Management of patients with diabetes and CKD : conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

Perkovic, Vlado

2016-12

Perkovic , V , Agarwal , R , Fioretto , P , Hemmelgarn , B R , Levin , A , Thomas , M C , Wanner , C , Kasiske , B L , Wheeler , D C , Groop , P-H & Conf Participants 2016 , ' Management of patients with diabetes and CKD : conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference ' , Kidney International , vol. 90 , no. 6 , pp. 1175-1183 . https://doi.org/10.1016/j.kint.2016.09.010

http://hdl.handle.net/10138/172966
https://doi.org/10.1016/j.kint.2016.09.010

Management of patients with diabetes and CKD: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

Vlado Perkovic[1,2], Rajiv Agarwal[3], Paola Fioretto[6], Brenda R. Hemmelgarn[7,8,9,10], Adeera Levin[11,12,13], Merlin C. Thomas[4,5], Christoph Wanner[14], Bertram L. Kasiske[15], David C. Wheeler[16] and Per-Henrik Groop[4,17,18,19]; for Conference Participants[20]

[1]George Institute for Global Health, University of Sydney, Sydney, NSW, Australia; [2]Royal North Shore Hospital, Sydney, New South Wales, Australia; [3]Department of Medicine, Indiana University School of Medicine and Richard L. Roudebush Veterans Administration Medical Center, Indianapolis, Indiana, USA; [4]Diabetic Complications Division, Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia; [5]Department of Medicine, Monash University, Melbourne, Victoria, Australia; [6]Department of Medicine, University of Padova, Italy; [7]Department of Medicine, University of Calgary, Calgary, Alberta, Canada; [8]Interdisciplinary Chronic Disease Collaboration, Calgary, Alberta, Canada; [9]Libin Cardiovascular Institute and Institute of Public Health, University of Calgary, Calgary, Alberta, Canada; [10]Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada; [11]Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada; [12]BC Provincial Renal Agency, Vancouver, British Columbia, Canada; [13]Centre for Health Evaluation and Outcomes Research, St. Paul's Hospital, Vancouver, British Columbia, Canada; [14]Renal Division, University Hospital of Würzburg, Würzburg, Germany; [15]Division of Nephrology, Hennepin County Medical Center, Minneapolis, Minnesota, USA; [16]University College London, London, UK; [17]Folkhälsan Institute of Genetics, Folkhälsan Research Center, Helsinki, Finland; [18]Diabetes and Obesity Research Program, Research Programs Unit, University of Helsinki, Helsinki, Finland; and [19]Abdominal Center Nephrology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

The prevalence of diabetes around the world has reached epidemic proportions and is projected to increase to 642 million people by 2040. Diabetes is already the leading cause of end-stage kidney disease (ESKD) in most developed countries, and the growth in the number of people with ESKD around the world parallels the increase in diabetes. The presence of kidney disease is associated with a markedly elevated risk of cardiovascular disease and death in people with diabetes. Several new therapies and novel investigational agents targeting chronic kidney disease patients with diabetes are now under development. This conference was convened to assess our current state of knowledge regarding optimal glycemic control, current antidiabetic agents and their safety, and new therapies being developed to improve kidney function and cardiovascular outcomes for this vulnerable population.

Kidney International (2016) **90,** 1175–1183; http://dx.doi.org/10.1016/j.kint.2016.09.010

KEYWORDS: antidiabetic agents; cardiovascular disease; chronic kidney disease; diabetes; glycemic control; renoprotection

Correspondence: *Vlado Perkovic, The George Institute for Global Health, 321 Kent Street, Sydney NSW 2000, Australia. E-mail: vperkovic@georgeinstitute.org.au; or Per-Henrik Groop, Abdominal Center Nephrology, University of Helsinki and Helsinki University Hospital Biomedicum Helsinki, Haartmaninkatu 8, 00290 Helsinki, Finland. E-mail: per-henrik.groop@helsinki.fi*

[20]See Appendix for list of other conference participants.

Received 5 August 2016; revised 16 September 2016; accepted 22 September 2016

The prevalence of diabetes around the world is expected to reach 642 million people by 2040.[1] About 40% of people with diabetes will develop chronic kidney disease (CKD),[2] including a significant number who will develop end-stage kidney disease (ESKD).

Diabetes is the leading cause of ESKD in most developed countries, and has driven growth in ESKD globally over recent decades.[3–5] There is a strong economic and health imperative to improve outcomes for people with diabetes and kidney disease.

The identification of renin-angiotensin system (RAS) blockade as an effective strategy for the prevention of ESKD in diabetes was a major step forward,[6–8] but subsequent research has had limited success in building upon these gains. A number of promising treatments have been found to be ineffective or harmful, many of which have now been abandoned in this population.[9–14] One common feature of these failures has been the emergence of unexpected adverse effects, highlighting the importance of safety monitoring in future trials and review of what is known about the safety of existing treatments in this patient population.

With a number of new agents under development targeting newly identified mechanistic pathways underlying

diabetic kidney disease (DKD), it is timely to reflect on what has been learned in order to better optimize both the care of affected patients as well as provide a road map for future research. Kidney Disease: Improving Global Outcomes (KDIGO) convened a Controversies Conference in Vancouver in February 2015 to bring together a multidisciplinary group of key experts from around the world to explore these issues. This report summarizes the key outcomes of this conference.

Lifestyle measures, including diet and exercise in DKD

Salt intake, obesity, and sedentary living have been linked to morbidity and mortality in multiple epidemiological studies.[15] Dietary sodium restriction has been demonstrated to reduce blood pressure (BP) and albuminuria[16–19] and enhances the effects of RAS inhibition. However, optimal dietary sodium intake in DKD remains controversial.

Other lifestyle interventions such as weight loss, and physical exercise, as well as supplementation with mono- and poly-unsaturated fats, have been shown to improve glycemic control, lower BP, reduce albuminuria, and alter high-risk biomarker profiles in the general population and are of interest in individuals with diabetes and CKD.[20–23] In the recently completed Look AHEAD study, patients randomized to a multifactorial lifestyle approach, including dietary advice and increased exercise, demonstrated slower progression of CKD than patients in the comparator group who received support and education[24] but the effects on cardiovascular (CV) events and mortality were disappointing. It is hoped that there will be further follow-up of these patients to determine if the renal benefits based on lifestyle interventions are sustained.

Glycemic control

The fundamental abnormality in diabetes is abnormal glucose metabolism, and the degree of abnormality predicts development of nephropathy,[25] but the role of intensive glycemic control on kidney outcomes remains controversial. Trials of intensive glucose control, such as the DCCT/EDIC trial in type 1 diabetes mellitus (T1DM), were inadequately powered to address this question. However, surrogate endpoints including albuminuria, and new-onset CKD or hypertension were attenuated by intensified glycemic control and sustained for more than 20 years after the end of the randomized phase of the study.[26]

In type 2 diabetes mellitus (T2DM), analyses from the ADVANCE trial found a >50% reduction in ESKD in the group randomized to intensive glycemic control that persisted out to 10 years.[27–29] Event numbers were modest, and no reduction in ESKD has been reported in other trials,[30,31] but benefits on endpoints such as albuminuria were shown. Together, these findings build on epidemiological data supporting the relationship between glycemic control and nephropathy in diabetes.[32,33]

Additional opportunities to further define the link between glycemic control and kidney disease may be provided by ongoing studies including the follow-up of the TODAY trial, which focused on youth and adolescents with early onset T2DM who have a higher incidence of kidney disease.[34] Furthermore, ongoing follow-up of participants in several diabetes intervention and prevention studies of more than 10 years duration should provide additional data on the impact of glycemic control on various complications of diabetes, including kidney disease.[35,36]

Glucose-lowering agents. The availability of a growing range of medications to manage T2DM has highlighted knowledge gaps that still have not been resolved. Metformin is an important therapy that is underutilized in patients with CKD largely because of the risk of lactic acidosis in this setting.[37] It may be possible to use reduced doses of metformin (≤ 1 g per day) in patients with stable impaired renal function, with a plan to discontinue therapy and seek review in the event of significant intercurrent illness.[37] Although the safety of this strategy has been questioned, many guidelines now suggest the use of metformin down to a glomerular filtration rate (GFR) of 30 ml/min/1.73 m^2.[38–41]

Preclinical and *post hoc* clinical analyses from early trials suggest that glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter 2 (SGLT2) inhibitors may afford renal protection, partly independent of their glycemic effects.[42,43] Although most trials are designed to address CV safety in order to meet the requirements of regulatory agencies, there are likely to be sufficient renal endpoints in some to determine whether these new approaches to lower glucose will confer renal benefits.

SGLT2 inhibitors are of great interest, particularly due to the marked reduction in CV mortality and renal risk as reported from the EMPA-REG OUTCOME trial, and suggested renoprotection from the CANTATA-SU trial.[44–46] Of note, the balance of risks and benefits in people with CKD will be important to define separately, particularly as the glucose-lowering effects decline as estimated glomerular filtration rate (eGFR) falls although similar weight loss and BP reductions are observed, at least in CKD stage 3 patients. The CREDENCE trial will assess whether the SGLT2 inhibitor canagliflozin prevents ESKD in patients with T2DM and nephropathy (clinicaltrials.gov: NCT02065791).

Glucose lowering has generally been disappointing in terms of CV protection in the context of diabetes mellitus. Because kidney function is closely linked to CV events and mortality, it is hoped that analysis of data from future trials will allow assessment of whether CKD stage modifies CV protection associated with use of glucose-lowering agents. There are a number of large ongoing studies being conducted in the CKD population that will help to address this issue (clinicaltrials.gov: NCT01897532, NCT01989754).

Monitoring glycemic control in CKD. HbA1c is problematic in CKD due to reduced red cell survival time, use of erythropoietin, modifications of hemoglobin (e.g., carbamylation)[47] and mechanical destruction of red blood cells on dialysis. Thus, clinicians may often need to rely more on random or continuous home blood glucose monitoring. This is a tedious, inconvenient approach in people with CKD, who are often sick and frail.

Thus, alternatives to HbA1c have been sought. These include fructosamine, glycated albumin, and 1,5-anhydroglucitol. The results of ongoing studies are required to ascertain whether any of these alternative approaches are useful and whether they may be particularly relevant in certain stages of CKD.

Hypoglycemia. A major challenge in the management of DKD is the increased risk of hypoglycemia. In the ACCORD study, hypoglycemia in the intensively treated group was associated with an increase in mortality.[48] The authors could not demonstrate whether hypoglycemia *per se* was causative, but this issue remains a concern particularly in the CKD population, which has a higher risk of hypoglycemia and CV events and mortality. The increased risk of severe hypoglycemia in CKD[49] reflects altered insulin and drug pharmacology including metabolite accumulation, inadequate compensatory gluconeogenesis, and flattening of the relationship between mean glucose control and HbA1c. Therefore, careful individualized glycemic control targeting, medication prescription, patient education, therapeutic planning, and vigilance for hypoglycemia are all important components in the management of patients with DKD.

Data from both trials[49] and epidemiological studies[50] have demonstrated the adverse impact of the combination of hypoglycemia and CKD on mortality in T2DM. There are a limited number of glucose-lowering agents that are not associated with hypoglycemia that can be used in CKD. New trials of these agents will help to define clinical benefits in the context of a lower risk of hypoglycemia. The recently published LEADER study demonstrates the potential of these drugs to reduce CV risk in patients with T2DM, but whether such benefits extend to patients with CKD needs to be explored.[51] Similarly, the EMPA-REG OUTCOME trial has demonstrated that empagliflozin, a SGLT2 inhibitor, was associated with slower progression of kidney disease and a reduction of clinically relevant renal events in patients with eGFR of at least 30 ml/min/1.73 m^2.[45]

Other renoprotective therapies: dual RAS blockade and beyond. The benefits of RAS blockade for slowing kidney disease progression with or without diabetes is well established. Trials attempting dual RAS blockade (ONTARGET, ALTITUDE) found increased rates of adverse events (i.e., hyperkalemia, acute kidney injury [AKI]).[12,13,52] More recently, the VA-NEPHRON-D trial[10] evaluated losartan alone versus losartan and lisinopril in stage 2 to 3 DKD with albuminuria, and was also terminated early due to hyperkalemia and AKI. Despite accumulating only 37% of the projected 739 endpoints, the hazards ratio for ESKD was 0.66 ($P = 0.07$), suggesting a potential emerging signal for renal protection. A network meta-analysis has also identified dual RAS blockade as the most promising potential therapy if it can be offered safely.[53] Novel therapies in sequestering potassium in the gut may mitigate the risk for hyperkalemia and permit further important clinical trials to proceed.[54] The risk for AKI may also be reduced by withholding RAS blockade during high-risk periods.

Aldosterone/mineralocorticoid inhibition may be a promising approach to test in this regard. Aldosterone blockade reduces CV mortality in patients with heart failure[55] and reduces albuminuria.[56,57] The effectiveness of aldosterone antagonism in reducing CV and renal events in DKD is being tested with finerenone (clinicaltrials.gov: NCT02540993).[56] Potential mechanisms of action include promotion of salt and water loss, potentially improving volume and BP management, with anti-fibrotic effects demonstrated in animal studies.[58]

Other potential mechanisms by which intraglomerular pressure could be reduced, independent of the RAS system, are also being assessed. For example, atrasentan has been shown to reduce albuminuria in DKD[59] and is now being tested in SONAR, a large outcome trial that will examine the effects on kidney failure using an enrichment design. This study will also help define whether a reduction in albuminuria can be used to predict clinical benefits such as slowing of progression of CKD (clinicaltrials.gov: NCT01858532). SGLT2 inhibitors may also reduce intraglomerular pressure by enhancing glomerular afferent arteriolar constriction[60] and may prevent ESKD.[45]

Strategies targeting fibrosis, inflammation, and other processes in the kidney may also have clinical benefits, but are at an early stage of development.

Cardiovascular and other outcomes

Patients with diabetes and kidney disease are at high risk for cardiovascular disease (CVD)[61–64] through both atherosclerotic and nonatherosclerotic mechanisms;[65] thus, multipronged strategies are required to reduce such risk. The relative contribution of traditional and nontraditional risk factors, as well as CKD complications such as mineral bone disorder, anemia, and fluid retention, to the excess CV burden in DKD at different stages of CKD requires further study.

Traditional risk factors including BP and dyslipidemia are important, and there has been progress in assessing interventions addressing these on CV outcomes in CKD. Recent KDIGO guidelines on BP[66] and lipid management[67] have recommended evidence-based treatment strategies that warrant uptake into clinical practice. These include single-agent RAS blockade and BP targets below 130/80 mm Hg in patients with diabetes and albuminuria (urinary albumin:creatinine ratio >3 mg/mmol or >30 mg/g), along with

routine treatment with fixed-dose, moderate-intensity statin with or without ezetimibe in DKD. However, the high residual CV risk in DKD highlights the unmet need for new strategies.

Volume control. The prevalence of volume overload in patients with CKD is well described.[68] There are several reasons why patients with T2DM retain salt and water, including insulin therapies, aldosterone escape on RAS blockers, potential increased activity of SGLT2 cotransporters,[69] and reduced GFR itself. However, the extent to which volume overload contributes to CVD morbidity and mortality is not well described. There are no studies that have examined intensified diuretic therapy targeted at objectively assessed volume overload, assessing harms and benefits of this strategy. The reductions in CV mortality and heart failure reported with SGLT2 inhibitors support the importance of volume control.[46,70] Further trials of targeted interventions would be of value.

Lipid lowering. Pharmaceutically based lipid lowering has been shown to safely reduce CV events in CKD,[71] and guidelines now recommend moderate-intensity therapy, with fixed dose and no additional measurements.[67] Recommended treatments incompletely mitigate excess CV risk in DKD, in which diverse lipid profiles are observed.[72]

The role of intensified therapies aimed at abnormalities of lipoprotein(a), low high-density lipoprotein cholesterol, and high triglyceride concentrations requires further study. Novel agents such as proprotein convertase subtilisin/kexin type 9 inhibitors and perhaps cholesterylester transfer protein inhibitors are of interest in this regard. New studies could explore whether the risk conferred by dyslipidemias in DKD is similar to dyslipidemias in those without CKD, and characterize the response to therapy and whether that response confers the same benefit.

Antiplatelet/antithrombotic therapy. The use of antiplatelet and antithrombotic agents in patients with DKD or CKD for prevention of CVD has not been robustly studied. A *post hoc* analysis of the HOT trial indicated net benefit for prevention of CV events for aspirin in patients with CKD and high BP, but predominantly included patients with relatively mild CKD.[73] *Post hoc* analyses of trials of other antiplatelet agents have raised questions of whether the balance of benefit and harm is the same in patients with diabetes and/or CKD[74] and whether some agents may be more effective in CKD than others.[75] These results need to be interpreted with caution, as most participants with CKD had mild GFR reductions.

There are potential harms associated with antiplatelet/antithrombotic agents, so an improved understanding of when to use these agents, in whom, and for what duration, is critical. Given the very high rates of thrombotic and embolic events (venous and arterial), particularly in advanced CKD, use of these therapies and novel oral anticoagulants requires further evidence.

Atrial fibrillation is highly prevalent in CKD and dialysis,[76] but treatment with warfarin is likely to increase risks of bleeding, vascular calcification, and calciphylaxis.[77] The role of both warfarin and novel oral anticoagulants (which do not need regular monitoring and may have lower complication rates) is a key research question. As the risk of bleeding in peritoneal dialysis and predialysis CKD may be less than hemodialysis, testing different anticoagulant strategies in advanced CKD, peritoneal dialysis, and hemodialysis populations should be a research priority.

An updated development path for new treatments?

The regulatory requirement for demonstrating clinical efficacy using hard endpoints, such as doubling of creatinine, ESKD, or death, in DKD has encouraged the design of large, operationally challenging clinical trials that selectively recruit patients with established DKD. Alternative strategies should be considered to complement this approach and grow the evidence base for the management of DKD.

Better identification of potentially useful treatments. The failure of many recent trials suggests that there may also be substantial variation between individuals in the molecular pathways driving disease progression and safety. Accordingly, the development of new medicines may require investigators to focus more on mechanisms operative within susceptible individuals rather than across populations.[78] This will necessitate advances in our understanding of these mechanisms and require access to kidney tissue.[79]

Albuminuria and eGFR are the best currently available risk markers for DKD but have less value in early stages. GFR in early DKD is typically normal or elevated, and albuminuria frequently regresses spontaneously.[80,81] Moreover, significant structural lesions often exist before the appearance of elevated albuminuria, so its absence does not preclude the presence of DKD.[82–84] Alternative markers are needed to more accurately identify early disease. The development of biomarkers for later-stage DKD is equally important, but few markers have emerged as independent predictors after accounting for albuminuria and GFR.[85] Furthermore, the association may vary across different outcomes assessed (e.g., ESKD vs. death).[85]

Combining morphometric evaluations of serial kidney biopsies with "-omic" studies (i.e., genomic, transcriptomic, epigenomic, proteomic, and metabolomic) in well-characterized cohorts of high-risk persons with diabetes may allow definition of mechanisms of progression and simultaneously identify markers of early structural lesions, which can be used to stratify risk of progression, and as endpoints for clinical trials. This approach may be particularly useful in T2DM, which increasingly affects young people[86] in whom it has a more aggressive course than does T1DM[87,88] and may also be more treatment-resistant.[34,89–91]

It should be noted that this approach also has challenges. In T1DM, histological changes are well described, typically homogenous, and predict adverse outcomes,[92–94] but the

lesions are more heterogeneous in T2DM.[82,95] Whether natural history varies by histologic lesion remains unknown, although longitudinal studies suggest a relationship with GFR decline.[83,96] Nevertheless, the failure to date to provide better diagnostic and therapeutic tools for DKD suggests that bold action is needed.[97] While some may have concerns about the use of research biopsies to define DKD natural history and mechanisms, they are safe in experienced hands,[98,99] and have been used successfully in previous studies.[100,101]

Combining serial kidney biopsies with collection of blood and urine specimens, and perhaps other tissue specimens such as skin fibroblasts, is important. In addition, novel imaging techniques (e.g., quantifying fibrosis in the kidney)[102] could be utilized and correlated with biopsy findings. By identifying important molecular pathways to disease and noninvasive markers to differentiate susceptible from nonsusceptible high-risk individuals, we may be able to target drugs more effectively and achieve the therapeutic breakthroughs that have proven so challenging.

Better trials of promising therapies. There is an urgent need to develop therapies that benefit patients earlier. An approach used successfully by regulators in the United States in the search for efficacious medicines for other major illnesses is to grant "subpart H" marketing approval for medicines with potential benefits based on assessment of surrogate endpoints. As part of this initial conditional approval, large safety and efficacy trials are mandated and must demonstrate a reduction in hard clinical endpoints to achieve final approval.

This approach may encourage adoption of therapies at an earlier stage of disease, with potential population-wide benefits. In the future, new biomarkers that reflect early hard endpoints may be identified, permitting final regulatory approval of new medicines for early DKD without the need for subpart H-type approvals.

Novel approaches to trial conduct. A common theme that needs to be addressed for CKD patients with diabetes is whether targeting levels of specific risk factors (vs. processes) through the use of intensified specific therapies (vs. multipronged strategies) is more effective.

To maximize efficiency, the conference attendees felt strongly that people with DKD should be randomized in multiple concurrent studies addressing important questions about the harm and benefit of several interventions. Cluster randomized approaches, rather than individual participant randomization, and other pragmatic trial designs may be more appropriate for strategy and lifestyle-type interventions (e.g., weight loss and exercise) and also to trials of new uses for existing medicines.[103]

In addition, novel designs for randomized control trials widely used in other fields are starting to be applied to DKD. These include enrichment approaches or randomized trials conducted within a registry context. The latter may be particularly suitable for dialysis trials.

Safety as a key priority

Adverse drug reactions are common in CKD, reflecting pill burden, altered pharmacokinetics and pharmacodynamics, interactions with abnormal physiology, and frequently inadequate dose adjustments.

Safety is particularly important during intensification of glucose control in patients with DKD, as each glucose-lowering agent has limitations (Table 1). Other treatments also carry important risks (e.g., hypotension, dizziness, and falls when lowering BP, bleeding when using anticoagulants, and excessive sedation with sedative use in CKD). These factors not only have a direct effect on patient health and quality of life but may also impact medication adherence. Therefore, appropriate targeting, cautious prescribing, judicious dosing, and close monitoring are necessary for all therapies in patients with DKD. Given the sheer complexity of multifactorial management, optimal care is best delivered by comprehensive multidisciplinary teams targeted to individual patient needs.

There is a need for more pragmatic studies in real-world clinical practice to refine indications and identify potential modifiers of both treatment effects and safety that had been missed in clinical trials. These studies may include clinical trials performed in more relevant heterogeneous populations and/or formally evaluating safety in specific at-risk populations (e.g., studies specifically in patients with CKD). Many of the interventions in pragmatic trials could be considered complex in that there may be a number of interacting components within the experimental and control interventions, targeting a number of groups, and with a number of outcomes. The Medical Research Council has developed a framework to help researchers recognize and

Table 1 | Potential limitations of glucose-lowering agents in patients with diabetic kidney disease

Drug	Limitations
Metformin	• Dose modification required at reduced eGFR, discontinuation at low eGFR • Increased gastrointestinal side effects, hyperlactatemia, lactic acidosis
Sulphonylureas	• Increased risk of hypoglycemia, accumulation of parent or active metabolites (with glibenclamide, glyburide, glimepiride), each require discontinuation at low eGFR
Thiazolidinediones	• Fluid retention, increased risk of congestive heart failure
Dipeptidyl Peptidase (DPP-4) inhibitors	• Dose modification (except linagliptin), possible heart failure
Glucagon-Like Peptide (GLP) 1 agonists	• Discontinuation at low eGFR (exenatide), increased gastrointestinal side effects (nausea, vomiting, etc.)
Sodium Glucose coTransporter (SGLT) 2 inhibitors	• Reduced efficacy at low eGFR, hypovolemia, interaction with loop diuretics
Insulin	• Increased risk of hypoglycemia, prolonged insulin half-life

eGFR, estimated glomerular filtration rate.

Table 2 | Research recommendations

- Studies should examine optimal strategies for maintaining adherence to lifestyle or therapeutic interventions; a large, simple trial of reduced salt intake assessing patient-level outcomes in patients with diabetes and CKD (by degrees of CKD severity) is one such example.
- Studies should ascertain the safety of metformin in patients with CKD stage 3b and the utility of "sick day rules" for discontinuing the drug when patients become unwell.
- Studies should explore alternative approaches to the use of HbA1c as a measure for long-term glycemic control in patients with CKD and diabetes.
- With the advent of new hyperkalemia therapeutics, further studies should be conducted to ascertain safety and benefits of dual RAS blockade in patients with CKD and diabetes.
- Trials should examine the utility of increased diuretic therapy or targeted dialytic volume removal for reductions in CVD (atrial fibrillation in particular).
- Future research should elucidate the clinical benefits and mechanisms of action of SGLT2 inhibitors (glycosuric vs. natriuretic effects) in individuals with CKD and diabetes specifically with respect to cardiovascular and renoprotection.
- Studies should ascertain the extent of CVD benefits associated with use of new lipid modifying agents (e.g., PCSK9 inhibitors, CETP inhibitors) in patients with diabetes with various degrees of CKD severity; studies should also compare effects on the profile of lipid abnormalities observed in CKD or dialysis populations.
- The role and utility of antiplatelet and antithrombotic therapies should be further clarified; specifically, are benefit-risk ratios significantly different between patients with CKD and diabetes (or CKD) versus general population?; studies on NOACs in advanced CKD, HD, or PD should be undertaken to inform use.
- Multilevel "-omic" studies should be undertaken in patients with advanced CKD and diabetes to identify potential biomarkers for identifying high-risk individuals.
- Safety of antidiabetic combination therapies should be examined; ongoing large clinical trials and databases should be used to monitor for effect of severe hypoglycemia (and mild hypoglycemia) on outcomes in individuals with CKD.

CETP, cholesterylester transfer protein; CKD, chronic kidney disease; CVD, cardiovascular disease; HD, hemodialysis; NOAC, novel oral anticoagulants; PCSK9, proprotein convertase subtilisin/kexin type 9; PD, peritoneal dialysis; RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter 2.

adopt appropriate methods for trials with complex interventions.[104]

Another useful tool is post-marketing surveillance using electronic health records, administrative health data, or patient registries.[105,106] Through distributed network audit and database access, large numbers and a broader range of patients could be enrolled inexpensively and rapidly in nonexperimental studies, providing a statistically powerful method to identify drug safety signals in specific at-risk populations. When conducted appropriately, observational studies with high external validity have the potential to provide useful information about real-world consequences of interventions that should augment—rather than compete—with considerations of net effects or internal validity.

Other important areas of research to reduce the risk of adverse drug reactions include point-of-care strategies that enable the use of risk stratification/prognostic tools, dedicated risk assessment and safety education programs, and the implementation of self-management tools, such as self-monitoring and "sick day" protocols for drug discontinuation. There is also a need for more research in vulnerable populations such as young adolescents with type 2 diabetes and ethnic minorities who present many unique management issues and in whom CKD is over-represented.

Conclusion

The large and growing global burden of DKD needs urgent attention to identify novel treatment strategies to prevent progressive kidney failure and its complications. Several existing strategies are supported by evidence, and studies to ensure their appropriate implementation are urgently required. In addition, the efficacy of a number of newer therapies are currently being evaluated, while other treatments shown to be effective in the general population will also need to be studied in DKD in order to understand the balance of risks and benefits in this group. Novel approaches are required to identify potentially valuable treatments and to test the effects of these interventions. Careful consideration of the safety of these interventions is also crucial. To this end, a listing of research recommendations has been proposed to address the knowledge gaps enumerated in this report (Table 2) and help pave the way for future studies and further advance the evidence base in this area.

DISCLOSURE

VP declared having received consultancy fees from Abbvie, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Novo Nordisk, Pharmalink, Relypsa, and Servier; speaker honoraria from International Diabetes Federation, Pfizer, and Sanofi; and research support from Abbvie, Jannsen and Pfizer. All monies were given to The George Institute. RA declared having received consultancy fees from Abbvie, Bayer, Celgene, Daiichi Sankyo, Janssen, and Takeda, and research support from the National Heart, Lung, and Blood Institute and Veterans Administration. MCT declared having received consultancy fees from AstraZeneca, Boehringer Ingelheim, and Eli Lilly, and speaker honoraria from AstraZeneca, BGP, Boehringer Ingelheim, Eli Lilly, Merck Sharpe & Dohme, Novartis, and Servier. CW declared having received consultancy fees from Boehringer Ingelheim and Janssen and speaker honoraria from Boehringer Ingelheim. DCW declared having received consultancy fees from Akebia, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Otsuka, UCB Celltech, and Vifor; speaker honoraria from Amgen, Fresenius, Janssen, Vifor, and ZS Pharma; and research support from British Heart Foundation, Healthcare Quality Improvement Partnership, Kidney Research UK, National Institute for Health Research, and Australian National Health & Medical Research Council. All the other authors declared no competing interests.

The conference was sponsored by KDIGO and supported in part by unrestricted educational grants from AbbVie, AstraZeneca, Bayer HealthCare, Boehringer Ingelheim, Fresenius Medical Care, Janssen, Merck, Roche, Takeda, and ZS Pharma.

REFERENCES

1. International Diabetes Federation. *IDF Diabetes Atlas*. 7th Edition, 2015.
2. American Diabetes Association. Standards of medical care in diabetes–2014. *Diabetes Care*. 2014;37 Suppl 1:S14–S80.
3. Villar E, Chang SH, McDonald SP. Incidences, treatments, outcomes, and sex effect on survival in patients with end-stage renal disease by

diabetes status in Australia and New Zealand (1991 2005). *Diabetes Care*. 2007;30:3070–3076.
4. U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Available at: http://www.usrds.org/2013/pdf/v2_ch12_13.pdf (p. 340).
5. Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet*. 2015;385:1975–1982.
6. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851–860.
7. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med*. 1993;329:1456–1462.
8. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861–869.
9. de Zeeuw D, Akizawa T, Audhya P, et al. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N Engl J Med*. 2013;369:2492–2503.
10. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med*. 2013;369:1892–1903.
11. Mann JF, Green D, Jamerson K, et al. Avosentan for overt diabetic nephropathy. *J Am Soc Nephrol*. 2010;21:527–535.
12. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet*. 2008;372:547–553.
13. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. 2012;367:2204–2213.
14. Tobe SW, Clase CM, Gao P, et al. Cardiovascular and renal outcomes with telmisartan, ramipril, or both in people at high renal risk: results from the ONTARGET and TRANSCEND studies. *Circulation*. 2011;123:1098–1107.
15. Ezzati M, Riboli E. Behavioral and dietary risk factors for noncommunicable diseases. *N Engl J Med*. 2013;369:954–964.
16. He FJ, Marciniak M, Visagie E, et al. Effect of modest salt reduction on blood pressure, urinary albumin, and pulse wave velocity in white, black, and Asian mild hypertensives. *Hypertension*. 2009;54:482–488.
17. Ekinci EI, Thomas G, Thomas D, et al. Effects of salt supplementation on the albuminuric response to telmisartan with or without hydrochlorothiazide therapy in hypertensive patients with type 2 diabetes are modulated by habitual dietary salt intake. *Diabetes Care*. 2009;32:1398–1403.
18. Slagman MC, Waanders F, Hemmelder MH, et al. Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. *BMJ*. 2011;343:d4366.
19. McMahon EJ, Bauer JD, Hawley CM, et al. A randomized trial of dietary sodium restriction in CKD. *J Am Soc Nephrol*. 2013;24:2096–2103.
20. Ndanuko RN, Tapsell LC, Charlton KE, et al. Dietary patterns and blood pressure in adults: a systematic review and meta-analysis of randomized controlled trials. *Adv Nutr*. 2016;7:76–89.
21. Navaneethan SD, Yehnert H, Moustarah F, et al. Weight loss interventions in chronic kidney disease: a systematic review and meta-analysis. *Clin J Am Soc Nephrol*. 2009;4:1565–1574.
22. Schwingshackl L, Dias S, Hoffmann G. Impact of long-term lifestyle programmes on weight loss and cardiovascular risk factors in overweight/obese participants: a systematic review and network meta-analysis. *Syst Rev*. 2014;3:130.
23. Schwingshackl L, Strasser B, Hoffmann G. Effects of monounsaturated fatty acids on glycaemic control in patients with abnormal glucose metabolism: a systematic review and meta-analysis. *Ann Nutr Metab*. 2011;58:290–296.
24. Look AHEAD Research Group. Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a secondary analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol*. 2014;2:801–809.
25. Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int*. 2003;63:225–232.
26. de Boer IH. Kidney disease and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. *Diabetes Care*. 2014;37:24–30.
27. Perkovic V, Heerspink HL, Chalmers J, et al. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. *Kidney Int*. 2013;83:517–523.
28. Wong MG, Perkovic V, Chalmers J, et al. Long-term benefits of intensive glucose control for preventing end-stage kidney disease: ADVANCE-ON. *Diabetes Care*. 2016;39:694–700.
29. Zoungas S, Chalmers J, Neal B, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med*. 2014;371:1392–1406.
30. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360:129–139.
31. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet*. 2010;376:419–430.
32. Skupien J, Warram JH, Smiles A, et al. Improved glycemic control and risk of ESRD in patients with type 1 diabetes and proteinuria. *J Am Soc Nephrol*. 2014;25:2916–2925.
33. Shurraw S, Hemmelgarn B, Lin M, et al. Association between glycemic control and adverse outcomes in people with diabetes mellitus and chronic kidney disease: a population-based cohort study. *Arch Intern Med*. 2011;171:1920–1927.
34. TODAY Study Group. Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: the TODAY clinical trial. *Diabetes Care*. 2013;36:1735–1741.
35. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009;374:1677–1686.
36. Look AHEAD Research Group, Wing RR, Bolin P, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;369:145–154.
37. Inzucchi SE, Lipska KJ, Mayo H, et al. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA*. 2014;312:2668–2675.
38. FDA Drug Safety Communication. FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm.
39. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38:140–149.
40. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. NICE guideline, 2 December 2015. Available at: http://nice.org.uk/guidance/ng28.
41. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3:1–150.
42. Groop PH, Cooper ME, Perkovic V, et al. Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction. *Diabetes Care*. 2013;36:3460–3468.
43. Udell JA, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes and moderate or severe renal impairment: observations from the SAVOR-TIMI 53 Trial. *Diabetes Care*. 2015;38:696–705.
44. Heerspink HJ, Desai M, Jardine M, et al. Canagliflozin slows progression of renal function decline independently of glycemic effects [e-pub ahead of print]. *J Am Soc Nephrol*. http://dx.doi.org/10.1681/ASN.2016030278.
45. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375:323–334.
46. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.
47. Chachou A, Randoux C, Millart H, et al. Influence of in vivo hemoglobin carbamylation on HbA1c measurements by various methods. *Clin Chem Lab Med*. 2000;38:321–326.
48. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545–2559.

49. Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med*. 2010;363:1410–1418.
50. Kong AP, Yang X, Luk A, et al. Severe hypoglycemia identifies vulnerable patients with type 2 diabetes at risk for premature death and all-site cancer: the Hong Kong diabetes registry. *Diabetes Care*. 2014;37:1024–1031.
51. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311–322.
52. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1547–1559.
53. Palmer SC, Mavridis D, Navarese E, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. *Lancet*. 2015;385:2047–2056.
54. Packham DK, Rasmussen HS, Singh B. New agents for hyperkalemia. *N Engl J Med*. 2015;372:1571–1572.
55. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709–717.
56. Bakris GL, Agarwal R, Chan JC, et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *JAMA*. 2015;314:884–894.
57. Bolignano D, Palmer SC, Navaneethan SD, et al. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev*. 2014:CD007004.
58. Haller H, Bertram A, Stahl K, et al. Finerenone: a new mineralocorticoid receptor antagonist without hyperkalemia: an opportunity in patients with CKD? *Curr Hypertens Rep*. 2016;18:41.
59. de Zeeuw D, Coll B, Andress D, et al. The endothelin antagonist atrasentan lowers residual albuminuria in patients with type 2 diabetic nephropathy. *J Am Soc Nephrol*. 2014;25:1083–1093.
60. Cherney DZ, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation*. 2014;129:587–597.
61. Tonelli M, Muntner P, Lloyd A, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet*. 2012;380:807–814.
62. de Boer IH, Katz R, Cao JJ, et al. Cystatin C, albuminuria, and mortality among older adults with diabetes. *Diabetes Care*. 2009;32:1833–1838.
63. Ninomiya T, Perkovic V, de Galan BE, et al. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *J Am Soc Nephrol*. 2009;20:1813–1821.
64. Fox CS, Matsushita K, Woodward M, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet*. 2012;380:1662–1673.
65. Rigatto C, Levin A, House AA, et al. Atheroma progression in chronic kidney disease. *Clin J Am Soc Nephrol*. 2009;4:291–298.
66. Wheeler DC, Becker GJ, Summary of KDIGO guideline. What do we really know about management of blood pressure in patients with chronic kidney disease? *Kidney Int*. 2013;83:377–383.
67. Wanner C, Tonelli M. KDIGO Clinical practice guideline for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int*. 2014;85:1303–1309.
68. Agarwal R. What are the consequences of volume expansion in chronic dialysis patients?: Hypertension as a manifestation of volume overload in hemodialysis patients. *Semin Dial*. 2015;28:231–232.
69. Lambers Heerspink HJ, de Zeeuw D, Wie L, et al. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. *Diabetes Obes Metab*. 2013;15:853–862.
70. Fitchett D, Zinman B, Wanner C, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. *Eur Heart J*. 2016;37:1526–1534.
71. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377:2181–2192.
72. Attman PO, Samuelsson O, Alaupovic P. The effect of decreasing renal function on lipoprotein profiles. *Nephrol Dial Transplant*. 2011;26:2572–2575.
73. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet*. 1998;351:1755–1762.
74. Montalescot G, Silvain J. Ticagrelor in the renal dysfunction subgroup: subjugated or substantiated? *Circulation*. 2010;122:1049–1052.
75. James S, Budaj A, Aylward P, et al. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation*. 2010;122:1056–1067.
76. Kulkarni N, Gukathasan N, Sartori S, Baber U. Chronic kidney disease and atrial fibrillation: A contemporary overview. *J Atrial Fibrillation*. 2012;5:62–70.
77. Jun M, James MT, Manns BJ, et al. The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study. *BMJ*. 2015;350:h246.
78. de Zeeuw D, Heerspink HJ. Unmet need in diabetic nephropathy: failed drugs or trials? *Lancet Diabetes Endocrinol*. 2016;4:638–640.
79. Martini S, Nair V, Keller BJ, et al. Integrative biology identifies shared transcriptional networks in CKD. *J Am Soc Nephrol*. 2014;25:2559–2572.
80. Perkins BA, Ficociello LH, Silva KH, et al. Regression of microalbuminuria in type 1 diabetes. *N Engl J Med*. 2003;348:2285–2293.
81. Araki S, Haneda M, Sugimoto T, et al. Factors associated with frequent remission of microalbuminuria in patients with type 2 diabetes. *Diabetes*. 2005;54:2983–2987.
82. Fioretto P, Mauer M, Brocco E, et al. Patterns of renal injury in NIDDM patients with microalbuminuria. *Diabetologia*. 1996;39:1569–1576.
83. Nosadini R, Velussi M, Brocco E, et al. Course of renal function in type 2 diabetic patients with abnormalities of albumin excretion rate. *Diabetes*. 2000;49:476–484.
84. Caramori ML, Fioretto P, Mauer M. Low glomerular filtration rate in normoalbuminuric type 1 diabetic patients: an indicator of more advanced glomerular lesions. *Diabetes*. 2003;52:1036–1040.
85. Agarwal R, Duffin KL, Laska DA, et al. A prospective study of multiple protein biomarkers to predict progression in diabetic chronic kidney disease. *Nephrol Dial Transplant*. 2014;29:2293–2302.
86. Pavkov ME, Bennett PH, Knowler WC, et al. Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. *JAMA*. 2006;296:421–426.
87. Yokoyama H, Okudaira M, Otani T, et al. Higher incidence of diabetic nephropathy in type 2 than in type 1 diabetes in early-onset diabetes in Japan. *Kidney Int*. 2000;58:302–311.
88. Dart AB, Sellers EA, Martens PJ, et al. High burden of kidney disease in youth-onset type 2 diabetes. *Diabetes Care*. 2012;35:1265–1271.
89. TODAY Study Group, Zeitler P, Epstein L, et al. Treatment options for type 2 diabetes in adolescents and youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes. *Pediatr Diabetes*. 2007;8:74–87.
90. TODAY Study Group. Effects of metformin, metformin plus rosiglitazone, and metformin plus lifestyle on insulin sensitivity and beta-cell function in TODAY. *Diabetes Care*. 2013;36:1749–1757.
91. TODAY Study Group. Lipid and inflammatory cardiovascular risk worsens over 3 years in youth with type 2 diabetes: the TODAY clinical trial. *Diabetes Care*. 2013;36:1758–1764.
92. Steinke JM, Sinaiko AR, Kramer MS, et al. The early natural history of nephropathy in Type 1 Diabetes: III. Predictors of 5-year urinary albumin excretion rate patterns in initially normoalbuminuric patients. *Diabetes*. 2005;54:2164–2171.
93. Perrin NE, Torbjornsdotter T, Jaremko GA, et al. Risk markers of future microalbuminuria and hypertension based on clinical and morphological parameters in young type 1 diabetes patients. *Pediatr Diabetes*. 2010;11:305–313.
94. Caramori ML, Parks A, Mauer M. Renal lesions predict progression of diabetic nephropathy in type 1 diabetes. *J Am Soc Nephrol*. 2013;24:1175–1181.
95. Osterby R, Gall MA, Schmitz A, et al. Glomerular structure and function in proteinuric type 2 (non-insulin-dependent) diabetic patients. *Diabetologia*. 1993;36:1064–1070.
96. Moriya T, Suzuki Y, Inomata S, et al. Renal histological heterogeneity and functional progress in normoalbuminuric and microalbuminuric Japanese patients with type 2 diabetes. *BMJ Open Diabetes Res Care*. 2014;2:e000029.

97. Gonzalez Suarez ML, Thomas DB, Barisoni L, et al. Diabetic nephropathy: Is it time yet for routine kidney biopsy? *World J Diabetes*. 2013;4:245–255.
98. Corapi KM, Chen JL, Balk EM, et al. Bleeding complications of native kidney biopsy: a systematic review and meta-analysis. *Am J Kidney Dis*. 2012;60:62–73.
99. Tondel C, Vikse BE, Bostad L, et al. Safety and complications of percutaneous kidney biopsies in 715 children and 8573 adults in Norway 1988-2010. *Clin J Am Soc Nephrol*. 2012;7:1591–1597.
100. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med*. 2009;361:40–51.
101. Weil EJ, Fufaa G, Jones LI, et al. Effect of losartan on prevention and progression of early diabetic nephropathy in American Indians with type 2 diabetes. *Diabetes*. 2013;62:3224–3231.
102. Zhang JL, Morrell G, Rusinek H, et al. New magnetic resonance imaging methods in nephrology. *Kidney Int*. 2014;85:768–778.
103. Pocock SJ, Gersh BJ. Do current clinical trials meet society's needs?: a critical review of recent evidence. *J Am Coll Cardiol*. 2014;64:1615–1628.
104. Craig P, Dieppe P, Macintyre S, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*. 2008;337:a1655.
105. Suissa S, Henry D, Caetano P, et al. CNODES: the Canadian Network for Observational Drug Effect Studies. *Open Med*. 2012;6:e134–e140.
106. Platt R, Carnahan RM, Brown JS, et al. The U.S. Food and Drug Administration's Mini-Sentinel program: status and direction. *Pharmacoepidemiol Drug Saf*. 2012;21 Suppl 1:1–8.

APPENDIX

Other Conference Participants

George L. Bakris, USA; Dong-Wan Chae, Korea; Mark E. Cooper, Australia; Michael H. Davidson, USA; Ian H. de Boer, USA; Dick de Zeeuw, The Netherlands; Alessia Fornoni, USA; Luigi Gnudi, UK; Charles A. Herzog, USA; Adriana M. Hung, USA; Tazeen Hasan Jafar, Singapore; Meg Jardine, Australia; Vivekanand Jha, India; Linong Ji, China; Steven E. Kahn, USA; Robyn G. Langham, Australia; Edgar V. Lerma, USA; Ronald C.W. Ma, Hong Kong, China; Hirofumi Makino, Japan; Michel Marre, France; Michael Mauer, USA; Kaj Metsärinne, Finland; Robert G. Nelson, USA; Roberto Pecoits-Filho, Brazil; Carol A. Pollock, Australia; Mohan Rajapurkar, India; Peter Rossing, Denmark; Ivan Rychlík, Czech Republic; Kumar Sharma, USA; Robert C. Stanton, USA; Vladimír Tesař, Czech Republic; Ilkka Tikkanen, Finland; Charlie R.V. Tomson, UK; Robert D. Toto, USA; Yusuke Tsukamoto, Japan; Katherine R. Tuttle, USA; Takashi Wada, Japan; Winfred W. Williams, USA; Hong Zhang, China; Sophia Zoungas, Australia