KDIGO Controversies Conference on Central & Peripheral Arterial Diseases in CKD
- Public Review Comments -

As of January 15, 2020
Industry comments are highlighted in blue

Andrew Davenport - University College London (Doctor / Physician)
1. role of monitoring with pulse wave velocity
2. role of lipid lowering strategies
3. Vitamin K2/ 25 OH vitamin D3 and Mg in preventing vascular calcification
4. interaction between osteoporosis and vascular calcification
5. role of shared/self-care

Dwarakanathan Ranganathan - Royal Brisbane & Women's Hospital (Doctor / Physician)
Peripheral artery disease Is there a difference in managing a patient with Diabetes Mellitus and CKD and CKD due to other causes

Cibele Isaac Rodrigues - Pontifícia Universidade Católica de São Paulo (Doctor / Physician)
Agree with the scope. It's important to clarify if the best evidence available supports or not renal revascularization for patients with high-risk clinical features: RAS of > 80% with a significant translesional pressure gradient; resistant and refractory hypertension, especially in younger patients; type of stenosis; rapid deterioration of renal function; flash pulmonary edema; and post-transplant RAS. There are several trials coming soon: https://clinicaltrials.gov/ct2/results?cond=Renal+Artery+Stenosis&Search=Apply&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=. All issues are important.

Girish Kumthekar - Star Hospital Hyderabad (Doctor / Physician)
A new look at lipid disorders in hemodialysis dependent patients
Introduction: Atherosclerotic cardiovascular disease is a major cause of mortality and morbidity in dialysis patients. Compared to general population, dialysis patients have lower lipid levels and higher vascular events. This paradox is popularly known as reverse epidemiology. This study is an attempt to understand reasons for low lipids in dialysis patients.
Material and methods: This is a prospective observation multicentric study involving three phases across six dialysis units with Care Hospitals, Hyderabad, India. 140 maintenance haemodialysis patients are studied with fasting lipid profiles [TC,LDL-c,HDL-c & TG],pre dialysis blood lipids ,post dialysis blood lipids and effluent water lipid profiles. Other parameters studied are vintage dialysis, presence of diabetes, coronary artery disease, use of statins, interdialytic weight gain and ultrafiltration. All patients had uniform dialysis protocols regarding filter used and dialysis duration.
Results: We observe significant rise in post dialysis total cholesterol [TC], LDL and HDL [$p < 0.01$] and likewise fall in lipids during interdialytic period [$p < 0.01$] just before the next dialysis. Lipids are least filtered across the membrane except HDL, which is found in effluent water for more than 60% of patients. Re use of dialyser is associated with higher rise in lipids post dialysis as well as HDL getting filtered in effluent [$p=0.24$]. Re use is also associated with lower BMI . Hemoglobin [$p=0.04$] and serum albumin[$p=0.92$] show increasing trend with increasing dialysis vintage. Rosuvastatin associated with lower lipid values[$p=0.08$] and BMI [$p=0.19$].
Conclusions: Low lipid levels in dialysis patients are due to dilution of plasma. These spuriously low lipid levels are due to dilutional hypolipidaemia and needs correction with an equation proposed in present study. Corrected lipids should be used for risk stratification and deploying treatment.

Deepak Sharma – Ketav Kalp Healthcare & Research (Doctor / Physician)
A well-conceived, compiled, and covered scope of work

Peter McCullough - Baylor University Medical Center (Doctor / Physician)
1) Add Lp (a) as novel risk factor for atherosclerosis in CKD
2) Add evidence for statins, exetimibe, PCSK9-9 inhibitors, EPA, and control of C P PTH, and future therapies including 6 inosine monophosphate
3) Add evidence review for percutaneous and surgical outcomes for critical limb ischemia

4) Add global variation in amputations as a focus topic and the need for technological advancement in percutaneous intervention for limb salvage

Pradeep Kumar Rai - Opal Hospital (Doctor / Physician)
Central and peripheral arterial disease is not very uncommon problem in CKD population. It is mainly because of atherosclerosis and arterial calcification due to mineral bone disease. It is seen commonly in those patients where CKD is secondary to Diabetes Mellitus. Other risk factors are Smoking, hyperuricemia, hypertension and hyperlipidemia. Commonest cause of death in CKD population is CVD. Keeping these points in mind I suggest the KDIGO experts to organise conference on central and peripheral arterial disease in CKD patients.

Kenneth Woodside - University of Michigan (Doctor / Physician)
CAD and PAD also significantly impact kidney transplant eligibility and peritransplant morbidity. The conference should be sure to address that, as well as the impact of vascular calcifications on transplantability.

Hideki Ishii - Nagoya University (Doctor / Physician)
Evaluation of the abdominal aortic calcification (AAC) can predict adverse clinical outcomes among CKD patients (Atherosclerosis. 2015 Dec;243(2):349-55). In addition, the AAC progression rate is significantly accelerated in patients with advanced CKD. Moreover measuring PTH is useful to evaluate both bone turnover and AAC progression in patients with advanced CKD (Atherosclerosis. 2016 Oct;253:15-21). Therefore, such measurement might be useful in the clinical settings.

Sreedhar Mandayam - UT MD Anderson Cancer Center (Doctor / Physician)
Very interested in the central aortic disease portion of this workshop. We had investigated the risk factors for AKI after TAA surgery at the Texas Medical Center and found strong co-relations between protected and unprotected renal times and dialysis dependent AKI occurrence with no real reductions in AKI over the years despite changes in OR management. Also curious to study the impact of EVARs in patients with CKD and risk for AKI or progression to ESRD

Vanessa Cullen - KHA-CARI Steering Committee and PKD Australia (Patient)
Please also look into the impact of positive diagnosis upon the emotional wellbeing and lifestyle of the patient, the management of these impacts and upon potential positive lifestyle intervention guidelines to empower patients.

Charles O'Neill - Emory University (Doctor / Physician)
I think any analysis of PAD has to include vascular calcification, specifically medial arterial calcification, which we have shown to be the principal lesion (Prevalence of non-atheromatous lesions in peripheral arterial disease. Arteriosclerosis, Thrombosis, and Vascular Biology 35:439-447, 2015) and which I believe plays a major role. We have shown a strong correlation between medial calcification elsewhere and amputation/revascularization in ESRD (Clinical significance of medial arterial calcification in end-stage renal disease in women. Kidney International 87:195-199, 2015). More recently, we have found that warfarin accelerates this calcification and probably should be used with caution in ESRD.

Manish Sood - University of Ottawa (Doctor / Physician)
Some recommendations for scope of work include Group 1: Clinical outcomes after stroke events: acute volume/dialysis management, risk of other cardiovascular events, functional status and all-cause mortality Functional recovery and rehabilitation by CKD stage/ dialysis/transplant Prediction scores/predictors of stroke specific to kidney disease may want to separate treatments specifically for hemorrhagic vs ischemic stroke

Mariana Murea - Wake Forest School of Medicine (Doctor / Physician)
Additional point of discussion for consideration
Group 1: Atherosclerotic Cerebrovascular Disease 1. The effects of different renal replacement modalities (PD, in-center thrice-weekly HD, in-center frequent HD, home HD) on incidence of stroke, markers of dysregulated cerebral perfusion during dialysis 2. The effects of different HD prescriptions on cerebral perfusion during dialysis (dialysate temperature, ultrafiltration rate in ml/kg/hr) 3. Subclinical strokes in patients on dialysis and attendant clinical consequences
Group 2: Central Aortic Disease 1. Differences in natural history of AAA (annual growth rate, risk of rupture or leak at lower dimension) in patients with and without CKD, and between patients with different CKD stages, adjusted for comorbidities

Group 4: Peripheral Arterial Diseases 1. Prevalence of PAD in the arterial bed of upper extremities in patients with known PAD in the arterial bed of lower extremities in the context of CKD/dialysis 2. Impact of PAD on the success of arteriovenous (AV) access creation in CKD/dialysis population 3. Would screening for upper extremities PAD be warranted as part of workup during planning for AV access placement?

DanielWeiner - Tufts Medical Center (Doctor / Physician)
One item to consider, although it may be in more access specific meetings, is the interaction between PAD and hemodialysis access, specifically fistulas and grafts. This is one of the more common peripheral artery disease scenarios that nephrologists and kidney patients confront on a regular basis. Thanks.

Sandro Mazzaferro - Sapienza University of Rome (Doctor / Physician)
Very important point to be considered for guidelines. Scope of coverage seems adequate.

EmilioRodrigo - University of Cantabria (Doctor / Physician)
I think that the issues proposed in each of the groups are relevant and encompass most of the fundamental aspects of each topic. In addition, I would like some more questions to be incorporated where there may be some doubts or as a reason for future research:
Group 1: Atherosclerotic Cerebrovascular Disease (excluding intracerebral disease) - Influence of stroke and its therapeutic procedures, such as intravenous thrombolysis and endovascular thrombectomy, in the development of AKI (Diprose WK et al. Contrast-Associated Acute Kidney Injury in Endovascular Thrombectomy Patients With and Without Baseline Renal Impairment. Stroke 2019; Gadalean F et al. The impact of acute kidney injury on in-hospital mortality in acute ischemic stroke patients undergoing intravenous thrombolysis. PLoS One 2017) - Influence of stroke-related-AKI on morbidity and mortality after stroke (Arnold J et al. Incidence and impact on outcomes of acute kidney injury after a stroke: a systematic review and meta-analysis. BMC Nephrol 2018)
Group 3: Renovascular Disease - Review of novel therapeutic strategies (trying to ameliorate renal inflammation or improving microvascular remodeling and/or mitochondrial injury) for renovascular disease in order to recommend further research on this field (reviewed by Eirin A, Textor SC, Lerman LO. Curr Opin Nephrol Hypertens. 2019)

Group 4: Peripheral Arterial Diseases - Although both decreased GFR and albuminuria are independent risk factors for PAD and some other non-traditional risk factors may also play a role on its development, I would like to highlight the importance of diabetes and smoking in its development and aggravation (Kaminski MR et al. Risk factors for foot ulceration and lower extremity amputation in adults with end-stage renal disease on dialysis: a systematic review and meta-analysis. Nephrol Dial Transplant 2015) - Reamputation risk in CKD: impact and risk factors (Czerniecki JM et al. Predicting reamputation risk in patients undergoing lower extremity amputation due to the complications of peripheral artery disease and/or diabetes. Br J Surg 2019)

Joris Rotmans - Leiden University Medical Center (Doctor / Physician)
Dear KDIGO-coordinators, thank you for reaching out in preparation for the KDIGO meeting on the very important of arterial disease in CKD patients. Below my suggestions/comments with regard to key issues relevant to the optimal detection, management and treatment of arterial disease.
- indications for diagnostic evaluation and treatment of renovascular disease.
- anticoagulation (DOAC, Vit K antagonist) for atrial fibrillation in advanced CKD.
- risk/benefits of surgical reconstruction of aortic/iliac stenosis to enable options for kidney transplantation in ESKD patients.
- indications for ICD-implantation in ESKD patients.
- statin therapy: hit and run versus LDL target levels. - optimal blood pressure target after stroke in ESKD patients.
- indications for acetylsalicylic acid (or is clopidogrel always better?)

Allen Hamdan - Beth Israel Deaconess Medical Center (Doctor / Physician)
Atherosclerotic Cerebrovascular Disease (excluding intracerebral disease)
How do we extrapolate information from large studies where CKD patients are excluded?
How does CREST I and II factor into our decisions?
How does TCAR fit into procedural algorithm?
Peripheral Arterial Diseases
How do we medically manage asymptomatic PAD?
Should we be screening for asymptomatic PAD?
Are there types of patients who should have primary amputation?
Multidisciplinary care in critical limb ischemia
Role of palliative care in last year of life/amputation decisions
Treatment of PAD in patients with functioning allograft

Alvaro Garcia (Doctor / Physician)

Group 3: Reno vascular Disease

1.What is the epidemiology in the context of CKD/dialysis? Reno vascular Disease includes renal artery stenosis (RAS), Reno vascular hypertension (RVH) and azotemic Reno vascular disease (ischemic nephropathy). Reno vascular hypertension is the result of RAS; it is the most common cause of secondary hypertension, and occurs in 1 to 2% of all causes of arterial hypertension (HTA) in the general population and in 5.8% of all cases of secondary HTA; its frequency is directly proportional to the degree of hypertension that patients present. In 2008 the American Heart Association defined a significant stenosis a 60% decrease in the luminal diameter of the renal artery; but the SAR can be found with stenosis > 70% or 50% in post dilation stenosis. It is important to individualize RAS and RVH; the latter is the summation of RAS + activation of RAAS (renin-angiotensin-aldosterone system); + sympathetic nervous system and active vessel hormones. Its summation results in a systemic HTA with very well defined characteristics; if it is a RAS with one renal artery compromise or, if its compromise is bilateral. By means of invasive or non-invasive diagnostic aids, we can find RAS in 5% of patients > 65 years old, and in 42% in those over 72 years old. In those who underwent renal arteriography, a RAS > 50% in 35% of patients with CKD, 20 to 35% in patients with Central Aortic Disease, 15 to 40% of the Peripheral Arterial Diseases and 5-20% in Coronary Artery disease. RAS may have several etiologies, atherosclerosis represents 90% of all causes and the rest 10% may be secondary to: fibro muscular disease of the media, Takayasu arteritis, and giant cell vasculitis, primary or secondary anti phospholipid syndrome, renal artery stenosis in post transplantation, among others. RAS is considered as an etiological agent of CKD in patients with HTA of difficult control more than 3 hypotensives for its control; hypertensive crisis, pulmonary edema flash, rapid and progressive deterioration of GFR: more than 0.5 mg in Cr or loss of 30% of GFR (< 3 months), which can lead to ESRD, or aggravate the vascular pattern in dialysis patients; endovascular treatment improves the pattern by 35 to 40% (see RAS treatment). On the other hand, it has been observed in patients with (RVH) followed by ultrasound - an incidence at two years of renal atrophy of approximately 5% in the cases in which the initial ultrasound was reported as normal, 12% of atrophy when the stenosis was < 60% and 21% when it was related to stenosis > 60%. The mere presence of RVH or end-stage renal disease reflects pathological states of poor prognosis for the patient's survival. Survival decreases as stenosis progression increases; survival is estimated at close to 96% for unilateral stenosis, 76% for bilateral stenosis, and 46% for occlusion or stenosis in a solitary kidney. Similarly, creatinine elevation decreases survival inversely; survival > 90% is expected when creatinine is below 1.4 mg/dL, 74% when creatinine is between

1.5 and 1.9 mg/dL, and 51% when creatinine is elevated above 2 mg/dL. Disease progression is slow and with a low tendency to develop occlusion (1, 2).
2. What is the pathophysiology? (e.g., role of hypoxia, inflammation, etc.; novel biomarkers?) The models of Harry Goldblatt and Erwin Hass, one, or two clip (one, or two kidneys) not only highlighted the role of RAAS, + the activation of the sympathetic nervous system and vase active hormones in the pathophysiology of VHR; in addition these works revealed the renal ischemic model, of renal damage; depending on the degree of stenosis, of the blood flow, the levels of 02, and inflammatory cytokines, as causes of the physiopathology of the Atherosclerotic Reno vascular disease (ARVD). However, it is believed that severe or prolonged vascular occlusion may surpass the adapted mechanisms of the kidney and activate an inflammatory cascade, culminating in micro vascular alteration and irreversible renal fibrosis. Venous blood analysis of stenosis kidneys reveals significantly higher levels of pro-inflammatory mediators such as attractive monocyte chemo protein 1 (MCP-1), interleukin-6 (IL-6), interferon-α (IFN-α) and tumor necrosis factor β (TNF-β) compared to the kidneys of patients with essential hypertension, despite similar control of blood pressure and blockage of the renin-angiotensin system. This cytosine mediate the migration of inflammatory cells such as macrophages and B and T lymphocytes within the renal parenchyma, leading to matrix accumulation, collagen deposition, micro vascular alteration, and irreversible renal fibrosis (ischemic nephropathy) (3,4,5) Reno vascular disease (ARVD). The relationship between blood flows (RBF), tissue oxygenation, and inflammatory injury in Atherosclerotic Reno vascular disease (ARVD), is poorly studied; few papers refer to this topic. Abumoawad A, et al (6) conducted a study in 48 patients with ARVD, Kidney simplex who are determined RBF, GFR; and tissue hypoxia. The sGFR was determined by Iotholamate, oxygenation was measured by Magnetic Resonance Image (BOLD MRI) which comes from an index of the level of Oxi- hemoglobin, in a volume of tissue (R2*).sGFR, correlated with RBF and with the degree of stenosis (determined by Duplex velocities); in addition values were determined in the renal vein of Neutrophil-Gelatinize-associated-Lipocalin (NGAL) and Monocyte-Chemoattractin protein-1 (MCP-1) which were high; but the correlation of R2* cortical, RBF and sGFR, was only evident when the sGFR falls below 8 ± 3ml with an R= -0.1; evidencing the high power of renal tissue tolerance to the decrease of RBF concentrations and saturation of 02; but when hypoxia occurs, there is liberation of inflammatory cytokines. There are few novel biomarkers in ARVD that reveal the entity and quantify the damage caused by it. In the Reno vascular Salford Study, several biomarkers and the final outcome were analyzed in a follow-up time: FGF-23, Cystatin C, Kidney Injury Molecule-1, Myeloperoxidase, neutrophil gelatinase-associted-lipocalin, m-terminal pro-hormone of brain Natriuretic peptide (Nt-proBNP), high-sensitivity troponin T, and anti-Apo lipoprotein A1 IgG; using a Cox

proportional hazards model and net reclassification index and the individual effect of biomarkers on predicting death, end-stage kidney disease and cardiovascular events. A total of 112 patients were followed for 59.9 months; 75 patients died, 21 progressed to ESRD and 36 suffered a cardiovascular event. Only NT-proBNP maintained statistical significance with all end-points (Death: HR 1.62, 95% CI 1.26-2,10, p < p,0005), end stage kidney disease:(HR:1.51, 95% CI 1.19-1,91, p=0.001) and cardiovascular event: (HR 1.56 , 95% Ci 1.23-1.97, p < 0.0005), in the panel of biomarkers when the concentration of NT-proBNP is > 300 ng/ml, revascularization is superior to medical treatment and correlates more efficiently all these catastrophic events secondary to ARVD. (7) Hipoxia, there is release of inflammatory cytokines.

3. What are the means for diagnosis and optimal evaluation, including value of duplex ultrasound, CT, MRI and angiography? All patients > 55 years old, with risk factors such as: 1- cardiovascular or peripheral arterial disease, malignant hypertension, or difficult to control with more than three antihypertensive drugs, sudden worsening of HTA, or renal function, flash pulmonary edema. 2- Presence of a systolic murmur in the renal fossae during physical examination, ankle-brachial index < 0.9 and presence of retinopathy. 3- HTA in women < 30 years or, in other cases if the patient presents sudden deterioration of renal function associated with the intake of angiotensin II converting enzyme inhibitors (IECAS) or the AT receptor (IARA II), or difference in size between kidneys > 1.5 cms. In all these cases it is recommended to perform diagnostic evaluation of (RVH), in order to evidence and quantify the degree of renal artery stenosis. Eco Doppler color. Of greater availability, it is of low cost, the disadvantage is to be a dependent operator. It has a sensitivity of 84-98% and a specificity of 62- 90%, its utility has a Class IB level of evidence for the diagnosis of renal artery stenosis. The CORAL study included as entry criteria Doppler velocities > 300 cm/sec, ensuring that values below that flow rate did not correlate with hemodynamically significant stenosis (> 60%). The resistance index is the ratio measured between the systolic and diastolic peaks (PS-PD/PS), its normal value is below 80, it is related to the hemodynamic response after renal revascularization and can be used as a predictor of response to treatment. The aortic renal index > 3.5 is related to a stenosis > 60% and a diastolic peak > 150 cm/sec, with a stenosis of ± 70%. Renography with captopril. It is a hemodynamic study that measures renin-dependent GFR, requires the suspension of the intake of IECAS and AT II inhibitors, provides functional information about renal perfusion and assesses the dependence of glomerular filtration rate on angiotensin II; it has a sensitivity of 74%, specificity of 59%, positive predictive value of 58%, and negative predictive value of 75%. This method has an evidence level III C for the diagnosis of Reno vascular hypertension and should not be used as the only study for decision making given its specificity. Magnetic resonance

angiography. Its limitation is cost, but this method provides information about the size, morphology, renal artery flow, filtration rate and vascular anatomy of each kidney in 3D; it has sensitivity of 97% and specificity of 93%. This method has a Class IB level of evidence for the diagnosis of renal artery stenosis.
Angiotomography. This imaging methodology is highly effective in allowing the visualization of the renal parenchyma, as well as the vascular anatomy, 3D reconstructions can be obtained. It has sensitivity of 98% and specificity of 94%, in detecting significant stenosis in the renal artery, with the application of a moderate amount of contrast material. Its use has Class IB evidence level for the diagnosis of renal artery stenosis. Arteriography. It continues to be the Gold standard in determining more precisely renal vascular anatomy, can detect stenosis in intraparenchymal branches and allows early diagnosis in cases of fibromuscular dysplasia (FD), has Class IB evidence level, is a solution in cases where non-invasive methods are inconclusive, also provides the alternative of offering an endovascular therapeutic procedure if necessary. (3, 4, 8)
4. What are the management and indications for treatment? (e.g., surgical Revascularization, medical, vs. stenting) Recent prospective trials of ARVD have shown that revascularization does not confer any additional benefit to optimal medical treatment in unselected populations and this has led to a decrease in the number of revascularization procedures performed. However, there is observational evidence that subgroups of patients with a so-called "high-risk" phenotype, such as patients with recurrent pulmonary edema, refractory hypertension, or rapidly decreasing renal function, benefit from revascularization (8,9,10). Several studies have been conducted in recent decades to determine whether kidney revascularization confers any additional benefit to medical therapy. A meta-analysis of 3 RTCs, in (210) patients randomized to percutaneous transluminal angioplasty (stenting) or medical therapy, with blood pressure control as the primary endpoint, showed that revascularization does not improve blood pressure or renal function, (11,12). A subsequent study, the STAR trial, assigned 140 patients to medical therapy alone or in combination with angioplasty and stenting. The primary endpoint was to improve eGFR-cr at 24 months. This study again showed that revascularization did not exert any additional benefit compared to medical therapy [18]. Importantly, all these studies showed considerable risks associated with revascularization. The STAR trial showed a perirevascularization mortality rate of 3%; and the prevalence of more frequent complications in contemporary clinical practice is about 0.5-10% [11, 14]. These small studies were followed by two large, landmark RCTs that provided more robust data on the role of renal revascularization. The UK-based trial (ASTRAL) randomized 806 patients with ARVD to medical therapy alone or in conjunction with revascularization. The primary endpoint was change in renal function from baseline. Patients were

included in the trial if they had renal artery stenosis and would be assessed for benefit from revascularization. In fact, in the study population, 40% were found to have stenosis below (50-70%) on angiography and 17% of patients randomized to stenting did not receive the intervention, because they had no identifiable stenosis. After a 34-month follow-up, the results showed that revascularization had no impact on improving renal function or blood pressure control, such as on the incidence of cardiovascular events or on mortality (secondary endpoints). Revascularization was also associated with a 6.8% complication rate (15). The U.S.-based Cardiovascular Outcomes in Atherosclerotic Kidney Lesions (CORAL) trial randomized 947 patients to stenting and best medical therapy or best medical therapy alone. The primary endpoint was a combination of major cardiovascular events, progressive deterioration of kidney function, and death from cardiovascular or renal causes. The initial design of CORAL was aimed at overcoming the defects observed in ASTRAL; only patients with hemodynamically confirmed severe renal artery stenosis and a systolic blood pressure > 155 mm Hg or more of 2 antihypertensive agents were chosen. The degree of stenosis was standardized by angiographic evaluation and translesional gradient measurement; severe stenosis was defined as at least 80% but less than 100% angiographic stenosis or 60-80% stenosis with a translesional systolic pressure gradient of at least 20 mm Hg. At the end of the study, average angiographic stenosis was 67%, similar to that of ASTRAL and only 20% of patients had > 80% stenosis. After 43 months follow-up, revascularization did not confer any clinical benefit over medical therapy itself (16) The current focus of ARVD treatment has shifted to medical therapy with the use of optimal treatment: use of angiotensin converting enzyme II inhibitors (ACEI) or angiotensin receptor AT (IARAII), ββ, statins, or antiplatelet agents; it also highlights the importance of hypertension and diabetes control as relevant and important agents in this pathology (16). The pleiotropic effects of statins extend beyond the reduction in lipid levels and have been shown to be associated with improved patient survival (HR = 0.131 (0.039-0.438), p = 0.001) and renal survival (HR = 0.211 (0.070-0.637), p = 0.006) (17), along with a reduced risk of disease progression (RR = 0.28 (0.10-0.77) (18). Evidence from two separate observational studies shows that renin-angiotensin blockade is associated with a reduced risk of death (HR = 0.61 (0.40-0.91), p = 0.02) [19] and improved survival (HR = 0.24 (0.08-0.71), p = 0.0098) [20]. Renin-angiotensin blockade helps to mitigate intrarenal parenchymal injury, decrease the degree of proteinuria, and improve renal outcomes while conferring significant cardiovascular protection. However, the "optimal" medical therapy regimen for patients with ARVD remains undefined to date: medical treatment alone, or revascularization (endovascular-stent), or both or other modalities to be developed?

5. How may management differ in special populations? (e.g., non-dialysis patients; stenosis in kidney transplants) Patients with ARVD, with CKDND that is not on dialysis, may be candidates for kidney revascularization (endovascular/stent therapy), those called high-risk, who have the following characteristics: - Sudden recurrent pulmonary edema. - Difficult to control systemic arterial hypertension (more than three antihypertensive drugs). - Elevation of azoids related to the intake of ACE inhibitors and in association with cardiovascular disease that will require this medication. - Rapidly progressive deterioration of renal function in relation to bilateral renal artery stenosis or in the solitary kidney. - Hypertensive crisis. - Unilateral stenosis associated with a glomerular filtration rate < 40%. - Impaired renal function that does not respond to the best medical treatment. Surgical treatment has the following indications associated with stenosis > 60% of the renal artery (IB evidence level): Once an adequate surgical revascularization has been performed, an immediate improvement in renal function is expected between 26 and 58% of patients. Conversely, a worsening in renal function between 3 and 27% can be observed, requiring early hemodialysis in up to 4%; of this group, up to 50% will require definitive replacement treatment of renal function and improvement in relation to renal function between 14 and 57%. (21,22) A retrospective observational study conducted on 237 patients with at least 50% RAS and one or more of the "high risk" characteristics mentioned above. About one-quarter (24%) of these patients underwent revascularization, and the clinical results for this subset of patients were compared with those of similar patients who were treated exclusively medically. The results showed that revascularization was associated with better outcomes in "high-risk" patients (22, 23). The etiology of post-transplant renal artery stenosis is multiple and its treatment depends in part on it: (peri vascular inflammation, fibrous rings, atherosclerosis, chronic rejection and layering that functionally behaves like a stenosis, BKV. As it can be deduced, some of the treatments are surgical, including reimplantation or extra renal revascularization, another involves the use of immunosuppresses or other therapies: reports of angioplasty alone or combined with stenting, are few but they show good results: Between Oct 2009 and July 2015, out of 660 patients with renal Tx, 22 cases of RA stenosis, diagnosed by 1- lumen diameter reduction > 50% and 2-pressure gradient > 15 mm Hg-, improved by 100% after angioplasty and e-GFR. (24) With regard to the treatment of patients with fibro muscular dysplasia and renal artery stenosis: in a study where 47 angioplasty studies (1616 patients) and 23 surgery studies (1014 patients) were selected, combined rates of hypertension were determined, according to criteria selected in each study, after angioplasty or surgery was estimated to be 46% (95%CI : 40% to 52%) and 58% (95% CI: 53% to 62%) respectively; cure of hypertension was poor (TA <140/90 mm hg without treatment) was 36 to 54% after angioplasty or surgery respectively. Per procedural

complications were 12% and 17% respectively. In conclusion, angioplasty or surgery provides a moderate benefit in this entity (25).

Bibliography 1-Samadian F, et al. New insights into pathophysiology diagnosis, and treatment of Reno vascular hypertension. Iran J Kidney Dis. 2017 Mar; 11(2):79-89 2-Hirsch AT. ACC/AHA Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic). J Am College Cardiol 2006; XX(X). 3. Herrmann SMS, Saad A, Textor SC. Management of atherosclerotic renovascular disease after Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL). Nephrol Dial Transplant 2014; 30: 366-75. 4-Charles ER, Lui D, Delf J, et al. Editor's Choice - The Impact of Endovascular Aneurysm Repair on Long Term Renal Function Based on Hard Renal Outcomes. Eur J Vasc Endovasc Surg 2019; 58: 328-333. 5. Textor SC and Lerman LO. Chapter 47: Approach to the patient with chronic kidney disease and renovascular disease. In: Chronic Renal Disease, second edn, p. 753-770, 2020. 6. Abumoawad A, Saad A, Ferguson CM, et al. Tissue hypoxia, inflammation, and loss of glomerular filtration rate in human atherosclerotic renovascular disease. Kidney Int 2019; 95: 948-957. 7- Vassallo D, et al. Association of novel biomarkers with mayor clinical outcomes in a cohort of pattients with atherosclerotic renovascular disease. Ann Clin Biochem. 2019 Jul , 56 (4) 488-501 8. Raman G, Adam GP, Halladay CW, et al. Comparative Effectiveness of Management Strategies for Renal Artery Stenosis: An Updated Systematic Review. Ann Intern Med 2016; 165: 635-649. 9- Hagemann R, et al. Attenuation of renal functional Decline Following Angioplasty a stenting in atherosclerotic Renovascular disease. Nephrol 2017, 135 (1). 15-22 10- Vasallo D Et al. Atherosclerotic Renovascular disease- epidemiology, treatment and current challenges. Advances in interventional cardiology 2017, 13, 3 (49).191-201, 2014.pp 11- Misra S. Endovascular treatment of renal artery stenosis.In Learman LO, Textor SC, editors. Renal Vascular disease. London: Springer-Verlag, 2014.pp 317-23 12-Folt Da, et al. Regional and physicians specialty –associated variation in the medical management of atherosclerotic renal-artery stenosis. Am Soc Hypertens. J Am Soc Hypertens.2015; 9: 443-52 13. Bax L, Woittiez A, Kouwenberg H, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function. Ann Intern Med 2010; 150: 840-8. 14. Burke CT. A review of the prevention and management of catastrophic complications during renal artery stenting. Vasc Dis Manag 2007; 4: 6-11. 15. Wheatley K, Ives N, Gray R, et al. Revascularization versus medical therapy for renal-artery stenosis. N Engl J Med 2009; 361: 1953-62. 16. Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. N Engl J Med 2014; 370: 13-22. 17. De Silva R, Nikitin NP, Bhandari S, et al. Atherosclerotic renovascular disease in chronic heart failure: should we intervene? Eur Heart J 2005; 26: 1596-605. 58 18. Cheung CM, Patel A, Shaheen N, et al. The effects of statins on the

progression of atherosclerotic renovascular disease. Nephron Clin Pract 2007; 107: 35-42. 19. Chrysochou C, Foley RN, Young JF, et al. Dispelling the myth: the use of renin-angiotensin blockade in atheromatous renovascular disease. Nephrol Dial Transplant 2012; 27: 1403-9. 20. Losito A, Errico R, Santirosi P, et al. Long-term follow-up of atherosclerotic renovascular disease. Beneficial effect of ACE inhibition. Nephrol Dial Transplant 2005; 20: 1604-9. 21. Kalra P, Chrysochou C, Green D, et al. The benefit of renal artery stenting in patients with atheromatous renovascular disease and advanced chronic kidney disease. Catheter Cardiovasc Interv 2010; 75: 1-10. 71. 22-Chrysochou C, Mendichovszky IA, Buckley DL, et al. BOLD imaging: a potential predictive biomarker of renal functional outcome following revascularization in atheromatous renovascular disease. Nephrol Dial Transplant 2012; 27: 1013-9. 23. Ritchie J, Green D, Chrysochou C, et al. High-risk clinical presentations in atherosclerotic renovascular disease: prognosis and response to renal artery revascularization. Am J Kidney Dis 2014; 63: 186-97. 24-Wang L, et al. interventional therapy for transplant renal artery stenosis is safe and effective preserving allograft function and improving hypertension. 16. Trinquart L, Mounier-Vehier C, Sapoval M, et al. Efficacy of revascularization for renal artery stenosis caused by fibromuscular dysplasia: a systematic review and meta-analysis. Hypertension 2010; 56: 525-32. Vas Endovascular surg Jan; 51(1):4-11 25. Trinquart L, Mounier-Vehier C, Sapoval M, et al. Efficacy of revascularization for renal artery stenosis caused by fibromuscular dysplasia: a systematic review and meta-analysis. Hypertension 2010; 56: 525-32.

Judy Savige - University of Melbourne (Doctor / Physician)

You have not considered small vessel disease in CKD - only medium vessel disease. Small vessel disease affects the vessels that result in progressive renal failure in hypertension, diabetes etc…cause vascular dementia, heart failure, possibly atrial fibrillation. This is the cause of heart failure in those 90 year old women who have never had an AMI...The vessels are visible in the retina... we have done some work that demonstrates small vessel disease gets progressively worse with CKD stage and does not improve after transplantation...however calibre is reversible with better blood pressure control

Rommel Bataclan - University of the East Ramon Magsaysay Memorial Medical Center (Doctor / Physician)

By Atherosclerotic cerebrovascular Disease, I have the impression that it only involves the Infarct type. Hemorrhagic strokes should also be included and its possible related problems (i.e. Aneurysm).

Dustin Dunham - GE Healthcare (Industry / Medical Affairs)

Thank you for encouraging submission statements regarding scope of work for the 2020 KDIGO Controversies Conference on Central & Peripheral Arterial Diseases in CKD. We would like to submit the below topics and literature for consideration with special attention to Breakout Group 2: Central Aortic Disease;

•#3. What are the means for diagnosis and optimal evaluation in CKD, including the value of duplex ultrasound, CT, MRI and angiography?

•#4. What is the optimal management (e.g., open surgery vs endovascular) indication for treatment of aortic disease including prevention of periprocedural kidney failure? As a minimally invasive alternative to traditional open repair, the use of catheter intervention technology for endovascular aneurysm repair (EVAR) for abdominal aortic aneurysm (AAA) has evolved into first-line treatment, predominately in the elective setting. Systematic review and meta-analysis of early and late outcomes of open and endovascular repair of AAA have demonstrated early and intermediate outcomes similar or superior to open repair, including potential for significantly lower 30-day or in-hospital mortality rates [1]. As such, review of the National Inpatient Sample reveals utility of EVAR has risen sharply in recent years, representing 74% of AAA repairs by 2010 [2]. However, patients undergoing EVAR still remain at risk for complications such as endoleak, stent graft migration, endograft limb occlusions, and acute kidney injury (AKI), predominantly owing to contrast nephrotoxicity [3]. The incidence of AKI post-EVAR has been reported to be 10-20% and is thought to increase in parallel with complexity of the procedure [4]. The exact etiology of AKI in perioperative EVAR setting is multifactorial, with kidneys being subjected to variety of hemodynamic, mechanical, and pharmacologic insults [5]. Risk factors include pre-existing renal impairment, diabetes, periprocedural intravascular depletion, congestive heart failure (CHF), concomitant use of nephrotoxic medications, and both volume & type of contrast media utilized [5]. Acute renal injury post-EVAR has significant clinical consequences; subsequently impacting mortality, cardiovascular morbidity, long-term renal function, hospital length of stay, and associated costs [3, 6]. Due to the frequency and poor prognostic implications posed by AKI, short-term adverse events, long-term adverse events, and potential financial burden, we recommend that comprehensive mitigation strategies be developed and employed. Further, AKI should be considered an important quality metric for healthcare systems as it is of strong clinical relevance, measurable with persistent gap, actionable, and prevention of AKI results in improved downstream outcomes. The Society for Vascular Surgery's (SVS) current practice guidelines on the care of patients with AAA acknowledge the potential for uniformly poor outcomes of aortic aneurysm repair in presence of severe renal dysfunction, regardless of the type of repair [7]. As such, Chaikof et al. suggest comprehensive multiprong strategies to minimize

renal injury after endovascular or open repair, including importance of periprocedural hydration to ensure euvolemia, temporarily withholding nephrotoxic medications, and limiting total volume of administered contrast media. Additionally, due to the association of ACE inhibitors and angiotensin receptor antagonists with hypotension on induction of anesthesia, these medications should be held the morning of surgery and restarted after the patient is euvolemic [7]. Although recognizing the potential of higher osmolality contrast agents to display increased nephrotoxicity, the SVS guidelines do not currently recommend consideration toward alternate types of contrast media (iso-osmolar vs. low-osmolar), however, reference dated publications from ten + years ago, further emphasizing data from coronary interventions rather than open/endovascular aortic repair [8,9,10]. As such, we would like to highlight emerging data presented during 2019 session of Transcatheter Cardiovascular Therapeutics (TCT) and published within corresponding supplement of Journal of the American College of Cardiology [11]. As one of the first ever attempts to compare rate of major adverse renal or cardiac events (MARCE) with iso-osmolar contrast media (IOCM) versus low-osmolar contrast media (LOCM) in patients undergoing EVAR, Amin et al retrospectively gleaned real-world data from the Premier Hospital Database from September 2012 to June 2018. Only patients deemed at high-risk were included as each were age ≥75 years or had 1 or more of the following comorbidities: diabetes, anemia, chronic kidney disease (CKD), and/or congestive heart failure. Conversions from endovascular to open repair were excluded. Using multivariate regression analysis, investigators compared the primary endpoint of MARCE (composite of AKI, acute kidney injury with dialysis, acute myocardial infarction, stent occlusion or thrombosis, stroke or transient ischemic attack, and death) for IOCM versus LOCM. Among 15,777 visits meeting inclusion criteria (LOCM, n=8,417; IOCM, n=7,360), the majority (81.1%) were elective procedures. The overall absolute unadjusted difference in incidence of MARCE was 1.4% (7.4% with LOCM vs. 6.0% with IOCM). After multivariate modeling, use of IOCM was associated with a 1.8% (p=0.0159) lower risk for MARCE (24% relative risk reduction, number needed to treat=56). The above emerging EVAR-specific assessment [11] complements several meta-analyses [12,13,14] and systematic review [14] suggesting favorable risk reduction of adverse renal events with utilization of iso-osmolar vs. low-osmolar contrast, most notably within intra-arterial procedures. Given the totality of data and recent supplementary evidence from EVAR-dedicated assessment, we suggest that selection of iso-osmolar contrast media be considered as recommendation for high-risk patients undergoing aortic aneurysm repair to complement comprehensive multiprong mitigation strategy encompassing individual risk assessment, periprocedural hydration, withholding of nephrotoxic medications, and judicious use of contrast in highest-risk patients. Thank you for your consideration.

References: 1. Stather et al. Br J Surg. 2013 Jun;100(7):863-72. https://www.ncbi.nlm.nih.gov/pubmed/23475697 2. Dua et al. J Vasc Surg. 2014 Jun;59(6):1512-7. https://www.ncbi.nlm.nih.gov/pubmed/24560865 3. Jhaveri et al. Kidney Int. 2017 Jun;91(6):1312-1323. https://www.ncbi.nlm.nih.gov/pubmed/28318632 4. Kasipandian et al. Continuing Education in Anaesthesia Critical Care & Pain. 2012 (12): 312-316. https://academic.oup.com/bjaed/article/12/6/312/279823 5. Wong et al. Br J Anaesth. 2016 Sep;117 Suppl 2:ii63-ii73. https://www.ncbi.nlm.nih.gov/pubmed/27566809 6. Saratzis et al. Clin J Am Soc Nephrol. 2015 Nov 6;10(11):1930-6. https://www.ncbi.nlm.nih.gov/pubmed/26487770 7. Chaikof et al. J Vasc Surg. 2018 Jan;67(1):2-77.e2. https://www.ncbi.nlm.nih.gov/pubmed/29268916 8. Aspelin et al. N Engl J Med. 2003;348:491-9. https://www.ncbi.nlm.nih.gov/pubmed/12571256 9. Pannu et al. JAMA. 2006;295:2765-79. https://www.ncbi.nlm.nih.gov/pubmed/16788132 10. Pannu et al. Curr Opin Nephrol Hypertens. 2006;15:285-90. 11. Amin et al. J Am Coll Cardiol. 2019 Oct, 74 (13 Supplement) B598. http://www.onlinejacc.org/content/74/13_Supplement/B598 12. McCullough et al. Cardiorenal Med. 2011;1:220-234. https://www.ncbi.nlm.nih.gov/pubmed/22164156 13. Dong et al. J Nephrol. 2012;25:290-301. https://www.ncbi.nlm.nih.gov/pubmed/22252847 14. Eng et al. Ann Intern Med. 2016;164(6):417-424. https://www.ncbi.nlm.nih.gov/pubmed/26830055

Marco Virgilio Usai - Uniklinikum Muenster (Doctor / Physician)

Group 1: Atherosclerotic Cerebrovascular Disease (excluding intracerebral disease)
What is the epidemiology in the context of CKD/dialysis? (e.g., types of strokes, risk factors, outcomes of interest)
Response: Although only scant data regarding this issue exist, it is already known that renal function impairment is associated with greater neurological deficits. Moreover, there is a higher risk of hemorrhagic transformation of the cerebral ischemic zones. It could be interesting to associate the degree of infarct demarcation with the stage of CKD to research on possible risk factors. Which subgroup of patients are prone to develop hemorrhagic transformation.
What are the pathophysiology and potential differences compared with non-CKD patients? (e.g., management of atrial fibrillation in CKD/dialysis)
Response: The pathophysiology of stroke in CKD is probably multifactorial with perfusion anomalies or reduction due to the vascular disease itself, but also intracellular altered pathways triggered by circulating uremic toxins and leading to

an impaired cell wall function. Another possible culprit for the development of stroke in CKD is the alteration in cardiovascular flow during dialysis. Data confirming this hypothesis are scant. This could be another interesting research item.

What are the means for its diagnosis and optimal evaluation in CKD? Role of imaging and biomarkers?

Response: There is a plethora of studied biomarkers associated with CKD, to date there is no consensus regarding specific markers associated with increased risk of stroke. To be honest, even if there is one, it's applicability in the all-day practice should be carefully proven. The same goes for example for tumor markers, which are knowingly not specific. Of more interest is the application of novel imaging technologies such as PET-MRI or Perfusion-CT, or evaluation of the degree of Leukoaraiosis in CKD patients.

What are the factors governing conservative management; endovascular vs surgical treatment; pharmacotherapies?

Response: Factors influencing the decision making for the treatment of extracranial cerebrovascular disease are for sure the degree of stenosis and the presence or not of symptoms. Not to mention, the degree of infarction in case of documented stroke and the prognosis. Surgical treatment is according to the current guidelines the first choice for asymptomatic and symptomatic carotid disease. CEA in CKD patients it known to deliver protection against stroke. Stenting is chosen in selected cases, because related to higher stroke rates. Best medical treatment is to date the treatment of choice in asymptomatic patients. How may ethnic differences differ for all of the above? Are there management differences in different populations? (e.g., women). Population studies on patients with chronic kidney disease are pretty univocal demonstrating a higher risk of stroke, but also all-cause mortality. How different ethnic groups could be proner to worse outcomes is unknown.

Group 2: Central Aortic Disease

1. What is the epidemiology in the context of CKD/dialysis? Bidirectional nature: CKD as a risk factor for AAA vs AKI/CKD as a consequence of AAA (e.g., CKD after EVAR)?

Response: Multiple studies confirmed the association between CKD and development of AAA, an impaired glomerular filtration rate and elevated albuminuria are independently associated with greater incidence of AAA and larger aneurysms diameters. Pathophysiological reasons are not clear, but a small-vessel-disease component is certainly one of those. On the other hand also patients with normal renal function develop aneurysms, data pooled from population studies showed a incidence of approximately 0.4 to 0.67 percent in Western populations. The risk of developing a AAA in CKD goes up to 2-Fold. It is controversial whether a microalbuminuria is an independent factor for AAA, because this is mostly

associated with diabetes. However, it has been postulated that diabetes is a protecting factor against AAA. Nevertheless, recent data suggest that the treatment with metformin could be the real protecting factor against AAA. The role of Metformin on protecting against AAA in CKD patients is unknown und should be scope of future studies. Also known is the decline in renal function in patients with AAA with or without surgical/endovascular treatment. The factors are multiple such as cholesterol microemboli, circulating growing factors, procedural factors such as suprarenal aortic cross-clamping, clamping time, need for transfusion. But also for endovascular treatment the use of suprarenal fixation devices or fenestrated/branched prosthesis are risk factors.

What are the pathophysiology and potential differences compared with non-CKD patients?

Response: The common cardiovascular risk factors are certainly implicated in the development of AAA. Arterial hypertension and smoking are the most common factors. However, CKD patients develop a far more aggressive micro-vascular disease compared to patients with normal renal function. This could explain the differences in the pathways of AAAs. The disfunction in the Renin-Angiotensin system is directly connected to CKD, as a dysregulation of the normal mechanism of the nephron. Diverse studies on the use of ACE inhibitor demonstrated controversial results over an hypothetical protective function against the growth of AAA. This issue should be further investigated with regard to the CKD population.

What are the means for diagnosis and optimal evaluation in CKD, including the value of duplex ultrasound, CT, MRI and angiography?

The use of diagnostic tools has a screening, planning and follow-up value. Depending on the reason, the use of the singular methodic acquires or loses meaning. Duplex ultrasound plays an important role in detecting abdominal aortic aneurysms, albeit those including the visceral segment of the aorta are more difficult to detect or impossible depending on the BMI of the patient. Ultrasound is helpful in detecting concomitant renal artery stenosis and measuring doppler flows in the kidneys. Duplex has a role in the follow-up after conventional abdominal aortic surgery but also EVAR. It can be combined with microbubbles contrast medium, in fact contrast enhanced ultrasound has a high diagnostic power in detecting any kind of endoleaks and it is safe for patients with CKD. Duplex loses meaning for thoracic aneurysms. Therefore, CT is the gold-standard as it gives informations about the morphology, giving the opportunity to process the images in specific computer softwares for an optimal preoperative planning. Of course, the need for contrast medium represents a draw-back in particular for patients with CKD. However, while in cases open surgery CT can be replaced by an MR-Angio, for EVAR or complex endovascular repair it has a scarce value, since the reconstruction of the images and the quality is questionable. At the end of the day one should

unfortunately accept the risk for a contrast induced nephropathy if the need for treatment overcomes the risk of a permanent renal injury. MRA is mostly safe but useful as diagnostic or follow-up tool, in particular to detect endoleaks. But the endoprosthesis should be MR-friendly. Some devices do not allow the use of MR or only with a certain degree of Tesla. New safer methodics for CKD patients have not yet been developed.

What is the optimal management (e.g., open surgery vs endovascular) indication for treatment of aortic disease including prevention of periprocedural kidney failure?

This is a really controversial issue. Open surgery is related in the short term to higher mortality and morbidity rates but, delivers longer durability. EVAR is faster and safer in the short term, but is related to equal, if not, worse outcomes in the long run. Thus, the answer would be, it depends on the patient. Nevertheless, the new NICE guidelines will cause turmoil in the vascular community, giving open surgery a second golden era. Periprocedural prevention of kidney failure do not exist. For thoraco-abdominal open aortic repair, a shorter operative time and cold perfusion of the kidneys seems to be protective against renal injuries.

How may management differ in special populations? (e.g., in cases of acute ruptures; care of the older adults >75 yrs)

Response: there is a certain agreement regarding ruptured aortic aneurysms, those feasible with EVAR should always be performed in this fashion. Open surgery for rAAA is nowadays acceptable only in cases of contained rupture with stabile patient, and in cases of anatomies deemed not treatable via EVAR. Nevertheless, by aortic ruptures a laparotomy is often necessary to treat or prevent abdominal compartment syndromes. In the elderly EVAR is the first treatment option, in particular those with multiple comorbidities and deemed unfit for surgery. However, the way of classifying a patient unfit is at discretion of the surgeon and less due to predefined risk criteria. Frailty is a new method of characterization of the fitness of the patients which could help in the decision making. In cases of juxtarenal aneurysms in which open surgery could be performed with infrarenal aortic cross clamping, the risk of renal injury is perhaps lower as that of the complex endovascular repair such Chimney-EVAR, Fenestrated-EVAR due to the higher risk for acute kidney injury and mandatory renal artery stenting. Other strategies aiming to reduce the contrast medium burden will improve the outcomes even in the over 75 with CKD.

Group 3: Renovascular Disease

1. What is the epidemiology in the context of CKD/dialysis?

A recent population-based study utilizing duplex ultrasound demonstrated that 5% of patients presented a minimal mono or bilateral renal artery stenosis without clinical significance, whereas a significant stenosis was detected in in 6.3% of patients. In another study was found that renal artery stenosis is independently

associated with age, hyperlipidemia, and hypertension. About 12% of patients with renal artery stenosis shows progression of the disease when associated with other risk factors like hypertension, diabetes mellitus and severe renal artery stenosis. Those patients are prone to develop an end stage renal disease. In this population survival rates are worse when compared to other etiologies.

2. What is the pathophysiology? (e.g., role of hypoxia, inflammation, etc.; novel biomarkers?)

Current knowledge about the pathophysiology of renal damage due to atherosclerotic disease recognizes the role of hypoxia. The limitation in renal tissue oxygen delivery leaves the kidney susceptible to hypoxia and has long been recognized as an important factor in the pathogenesis of acute renal injury. Renal hypoxia means oxygen deprivation but also induces regulatory mechanisms and has a profound influence on gene expression. In particular, the transcription factor hypoxia inducible factor (HIF) is involved in cellular regulation of angiogenesis, vasotone, glucose metabolism, and cell death and survival decisions. HIF has been shown to be activated in renal disease and presumably plays a major role in protective responses to oxygen deprivation. The role of the renin-angiotensin-aldosterone plays a crucial role in the pathogenesis of renal hypertension. Recent research tried to find biomarkers capable of identifying or characterizing the degree of renal damage, for example Asymmetric Dimethylarginine, Symmetric Dimethylarginine, Uromodulin, Kidney Injury Molecule-1, Neutrophil Gelatinase-Associated Lipocalin. This plethora of biomarkers is required to diagnose CKD with high sensitivity and specificity and to identify persons at high risk of progression. However further studies are mandatory to detect the efficacy, sensitivity and specificity as well as the reduction in analysis costs is required.

3. What are the means for diagnosis and optimal evaluation, including value of duplex ultrasound, CT, MRI and angiography?

Duplex ultrasound represents the tool of choice for the diagnosis of renal artery stenosis, it gives a lot of information about morphology, perfusion and grade of stenosis of the renal artery. A peak systolic velocity of more than 180 or 200 cm/second is defined as severe. Moreover, another useful marker is the renal aortic ratio, which is calculated by dividing the peak systolic velocity of the renal artery by the peak systolic velocity of the adjacent aorta. A normal ratio is ,3.5. The sensitivity and specificity of a renal aortic ratio .3.5 as compared to contrast arteriography has been estimated at 84% and 97%, respectively. CTA represents an important tool when an invasive therapy is planned, but also gives information about the adjacent structures, MRA gives similar information but has a less nephrotoxic contrast medium. However, it is more expensive and contraindicated with devices such pacemakers or joint implants. Angiography is nowadays used only for interventions and rarely for diagnostic scopes.

What are the management and indications for treatment? (e.g., surgical revascularization, medical, vs stenting)
Response: Therapy of choice of atherosclerotic renal artery stenoses is best medical treatment, only when this one fails there is indication to invasive treatment. The gold standard is PTA with stenting of the renal artery, rarely is a PTA alone enough while followed by high restenosis rates. Open revascularization is indicated in selected cases with complex renal artery stenosis, or simultaneous aortic reconstruction or failed endovascular treatment. How may management differ in special populations? (e.g., non-dialysis patients; stenoses in kidney transplants)
Patients already on dialysis without chances of recovering the renal function would not receive any invasive or surgical treatment. The treatment of stenosis of transplanted renal arteries varies from conservative to surgical. Medical treatment is indicated in cases of stenosis considered not hemodynamically significant or where an invasive treatment is considered to be related to graft loss. Surgical treatment is indicated in cases of kinking of the renal artery, this is related to high failure rates of graft loss ranging from 10 to 30%. PTA with Stenting is considered based on the anatomy and risk for graft loss. This methodic is surely less invasive than surgery and can be performed without iodinated contrast using CO2. Data regarding this treatment are poor. A recent study reported on long term results after surgical repair of renal artery stenoses concluded that surgical intervention is safe and effective on graft survival and graft function and has to be considered for patients unsuitable for endovascular repair.
Group 4: Peripheral Arterial Diseases
1. What is the epidemiology in the context of CKD/dialysis? (e.g., types of PAD)
Response: Peripheral artery disease has a high incidence in hemodialysis patients (400 per 1,000 patient-years). In an international collaborative metanalysis over 800000 patients, mild to moderate CKD conferred 1.5 to 4 times higher risk of PAD beyond traditional risk factors. Lately eGFR and albuminuria are becoming recognized markers of degree of peripheral artery disease.
2. What are the pathophysiology and potential differences compared with non-CKD patients? Role of inflammation, oxidative stress, uremic toxins?
There are several possible patho-mechanisms relating CKD to peripheral artery disease. One of those is the dysregulation of renin-angiotensin system, an elevated oxidative stress, inflammation, hypercoagulability, abnormal calcium-phosphate metabolism, elevation of lipoprotein(a), and accumulation of uremic toxins. Moreover, albuminuria is linked to endothelial dysfunction and/or microvascular damage. This would explain the direct connection between albuminuria and leg amputation.
3. What are the means for its diagnosis and optimal evaluation in CKD?

The Means for diagnosis for PAD in CKD are not much different compared to the non-CKD population. The clinical classification represents always the first approach and helps in the decision of the next steps. Duplex ultrasound represents always the first approach, aiming to localize anatomically the culprit and evaluating the degree of stenosis with Peek Systolic velocities. A different point in this specific population is the measurement of the ankle brachial Index, since false negative results occurs due to the media sclerosis or calcification in the arteries below the knee. In this case an Ankle-Toe index with different cut-off is helpful in the diagnostic work-up. Transcutaneous Pulse-Oxymetry represent another essential tool in particular when a critical limb ischemia is under suspicion. MRA is for complex disease such as aortic and iliac vessels PAD the method of choice in this population because of the safety regarding renal function in comparison to CTA. Although not every patient can undergo MR-Angio because of Metal implants, or chlaustrophobie.

4. What are the means for its management and treatment in CKD?

Means of treatment in CKD patients differs not much from the normal population, although CKD patients have more often a below-the-Knee disease and higher stages of Rutherford or Lerich-Fontaine. Those patients requires complex endovascular infragenicular interventions or surgical crural or pedal bypasses.

5. How may management differ in special populations? (e.g., chronic limb threatening ischemia; patients with polyvascular disease; PAD as predictor for allograft failure)

Response: Despite advances in surgical techniques, there has been scarce improvement in outcomes for CKD patients. Reported survival rates for this cohort after lower extremity bypass ranges from 23% to 52% at 2 years. This is unfortunately a draw-back, because even with patent bypass those patients die often from other causes with only 1/4 surviving at 5 years. Apparently, there is no influence of the methodic on the overall survival of those patients, hence endovascular or surgical means are similar in this setting. But as demonstrate in a recent study the presence of Coronary artery disease, COPD, age over 80 and a non ambulatory status before the operation are all factors associated with high mortality, namely 3 of those risk factors relate with a mortality of >60 % at 2 years. Therefore, it is good to keep this in mind when choosing the treatment modality. Moreover, there is no difference in patency rates between open and endovascular treatment at 2 years with a better trend in favor of endovascular strategies.

Filippo De Stefano (Doctor / Physician)

In CKD patients is very important to study the arterial disease: the incidence of atherosclerotic vascular lesions and hypertension in CKD can modify the prognosis of this patients so can grow the risk of stroke accidents. Can be important to follow

guidelines to prevent the risk and the incident of vascular injuries in CKD. But are atherosclerosis and hypertension the only target to follow in CKD patients to prevent stroke?

Kazunori Toyoda - National Cerebral and Cardiovascular Center (Doctor / Physician)
It would be better to introduce some comments on "the association of CKD with cognitive impairment" in "Cerebrovascular Disease" section. Please check my review (Toyoda & Ninomiya: Lancet Neurol 2014;13:823-33) that has a chapter on "Does CKD affect cognitive function?"

Zanfina Ademi Delaney - Monash University (Doctor / Physician)
There is no discussion proposed around what are the most cost-effective ways to treat patients with PAD/CKD/including other atherosclerotic diseases. What is the evidence around?

Michael Criqui – UCSD (Doctor / Physician)
I have reviewed the Conference Scope of Work. My expertise is in the epidemiology of peripheral arterial diseases, and I think the questions addressed in Group 4 are relevant and timely. For example, question 3 under Group 4, the diagnosis of PAD in CKD, is quite important since a PAD diagnosis in CKD patients is more problematic than in non-CKD patients due to frequent peripheral arterial stiffness in CKD. Our group has also studied the epidemiology of aortic disease, both aneurysmal disease and aortic atherosclerosis.

Angela Wang - University of Hong Kong (Doctor / Physician)
Group 1.

1) Should we include discussions on both ischemic and hemorrhagic stroke as they are both important complications in CKD. Is there a reason why intracerebral disease is excluded as they are important causes for cognitive impairment in CKD. Should this group include discussions on cognitive impairment in CKD?
2) Should this group discuss primary and secondary prevention of stroke in CKD and review evidence on efficacy of various strategies including Blood pressure control, lipids, DM control, proteinuria and use of aspirin?

3) Assessment and , of stroke risk in CKD – how useful are those scores used in general population in CKD and dialysis? Such as CHADSVASC2 score? HasBled score etc.
4) AF is an important risk factor for thromboembolic stroke or ischemic stroke in CKD. How best to treat this population remains controversial. Should this group discuss this and review this topic – anti-coagulation (risk versus benefits)

Group 2.

1) Should this group include discussion about the entity 'abdominal aortic calcification'? This is a frequent complication in CKD.
2) Review risk factors for central aortic disease.

Group 4.

1) Should there be discussions on risk factors for PAD in CKD ? and how to modify these risk factors?
2) Medical treatment of PAD versus surgical treatment? Cilostazol.
3) Role of multidisciplinary team in the treatment of PAD?
4) Role of smoking cessation?
5) Should there be specific discussions on diabetic PAD? Should there be screening for PAD in at risk populations ? And how to screen for PAD ?

Additional comments: Which group will cover arterial stiffness? This is an important topic. Or has it been covered in another conference?
How to define vascular stiffness? How to assess arterial stiffness? And how best to manage arterial stiffness ? Why is it important ? should there be screening ?

Rajasekara Chakravarthi (Doctor / Physician)

Thank you for the request for comments on the KDIGO consensus conference on Aortic and peripheral arterial disease in CKD. Below is a list of points which I think need discussion. India like other developing countries is seeing a huge burden of aortic and peripheral arterial disease in the CKD population which comprises almost 18% of the population. Though the no of specialists like CT surgeons and Vascular surgeons is increasing in the subcontinent, they are primarily involved in the care of patients with advanced disease. There is a lot to be done in the area of prevention.

1. Etiology of CKD in patients with CV, central aortic and PAD with special reference to Diabetes mellitus
2. Pattern of disease: for cerebrovascular: aortic vs carotid vs intracranial disease

3. Pattern of disease for peripheral arterial disease: Is tibial disease more prevalent? Is calcification more prevalent and the impact of it on intervention and outcomes.
4. Evaluation of disease in CKD patients: Imaging: Non contrast MR angiography avoids use of contrast.
5. Use of CO2 for endovascular interventions
6. Use of IVUS for aortic interventions
7. Use of hydration with saline prior to endovascular interventions
8. Role of Mannitol / N acetylcysteine in reducing renal injury prior to clamping for aortic surgery