KDIGO Controversies Conference on Blood Pressure & Volume Management in Dialysis

- Public Review Comments -

As of January 7, 2019
Industry comments are highlighted in blue

Laura Sola (CASMU, Montevideo, Uruguay)

It is a very comprehensive scope of coverage that you had prepared. I have 2 comments:

For working group 1, included in the pharmaceutical approach, when discussing anti-hypertensive agents to be used, should we discuss: should diuretics be used for blood pressure or volume control, if yes, which ones and doses.

For working group 2, when discussing the best strategies to lower UF rates and RKF, Should we include in the discussion: What method for measuring RKF should we use, with urine collection or only serum measures as beta trace protein?

Martin Wilkie (Sheffield Teaching Hospitals, UK)

I would suggest that relevant to these discussions are the following points:

1) the relationship between co-morbidity (specific co-morbidities) and extracellular fluid (I note co-morbidity is not mentioned in the scope, although frailty is). This has been raised in several fora - see Maria-Eleni Roumelioti et al. Fluid balance concepts in medicine: principles and practice. World Journal of Nephrology 2018 Jan 6;7(1):1-28

2) that incident (baseline) measures of extracellular volume represent the patient's clinical condition rather than the impact of the dialysis itself eg as observed in the baseline IPOD study paper - Ronco C et al NDT 2015 30:849-58.

3) that the use of measures longitudinally for individual patients provides different and theoretically more relevant data than the placement of an individual's measurement within a cross-sectional population of measures.

Andrew Davenport (University College London, UK)

I think one area not covered is the role of preserving residual renal function

Anthony Bleyer (Wake Forest School of Medicine, USA)

I think this is a really great idea, and I look forward to hearing the outcomes.

Hideki Kawanishi (Tsuchiya General Hospital, Japan)

I believe that this KDIGO Controversies Conference draws important conclusions and can do CVD prevention for dialysis patients. My personal opinions and interest are related to the dialysis modality selections.

Peritoneal dialysis (PD) is well known to maintain the events of CVDs and BP drop. Moreover, the preservation of RKF by PD was believed to maintain of fluid balance and mortality for patients (1). However, the several evidences showed that the PD patients was maintained on the overhydration condition and LVH due to the purpose of preservation of RKF (2,3). The NECOSAD study showed the RKF was not related the hydration condition(4). The BIA in PD was showed the fluid overload was not related the RKF maintained (5). These data doubt the usefulness of RKF for CVDs management in PD. The ISPD Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis was emphases the point and recommended the define “Dry Weight” for PD patient (6). Although this indication was presented in 2000, it has not been widely accepted even 18 years later. The cause is that it is difficult to control the UF in the PD, but now it is possible to set the DW by using the Icodextrin-PDF or Hybrid PD+once HD/wk (7). I hope to discuss the importance of “Dry Weight” setting in PD patients again.

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2) Nakayama M, Kawaguchi Y. Multicenter survey on hydration status and control of blood pressure in Japanese CAPD patients. Perit Dial Int. 2002 May-Jun;22(3):411-4.
3) Enia G, Mallamaci F, Benedetto FA, Panuccio V, Parlongo S, Cutrupi S, Giacone G, Cottini E, Tripepi G, Malatino LS, Zoccali C. Long-term CAPD patients are volume expanded and display more severe left ventricular hypertrophy than haemodialysis patients. Nephrol Dial Transplant. 2001 Jul;16(7):1459-64.
4) Jansen MA, Hart AA, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT. Predictors of the rate of decline of residual renal function in incident dialysis patients. Kidney Int. 2002 Sep;62(3):1046-53.
5) McCafferty K, Fan S, Davenport A. Extracellular volume expansion, measured by multifrequency bioimpedance, does not help preserve residual renal function in peritoneal dialysis patients. Kidney Int. 2014 Jan;85(1):151-7.
6) Mujais S, Nolph K, Gokal R, Blake P, Burkart J, Coles G, Kawaguchi Y, Kawanishi H, Korbet S, Krediet R, Lindholm B, Oreopoulos D, Rippe B, Selgas R. Evaluation and management of ultrafiltration problems in peritoneal dialysis. International Society for Peritoneal Dialysis Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis. Perit Dial Int. 2000;20 Suppl 4:S5-21.
7) Kawanishi H, McIntyre, Complementary use of peritoneal and hemodialysis: Therapeutic synergies in the treatment of end-stage renal failure patients. Kidney Intern 2008; 73:S63-S67

Hemodiafiltration (HDF) is controversial for the maintain the Dialysis-Related Hypotension (DRH). Although the several mechanism such as the Gibbs-Donnan, and low-temperature dialysis effects were discussed (1), these effect of HDF was denied by RCT (2). However, intermittent infusion HDF (IHDF) has been proposed as a new modality for prevent the DRH. The basic principal of IHDF is intermittent infusion used by back-filtrations, and the small size study showed that effects (3,4). It is meaningful to discuss these new therapies.

1) Kawanishi H. Is There Enough Evidence to Prove That Hemodiafiltration Is Superior? Blood Purif. 2018;46(1):3-6.
2) Smith JR, Zimmer N, Bell E, Francq BG, Mc-Connachie A, Mactier R: A randomized, single-blind, crossover trial of recovery time in high-flux hemodialysis and hemodiafiltration.Am J Kidney Dis 2017; 69: 762–770.
3) Koda Y, Aoike I, Hasegawa S, Osawa Y, Nakagawa Y, Iwabuchi F, Iwahashi C, Sugimoto T, Kikutani T. Feasibility of intermittent back-filtrate infusion hemodiafiltration to reduce intradialytic hypotension in patients with cardiovascular instability: a pilot study. Clin Exp Nephrol. 2017 Apr;21(2):324-332.
4) Mineshima M, Eguchi K, Shishido K, Takahashi S, Kubo T, Kawaguchi H, Shitomi K, Shibagaki K, Suga K, Nagao H, Takada M, Taoka M, Sato T. Clinical Effectiveness of Intermittent Infusion

Hemodiafiltration Using Backfiltration of Ultrapure Dialysis Fluid Compared with Predilution On-Line Hemodiafiltration. Contrib Nephrol. 2017;189:24-29

The effectiveness of frequent HD has been proven in many studies, but the adaptation at the center is not clear. Although the quasi-intensive center HD was introduced in the ANZDATA (1), the reactive (rescue) indication of intensive center HD is not yet clear evidence (2). However the effectiveness of this therapy is inferred and needed the further discussions.

1) Marshall MR, Polkinghorne KR, Kerr PG, Hawley CM, Agar JW, McDonald SP: Intensive hemodialysis and mortality risk in Australian and New Zealand populations. Am J Kidney Dis 2016; 67: 617–628
2) Banshodani M, Kawanishi H, Moriishi M, Shintaku S, Tsuchiya S. Increased Frequency of In-Center Hemodialysis as Rescue Therapy: Impact on Hospitalization for Acute Cardiovascular Events. Blood Purif. 2018 Nov 22:1-8.

Finally, I hope that the discussion at KDIGO will contribute to the improvement of the life prognosis/QOL of dialysis patients

Fan Fan Hou (Nanfang Hospital, Southern Medical University, China)

The scope of coverage is very comprehensive, including almost all crucial issues about dialysis. I would like to suggest two more questions being considered.

1. How might lifestyle modifications be beneficial for hypertension management in dialysis patients? If yes, which strategy should be recommended? (dietary pattern, exercises, body-weight, etc.)

2. What is the optimal BP target for pediatric dialysis patients? Does the definition apply across all patients? If not, how should targets be individualized?

Geoffrey Block (Reata Pharmaceuticals)

I applaud the conference agenda! I have just a few thoughts/comments for consideration.

- in-center HD patients get 48 BP measurements/month (sitting/standing, pre-post 12 sessions/month)- it is really unclear IF these should be used and If so, how does the clinician integrate the multitude of measurements in his/her head while rounding?

- I didn't see anything about the TREATMENT of intradialytic hypertension- should it be treated? ignored? should EPO be given to patients who develop intradialytic hypertension?

- I didn't see anything on the very common problem of diabetic autonomic neuropathy resulting in profound orthostatic hypotension BUT severe pre-dialytic HTN- it is totally unclear how to Rx these individuals

- regarding dialysis Rx- how should (or should it) be modified for intradialytic hypER tension?

- is hypotension in PD patients really a problem that needs to be addressed at this conference? doesn't seem like a tremendous (or complicated) issue clinically

- the conference should address somewhere the concept of a 'Max UFR' strategy- should clinics enforce a maximum UFR in ml/kg/hr given the risk above 10 and if so, should this be subject to a randomized trial (pragmatic would work well) versus Standard Therapy? This relates to the clinical manifestations/outcomes- those questions should consider how these could be implemented in a clinical trial which randomizes to a Max UFR strategy vs. standard- of course hospitalization would be measured and presumably some objective measure of stunning/ cognition

- I didn't see anything about the implementation issues with a dialysate temp (0.5 below core temp) strategy and how it can be done/assessed

- should we use serial imaging to document the adverse effects of poor BP managment? should we get serial LV assessments, tests of cognition/executive function?

- I'm sure it is in here but should we use the NON-dialysis day BP self-assessed by patient over 2 days as the standard? if so, how does the clinician handle the CQI aspect of BP control? How should BP control be assessed in a CQI program? It's not currently- only UFR

Mona Alrukhaimi (Dubai Medical College, UAE)

I agree with the scope of work and have nothing to add

Michael Germain (Baystate-U Mass Med School, USA)

1) More detail on the relatively rare intra dialytic HTN. Causes and treatment

2) discuss the changes in BP on the different days of the week

3) more discussion on how over likel 1/3 of pts have a too high DW, 1/3 too low DW and how we can better determine correct DW

4) perhaps the biggest gap in the SOW IS cardiac and vascular issues WHICH are intimately in wined with volume status, physiological response to UF, BP and cardiac issues, use of meds for HTN on cardiac issues

Mariano Arriola (Hospital Cullen, Argentina)

Very interesting meeting. I am waiting the results.

Thomas Golper (Vanderbilt University Medical Center, USA)

The physiologic side is very important, but please discuss strategies for a more holistic approach as well. A separate component is the behavioral/psychological aspect to volume management vis a vis Na and fluid intake. Obviously, part of that is cultural and educational.

Eduardo Aguilera (Instituto Mexicano del Seguro Social, Mexico)

In regard to management of BP and volume control in dialysis patients, it should be an individualized approach given the fact that almost every patient is different and there should be considered comorbidities other than the renal disease to make a satisfactory treatment such as concomitant atrial fibrillation, LVH, CHF as these are modifiers to the liquid overload or difficult control hypertension. Other factors include the weight, age and sex of the patient, it should be considerd the “dialysabilty” of antihypertensive agent and if the hypertension is volume dependent or other factors are intervening. Thank you

Rolando Claure-Del Granado (Universidad Mayor de San Simon, Bolivia)

How to utilize team care? This is a question that should be addressed during the conference in order to optimally treat hypertension and fluid overload in dialysis patients: the team of nephrologist, nurses and renal dietitian need to apply a multidisciplinary approach to optimize dialysis prescription and determine appropriate use of anti-hypertensive regimens as well as to advise and empower patients to the appropriate individualized dietary fluid and salt intake to optimize balance.

Clarissa Havel (RPh-on-the-go, USA)

Good review and seminar, symposium topics of blood pressure and volume management. Mirrors the ACCP PSAP for pharmacist Board Re-certification.

Meg Jardine (The George Institute for Global Health, Australia)

Thank you for the opportunity to comment on this important area. Fortunately we are at last seeing a rise in randomised trials being planned and undertaken in these areas which will help address knowledge deficits. The KDIGO conferences have the opportunity to inform new and ongoing trials by defining current knowledge but, more importantly, defining knowledge gaps and priority research areas. It will be important in this conference as in all of them, to distinguish between the current state of knowledge and the significance of any given area. For example, time to recovery post dialysis is a high significance topic but one where there is still an evidence gap for interventions. The considered statements by KDIGO CCs are very valuable in funding and IRB applications as they provide a consensus, independent view from an august body. By articulating areas of evidence gap, the Conference statement will assist research prioritisation and funding application success for issues of importance to the nephrology community. In my own areas of research activity I would nominate 3 priority areas.

1) Dialysate sodium. The current evidence (small to large observational and small randomised studies) for benefit is conflicting. There is small and indirect evidence on the patient experience (intradialytic hypotension) which suggests harm. There is evidence that individualisation increases prescribing mistakes. The area is ripe for a considered and thoughtful summary of the current evidence and, importantly, the evidence gaps. The RESOLVE trial I lead has commenced which will provide definitive evidence.

2) Haemodialysis hours. I don't think I saw this on the preliminary statement and I think it is important to include. Extended/nocturnal/frequent dialysis is a potential means to enable haemodynamic stability during and between dialysis sessions. Surprisingly little of the observational data reports on haemodynamic stability or the patient experience of intradialytic hypotension. We have completed the ACTIVE Dialysis study which is the largest RCT globally of extended dialysis hours with 200 patients in which we assessed multiple factors including Blood pressure, intradialytic weight gain, blood pressure lowering medications. Importantly, we also included the most comprehensive assessment of patient reported outcome measures of these trials, including EQ5d, SF-6D, SF36 MCS, SF36 PCS, KDCS and its components (articles in press/presented at conference presentations). The combined evidence from the ACTIVE, FHN and Alberta trials now provides at least some evidence to provide guidance in this area for haemodynamic management and the patient experience.

3) Haemodiafiltration. The evaluation of the impact of haemodiafiltration requires a careful evaluation and a nuanced statement. We have the benefit of some large completed trials and there have been useful publications arising. There were also some particular characteristics of reporting in some that have been described in systematic reviews from my group (Wang et al) and others (Nistor et al). There are further trials to report including our own completed trial which will report in 2019. More importantly, a large RCT is ongoing in the UK which represents a vital opportunity to address some of the uncertainties that remain.

Guillen Miguel-Ange (**Private Nephrology & Epicura, Belgium)**

1/ blood volume monitoring: recommandation to minimal use ? , minimal composant of monitor .?

2/ blood volume monitoring: nurse education ?

3/ Ultrafiltration rate and duration of hemodialysis ?

4/ blood pressure monitoring in legs : value/comment ?

5/ biofeedback with multiple cession analysis data : research to future approach of blood pressure stability...

Claire Gardiner (British Dietetic Association,UK)

I am responding on behalf of the British Dietetic Association Renal Nutrition Group. I have had a read through the document and it is very comprehensive. A lot of the questions should direct discussions around the factors we have discussed when developing the fluid management document on behalf of the Renal Association. Group 4 will focus on QOL and the role of salt and fluid management, although it is more directed at evidence relating to counselling, education and how we empower the patient. What is not clear from the questions is how the decision is made about individualising total fluid intake (based on body size and gender) and what salt recommendations are referred to. There are no questions that I can see that would direct that conversation and advise for further research in this area. I believe that there is inconsistencies in fluid management and although there is a not one size fits all approach there should be some agreement in how and when the decision is made regarding fluid allowance (rather than reducing salt intake first), especially in the interest of protecting RRF in this group. The questions asked will hopefully direct discussions around resources that may be used to educate and empower the patient which is paramount to the management of volume in dialysis patients.

Philip Zager (Dialysis Clinic Inc., USA)

Current recomendations on BP guidelines in HD patients have been largely extrapolated from the general population. We recently published the results of a successful pilot RCT comparing ususal vs. intensive control of BP. Although we obtained separation in SBP this was largely accomplished with medications rather than volume control. Since the pilot demonstrated feasibility and safety it seems time for an adequately powered, full-scale, RCT. It would require close attention to volume. Possible steps to control volume include, low salt diet, individualized dialysate sodium concentrations, longer or more frequent treatments. Given the high mortality on the day after the long interval a pilot of every other day dialysis seems warranted.

Maria Fernanda Slon Roblero (Complejo Hospitalario de Navarra, Spain)

I believe volume control is a very important issue in the field of dialysis and I am glad to know that we will have very valuable information on it at the end of this meeting! It is increasingly evident that volume control must be a fundamental aspect in dialysis adequacy and directly related to the survival of our patients; so this controversy will help to improve the knowledge of Nephrologists, updating and reinforcing knowledge related to this topic. I have reviewed the

different aspects to deal with during the controversy and it seems to me that it is very broad and complete. Thank you for your work and I hope to have the information available soon.

Patricia Ferreira Abreu (Universidade Federal de São Paulo, Brazil)

Dear colleagues, Congratulations for this topic; it is fundamental in daily clinical practice I would like to suggest the role of spirolactone to treat high blood pressure and heart failure Aspects about Drug and removal during dialysis Correlation between fluid withdrawal and online hematocrit Best regards

Alvaro Garcia (Colombia

Group 1: Blood Pressure (BP) Measurement and Targets and Pharmacologic Approaches to BP Management among Individuals Receiving Maintenance Dialysis BP Measurement

1. How and when should BP be measured among individuals receiving dialysis?

a. What approach, if any, is considered the gold standard to measure BP among individuals receiving dialysis? Does the approach differ by dialysis? Modality?
A typical dialysis therapy for patients in G5 is: hemodialysis 3 times a week in the dialysis unit; with frequent measurements of blood pressure (BP), at each visit; this peri-dialysis measurement of BP is used by most of the nephrologist as a diagnosis and treatment of BP, a frequent complication of CKD (Chronic Kidney disease). Recent data show that BP measurements in sites other than the dialysis units are superior in the diagnosis and treatment of the BP of the patient in RRT. The Gold standard to measure BP in dialysis patients, is an extrapolation of the methods used for the diagnosis of BP in the general population (Home BP and Ambulatory BP monitoring [ABPM]), not only makes the diagnosis more accurate but also correlates in a high % of accuracy with cardiovascular adverse events, which cause 60% of the deaths of patients on dialysis

b. When gold standard measurements are not available, what alternative BP measurements should be used to diagnose hypertension?
It is difficult to apply in 100% the Gold standard measure the BP for (expensive infrastructures, patient displacements, comfort, etc.), that is why other alternatives have arisen: like the home BP, which is based on a self-serial monitoring of BP measurements by the patient at home: on 7 days a week, it is measured twice a day (in the morning before breakfast and in the afternoon

before the meal and the supply of the hypo tensors); it is suggested to maintain the SBP between 120-135 and only use the ABPM, in those patients with pre-dialysis hypotension - post-dialysis hypertension, and with use of more than 3 hypo tensors, all to establish a profile of BP behavior in 24 hours .

c. Should in-center BP measurements ever be used to manage? Hypertension?
Having an Out-of-Clinic BP in the management of hemodialysis patients, is striking to which patients could attend in the interdialytic periods, and to be able to apply previously established protocols, for a standard diagnosis and treatment would be the standard Gold; but an Analysis Performed by the U.S. Agency for Health Care Research and Quality, determined that to measure and compare it with other modalities of study and treatment of BP and cardiovascular risk, the statistically significant sample for this would be a prospective study with 59,000 patients in a 10-year follow-up period, in order to obtain conclusive data and statistical weight.

The Blood Pressure (BP) targets in hemodialysis patients:
• K-DOQI- 2005: Predialysis < 140/90 mm Hg, post dialysis <of 130/80 mm Hg
• Proposed Approach:
• Home BP(BP measurement twice daily for 7 days): Target SBP 120-135mm Hg, and Target DBP 60-80 mm Hg
• Standardized clinic BP on non-dialysis (alternative when BP is not available): Target SBP < 140, Target DBP 60- 80 mm Hg
• Standardized dialysis unit BP: Target predialysis SBP 130-159 mm Hg y DBP 60-99 mm Hg; Target postdialysis: SBP 120-139 mm Hg y DBP 70-89 mm Hg

Definitions of Hypertension, Intradialytic Hypotension and Hypertension

2. What is the optimal definition of intradialytic hypotension? Based on what Evidence?
Intradialytic hypotension (IDH) is a medical complication with a high morbidity and mortality rate; its causes are multiple, it may be associated with subsequent vascular access thrombosis, inadequate dialysis dose, and mortality. Generally it is reported in a very wide range 15 to 50% of ambulatory HD session. This wide range implies the different criteria for its definition. The (KDOQI) Guidelines define HDI, as a sudden decrease in systolic pressure (SBP) of ≥ 20 mm hg or ≥ 10 mm hg (SBP), with symptoms attributed to it (Cramping, dizziness, headache). There are multiple studies and definitions regarding the percentage of PB drop, accompanied by symptoms or not and that respond to saline bolus administration, ultrafiltration (UF) reduction, or blood flow reduction. Some definitions are based on the reduction of SBP during dialysis treatment (20, 30, 40 mm Hg), or drops of the SBP, to points lower than the lower limit of the normal accepted SBP (90, 95,100), with symptoms of IDH, which are recovered with specific

measures already noted. A Secondary analysis of the HEMO study, referring to IDH according to the drop of SBP and its symptomatology was associated with a high risk of mortality.

a. Does this definition applies across dialysis modalities?
This pathology is fully defined and studied in patients on hemodialysis (but it can occur in any dialysis modality); the basic cause is the increase of ultrafiltration (UF), in a patient with water overload, in which large amounts of fluid are removed from the vascular and interstitial space, causing cardiovascular, electrolyte, neurological alterations, death arrest, when trying to lead the patient to his dry weight in a short time.

b. Should the definition vary depending on its planned use (identification ofPhenotype/ pattern vs. an episode)? To avoid IDH episodes, and cardiovascular decompensating, there are several studies, in which the allowed volume of UF per minute is shown according to the patient's dry weight 10-12 ml / Kg of weight / hour, during the time scheduled (average 4 hours). The central point of the problem is the control of the dry weight of the patient in dialysis, especially in those who do not have residual renal reserve and are auric. Interdialytic gain cannot be more than 2% of its dry weight; a continuous hydration of the patient in a chronic form (2.5 to 3 liters more), leads to the presence of SBP and develop cardiovascular disease, with a high risk of death at 2 years.

3. What is the optimal definition of intradialytic hypertension? Based on what Evidence?
The control of blood pressure is a condition that cannot be excluded as part of the treatment of patients with CKD and ESKD on dialysis. The high prevalence of fluid overload (FO) in chronic form, in this population, is one of the most important causes of the increase in SBP and the risk of death. Through the Whole-Body Bioimpedance Spectroscopy (BCM), it has been possible to correlate that a chronic over hydration ≥15% in men and 13% in women, that is to say more than 2.5 liters, represent risk and increase the levels of SBP and the inherent risks thereto. The optimal blood pressure values in pre dialysis are determined between 130-160 mm Hg; the risk of secondary mortality is 6% with low BP to 26% in those with high BP; as we can see, diastolic pressure (DBP) is practically not taken into account for this decision, its range varies between 60 to 90 mm Hg.

a. Does this definition apply across dialysis modalities?
High levels of BP, atherosclerosis, endothelial dysfunction, arterial stiffness, structural changes in the heart and brain increase the risk of death in hypertensive patients. The mechanisms responsible for endothelial dysfunction in the patient with CKD and ESKD, Dialysis is different from that of the general hypertensive population; in them are increased the levels of: Asymmetric Dimethylarginine, fibroblast growth factor 23, increased arterial stiffness owing to

procalcifying pathways, and impaired bone mineral metabolism. In addition, a pattern of diffuse myocardial fibrosis secondary to uremic toxins ,has been found in dialysis patients. Thus, hypertension is not part of the dialysis modality that is typical of CKD, but may be more frequent in a dialysis modality due to the water overload and the UF levels obtained.

b. Should the definition vary depending on its planned use (identification ofPhenotype/ pattern vs. an episode)?
Based on adjusted patient's models in dialysis and study and monitoring patterns, we can conceptualize that the target of the BP pre-dialysis is 130 to 159/60 to 99 mm Hg and BP post-dialysis of 120/70 to 89 mm Hg Patients who present pre-dialysis hypotension patterns - post dialysis hypertension, or who need more than 3 hypotensors, it is mandatory to evaluate other diagnostic forms and a pressure pattern in 24 hours, including sleep.

4. What is the optimal BP target for dialysis patients?
It is not clearly defined but a range between 130 -160 mm Hg (SBP) and a DBP between 90-60, has shown less comorbidities and good tolerance for patients a-Does this definition apply across dialysis modalities? Across all patients?If not, how should targets be individualized?- It is too complicated to have reference values of arterial hypertension, according to the therapeutic modality applied (HD, PD) - the intimate mechanism of BP is the vasculopathy characteristic of the patient with CKD, but BP levels are greatly influenced by the dry weight, water overload, UF, their ranges graphically form a U, and the risk of mortality increases at the extremes.

Pharmacologic Approaches to BP Abnormalities

5. When should anti-hypertensive agents be used?
Once the patient complies with the Optimal Dialysis Parameters and controls the established dry weight continuously; also, if the BP levels are persistently outside the established ranges; this would be the time to start the hypotensive medicines.

6. How should anti-hypertensive agents be selected?
There are several parameters to take into account.
• They are dialyzable
• Action time, long or short
• Hypo tensor efficacy
• Comorbidity of the patient to be treated, heart disease, water overload etc.
• Monotherapy or accompanied by others, (adverse effects use of β blockers + calcium antagonists=risk of AV block, increase K levels, hirsutism), it is important to keep in mind.

• Residual Kidney Function RKF
• Hepatic or kidney disposal route

a. Comparative effectiveness of anti-hypertensive agents?
The peripheral vasodilators are powerful hypo tensors, such as hydralazine and Minoxidil- they act directly producing arterial dilation, without venous compromise- the problem is that the time of action of the first one is short and requires several doses during 24h; Minoxidil is a powerful vasodilator but produces fluid retention, edema, may present pericardial effusion, and hirsutism, among others, its action time is 24h.

2. The Angiotensin -converting enzyme inhibitors (ACEis), and angiotensin II receptor blockers (ARBs), they are excellent hypo tensors, but their use is more targeted in the treatment of the patients with CKD (pre dialysis) with depurations between 60 a 30 ml/min71.73 m2 and significant proteinuria; they are dialyzable, their use in hemodialysis is good, they are powerful hypotensive, there are several jobs with the use of Lisinopril, Trandolopil, 3 times a week, post dialysis, with excellent results; one of the problems to consider is hyperkalemia.

3. Theβ- adrenergic Blocking agents (BABAs) originally were related to the treatment of heart disease (cardiopathy) and HF (cardiac failure when modifying cardiac output).The Hypertension in hemodialysis patient's treatment with Atenolol or Lisinopril (HDPAL)trial, showed its hypotensive effect in patients in dialysis, and left ventricular hypertrophy (LVH). There are many jobs where it is used as the first line of treatment for BP in dialysis to the BABA, 3 times a week.

4. Calcium antagonists are excellent hypotensive, on all long-acting dehydroperidines such as nefidipine, felodipine; their problemlies in the presence of edema. They are of hepatic metabolism. The non-dehydroperidines type Verapamil/Diltiazem, in many groups its prescription is abolished, due to the risk of AV block, when used in conjunction with the BBAs, they also decrease cardiac output, edema, constipation, etc.

5. Diuretics, (Thiazide and Loop Diuretics) and their use as hypotensors.
The Thiazide type, which blocks the co-transporter of Na-Cl in the distal convoluted tubule, responsible for 5% of the absorbed sodium and the loop diuretics which inhibit the Na-K-Cl co-transporter, present in the Thick ascending limb of the loop of Henle, responsible for 25% of total Na absorption, have no hypotensive effect in patients with dialysis.

6. Mineralocorticoid Receptor Brooches.
The aldosterone blockers type Spironolactone/Eplerenone, are excellent antihypertensive, cardio protective, antiproteinuric; its use in hemodialysis is conditioned by secondary hyperkalemia.

7. Centrally Actingα-Agonists
They are powerful peripheral vasodilators (Clonidine / Guanfacine) and frequently used in the control of BP in hemodialysis; but they have many side effects: dry mouth, sedation, bradycardia, and rebound hypertension when stopped abruptly.

b. How does dialysis modality factor into anti-hypertensive agent selection?
In general terms, it is Little what influences the anti-hypertensive agent and the dialectic method to choose, this is more related to the comorbidities of the patient, displacement to the dialysis unit, dialytic access, and adherence, among others. It is recommended to have a defined plan of antihypertensive stratified as follows: In the first line BABAs, Atenolol type for its long action and hypotensive power. In second line, calcium antagonists (DHP-CCBs). Third line is not established the role of diuretics in hemodialysis, the ACEIs / ARBs could be evaluated. In the fourth line, the peripheral vasodilators are powerful hypotensive.

c. How can anti-hypertensive therapy strategies be individualized?
It is important to determine the comorbidities of the patient, to take into account, in order to avoid further deterioration of them; for example, to prefer the use of BABAs, ACEIs or ARBs, in patients with CVD, due to its beneficial effect and to avoid the use of calcium antagonists. In patients with difficulty maintaining their weight, do not use-Centrally Acting α-Agonists, due to its dry mouth effect, which forces the patient to constantly consume water and thus it is not possible to control his dry weight. To avoid using ACEIs o ARBs,in those with tendency to hyperkalemia, etc.

7. What is the optimal timing of anti-hypertensive administration?
When are used anti-hypertensivedialyzabletype BABAs, ACEIs or ARBs, it is recommended to supply them 3 times a week after the dialysis.

a. How does dialysis modality factor into timing of anti-hypertensive agent Administration?
The blood bioavailability of the hypotensive agent is important in the control of BS, during 24 hours; it is important to take into account its excretion via (hepatic, kidney, other), protein binding 90 a 100%, if it is dialyzable or not, residual kidney function, etc. This will allow us not only to select the type of medicine, taking time (post dialysis), and time intervals.

8. What gaps remain in our understanding of antihypertensive medications in Dialysis and what type(s) of research is (are) needed to fill these gaps?
The patient in dialysis is polymedicated, in most of the times he takes> of 3 hypo tensors to control BP, with frequent side effects; it would be important the combination of potent, non-dialyzable hypotensive agents, which can be delivered periodically without considering the dialysis day, this added to a rational UF, would allow the patients to maintain BP in acceptable ranges and in this way decrease the risk of acute morbidity or death due to CVD.

9. Should pharmacologic agents be used to raise BP?
There are no systematic reviews or RCTs that evaluate this topic; the few reports are anecdotal in their majority. Only in specific pathologies such as hyporeninemichypoaldosteronism, has a specific therapy even in dialysis patients; daily doses of Fludrocortisone (0.025 to 0.05 mgs / day), with controls of Na, K, and dry weight, are recommended.

a. If, yes, in what clinical situations and what agents? If, no, why, and what are alternative management strategies?
It is fully demonstrated that the periodic supply of fluodrohydrocortizone not only corrects the defect of Na/K, but also increases the BP averages, by expanding the intravascular and interstitial space in patients with hyporeninemichypoaldosteronism. Its effect is more potent than the supply of salt capsule or use of other mineralocorticoids. The hypotensive patient deserves an extensive nutritional evaluation to determine albumin / total protein levels, a control of their dry weight, and moderate UF previously established, according to their BCM.

b. Comparative effectiveness of BP-raising agents?
Our experience with the use of hypertension in chronic form is null, we do not use any medication; in our hypotensive patients we make an evaluation of their pharmaceutical polypharmacy and their medical interactions, of their nutritional status, and of the use of a well programmed UF, in some occasions we transfer them from HD to a DP.

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Eugen Mota (University of Medicine and Pharmacy Craiova, Romania)

Routine dialysis unit systolic blood pressure measurements have significant limitations. The vast majority of dialysis clinics do not adhere to the American Heart Association (AHA) guidelines. Moreover, large inter and intra-patient variability has been reported, using routine dialysis unit blood pressure measurements. "Out of dialysis unit" blood pressure measures; eg, home blood pressure monitoring (HBPM) and ambulatory blood monitoring (ABPM) may be more strongly associated to clinical outcomes. However, adherence to HBPM and ABPM schedules has been noted to be poor. Furthermore, whether ABPM are the most reflective measures of a patient's true blood pressure remains controversial. Finally, current clinical guidelines for the diagnosis and treatment of hypertension in hemodialysis patients are based on routine pre-dialysis systolic blood pressure. Several biomarkers have been advocated as potential indicators of volume overload (atrial natriuretic peptide [ANP], brain natriuretic peptide [BNP] and cylic guanosine monophosphate [cGMP]). However, all are fraught with excessive variability and poor correlation with volume status. Since estimated dry weight (EDW) is difficult to assess by physical exam, other methods have been used to guide ultrafiltration; e.g., extracellular fluid volume (ECFV) measurement by bioelectrical impedance, ultrasonic measurement of the inferior vena cava diameter and collapsibility upon inspiration, ultrasound measurement of lung water, and continuous intra-dialytic blood volume monitoring. These measures suffer from operator dependence, low accuracy and/or precision, and impracticality. Furthermore, none is sufficiently reliable to justify routine use in clinical practice. Whether the blood pressure target identified by current clinical guidelines actually contributes to improved survival of hemodialysis patients remains controversial. A recent meta-analysis concluded that decreasing SBP in HD patients lowered the number of CVD events, as well as all cause- and CVD-mortality.

A RCT comparing intensive vs. standard hypertension control in HD patients is needed to assess the safety and efficacy of the KDOQI guidelines. The available evidence indicates that many HD patients with elevated BP may experience higher rates of cardiovascular events and mortality. The exception may be in HD patients prone to intradialytic hypotension (which may be from cardiomyopathy, slow' vascular refilling', autonomic dysfunction, other causes) or those with recurrent vascular access thrombosis / limited vascular access options. However, poor volume control can exacerbate hypertension and its myriad of detrimental effects on the cardiovascular system. Several studies support the association between fluid overload and all-cause and cardiovascular mortality. Fluid overload has also been associated with myocardial stunning, left ventricular hypertrophy and death. Perhaps in patients not at risk of acute hypertensive complications, it is prudent to initially determine and achieve the appropriate dry weight and fluid balance, before pharmacologic anti-hypertensive therapy is initiated or intensified. In order to optimally treat hypertension and fluid overload in dialysis patients, the nephrologist, nurse and renal dietitian will apply a multidisciplinary approach to optimize dialysis prescription and determine appropriate use of anti-hypertensive regimens as well as to advise and empower patients to the appropriate individualized dietary fluid and salt intake to optimize balance

Indranil Dasgupta (University Hospital Birmingham and Renal Association, UK)

First of all, I would like to congratulate the chairs for drawing up a very comprehensive scope of work. I have a few comments which I have listed below:

1. BP measurement - interdialytic ambulatory BP monitoring is considered gold standard but is not widely available and patients do not always agree to having this done. Interdialytic Home BP monitoring is considered second best but that too is not widely available especially in resource-constrained health systems, and also there are concerns about the accuracy of patient reported BP readings. On the other hand, pre and post HD (and sometimes intradialytic) BP measurements are recorded routinely. I feel a discussion needs to be had as to how effectively these routinely collected BP readings be used to manage hypertension in HD patients.

2. BP target - BP target will vary depending on the method of measurement (ABP/HBP/OBP) and timing of measurement (interdialytic/ pre/ post/ intra). Observational data suggest pre-dialysis SBP 130-160/170 mmHg is associated with lowest rates of CV events and mortality (Robinson 2012, Bansal 2017). Ideally, an adequately powered RCT using interdialytic BP readings will inform the ideal target BP in HD patients but this may not be possible in the foreseeable future given the complexity and cost of such a trial. The BID pilot study (Misculin JASN 2017) took a long time to recruit 126 patients to a trial comparing intensive (pre HD SBP

110-140 mmHg) vs standard (pre HD SBP 155-165) targets. There were safety signals in the intensive BP group with higher hospitalisation, intra-dialytic symptoms and vascular access thrombosis. This may add to the lack of equipoise among nephrologists to enrol to a substantive trial in the future. Therefore, we may have to go with the currently available observational data. A best practice guideline in this regard will be extremely useful.

3. Pharmacological approach in BP management - there is no head to head comparative trial available yet to inform what the best agent to treat BP in HD patients is. A few small trials suggest beta-blockers may be most beneficial. A recent large DOPPS study shows all commonly used agents are associated with lower mortality but ARBs may have a slight edge over the others (Karaboyas, KI 2018).

4. The other issue that must be considered is non-adherence to antihypertensive treatment which is very common (around 50%) among general hypertensives. With polypharmacy in HD patients, this may be even commoner. It is difficult to prove in HD patients as urine LCMS/MS assays are not possible and serum assays are costly and not widely available. Should we be recommending in-centre supervised administration of beta-blockers post HD (given what we know about their pharmacokinesis in HD patients) as first line therapy or where there is doubt about patient's compliance?

5. Management of intradialytic hypotension - there is growing evidence for the use of lower temperature dialysate in HD. Studies have shown it's benefit in reducing myocardial and cerebral stunning (Burton CJASN 2009, Odudu CJASN 2015, Eldehni CJASN 2015). Cognitive impairment is now a well-recognised complication of HD and recent evidence suggests it is associated with lower intradialytic cerebral blood flow (Findlay et al, JASN 2018). Our own work from DOPPS (Dasgupta et al, CJASN in press) shows that the routine use of low temp dialysate to prevent IDH is associated with a 24% lower risk of CV mortality. On the other hand, the use of sodium profiling was associated with higher all-cause mortality (36%), CV mortality (34%) and CV events (21%). These evidences need to be considered in developing a consensus statement in this regard and provide guidance to the clinician in the use of low temperature dialysate and tools to prevent/ mitigate IDH.

6. Extracellular Volume Management - our work mentioned above shows the variability in practice across the world; and the importance of regular and careful clinical assessment of target weight and fluid balance. Protocol that specified how often to assess dry weight (50% of 279 centres across the world) was associated with 22% lower all-cause and 28% lower CV mortalities. Moreover, the centres that use orthostatic BP measurement to assess target weight

have lower all-cause hospitalisation (14%) and CV events (15%). I believe the importance of careful clinical assessment for fluid status needs to be emphasised in the consensus statement.

7. Technology-Based Considerations Relevant to Volume Management - bioimpedance spectroscopy seems to have the best evidence with a number of observational studies and 2 small RCTs demonstrating better patient outcomes associated with its use to assess fluid volume in HD patients (Hur et al AJKD 2013, Onofrescu et al AJKD 2014). A large RCT is underway in the UK (BISTRO, Davies et al BMC nephrol 2017) assessing the importance of BIS guided fluid management in HD in protecting residual renal function with mortality and CV events among secondary endpoints. As for HDF, the data available are contradictory; a large adequately powered study is underway in the UK comparing HDF with HD (H4H) which is expected to address the issue convincingly in the near future. Until then it may not be wise to recommend its use. As for on-line blood volume monitoring, there are a few recent studies that suggest its use is associated with worse patient outcomes (Leung CJASN 2017). Our own data (Dasgupta CJASN in press) shows 19% higher all-cause mortality associated with the use of on-line volume monitoring. In the absence of technologies (or evidence of their benefit) to assist fluid volume management, especially in resource constrained-health systems, I strongly feel that the importance of regular and careful clinical assessment for fluid volume needs to be emphasised in the consensus document.

Thanks for giving me the opportunity to feedback on the scope.
Kind regards,
Indranil Dasgupta

Rommel Bataclan (University of the East Ramon Magsaysay Medical Center, Philippines)

I think it's important also to discuss if the treatment for hypertensive emergencies is similar to CKD 5D patients. The scope is comprehensive and a lot of issues though may be unresolved. Formulation of research gaps will help optimize treatment of hypertension among these patients.

Ansgar Conrad (Relypsa)

Thank you for providing us an opportunity to comment on the Scope of Work for the KDIGO Controversies Conference on Blood Pressure and Volume Management in Dialysis. We have reviewed the selected topics that will be covered during the meeting and would like to

recommend that the following clinically relevant questions be added and addressed during the controversies conference.

Group 1 Topics 5 to 9 in the proposed Scope of Work comment on pharmacologic approaches to blood pressure (BP) abnormalities in CKD patients receiving dialysis. A part of this discussion may focus on the emerging evidence of renin-angiotensin-aldosterone-system (RAAS) inhibitors, including angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor-blockers (ARBs), and mineralocorticoid-receptor-antagonists (MRAs) in dialysis and the need for further studies. Hyperkalemia (HK) has been reported in clinical trials with RAAS inhibitors in both patients with non-dialysis CKD and patients on dialysis and may limit the use of these medications. For these reasons, we suggest that the following questions be addressed within the proposed Scope of Work:
- To what extent may hyperkalemia may limit the use of RAAS inhibitors in dialysis patients?
- When (days, weeks), and how often should serum potassium be monitored in case an ACE inhibitor, ARB, or MRA is prescribed for the treatment of hypertension in patients on dialysis?
- How effective are current strategies for treatment of hyperkalemia in patients on dialysis receiving RAASi?
- In case hyperkalemia occurs while on RAAS inhibitors, what treatments should be prescribed to control BP in dialysis?
- What is the role for potassium binders in the management of RAAS inhibitor-associated hyperkalemia in patients on dialysis?

In a related discussion, Group 4 Topic 4 focuses on fluid and salt restrictions in BP and volume management. Part of the discussion may focus on salt-containing medications. We suggest that the following questions be addressed:
- Should sodium-containing medications be avoided in hypertensive patients receiving dialysis?
Rationale: Hypertension and volume overload are common clinical conditions among patients on dialysis and are often inadequately diagnosed and poorly controlled. Strategies to control volume and lower BP in these individuals may include nonpharmacological strategies such as controlling sodium by restricting dietary sodium intake, individualized dialysate sodium prescription and optimized duration of dialysis are first-line treatment, and, if BP remains uncontrolled, antihypertensive therapy (Georgianos & Agarwal, 2018). The association of RAAS inhibitors with improvement in clinical outcomes among those on hemodialysis is not clearly understood (Georgianos & Agarwal, 2016, 2018) and a subject of the present meeting. There is some evidence for the efficacy of ARBs (Takahashi et al., 2006, Zuzuki et al., 2008) and the combination of ACEi and ARBs (Cice et al., 2010) in dialysis while other studies have not demonstrated a benefit (Zannad et al., 2006, Iseki et al., 2013, Peters et al., 2014). Similarly, the safety and efficacy of MRAs in the treatment of dialysis patients is not well defined. Panagiotis

et al. (2017) conducted a systematic literature search of MEDLINE/PubMed and identified 11 randomized controlled clinical trials evaluating the efficacy and safety of MRAs in dialysis patients. The authors concluded that the MRAs spironolactone and eplerenone may be beneficial in improving several surrogate cardiovascular endpoints among dialysis patients. Properly designed, larger studies are needed to confirm the effects, including the ongoing Phase III ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST) (University Hospital, Brest, 2018). Hyperkalemia is a common electrolyte disorder among dialysis patients and is associated with increased risk of cardiovascular and arrhythmogenic death (Sanghavi et al., 2013). Given the high vulnerability of dialysis patients in developing hyperkalemia and the close association of this electrolyte disorder with adverse events, the potential cardioprotective properties of MRAs in the dialysis setting may be compromised by MRA-induced hyperkalemia (Panagiotis et al., 2017). For example, in the PHASE study (Walsh et al., 2015), 154 prevalent hemodialysis patients were randomly allocated to eplerenone (titrated up to 50 mg daily) or placebo for 13 weeks. The incidence of hyperkalemia (defined as pre-dialysis serum potassium >6.5 mEq/L) was 4.5-fold higher in eplerenone-treated participants than in placebo-treated participants [Relative Risk (RR): 4.5; 95% CI: 1.0-20.2]. There is no consensus on how often serum potassium should be monitored in case an ACE inhibitor, ARB, or MRA is utilized for the treatment of hypertension in patients on dialysis. In addition, discussion could be warranted on how effective current strategies for treatment of hyperkalemia in patients on dialysis receiving RAASi are, including if there could be a role for potassium binders. Another approach to controlling volume and BP of patients with CKD is reduced sodium intake. In fact, BP of patients with CKD is more sensitive to high sodium intake than persons with normal kidney function due to a diminished capacity to excrete sodium (Johnson et al., 2002). Mills et al. (2016) followed 3757 patients in the Chronic Renal Insufficiency Cohort (CRIC) Study for a median of 6.8 years and found that among patients with CKD, higher urinary sodium excretion was associated with increased risk of CVD. KDIGO guidelines (2013) recommend that CKD patients consume <2g (<90 mmol) per day of sodium (~5g of salt), unless contraindicated. Thus, a discussion may be warranted if high sodium-containing medications should be avoided in patients receiving dialysis to help control interdialytic weight gain and improve blood pressure control.

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Yusuke Tsukamoto (Itabashi Chuo Medical Center, Japan)

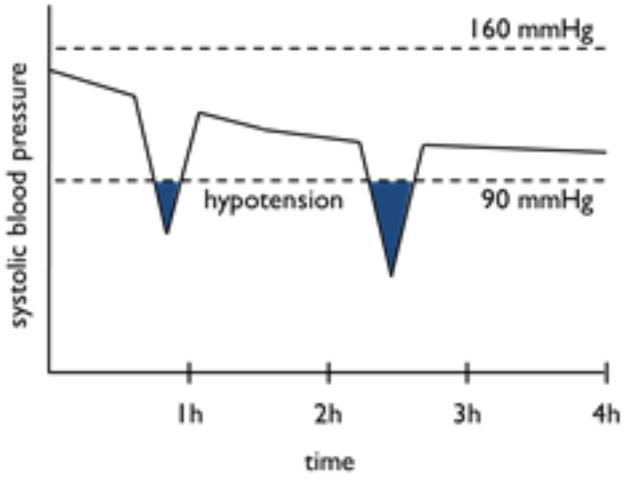
Effect of dialysis, comorbidities by BP derangement and its management are so much different between hemo and peritoneal. I would suggest separate group discussion to discuss hemo and PD.

Axel Dessal (TrioxBio, Inc.)

As developers of a drug to treat and prevent intra-hemodialytic hypotension, including hypotension in the immediate post-hemodialytic period, we are particularly interested in groups 1 and 2, more especially, in everything related to the definition of intra-hemodialytic hypotension and to its pharmacologic prevention. I think that given our ongoing discussions with the FDA, the EMA, clinical research organizations, dialysis organizations and potential investors, we could contribute to the conference with very valuable knowledge.

Based on our discussions with potential investors, I think that it is very important that KDIGO, as it intends, provides a new definition of intra-hemodialytic hypotension which "officially" replaces the one that KDOQI presented in 2005. We have adopted, and we continuously defend, the nadir-SBP-based definition proposed by Jennifer Flythe, Steven Brunelli and others in 2015, and the potential investors always ask whether this definition has already been accepted by the FDA, EMA, etc.

We have designed a phase 2 clinical trial which will indeed use nadir SBP as its primary endpoint, and we will even explore the practicality of other endpoints, for instance, the area above the SBP curve and below the IDH definition threshold (AACBDT), which might better correlate with mortality, as it takes into account how often, how deeply and for how long the patients have been hypotensive during the hemodialysis session. The beauty about this endpoint is that Flythe and Brunelli could compute it with the same data points that they used to compute nadir SBP in their work.



In our phase 2 clinical trial, we will also explore the ability of our drug to prevent orthostatic hypotension immediately following the hemodialysis session. I think that this topic could also

be included in your program. Although orthostatic hypotension immediately following the hemodialysis session is sometimes mentioned together with intra-hemodialytic hypotension as “hemodialysis-associated hypotension”, the truth is that there is not much information about its importance and its incidence.

In general, I think that the Scope of Work looks very good and that the timing for the conference is great!

Best regards,
Axel

Ezio Movilli (University of Brescia, Italy)

I would suggest to include in the “Ultrafiltration rate and treatment time“ section a discussion point on the role of “end-dialysis overweight” or “end-dialysis Hyper or hypo hidrationon” on morbidity and mortality.

There are some interesting observations suggesting an independent role of residual hyper or hypo hydration on all cause and cardiovascular mortality in patients on chronic HD treatment.

(Movilli E, Camerini C, Gaggia P, et al. Am J Nephrol. 2013;37(4):370-7; Flythe JE, Kshirsagar AV, Falk RJ, Brunelli SM: Clin J Am Soc Nephrol 10: 808–816, 2015; Assimon MM, Wang L, Flythe JE.J Am Soc Nephrol 29: 2178–2188, 2018.)