Summary of the 2018 ISN Frontiers Meeting: Kidney Disease and Cardiovascular Disease

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International Society of Nephrology (ISN) Frontiers meetings build on the success of the ISN Nexus and Forefronts series by bringing together basic scientists, clinicians, and practitioners in a unique setting. This new event was organized to make more innovative science available to a global audience by removing regional barriers in accessing the latest knowledge. The first ISN Frontiers meeting was organized in partnership between the Japanese Society of Nephrology and the Japanese Society for Dialysis Therapy, which was held in Tokyo in February 2018. The meeting focused on the topic “Kidney Disease & Cardiovascular Disease,” which covered a broad range of scientific and clinical fields, including nephrology, cardiovascular diseases, dialysis, transplantation, chronic kidney disease (CKD)–mineral bone disease (MBD), diabetes, pediatric nephrology, nutrition, pharmacology, and nursing. A total of 1584 active physicians and scientists from 64 countries attended the meeting, and a number of leading physician scientists from different and related disciplines of clinical and basic research described and reviewed recent discoveries. This report summarizes the main highlights of the meeting lectures.

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Overview of the 2018 ISN Frontiers Meeting

International Society of Nephrology (ISN) Frontiers meetings were initiated based on the significant achievements of the ISN Nexus and Forefronts series. The ISN Frontiers Meeting 2018 took place in Tokyo, Japan on February 22–25, 2018, and was organized in partnership between the Japanese Society of Nephrology and the Japanese Society for Dialysis Therapy, and was supported by a number of Japanese academic societies, including the Japanese Circulation Society, the Japan Diabetes Society, the Japanese Society for Pediatric Nephrology, the Japanese Society of Nephrology and Pharmacotherapy, the Japan Society of Metabolism and Clinical Nutrition, the Japan Diabetic Nephropathy Study Group, and the Japan Academy of Nephrology Nursing.

The meeting focused on the topic “Kidney Disease & Cardiovascular Disease,” and provided attendees with opportunities to attend a number of informative lectures, including 2 keynote lectures, 4 plenary lectures, 1 special lecture, and 14 symposiums (54 speakers). Twelve “Meet the Professor” sessions were held with approximately 100 young scientists. Among the 855 regular submissions, Young Investigator Awards were awarded to the top 8 abstracts, which were presented at the Young Investigator Network oral session. In addition, 765 abstracts on a broad range of topics from basic research to clinical case reports were presented in general poster sessions, and Top 10% and Top 10 Poster Awards were awarded, respectively. In addition, 54 travel grants were awarded to young investigators.

This report summarizes the main highlights of the lectures presented by senior physician scientists. The meeting program can be accessed at http://www.isnfrontiers.org/tokyo/program. All the organizing members are listed in the Supplementary Appendix S1, and Figure 1 is a photograph of the members at the closing ceremony.

Keynote Lectures

Takashi Kadowaki (Japan) and Vlado Perkovic (Australia) discussed the clinical importance of
multtarget intensive therapy for patients with diabetes and chronic kidney disease (CKD), respectively. First, Kadowaki introduced the recently published achievement of the Japan Diabetes Optimal Integrated Treatment Study for Three Major Risk Factors of Cardiovascular Diseases (J-DOIT3), which showed that diabetic macrovascular and renal events were less frequent in the intensified multifactorial intervention therapy group.

Similarly, Perkovic addressed the importance of multiple target intervention, including blood pressure, low-density lipoprotein (LDL) cholesterol, triglycerides (TGs), thrombosis, arrhythmias, and heart failure in managing CKD. These clinical achievements provided the audience with useful information on the future development of diabetes and/or CKD care, and raised novel issues in optimal goals to manage multiple risks for better health promotion of patients with diabetes and CKD.

**Plenary Lectures**

Osamu Nureki (Japan) discussed how CRISPR-associated endonuclease Cas9 could be directed to specific genomic loci by single-guided RNAs and their target DNA, and reviewed the current developments of the CRISPR/Cas9 system in their own research. Nureki and colleagues are now using the CRISPR/Cas9 system to develop therapeutics for unmet medical needs (e.g., hemophilia B, a congenital hemorrhagic disease caused by mutations in the coagulation factor IX gene). Their scientific achievements should shed a light on treating numerous genetic disorders.

Lisa Pettigrew (USA) talked about “Digital health solutions and new payment models.” With the development of an information technology society, patients are becoming informed consumers, and the location of care is changing. Thus, she proposed that successful health systems no longer consider “digital health” as optional. It may be the time for old processes of the medical care system to find a way to coexist with a rapidly developing information technology society, which may provide a better medical care system.

Peter Ratcliffe (UK) presented elucidation of oxygen-sensing pathways and their implications in kidney diseases. Long-standing research on the physiology of erythropoiesis has led to the discovery of a system of transcriptional regulation by oxygen. The hypoxia-inducible factor (HIF) pathway plays a central role in cell-adaptive mechanisms to combat hypoxic conditions. He overviewed the HIF transcriptional cascade under physiological and disease conditions, and a potential approach for therapeutic manipulation of the HIF pathway.

Mammals have evolved elaborate detoxification machinery associated with phase I to III classes of enzymes. Masayuki Yamamoto (Japan) reviewed the KEAP1-NRF2 system, a critical regulator of the phase II detoxification system. In addition, he discussed the therapeutic potency of the NRF2 pathway in several metabolic diseases, such as diabetes, diabetic kidney disease (DKD), and ischemic kidney injury, and the involvement of this system in cancer development. Activators and inhibitors of the NRF2 pathway are likely to be effective therapies for metabolic diseases and cancer, respectively.
Special Lecture
Christoph Wanner (Germany) presented a special lecture regarding sodium and glucose co-transporter 2 (SGLT2) inhibitors in diabetic vascular complications. He mainly introduced the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME) and Canagliflozin Cardiovascular Assessment Study (CANVAS) programs, both of which revealed health benefits of SGLT2 inhibitors in patients with diabetes with high risks for cardiovascular disease (CVD). Most importantly, the SGLT2 inhibitor improved the decline of the estimated glomerular filtration rate (eGFR), regardless of baseline albuminuria stages. SGLT2 inhibitors could be a promising therapy to cure all aspects of DKD, from the classic diabetic nephropathy characterized by increased albuminuria to the nonalbuminuric eGFR decline that has been recently and is often observed in patients with diabetes.7

Symposium 1—Acute Kidney Injury and Cardiovascular Disease
Yung-Chang Chen (Taiwan) reviewed the cardiorenal syndrome (CRS). As defined by Ronco and other experts, CRS has been divided into 5 subtypes. Chen focused on type 1 CRS, which is characterized by development of acute kidney injury (AKI) after acute cardiac illness. He discussed risk factors and biomarkers for AKI, such as angiopoietins, brain natriuretic peptide (BNP), soluble ST2 (sST2), neutrophil gelatinase-associated lipocalin (NGAL), Kidney Injury Molecule-1 (KIM-1), and aquaporin 2. He reported that serum cystatin C is 1 of the best indicators to predict AKI in critically ill patients. However, urinary NGAL and serum interleukin-18 are also associated with short-term mortality of these patients.

Yuichi Ando (Japan) discussed the guidelines for treatment of renal injury during chemotherapy. Oncology has emerged as a new field concerned with the management of nephrotoxicity during anticancer therapy. He mentioned the importance of risk assessment to prevent cisplatin-induced AKI. Furthermore, he introduced the relationship between novel classes of anticancer agents and AKI. Vascular endothelial growth factor (VEGF) inhibitor—induced AKI typically presents with hypertension and proteinuria, which can be reversed by stopping the use of the agents. Immune checkpoint inhibitors, such as a PD-1 inhibitor, also cause AKI. He suggested glucocorticoid therapy for the PD-1 inhibitor—induced AKI.

Joseph Bonventre (USA) discussed the molecular basis of the transition from AKI to CKD, with a focus on G2/M cell cycle arrest in proximal tubular cells. Reports have revealed a strong correlation between G2/M arrest and fibrosis. To investigate the mechanism of the AKI—CKD transition, Bonventre established an organoid system using human pluripotent stem cells and applied cisplatin, which suggested the therapeutic potency of inhibition of ataxia-telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related protein to ameliorate kidney fibrosis due to renal ischemia—reperfusion injury (IRI).

Tsuyoshi Inoue (USA) discussed the interaction between nervous and immune systems in AKI. Inoue studied the effect of vagus nerve stimulation on AKI. Vagus nerve stimulation induces a macrophage phenotype switch to the M2 type through \(7nAChR\) activation. Furthermore, restraint stress or optogenetic C1 neuron stimulation protected mice from AKI, which was reproduced by injecting mice with splenic T cells preincubated with noradrenaline or splenocytes harvested from stressed mice. Stress-induced protection against IRI was absent in a\(7nAChR^{-/-}\) knockout mice and reduced by destroying or inhibiting C1 neurons.

Symposium 2—Cardiorenal Syndrome (Joint With the Japanese Circulation Society)
Marcello Tonelli (Canada) discussed the influence of multiple comorbidities in older CKD patients in current clinical practice. The aging population has led to an increase in the prevalence of multiple comorbidities, such as heart failure, atrial fibrillation, artery diseases, arrhythmias, and aortic valve stenosis. All these comorbidities are also common in CKD patients. An increasing comorbidity burden is associated with an increased risk of death and long-term care placement, but reduces the likelihood of end-stage renal disease (ESRD), and the risks of increasing age are similarly incremental. Thus, among patients with CKD, older age and/or multiple comorbidities, death, and long-term care placement are more likely to occur than ESRD.

Catherine Shanahan (UK) talked about the role of premature vascular smooth muscle cell (VSMC) aging in vascular calcification (VC) and higher CVD prevalence in young hemodialysis patients. VSMCs in children who underwent hemodialysis showed senescence markers and oxidative DNA damage caused by calcium (Ca) and inorganic phosphate (Pi). Thus, dialysis vessels showed a premature aging phenotype even in a young population. Prelamin-A, the unprocessed form of the nuclear lamina protein lamin A, accumulated in the nuclear lamina protein lamin A, accumulated in the VSMCs of dialysis vessels, leading to vascular aging via pro-osteogenic cytokine secretion. Finally, she proposed that inhibition of DNA damage response kinases ataxia-telangiectasia mutated/ataxia telangiectasia and Rad3-related protein could block calcification and inflammation in VSMCs of dialysis vessels.
Katsuhito Fujiu (Japan) proposed a novel mechanism underlying CRS. Krüppel-like factor 5 is expressed in renal collecting ducts. Fujiu identified amphiregulin as a cardioprotective mediator produced by cardiac Ly6C macrophages. Dynamic interplay among the heart, brain, and kidneys is essential for adaptation to cardiac stress, and Krüppel-like factor 5 in collecting duct cells is involved in this process.

Minoru Satoh (Japan) examined involvement of altered nitric oxide (NO) metabolism and oxidative stress in glomerular endothelial cell dysfunction by in vivo real-time imaging. He demonstrated glomerular hypertension, together with renin-angiotensin system (RAS) activation, NAPDH oxidase activation, and endothelial NO synthase uncoupling in diabetes and/or hypertension models, which decreased NO production and increased oxidative stress. GTP cyclohydrolase I is the rate-limiting enzyme for biosynthesis of tetrahydrobiopterin, a cofactor for NO production. Diabetes-related glomerular hyperpermeability in Akita mice was improved by GTP cyclohydrolase I overexpression, whereas massive oxidative stress induced by endothelial cell-specific NOX2 overexpression elicited hyperpermeability. Finally, he suggested some pharmacological approaches to improve endothelial cell dysfunction.

Symposium 3—Phosphate Toxicity and CVD
Ziad Massy (France) discussed the role of Pi in cardiovascular calcification. Pi elevation is associated with all-cause and cardiovascular mortality. He introduced several experimental findings on the relationship between CKD-MBD and CVD. (i) Both fibroblast growth factor 23 (FGF23) knockout mice and Klotho knockout mice showed increased VC. (ii) M2 macrophages played a critical role in VC of CKD. (iii) A calcium-related phosphate binder caused VC, but a non-Ca-related phosphate binder did not. (iv) Soluble klotho treatment increased endothelial NO synthase activity in CKD model animals. Finally, Massy summarized the role of Pi in endothelial cell dysfunction and VC via multiple mechanisms.

Hirotaka Komaba (Japan) demonstrated the significance of phosphate binders in CKD patient care. VC is a strong risk for CVD events in dialysis patients. Maintaining serum Pi levels within an almost normal range is essential to prevent VC. The Accelerated Mortality on Renal Replacement (ArMORR) study showed that phosphate binders significantly improved the survival rate of dialysis patients. Restricting dietary phosphorus intake is essential for regulating Pi levels in CKD patients, but it may cause protein malnutrition. Phosphate binders can relax protein restriction and lead to a better nutritional status in CKD patients.

Tamara Isakova (USA) discussed whether FGF23 or Pi exacerbates CVD and CKD, both of which are elevated in CKD. Experimentally, Pi toxicity caused endothelial dysfunction and CKD progression, and had a direct adverse effect on the myocardium. In addition, VC was due to elevated levels of Pi, but not FGF23. However, elevated FGF23 in CKD patients was independently associated with a higher all-cause mortality risk, and elevated FGF23 exacerbated cardiac hypertrophy in an animal study, which suggested that FGF23 elevation is independently associated with CVD events. Thus, early intervention targeting both Pi and FGF23 levels is important to reduce the risk of CKD progression, CVD events, and even death.

Yusuke Sakaguchi (Japan) demonstrated that hypomagnesemia is a novel mortality risk in dialysis patients. Growing evidence has shown that magnesium (Mg) inhibits Pi-induced VC. Maturation of primary calcioprotein particles (CPPs) to secondary CPPs was promoted by higher Pi or lower fetuin A, which led to VC. Interestingly, this process was inhibited by Mg supplementation. Furthermore, Mg supplementation inhibited Pi-induced proximal tubular cell apoptosis. Clinically, a randomized clinical trial study showed improvement of VC in the Mg oxide group (3.0 mg/dl) compared with the control group (2.5 mg/dl). Hypomagnesemia predicted DKD stage progression, and Mg dissociated the relationship between Pi and CKD progression.

Symposium 4—CKD and CVD
John Cunningham (UK) discussed bone diseases in CKD patients. Bone metabolism disorders are associated with CVD, which leads to a higher mortality rate. In CKD patients, normal serum Pi levels are maintained despite a decline in the nephron mass, in part due to an FGF23-mediated compensatory increase in phosphaturia. The increased FGF23 levels appear to be independently associated with mortality among patients who are beginning hemodialysis treatment. Faul et al. reported that FGF23 inhibition attenuated left ventricular hypertrophy, which indicated that FGF23 plays a central role in the CRS of CKD patients. In addition, Cunningham introduced the therapeutic potential to reduce CVD in CKD patients through NaPi2b, NHI, and Wnt-Catenin inhibition.

Kunihiro Matsushita (USA) discussed how CKD guidelines differ in terms of risk classification. The American Heart Association/American College of Cardiology guidelines indicate “the contribution to risk assessment for a first CVD event during CKD is uncertain at present.” However, the guidelines from the European Society of Cardiology and Kidney Disease Improving Global Outcomes warn that “CKD is a high
risk for CVD.” Therefore, clinical guidelines are not consistent on how to incorporate information on CKD for CVD risk assessments. He showed data from Chronic Kidney Disease Prognosis Consortium (CKD-PC), which suggested that both eGFR and the albumin-creatinine ratio are useful to classify CVD risk, particularly for CVD mortality and heart failure. He emphasized that the albumin-creatinine ratio is a potent predictor of CVD and proposed some potential predictors of CVD in CKD patients.

Naoki Nakagawa (Japan) described the relationship between CVD and malnutrition in CKD patients. He also discussed the significance of atrial fibrillation (AF) in CKD management. CKD patients had a higher rate of AF, which was associated with a higher incidence of cerebral embolism. Thus, management of AF as well as traditional CVD risks should receive more attention to prevent stroke in CKD patients.

Paweena Susantitaphong (Thailand) focused on the prevalence of VC in CKD patients. Despite optimal control of traditional CVD risks, CKD patients are still at a high risk of CVD mortality due to nontraditional CVD risk factors, including VC. The severity of VC predicted CVD morbidity and mortality in CKD patients, and VC caused structural and functional changes in vessel walls, which led to vascular stiffness. Further information was provided, including: (i) the pathophysiological mechanism responsible for VC and vascular stiffness; (ii) the methods for detecting VC and vascular stiffness; and (iii) updated treatments for VC and vascular stiffness in CKD patients.

Symposium 5—DKD and CVD: Clinical
Keizo Kanasaki (Japan) examined the molecular basis underlying the currently available antidiabetic agent-mediated renoprotection in DKD. DPP4 expression increased in the endothelium of diabetic kidneys, which was associated with a phenotype change in endothelial cells, named EndoMT. Interestingly, this process was prevented by a DPP-4 inhibitor via suppression of the miRNA29-TGFβ-DPP4 vicious cycle in a fibrogenic signal. He also revealed that empagliflozin, an SGLT2 inhibitor, ameliorated fibrosis in mouse diabetic kidneys by decreasing diabetes-induced hyperactivation of pyruvate kinase M2, which was previously reported to be associated with DKD.

Per-Henrik Groop (Finland) provided a comprehensive lecture for DKD practice. (i) Effectiveness of intensive care for DKD was confirmed in Action in Diabetes and Vascular Disease Preterax and Diamicron MR Controlled Evaluation (ADVANCE) studies and J-DOIT studies. (ii) To achieve strict glycemic control without harmful hypoglycemia, DPP4 inhibitors are useful. The antialbuminuric effect of a DPP-4 inhibitor was observed in the Efficacy, Safety & Modification of Albuminuria in Type 2 Diabetes Subjects with Renal Disease with LINAgliptin (MARLINA-T2D) study, but its long-term benefits have not been confirmed yet. (iii) The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study showed that a GLP-1 analog improved cardiorenal outcomes. (iv) The EMPA-REG OUTCOME study showed that the addition of SGLT2 inhibitors to standard diabetes care further improved the decline in renal functions of DKD.

Mark Cooper (Australia) discussed the future direction of DKD care. A NOX4 inhibitor, GKT137831, ameliorated diabetic complications in mice; this inhibitor was recently administered to patients with type 1 diabetes. Receptor for advanced glycation end product overexpression accelerated kidney injury, whereas RAGE knockout improved kidney injury in apolipoprotein-E knockout mice. CDA1/CDA1BP amplified transforming growth factor β-mediated fibrogenesis, a final common pathway of CKD. CDA1 knockout mice showed less fibrosis in DKD. He also reviewed the therapeutic potency of CHA-061, a peptidic inhibitor of CD1A/CDA1BP interaction.

Juliana Chan (Hong Kong) introduced the state of diabetes management in Asia by showing data from The Hong Kong Diabetes registry (1995–2007). The study showed that multifactorial management, including statin use and strict blood pressure control, improved renal and CVD outcomes in diabetic patients. Furthermore, she showed data from the Hong Kong Diabetes Database (2000–2012), which revealed significant decreases in the incidence of cardiovascular renal complications and death, and corresponding improvements in risk factor control during a 13-year period. In addition, she provided evidence that genetic variations affect DKD progression and treatment responsiveness in DKD management.

Symposium 6—Hypoxia Biology in Kidney Disease and CVD
Kai-Uwe Eckardt (Germany) studied the role of HIFs in AKI and CKD. Hypoxia induces changes in transcriptional activity mediated by HIF-1 and -2. Fundamentally, HIF activation appeared to play a renoprotective role as a response to regional renal hypoxia. However, in CKD patients, such an analysis is much more complicated because hypoxia promotes epithelial-to-mesenchymal transition and occasionally fibrogenesis via HIF-1 activation. In clinical settings, renal oxygenation can be detected by blood oxygenation level-dependent magnetic resonance imaging, which revealed that low cortical oxygenation in
diseased kidneys is an independent predictor of renal dysfunction. This finding should encourage studies that will explore the therapeutic effect of improving renal oxygenation.

Roger Evans (Australia) discussed 2 ideas about a clinical problem—AKI in cardiac surgeries that requires cardiopulmonary bypass—(i) continuous intraoperative measurement of urinary pressure of oxygen (PO2) can be used to assess the risk of postoperative AKI; and (ii) perfusion conditions during cardiopulmonary bypass must be optimized to improve renal medullary oxygenation. In septic AKI, medullary and urinary hypoxia developed several hours earlier than the increases in the currently used biomarkers. He also developed a pseudo—three-dimensional model of oxygen transport in a rat renal cortex by incorporating both the axial and radial geometry of periglomerular circulation, as well as quantitative information regarding the surface areas and transport from the vasculature and renal corpuscles.

Tetsuhiro Tanaka (Japan) discussed recent discoveries of the regulatory mechanisms of HIF-1α activation in diseased kidneys. Hypoxia plays a critical role in renal fibrosis, inflammation, and CKD progression. HIF activity is modulated by multiple factors associated with CKD. Interestingly, hypoxia and/or myeloid cell–specific HIF activation attenuated inflammation in CKD. Therapeutic treatments based on HIF activation have been investigated for kidney diseases, and successful prevention has been reported in numerous experimental models.

Daisuke Nakano (Japan) introduced a novel role of tubular glucose metabolism regulated by SGLT2 and the glucose transporter 2 (GLUT2) in AKI–CKD progression as revealed by multiphoton laser microscopy. Both GLUT2 and SGLT2 play central roles in glucose uptake in kidneys. In mice, renal uptake of 2-NBDG, a fluorescent glucose analog, was suppressed by an SGLT2 inhibitor. In addition, a greater reduction in glucose uptake accompanied by decreased GLUT2 expression was observed in mice after renal IRI. In IRI mice, an SGLT2 inhibitor significantly lowered intracellular glucose levels in ischemic tubules, leading to renoprotective overexpression of VEGF.

Symposium 7—DKD and CVD: Basic
Katherine Tuttle (USA) discussed new strategies for DKD treatment. (i) SUSTAIN-6, LEADER, and AWARD-7 studies showed benefits of a GLP-1 analog in type 2 diabetic patients compared with conventional diabetes care. (ii) The effect of an Nrf2 activator (bardoxolone methyl) on improving the eGFR in DKD patients was discussed based on the BEACON trial and the TSUBAKI study. (iii) The effectiveness of inhibiting the MCP-1/CCR2 signal and a JAK1/2 inhibitor in DKD was introduced. Widespread innovation is continuously needed to further improve health outcomes of DKD patients.

Robyn Langham (Australia) discussed the usefulness and importance of a transcriptional array to identify new therapeutic targets of DKD, biomarkers of disease progression, and biomarkers to assess the effectiveness of therapy. Molecular mechanisms active early in DKD were revealed by correlating intrarenal transcripts with quantitative morphometry and long-term outcomes.

Sydney Tang (Hong Kong) discussed the role of inflammation in DKD. (i) Toll–like receptor-4 (TLR4) was overexpressed in human diabetic kidneys. TLR4 overexpression in diabetic mice promoted severe tubulointerstitial lesions, whereas TLR-4 antagonist CRX-526 improved DKD in mice. (ii) Transfer of the kallistatin gene, a kallikrein inhibitor, improved renal injury in type 2 diabetic db/db mice by suppressing advanced glycation end product–receptor for advanced glycation end product—induced oxidative stress. (iii) A mixed RNA/DNA aptamer that binds to human and mouse C5a improved fibrogenesis in an animal model of DKD. TLR4, kallikrein, and complement proteins in tubulointerstitial inflammation may be novel therapeutic targets for DKD.

Atsuko Nakatsuka (Japan) discovered a novel adipokine, vaspin, which improves obesity, diabetes, and atherosclerosis. She expanded the study to examine tissue-protective effects of vaspin in DKD. Growing evidence showed involvement of a dysfunctional autophagy–lysosomal system in the pathogenesis of DKD. Interestingly, she revealed that vaspin prevented kidney injury induced by endoplasmic reticulum stress and saturated fatty acids via activation of the autophagy–lysosomal pathway.

Symposium 8—Atypical Hemolytic Uremic Syndrome and Systemic Vascular Injury
Toby Coates (Australia) demonstrated involvement of the alloimmune response in the endothelium of patients with transplantation-related secondary thrombotic microangiopathy (TMA). After transplantation, disruption of endothelial glycocalyx by oxidative stress increased vascular wall adhesiveness and triggered TMA. If an abnormality was identified in the complement systems involving factor H or I, TMA recurrence was frequent. TMA also often occurs during immune suppression therapies, such as calcineurin inhibitor (CNI) treatment. Overexpression of VEGF exerted a renoprotective effect in experimental TMA. For patients with CNI-induced TMA, reduction of the responsible drug can help, and occasionally, a switch from tacrolimus to cyclosporine or vice versa may be beneficial.
Christine Sethna (USA) provided an overview of Shiga toxin-producing Escherichia coli—hemolytic uremic syndrome (STEC-HUS). Risk factors for STEC-HUS include an elevated white blood cell count, age younger than 10 years, and antibiotic administration.

Toshihiro Sawai (Japan) summarized the current knowledge of atypical hemolytic uremic syndrome (aHUS). Typically, a genetic mutation occurs in the complement system, including complement factors B, H, and I, and a membrane cofactor protein or C3 causes aHUS. Also, antifactor H antibodies can cause aHUS. With the introduction of eculizumab, it is now possible to control renal disease in aHUS.

Yoko Yoshida (Japan) established a diagnostic system for aHUS, including a quantitative hemolytic assay using sheep erythrocytes, anticomplement factor H (CFH), autoantibody screening, and genetic analysis of 7 candidate genes (CFH, CFI, C3, CFB, MCP, THBD, and DGKE). The hemolytic assay showed that patients with CFH variants or anti-CFH antibodies showed increased hemolysis of sheep red blood cells. As of December 2016, 120 patients have been clinically diagnosed with aHUS. Of these patients, 47 developed aHUS during adulthood; a male predominance was observed.

**Symposium 9—Dialysis and CVD: Clinical**

Xueqing Yu (China) introduced the current state of kidney cares in China. CVD is the leading cause of mortality in Chinese patients undergoing peritoneal dialysis (PD). The study identified various all-cause and/or CVD mortality risks, including fluid overload, glucose-based PD solution, high glycosylated hemoglobin (HbA1c), lipid abnormalities (e.g., a high TG/high-density lipoprotein cholesterol ratio), high uric acid levels, high declining rate of body mass index during the first year after the start of PD, a high malnutrition score, high serum C-reactive protein, peritonitis, lower hemoglobin levels, and higher serum phosphate. Assessment and management of modifiable risk factors are important to prevent CVD events in dialysis patients.

Jorge Cannata-Andia (Spain) discussed optimization of CKD-MBD management in hemodialysis patients, which was determined by the COSMOS study, a multicenter, open cohort, prospective, observational 3-year study carried out in 20 European countries from 2005 to 2007. The COSMOS study described the main characteristics of the European dialysis population, current practices for prevention, diagnosis, and treatment of CKD-MBD, and the differences across European regions. CVD and CKD-MBD were associated with higher mortality in dialysis patients, and the lowest mortality risk ranges based on the previous values were 3.6 to 5.2 mg/dl for serum phosphorus, 7.9 to 9.5 mg/dl for serum calcium, and 168 to 674 pg/ml for serum parathyroid hormone (PTH).

Vivekanand Jha (India) discussed an issue in clinical trials regarding CKD and CVD in Asian countries. Asia is highly diverse in terms of ethnic and sociocultural backgrounds. Some of this diversity is reflected by relatively young CKD patients, differences in dietary habits, causes of kidney disease, and access to care, which can be ascertained through large Asian cohort studies, such as the Chronic Kidney Disease Japan Cohort (CKD-JAC; Japan), the Chinese Cohort of Chronic Kidney Disease (C-STRIDE; China), the Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD; Korea), the Indian Chronic Kidney Disease (ICKD; India), CORE-CKD (Thailand), and TCKDS (Australia). Finally, he introduced ISN-iNET-CKD (International Network of Chronic Kidney Disease) cohort studies and ISN-ACT (Advancing Clinical Trials), which were recently launched by the ISN.

David Johnson (Australia) talked about CVD management in PD patients. CVD is highly prevalent and the primary cause of death in PD patients. He introduced the importance of optimized management of traditional risk factors (hypertension, dyslipidemia, obesity-related conditions, and smoking), nontraditional risk factors (anemia, fluid overload, inflammation, malnutrition, hyperuricemia, and CKD-MBD), and PD-specific risk factors (dialysis solution, residual kidney functions, and ultrafiltration failure) to mitigate CVD risks in PD patients.

**Symposium 10—CKD-MBD and CVD**

Recent reports on several bone-derived substances have shed new light on the bone—cardiovascular axis. Ravi Thadhani (USA) highlighted FGF23 and phosphate among these substances. The therapeutic potential of vitamin D for CVD has been studied in several clinical trials. In the OPERA trial, treatment with oral paricalcitol, a vitamin D analog, significantly improved secondary hyperparathyroidism, but it did not alter parameters of the left ventricular structure or improve functions in patients with severe CKD. In the Paricalcitol Capsules Benefits in Renal Failure Induce Cardiac Morbidity (PRIMO) study, therapy with paricalcitol neither altered the left ventricular mass index nor improved certain parameters of diastolic dysfunction in patients with CKD.

Takayuki Hamano (Japan) reviewed the ADVANCE and Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EOLVE) trials of cinacalcet. In the ADVANCE trial, cinacalcet slowed calcification of coronary arteries and the aortic valve. The EOLVE
trial showed no significant benefit of cinacalcet in primary composite outcomes, such as death or a first nonfatal myocardial infarction, in an intention-to-treat (ITT) analysis. This negative result could be attributed to the lower than predicted event rate, contamination between the 2 arms, and high drop-out rates, which led to an unexpected smaller statistical power. However, even in the ITT analysis, cinacalcet significantly reduced the incidence of heart failure and calciphylaxis, which was in line with the ADVANCE trial.

Calcification in vasculature and cardiac valves is a hallmark of CKD-MBD, which leads to increased stiffness and/or a tendency to rupture, and has severe effects on hemodynamics and cardiovascular functions. Cecilia Giachelli (USA) focused on the role of osteochondrogenic differentiation guided by Runx2 and type III sodium-dependent phosphate transporters in regulating VC.

Yoshitsugu Obi (USA) proposed a novel concept, “hidden hypercalcemia,” in CKD-MBD. Because serum calcium is bound to albumin, calculations of total serum Ca (tCa) are corrected by a predictive equation in clinical practice. However, both uncorrected and albumin-corrected tCa concentrations poorly predict hypo- or hypercalcemia in CKD patients. In a cohort study, approximately 70% of dialysis patients with ionized hypercalcemia were incorrectly categorized as normocalcemic using the conventional equation. These patients were considered to have hidden hypercalcemia, which was associated with higher mortality.

Symposium 11—Transplantation and CVD

Toby Coates (Australia) summarized antibody-mediated rejection (ABMR) after kidney transplantation. The mechanisms underlying the development of donor-specific antibodies (DSAs) and human leukocyte antigen (HLA) antibody-mediated kidney injury are complex via the multiple modulated intracellular pathways. A recent meta-analysis examined a management strategy for acute ABMR. Plasma apheresis and IV-IgG are the standard treatments for acute ABMR, and screening for DSAs is important to prevent acute ABMR. Kidney graft survival in patients with chronic ABMR is also associated with the existence of DSAs. No effective treatments for chronic ABMR have been suggested so far, but a promising therapeutic potency of immunoproteasome inhibition is now expected.

Adrian Liew (Singapore) discussed sequential changes of allograft survival rates and the current state of long-term allograft survival. (i) The quality of donor kidneys was important for better allograft survival. (ii) Older age and the time on dialysis were identified as rejection risks for the recipient, and HLA compatibility and anti-HLA immunization were important as immune-related factors for rejection. (iii) Delayed graft functions were commonly considered a risk factor for acute rejection. (iv) Optimization of immunosuppression therapy with CNIs by maximizing its effect on allograft rejection while minimizing contrast media-induced nephropathy–induced nephrotoxicity was discussed. (v) Finally, a poorly established strategy to predict the allograft rejection was raised as a problem to be resolved.

Philip Li (Hong Kong) stated that CVD mortality in kidney transplantation patients is better than that in hemodialysis patients, but it is still worse than that in the general population. Malnutrition, inflammation, and atherosclerosis/calcification syndrome, in addition to traditional CVD risks, were considered similar to other CVD risks in kidney transplantation patients. Hypertension was associated with 1-year survival and a modifiable risk. Calcium channel blockers were feasible for treating hypertension, but RAS blockade did not improve clinical outcomes in the kidney transplantation patients. For lipid management, a statin did not reduce CVD risk and mortality.

Tadashi Sofue (Japan) discussed marginal living donors in kidney transplantation. There is controversy regarding whether marginal donors are suitable for kidney transplantation in terms of donor safety and organ quality. The quality of donated kidneys directly affects recipient allograft functions and acute allograft rejection. Quality of donated kidneys has been evaluated based on physical or pathological assessment of donors and/or donated kidneys, which may facilitate a better allograft outcome.

Symposium 12—Pediatric Nephrology and CVD

Kandai Nozu (Japan) provided an overview of Alport syndrome (AS), a type IV collagen hereditary disease. Mutations in the COL4A5 collagen gene are responsible for the common X-linked dominant form of the disease. Kandai Nozu (Japan) provided an overview of Alport syndrome (AS), a type IV collagen hereditary disease. Mutations in the COL4A5 collagen gene are responsible for the common X-linked dominant form of the disease. Nozu retrospectively studied 52 genetically diagnosed male X-linked AS patients to evaluate differences in clinical characteristics and renal outcomes between 15 α5(IV)-positive and 37 α5(IV)-negative patients. In the study, approximately 70% of the patients had the X-linked form of the disease, 15% were autosomal recessive, and the remaining 15% were autosomal dominant. The male X-linked AS cases were reported to develop ESRD at a median age of 25 years.

Yutaka Harita (Japan) reviewed childhood steroid-sensitive nephrotic syndrome and steroid resistant nephrotic syndrome. B cells play a critical role in steroid resistant nephrotic syndrome. The risk of steroid-sensitive nephrotic syndrome is mediated by specific genetic risk variants in the MHC II gene HLA-DQA1, either alone or in response to yet unidentified
environmental triggers. Primary focal segmental glomerulosclerosis (FSGS) is purportedly caused by an unrecognized circulating factor. Soluble urokinase plasminogen activator receptor was identified as a circulating factor associated with FSGS. Causative genes in childhood nephrotic syndrome differ by race.

Rukshana Shroff (UK) discussed the role of vitamin D in childhood CKD-MBD. Dysregulation of mineral metabolism directly affects bone strength, mineralization, and architecture, leading to the spectrum of CKD-MBD. Children with CKD have a high likelihood of fracture. Regarding modifiable factors, higher PTH levels have been associated with a greater risk of fracture, whereas phosphate binder use has been shown to be protective. Another report indicated that calcium, iPTH, and 1,25(OH)2D are important and independently correlated with the CortBMD Z-score, and that calcium is particularly important in the growing skeleton. Cortical bone consists of 80% of skeletal mass, and children are more likely to fracture the cortical-rich appendicular skeleton.

Similar to adults, CVD is the leading cause of death in young adults diagnosed with kidney diseases during childhood. Christine Sethna (USA) discussed CVD risks in children with kidney diseases. In the Cardiovascular Comorbidity in Children with CKD Study, the prevalence of CVD increased from 24.4% in CKD stage 3 to 47.4% in CKD stage 5. The prevalence of left ventricular hypertrophy was also higher with each CKD stage. The office systolic blood pressure SD score was an independent factor associated with all surrogate markers of CVD. Early identification of modifiable risk factors and treatment may decrease long-term cardiovascular morbidity and mortality, but data in this population are lacking.

Symposium 13—Nutrition in Kidney Disease and CVD

Akihiko Kato (Japan) discussed the emerging clinical problem of sarcopenia in CKD. CKD causes sarcopenia that is associated with progression of CKD, development of atherosclerosis, and higher mortality. In addition to lifestyle- and age-related factors, uremia-related factors that promote sarcopenia should exist in CKD patients. The circulating irisin level is low in sarcopenia patients, which is associated with progression of arterial disease. Interestingly, in mice, exercise-induced irisin expression or recombinant irisin administration improved kidney functions. Irisin may explain the crosstalk among kidney injury, muscle weakness, and atherosclerosis.

Hiroko Segawa (Japan) focused on gastrointestinal handling of phosphate and its importance as a novel therapeutic target for hyperphosphatemia in CKD patients. Because phosphate binders have several adverse effects, such as severe constipation, alternative inhibitors of phosphate absorption from the intestines that block the Npt2 and PiT1/2-NHE3 interaction are being studied.

Angla Wang (Hong Kong) presented a comprehensive lecture on dietary management in CKD care and protein energy wasting as a novel problem in CKD management. Lifestyle modification, including dietary modification, is essential to prevent CKD progression. An experimental low protein diet improved kidney fibrosis, proteinuria, and eGFR. Clinically, a vegetarian low protein diet supplemented with ketoanalogues deferred dialysis initiation in patients with eGFRs of <20 ml/min. These observations were enhanced by a meta-analysis of all-cause mortality in CKD patients. In addition, Wang discussed the therapeutic effectiveness of high-fiber intake against CVD events in CKD patients. Moreover, trimethylamine-N-oxide, a gut microbe-dependent metabolite of dietary choline, phosphatidylcholine (lecithin), and L-carnitine, which was increased in the serum of CKD patients, exacerbated renal dysfunction in animal models.

Orson Moe (USA) reviewed phosphotoxicity and introduced its underlying molecular mechanism. Phosphotoxicity is due to excessive dietary intake of inorganic phosphorus that is included as food additives and can be more easily absorbed compared with organic and plant-based phosphorus. An epidemiological study revealed that high phosphatemia was associated with higher mortality. As mechanisms underlying phosphotoxicity, he discussed their previous findings that Klotho deficiency was a novel intermediate mediator of pathological cardiac remodeling.

Symposium 14—Specialization of Nephrology Nursing and Development of Multi-Occupational Collaboration

Hisaitsu Sato (Japan) reviewed the history and role of the Japan Academy of Nephrology Nursing. He discussed the experiences of the academy after the East Japan great earthquake disaster.

Noriko Koteda (Japan) discussed the history and role of dialysis care and management of CKD leading nurses.

Conclusion

The ISN Frontiers Meeting 2018 in Tokyo was intended to educate, to inform, to broaden, and to advance basic and applied renal science by drawing on expertise from the diverse fields of biology and clinical medicine, which was organized by the local committee members, including many young Japanese nephrologists under the supervision of the scientific program committee (Figure 1 and Supplementary Appendix S1). As can be
seen from the breadth of subjects covered in these summaries, we believe these goals were achieved. In addition, it was a unique opportunity to bring research scientists, clinical scientists, and nephrologists from Asia, Australia, Europe, and North America together in such a close, interactive format. The ISN Frontiers meeting 2018 attracted 1584 active physicians and scientists from 64 countries, and has and will lead to new exchanges and productive collaborations for innovation in nephrology research to improve clinical practice. We hope that the achievements will contribute to better health for all patients with kidney diseases.

DISCLOSURE
All authors declared no competing interests.

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SUPPLEMENTARY MATERIAL
Appendix S1. List of meeting organizers.
Supplementary material is linked to the online version of the paper at [www.kireports.org](http://www.kireports.org).

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