Peritoneal Dialysis International, Vol. 35, pp. 379–387
doi: 10.3747/pdi.2014.00279

0896-8608/15 $3.00 + .00

ISPD GUIDELINES/RECOMMENDATIONS

ISPD CARDIOVASCULAR AND METABOLIC GUIDELINES IN ADULT PERITONEAL DIALYSIS PATIENTS PART I – ASSESSMENT AND MANAGEMENT OF VARIOUS CARDIOVASCULAR RISK FACTORS

Angela Yee Moon Wang,[1] K. Scott Brimble,[2] Gillian Brunier,[3] Stephen G. Holt,[4] Vivekanand Jha,[5] David W. Johnson,[6,7] Shin-Wook Kang,[8] Jeroen P. Kooman,[9] Mark Lambie,[10] Chris McIntyre,[11] Rajnish Mehrotra,[12] and Roberto Pecoits-Filho[13]

Department of Medicine,[1] Queen Mary Hospital, University of Hong Kong, Hong Kong; St. Joseph's Healthcare,[2] McMaster University, Hamilton, Ontario, Canada; Lawrence S. Bloomberg Faculty of Nursing,[3] University of Toronto, Toronto, Ontario, Canada; Division of Nephrology,[4] The Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia; George Institute for Global Health India,[5] Postgraduate Institute of Medical Education and Research, Chandigarh, India; University of Queensland at Princess Alexandra Hospital,[6] Brisbane, Australia; Centre for Kidney Disease Research,[7] Translational Research Institute, Brisbane, Australia; Department of Internal Medicine,[8] College of Medicine, Severance Biomedical Science Institute, Yonsei University, Korea; Division of Nephrology,[9] University Hospital Maastricht, Maastricht, The Netherlands; Health Services Research Unit,[10] Institute for Science and Technology in Medicine, Keele University, Keele, Staffordshire, United Kingdom; School of Medicine,[11] University of Nottingham, Royal Derby Hospital Centre, Derby, United Kingdom; Harborview Medical Center,[12] Division of Nephrology/Department of Medicine, University of Washington, Washington, DC, United States; and School of Medicine,[13] Pontifícia Universidade Católica do Paraná, Curitiba, Paraná, Brazil

Cardiovascular disease contributes significantly to the adverse clinical outcomes of peritoneal dialysis (PD) patients. Numerous cardiovascular risk factors play important roles in the development of various cardiovascular complications. Of these, loss of residual renal function is regarded as one of the key cardiovascular risk factors and is associated with an increased mortality and cardiovascular death. It is also recognized that PD solutions may incur significant adverse metabolic effects in PD patients. The International Society for Peritoneal Dialysis (ISPD) commissioned a global workgroup in 2012 to formulate a series of recommendations regarding lifestyle modification, assessment and management of various cardiovascular risk factors, as well as management of the various cardiovascular complications including coronary artery disease, heart failure, arrhythmia (specifically atrial fibrillation), cerebrovascular disease, peripheral arterial disease and sudden cardiac death, to be published in 2 guideline documents. This publication forms the first part of the guideline documents and includes recommendations on assessment and management of various cardiovascular risk factors. The documents are intended to serve as a global clinical practice guideline for clinicians who look after PD patients. The ISPD workgroup also identifies areas where evidence is lacking and further research is needed.

***Perit Dial Int* 2015; 35(4):379–387 www.PDIConnect.com**
doi: 10.3747/pdi.2014.00279

KEY WORDS: Cardiovascular risk; residual renal function; volume; salt; glycosylated hemoglobin; hypertension; dyslipidemia; anemia; inflammation; obesity; hypokalemia; dialysate calcium; peritoneal dialysis.

Cardiovascular disease is a leading cause of death in peritoneal dialysis (PD) patients, according to various national and regional registries (1,2). Proper assessment and treatment of various cardiovascular risk factors is an essential part of the management of PD patients. However, it is recognized that cardiovascular risk profiles and their management in chronic PD patients may be different from those of chronic hemodialysis patients in several aspects. First, loss of residual renal function

Correspondence to: Angela Yee Moon Wang, Department of Medicine, Queen Mary Hospital, University of Hong Kong, 102 Pok Fu Lam Road, Hong Kong.
aymwang@hkucc.hku.hk
Received 1 November 2014; accepted 31 January 2015.
Supplemental material available at www.pdiconnect.com

contributes significantly to the overall mortality and cardiovascular mortality of PD patients (3). Second, PD solutions, the majority of which are glucose-based solutions, may incur significant adverse metabolic effects (4) and may thus further influence cardiovascular risk profiles in PD patients, especially in those with underlying diabetes. Third, volume control is an important predictor of outcome in chronic PD patients (5), and salt and fluid removal constitute a key component in the cardiovascular management of PD patients. Yet, strategies of fluid removal are obviously very different from those for hemodialysis patients. It is therefore imperative to develop a Cardiovascular and Metabolic Clinical Practice Guideline specifically for chronic PD patients covering these unique aspects. It has been several years since the last Global Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients were published by the Kidney Disease Outcome Quality Initiative (KDOQI) in 2005. We set out to review and reappraise the more recently available evidence and formulate an updated clinical practice guideline in relation to the management of various cardiovascular risk factors as well as different cardiovascular complications specifically for chronic PD patients.

To achieve this, the International Society for Peritoneal Dialysis (ISPD) commissioned a workgroup with representation from Asia, Australia, Europe, and North and South America in 2012 to formulate this series of recommendations regarding lifestyle modification, assessment and management of various cardiovascular risk factors, as well as management of various cardiovascular complications including coronary artery disease, heart failure, arrhythmia (specifically atrial fibrillation), cerebrovascular disease, peripheral arterial disease and sudden cardiac death, to be published in 2 documents. The documents are intended to serve as a global clinical practice guideline for clinicians who look after PD patients. We also aimed to identify areas where evidence is lacking, where there are gaps in knowledge and where further research is needed. We decided not to duplicate evidence review and clinical practice guideline formulation for topics that had already been comprehensively covered by the Kidney Disease Improving Global Outcomes (KDIGO). This included the KDIGO-published guidelines on chronic kidney disease-mineral bone disease (CKD-MBD), lipids, anemia, diabetes, and chronic kidney disease. Therefore, our workgroup focused on evidence review and clinical practice guideline formulation to address aspects of these areas that are specific for PD patients and not covered by the KDIGO.

The evidence for formulating all the recommendations within this Guideline has been evaluated using the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The modified GRADE system defines both the strength of recommendation of each guideline statement and the level of evidence on which each guideline statement is based. In brief, the GRADE system classifies a 'strong' recommendation as grade 1 and a 'weak' recommendation as grade 2. The strength of recommendation is based on the balance between benefits and risks, cost implication, as well as the burden of disease. The quality of level of evidence is graded as high (grade A), moderate (grade B), low (grade C) or very low (grade D). The level of evidence is graded according to study design, sample size, directness of evidence, and consistency of results. Grades of recommendation and quality of evidence may therefore range from 1A to 2D.

The development of the 2 guideline documents has proved challenging for several reasons. First, cardiovascular disease is a complex complication in PD patients, and the causes are usually multifactorial. Its manifestations are heterogeneous, and most aspects are not well studied in PD patients. Second, there are a limited number of randomized controlled trials dedicated to PD patients and also a tendency toward very small sample size, inadequate study power and short duration of follow-up. Third, very few clinical trials in PD patients have examined hard primary outcome measures (for example, mortality, various adverse cardiovascular outcomes, and hospitalization). Fourth, previous guidelines developed in this area have extrapolated from references largely based on studies in the general population or non-dialysis chronic kidney disease (CKD), or hemodialysis patients. It is uncertain whether the results of such studies are equally and truly applicable to PD patients as well.

In reviewing literature evidence, the workgroup conducted a Medline and PubMed search for the last 25 years, from 1989 through to March 2014. The search was limited to publications in English. For non-treatment related questions, namely questions related to diagnosis, screening, prevalence, natural history and risk relationship, the workgroup decided to include prospective observational studies of cross-sectional, case control, longitudinal cohort design or randomized studies with a sample size of at least 100 subjects. Retrospective studies were generally excluded from the evidence review due to the potential for significant bias. For questions relating to evaluation of treatment efficacy, our workgroup decided to include only prospective randomized controlled trials with a sample size of at least 50 subjects for surrogate outcomes and a sample size of at least 100 subjects for hard outcomes in the evidence review. Systematic reviews of randomized controlled trials were also included. Observational studies were not considered in the evidence review for treatment efficacy. As studies in PD patients were rather limited, we included studies conducted in hemodialysis patients that fulfill the study design and sample size criteria for our evidence review. In areas where the sample size of available randomized controlled trials was below that suggested in the inclusion criteria, if these studies were the only randomized trials available, the workgroup did include them in the evidence review but the evidence was taken with caution and the study quality was downgraded.

The ISPD Cardiovascular and Metabolic Clinical Practice Guidelines for PD patients are published in 2 documents. The first publication covers assessment and management of various cardiovascular risk factors and includes sections on lifestyle modification, residual renal function, volume control, glycemic control in diabetes, hypertension, inflammation, protein energy wasting, CKD-MBD, hypokalemia, obesity, dyslipidemia, and anemia. The second publication document covers assessment and management of various cardiovascular complications including coronary artery disease, left ventricular hypertrophy and dysfunction, heart failure, arterial stiffness, stroke, peripheral arterial disease, arrhythmia (specifically atrial fibrillation), and sudden cardiac death.

There are several areas where our workgroup felt there was insufficient evidence to formulate guideline recommendations. One of these relates to the ideal or 'target' body mass index (BMI) and obesity management in PD patients. Obesity is associated with higher mortality in the general population and a lower mortality in hemodialysis patients but it has an uncertain relationship with mortality in PD patients, where numerous large studies show conflicting results. It is therefore not possible to recommend any particular weight or BMI range for PD patients. In some situations it will be appropriate for PD patients to lose weight, such as for transplant listing. There have been some studies of interventions to minimize glucose loading, but there have been no consistent outcomes differentiating fat loss from fluid loss. The largest study of glucose minimisation found a trend toward less visceral fat with less dialysate glucose (6) but this did not meet the defined threshold for significance. Our workgroup therefore felt that it is currently not possible to recommend a target BMI for PD patients or recommend any particular PD prescription that may assist body weight control in this population.

The other area where our workgroup felt there was insufficient evidence to formulate guideline recommendations relates to guided fluid management in the volume control section. There is recent randomized trial evidence in hemodialysis patients showing that fluid management guided by a bioimpedance device that provides an estimate of the degree of overhydration may be associated with a reduction in left ventricular hypertrophy and an improvement in blood pressure control and pulse wave velocity (7). Another randomized controlled study also showed an improvement in patient survival (8). However, similar evidence of bioimpedance or guided fluid management is completely lacking in PD patients. Given the very different hemodynamic characteristics of hemodialysis and PD patients, it is not known whether the findings from hemodialysis patients can be directly extrapolated to PD patients. Therefore, awaiting further studies, our workgroup did not formulate a guideline statement in relation to guided fluid management.

In this first cardiovascular and metabolic clinical practice guideline publication, there are altogether 20 guideline statements of which 11 statements are graded as level 1 or 'strong' recommendations, 7 statements are graded as level 2 or 'weak' recommendations, and only 2 statements are ungraded. Each guideline statement is provided with a brief paragraph of rationale. Full detailed rationale and evidence review tables are presented online. In addition, a list of research recommendations is prepared at the end of all the guideline statements which aims to facilitate future research.

LIFESTYLE MODIFICATION

GUIDELINE 1. LIFESTYLE MODIFICATION

1.1 We recommend peritoneal dialysis patients undertake physical activity compatible with cardiovascular health and tolerance (aiming for at least 30 minutes, 5 times per week). (1D)

RATIONALE: Physical activity levels are strikingly reduced in patients on dialysis (9). There is overwhelming evidence from observational studies that regular exercise improves physical functioning, exercise capacity, and physical performance and has a favourable influence on metabolic profiles (10–11). Exercise includes cardiovascular and resistance training, and yoga in various combinations. In view of high-quality evidence in the general population, the workgroup recommends that all PD patients increase physical activity.

1.2 We recommend salt restriction (<2 g sodium or 5 g sodium chloride per day) for all peritoneal dialysis patients unless contraindicated or patients show evidence of volume contraction or hypotension. (1C)

RATIONALE: High-quality evidence in the general population shows that reduced sodium intake reduces blood pressure and has no adverse effects on blood lipids, catecholamine levels, or renal function (12). Lower sodium intake is also associated with a reduced risk of stroke and fatal coronary heart disease in adults. High salt intake is associated with an increased mortality risk in dialysis patients (13). Maintaining optimal volume status is an important issue in PD patients, and salt restriction plays a critical role (14). The totality of evidence suggests that most people with CKD, including those on PD, will likely benefit from reducing sodium intake (15). Therefore, despite the lack of high-quality randomized trial evidence in PD patients, the workgroup gives a strong recommendation on salt restriction in PD patients.

1.3 We recommend peritoneal dialysis patients who smoke cigarettes or use other forms of tobacco be advised to stop smoking. (1C)

RATIONALE: There is good evidence linking smoking to adverse clinical outcomes in the general population (16). There are observational studies that support similar associations in PD patients (17). There are no randomized controlled trials of smoking vs non-smoking, but since there is overwhelming evidence in the general population to suggest that smoking is harmful, it is unlikely that there ever will be a randomized controlled trial in PD patients.

ASSESSMENT AND MANAGEMENT OF VARIOUS CARDIOVASCULAR RISK FACTORS

GUIDELINE 2.1. RESIDUAL RENAL FUNCTION

2.1.1 We recommend monitoring residual renal function at least once every 6 months in peritoneal dialysis patients with urine output. (1C)

RATIONALE: Monitoring residual renal function (RRF), a predictor of important clinical outcomes, is necessary to guide changes to the PD prescription over time to ensure dialysis adequacy (18). Studies suggest that the rate of loss of RRF on PD varies between 1 and 4 mL/min/1.73m^2/year (19,20). It

therefore seems reasonable to monitor at least every 6 months in patients with RRF, anticipating a change in RRF of about 1 – 2 mL/min/1.73m^2 or renal Kt/V of about 0.2 – 0.4.

2.1.2 We suggest estimating residual renal function using the mean of the 24-hour urinary clearance of urea and creatinine. (2B)

RATIONALE: Measurement of the glomerular filtration rate using an exogenous substance such as inulin is considered the gold-standard but is impractical. The mean of 24-hour urea and creatinine, which takes advantage of the offsetting effects of overestimation by creatinine clearance and underestimation by urea clearance, has been shown to be a reasonable estimate of glomerular filtration rate as determined from inulin clearance (21). A simpler method to estimate RRF, such as serum cystatin C, has not been externally validated and is influenced by the intensity of dialysis (22).

2.1.3 We suggest peritoneal dialysis patients with significant residual renal function be treated with an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker as tolerated. (2C)

RATIONALE: There is a large body of evidence that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers retard the rate of loss of kidney function in individuals with and without diabetes mellitus (23). Two small randomized, open-label, controlled clinical trials have demonstrated that the benefit of these drug classes extends to levels of renal function seen in PD patients (24,25).

2.1.4 We suggest neutral pH, low glucose degradation product peritoneal dialysis solutions may be considered for better preservation of residual renal function if used for periods of 12 months or more. (2B)

RATIONALE: There are conflicting data on the impact of neutral pH, low glucose degradation product (GDP) PD solutions on RRF. The single largest randomized controlled trial did not find a positive effect of these solutions on RRF but demonstrated a significant delay in the time to anuria with neutral pH, low GDP PD solution (26). However, a systematic review of generally lower quality studies did suggest an improved preservation of RRF and greater 24-hour urine volume with the use of low GDP PD solutions when used for more than 12 months (27). Recognizing the limitations of the studies to date and the potential cost implications of using these more expensive solutions, neutral pH, low GDP PD solutions may be considered to preserve RRF when used for more than 12 months.

GUIDELINE 2.2. VOLUME CONTROL

2.2.1 We recommend hydration status be assessed clinically on a regular basis during every follow-up visit and more often if clinically indicated. (1D)

RATIONALE: Overhydration is prevalent in both hemodialysis and PD patients and is an important determinant of mortality. Although no study showed a direct relation between clinically assessed fluid overload and outcome in PD patients, there is wide consensus in the medical community that clinical examination forms an important basis for the assessment of hydration status in dialysis patients. The workgroup considers assessment of hydration status a vital component in the management of PD patients, which should be, in its opinion, an integral part of follow-up visits of PD patients.

2.2.2 We recommend regular monitoring of peritoneal ultrafiltration by timed dialysate collections at least once every 6 months and more frequently if clinically indicated. (1C)

RATIONALE: Several prospective observational studies showed that peritoneal ultrafiltration is an important predictor of patient survival (14,28). The workgroup decided not to set a fixed ultrafiltration threshold as a basis for more intensive monitoring, because the relation between peritoneal ultrafiltration and hydration state is also dependent on other factors such as dietary salt and fluid intake. The recommendation for the frequency of monitoring is opinion-based and in line with previous guidelines.

2.2.3 We recommend once-daily icodextrin be considered as an alternative to hypertonic glucose peritoneal dialysis solutions for long dwells in peritoneal dialysis patients experiencing difficulties maintaining euvolemia due to insufficient peritoneal ultrafiltration, taking into account the individual patient's peritoneal transport state. (1B)

RATIONALE: In 3 recent meta-analyses, an increase in peritoneal ultrafiltration volume as well as a reduction in episodes of uncontrolled fluid overload were observed with the use of icodextrin compared with conventional glucose PD solutions (27–29,30). The effect of icodextrin was most pronounced in patients with high/high-average transport state. No significant effects on technique failure or mortality were demonstrated (29). The effect of icodextrin on peritoneal ultrafiltration was significant in categories of patients ranging from low-average to high transport state, but not in those patients with low transport state (29). No significant effect on residual urine volume was reported in the meta-analyses. Therefore, in view of the positive benefit-risk relation, the workgroup made a strong recommendation for the use of icodextrin in patients experiencing difficulties maintaining euvolemia due to insufficient ultrafiltration, taking into account the membrane transport state of the patient.

GUIDELINE 2.3. GLYCEMIC CONTROL IN DIABETIC PD PATIENTS

2.3.1 We recommend glycosylated hemoglobin be measured at least once every 3 months in diabetic peritoneal dialysis patients to assess glycemic control. (1C)

RATIONALE: Even though glycosylated hemoglobin (A1C) levels can be influenced by various clinical factors including reduced red blood cell lifespan, recent transfusion, iron deficiency, metabolic acidosis, and the usage of erythropoietin-stimulating agents in end-stage renal disease patients, A1C still remains a reasonable glycemic metric in diabetic patients on dialysis. According to the American Diabetic Association Clinical Practice Recommendations, A1C should be tested at least twice a year in patients with well controlled glucose levels, while patients whose therapy has changed or who are not meeting glycemic control targets may be tested more frequently at 3-month intervals (31). Given the situation of continuous exposure to high glucose-containing dialysate, we suggest that A1C should be measured at least every 3 months in diabetic PD patients.

2.3.2 We suggest glycosylated hemoglobin be targeted around 7% (53 mmol/mol) in peritoneal dialysis patients with diabetes, and may be up to 8.5% (69 mmol/mol) in older diabetic peritoneal dialysis patients. (2D)

RATIONALE: The updated 2012 National Kidney Foundation KDOQI Clinical Practice Guideline for Diabetes and CKD recommends a target A1C of ~7.0% to prevent or delay progression of the microvascular complications of diabetes (32). However, it also recommends not treating to an A1C target of <7.0% in diabetic CKD patients at risk of hypoglycemia. Recently, the American Diabetic Association's Standards of Care also suggested that it is reasonable to set a target A1C goal of up to 8.5% for older diabetic patients with the presence of a single end-stage chronic illness such as stage 3 – 4 congestive heart failure or oxygen-dependent lung disease, CKD requiring dialysis, or uncontrolled metastatic cancer (33). The workgroup feels that a similar target of up to 8.5% is also reasonable for older diabetic PD patients to reduce the risk of hypoglycemia.

2.3.3 We suggest once daily icodextrin be considered as the long-dwell dialysis solution in diabetic peritoneal dialysis patients for better glycemic control. (2C)

RATIONALE: Glucose absorption via glucose-based PD solutions has been implicated with systemic metabolic abnormalities, including hyperglycemia, hyperinsulinemia, and dyslipidemia. Accumulating evidence indicates that the use of non-glucose-based PD solution (e.g. icodextrin solution) could lead to a reduction in glucose absorption through the peritoneal membrane, leading to an improvement in glycemic control in diabetic PD patients (6).

GUIDELINE 2.4. INFLAMMATION

2.4.1 We suggest peritoneal dialysis patients with persistently elevated C-reactive protein be investigated for any treatable cause of inflammation. (ungraded)

RATIONALE: Markers of inflammation such as C-reactive protein (CRP) are frequently elevated in dialysis patients and a single or sustained elevation in CRP is associated with an enhanced cardiovascular risk (34–36). What is lacking is any conclusive evidence on how to treat such patients, or that treating inflammation *per se* may reduce cardiovascular risk. It seems reasonable to investigate patients with very elevated CRP or sustained high CRP for any treatable causes of inflammation (37).

GUIDELINE 2.5. PROTEIN-ENERGY WASTING

2.5.1 We suggest nutritional status be assessed within 6 – 8 weeks after commencement of peritoneal dialysis, and monitored regularly at least once every 4– 6 months for peritoneal dialysis patients. (ungraded)

RATIONALE: Protein–energy wasting (PEW) is highly prevalent in patients on dialysis (33). Accumulating evidence indicates that PEW is an important predictor of morbidity and mortality in these patients. Therefore, constant monitoring of nutritional status, early detection, and institution of therapeutic strategies for the prevention and treatment of PEW form a crucial aspect in the management of PD patients. Body mass index, subjective global assessment, anthropometric measurements, biochemical parameters (such as serum albumin level) and dietary protein intake have traditionally been used in clinical practice (39). However, because no single method is precisely indicative of PEW, it should be cautiously interpreted by data combined from several parameters (40).

GUIDELINE 2.6. HYPERTENSION

2.6.1 We recommend blood pressure be evaluated by home blood pressure measurement at least once a week and at each visit to the clinic. (1C)

RATIONALE: Hypertension is extremely common in patients on PD, affecting more than 80% in prevalent patients, and is associated with poor outcomes (38,39). The relationship between hypertension and risk of adverse outcomes is well documented in the general population. However, the evidence associating hypertension with adverse outcomes in PD is limited. Nevertheless, the workgroup feels that extrapolation of these findings from the general and CKD population, along with the high prevalence of hypertension in PD patients, does justify the recommendation of active screening and periodic monitoring of blood pressure in this population.

2.6.2 We recommend peritoneal dialysis patients whose blood pressure is consistently >140/90 mmHg be treated to maintain blood pressure <140 mmHg systolic and <90 mmHg diastolic. (1D)

RATIONALE: A relationship between high systolic blood pressure and an increased risk of mortality has been reported in PD patients (40). However, at least 1 observational study showed that a systolic blood pressure of 110 mmHg or less was associated with an increased mortality, and a protective effect was

observed with a systolic blood pressure above 120 mmHg (41). Another study showed a variable relationship between blood pressure and mortality with time in that a higher blood pressure was associated with lower mortality early but with higher mortality in the longer term (42). There are no randomized studies examining different blood pressure targets in relation to clinical outcomes in PD patients. Nevertheless, based on data from the general population and CKD population, the workgroup recommends target blood pressure be below 140/90 mmHg in PD patients.

2.6.3 We recommend peritoneal dialysis patients with hypertension have volume status optimized before starting or increasing anti-hypertensive medications. (1C)

RATIONALE: Hypertension is associated with volume overload in PD patients (43). The initial approach to hypertension should therefore always involve assessment of volume status and treatment of hypervolemia as clinically indicated. Although the utility of hypertonic glucose PD solutions for volume removal in both continuous ambulatory PD and automated PD patients is not disputed, the workgroup emphasizes the minimization of PD glucose exposure by salt restriction, diuretic use among those with RRF, and use of glucose-sparing solutions to optimize volume control.

GUIDELINE 2.7. CHRONIC KIDNEY DISEASE – MINERAL BONE DISEASE (DIALYSATE CALCIUM)

2.7.1 We suggest a calcium-containing peritoneal dialysis solution of 1.25 mmol/L be used to avoid positive calcium balance or hypercalcemia. (2C)

RATIONALE: Several observational studies have demonstrated an association of higher serum calcium level with risk of death in patients undergoing maintenance dialysis; these studies have been done largely in patients undergoing hemodialysis (44). Dialysate calcium is a modifiable intervention and limited evidence suggests that lower-calcium PD solutions (1.25 mmol/L) can facilitate the use of calcium-based phosphate binders and/or activated vitamin D therapy and, at the same time, reduce the risk for positive calcium balance and hypercalcemia (45,46). Whether the reduction in the risk for positive calcium balance and hypercalcemia with the use of low calcium dialysate may reduce cardiovascular risk in patients undergoing PD is currently not known.

GUIDELINE 2.8. HYPOKALEMIA

2.8.1 We suggest serum potassium levels in patients undergoing peritoneal dialysis be maintained between 3.5 and 5.5 meq/L. (2C)

RATIONALE: The potassium gradient across the cardiac myocyte is vital for regulating the electrical activity of the heart. While low extracellular potassium increases the likelihood of re-entrant arrhythmia, increased serum potassium puts individuals at risk for ventricular fibrillation and asystole (47,48). Patients undergoing PD are at a significant risk for hypokalemia, and observational studies demonstrated a U-shaped relationship between serum potassium levels and mortality, with a higher population-attributable fraction to low rather than high serum potassium levels (49,50). It remains currently not known whether correcting serum potassium abnormalities may reduce cardiovascular risk in patients undergoing PD.

GUIDELINE 2.9. DYSLIPIDEMIA

The workgroup endorses the KDIGO lipid guidelines for managing dyslipidemia in peritoneal dialysis patients.

GUIDELINE 2.10. ANEMIA

The workgroup endorses the KDIGO anemia guidelines for the management of anemia in peritoneal dialysis patients.

RESEARCH RECOMMENDATIONS

I. LIFESTYLE MODIFICATION

- To examine the effects of regular exercise on muscle endurance, morphology and morphometrics, physical functioning, cardiovascular dimensions, nutrition (e.g. muscle mass), and systemic inflammation in PD patients.
- To examine the effects of regular exercise on depression, lipids, and glucose metabolism in PD patients.
- To study the effects of regular exercise on cardiovascular outcomes in PD patients.
- To evaluate the effects of different levels of salt intake on blood pressure and volume control, and cardiovascular structure, function, and clinical outcomes of PD patients.
- To evaluate the safety and efficacy of behavioural and pharmacological treatments that help PD patients to stop smoking.

II. ASSESSMENT AND MANAGEMENT OF VARIOUS CARDIOVASCULAR RISK FACTORS

SECTION 1: Residual Renal Function

- Research on the development of simple, inexpensive methods to measure RRF in patients undergoing PD that do not require 24-hour urine collection.
- Randomized controlled trials of sufficient power to evaluate the effectiveness of neutral pH, low-GDP solution therapy in delaying the loss of solute clearances and/or urine volume in patients undergoing PD.
- Determine the long-term effectiveness and safety of high dose diuretics in maintaining urine volume in patients undergoing PD.
- Randomized controlled trials to determine the long-term safety and effectiveness of keto-acid supplementation with

or without low-protein diets on the rate of decline of RRF in patients undergoing PD.

SECTION 2: Volume Control

- To assess the effect of icodextrin treatment on hard outcomes in PD patients.
- To assess the relationship between prescribed peritoneal ultrafiltration and outcomes in clinical trials.
- To assess the effect of guided fluid intervention using bioimpedance, vena cava echography, lung comets and natriuretic peptides on patient survival and other hard clinical outcomes in PD patients.

SECTION 3: Glycemic Control in Diabetic PD Patients

- Studies to examine the optimal interval of A1C measurement and optimal target of A1C that improves clinical outcomes of diabetic PD patients.
- Randomized controlled trials to determine the efficacy of dipeptidyl peptidase inhibitors in improving clinical outcomes of diabetic PD patients.

SECTION 4: Inflammation

- Investigations on the mechanisms driving inflammation in uremic patients with renal disease are needed.
- Study of the effect of the peritoneal inflammatory response on systemic inflammatory markers.
- A randomized controlled trial of the effect of various anti-inflammatory agents (e.g. statins, magnesium, zinc) on cardiovascular outcomes of PD patients.

SECTION 5: Protein-Energy Wasting

- Studies for the best method and optimal interval of nutritional assessment and interventions to treat PEW in PD patients.
- Randomized controlled trials to determine whether treatment of PEW may improve clinical outcomes of PD patients.

SECTION 6: Hypertension

- A randomized controlled clinical trial comparing different blood pressure targets in relation to clinical outcomes (including RRF, adverse cardiovascular events, and mortality) of PD patients.
- Randomized trials of different anti-hypertensive agents in relation to mortality and cardiovascular outcomes in PD patients.

SECTION 7: CKD-MBD (Dialysate calcium)

- To determine whether cardiovascular risk is best identified with serum calcium, uncorrected for serum albumin, or with albumin-corrected serum calcium. In that context, the effect of method of measurement of serum albumin (bromcresol green or purple or nephelometery) on the magnitude of adjustment for serum calcium for patients undergoing PD needs to be determined.
- Clinical trials to define the optimal target range of serum calcium for patients undergoing PD. Such studies should consider not only the effect on cardiovascular risk but also other meaningful patient-centered metrics such as risk for fractures.
- The effectiveness of low-calcium dialysate in maintaining serum calcium in the target range needs to be determined in adequately powered clinical trials with long-term follow-up.

SECTION 8: Hypokalemia

- Determine the effectiveness of different interventions (such as oral or intraperitoneal potassium supplements, aldosterone receptor antagonists) to ensure sustained increases in serum potassium.
- Determine the effectiveness of maintaining eukalemia in reducing cardiovascular risk, including sudden cardiac death.

SECTION 9: Dyslipidemia

- A randomized trial of statin use on mortality and cardiovascular outcomes in PD patients.
- Identify the true rate of triglyceride-related pancreatitis in PD patients.
- A randomized trial of PD glucose-minimisation strategies on lipid control in PD patients.

SECTION 10: Anemia

- A randomized controlled trial of anemia treatment in relation to overall mortality and cardiovascular outcomes in PD patients.
- Study to evaluate optimal target hemoglobin in PD patients.

SECTION 11: Obesity

- Large-scale observational studies to evaluate the effects of visceral and subcutaneous fat accumulation by a validated technique.
- Studies to evaluate the effects of other novel measures of obesity on hard outcomes in the PD population.
- If subsequent observational studies reliably define a group with higher mortality risk, conduct interventional studies of weight loss measures encompassing reliable body composition measures.

DISCLOSURES

AYMW has received research grants or speaker honoraria from Baxter, Sanofi, Fresenius Kabi and Abbvie. KSB has received research funding from Baxter. SH has received research grants,

consultant fees or honoraria from Amgen, Baxter, Gilead, Novartis and Shire. VJ has received research funding and is on the Advisory Board for Baxter. DJ has received consultancy fees from Baxter, Fresenius, Gambro, Amgen, Janssen-Cilag, Roche, Genzyme, Shire, Sigma, Sanofi-Aventis, Boehringer-Ingelheim, Lilley, Merck, Sharpe & Dohme, Bristol-Myers Squibb, and Novartis; speaker honoraria from Baxter, Fresenius, Gambro, Amgen, Janssen-Cilag, Roche, Servier, Shire, Merck, Sharpe & Dohme, Boehringer-Ingelheim, and Bristol Myers Squibb; research grants from Baxter Extramural, Fresenius, Roche Foundation for Anaemia Research (RoFar), Amgen, Janssen-Cilaz, Pfizer, and Abbott; and, travel sponsorships from Baxter, Fresenius, Gambro, Amgen, Janssen-Cilag, Roche, and Shire. JK has received unrestricted research grants from Fresenius FMC Europe, speakers' grants from Baxter healthcare and Fresenius FMC, and consultancy fees from Sanofi. ML has received unrestricted research grant from Baxter. CM has received research grant funding from both Baxter and Fresenius, honorariums from Baxter, Fresenius, Braun, Sanofi, and is an adviser for Astra Zeneca. RM hass received research support and/or honoraria from Baxter Healthcare and DaVita. RP-F has received speaker honoraria from Baxter, Renal Research Institute, Abbott, AMGEN, Astra Zeneca, research grants from Fresenius Medical Care, Baxter, and a consultancy fee from Novartis, AMGEN, Abbott, Astra Zeneca. GB and S-WK have no conflicts of interest to declare.

ACKNOWLEDGMENTS

We would like to acknowledge the clerical support and assistance provided by Miss Giorgia Manuzi and all the valuable input and comments from Drs. Simon Davies and Martin Wilkie for this guideline work.

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