medicine (EURECA-m)/European Renal Association–European Dialysis and Transplant Association (ERA-EDTA)/ ESH consider home or ABPM values of ≥135/85 mmHg on non-dialysis days and average BP≥130/80 mmHg over 24-hours respectively for hemodialysis patients and an office BP≥140/90 for PD patients to be diagnostic of hypertension.[58] The Kidney Disease Outcomes Quality Initiative (KDOQI) made a grade C recommendation for a pre-dialysis blood pressure target of less than 140/90 mmHg and post-dialysis blood pressure target of less than 130/80 mmHg.[59]

The pathophysiology of hypertension in dialysis-dependent ESKD patients is multifactorial. Proposed factors include salt and volume retention, RAAS and endothelial cell dysfunction, sleep apnea and use of erythropoietin agents.[53,60,61] A low sodium diet (2 grams per day) is recommended.[59] An attempt to optimize volume removal with aggressive ultrafiltration during hemodialysis has been shown to improve hypertensive control.[62] Data from meta-analysis suggests the use of pharmacological therapy is associated with CVD reduction and survival benefit.[63,64] While ACEi have shown efficacy in decreasing left ventricular mass as well as providing RAAS blockade, use may be limited due to side effects.[58,61] Multiple agents will mostly likely be required and should be individualized to each patient. Patients maintained on PD have also been shown to be chronically volume overloaded as evidenced by elevated atrial natriuretic peptide levels and left atrial volume by echocardiography. In general, this is managed by increasing the glucose concentration in the dialysate to promote a higher osmotic gradient to promote better ultrafiltration. However, a high peritoneal dialysate glucose concentration (PDGC) may induce metabolic syndrome, which has been associated with a higher CVD mortality in PD patients.[58,65] Further data on blood pressure targets and pharmacological regimens is lacking in PD patients.

Due to the lack of evidence from quality randomized controlled trials or strong recommendations from society guidelines, hypertension treatment in advanced CKD (stage 5) and dialysis-dependent ESKD is based on observational data and expert opinion.[46,63,64] Unfortunately, the lack of clarity on this issue most affects patients who are awaiting imminent transplantation, limiting the optimization of their medical management.

SUMMARY

This summary provides guidelines based on the limited available data in this vulnerable patient population. Given the high burden of CVD in the ESKD population and the multiple challenges these patients face, providing a multi-disciplinary approach to mitigate cardiovascular risks may result in improved clinical outcomes and benefit these patients while they wait on the long road to transplantation.

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