Diabetic kidney disease: a clinical update from Kidney Disease: Improving Global Outcomes

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The incidence and prevalence of diabetes mellitus (DM) continue to grow markedly throughout the world, due primarily to the increase in type 2 DM (T2DM). Although improvements in DM and hypertension management have reduced the proportion of diabetic individuals who develop chronic kidney disease (CKD) and progress to end-stage renal disease (ESRD), the sheer increase in people developing DM will have a major impact on dialysis and transplant needs. This KDIGO conference addressed a number of controversial areas in the management of DM patients with CKD, including aspects of screening for CKD with measurements of albuminuria and estimated glomerular filtration rate (eGFR); defining treatment outcomes; glycemic management in both those developing CKD and those with ESRD; hypertension goals and management, including blockers of the renin–angiotensin–aldosterone system; and lipid management.

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The incidence and prevalence of diabetes mellitus (DM) have grown significantly throughout the world, due primarily to the increase in type 2 DM (T2DM), which in turn is largely related to the increase in obesity.[1] This increase in T2DM disproportionately affects less developed countries, which also have fewer resources to deal with such patients.[1] The increase in the number of people developing diabetes will also have a major impact on dialysis and transplant needs. As such, it is important to develop cost-effective strategies at every step: (1) prevention of obesity; (2) screening for and prevention of diabetes in an at-risk population; (3) glycemic control once diabetes develops; (4) blood pressure (BP) control once hypertension develops; (5) screening for diabetic chronic kidney disease (CKD); (6) use of renin–angiotensin–aldosterone system (RAAS) inhibition/blockade in those with diabetic CKD; and (7) control of other cardiovascular (CV) risk factors such as management of low-density lipoprotein cholesterol (LDL-C).

The relationship between CKD and CV disease (CVD) remains complex. Increased urinary albumin excretion rates (AERs) and decreased glomerular filtration rate (GFR) are both associated with an increase in all-cause and CVD mortality independent of each other and of other CVD risk factors in general and high-risk populations.[2–4] The relationship between the presence of microalbuminuria and CVD mortality in diabetic individuals has been known for over 25 years[5] and the interrelationship between AER, GFR, and CVD mortality has been well-studied in diabetic individuals.[6,7] However, treatments that affect progression of CKD may not always have the same effect on the development/progression of CVD. Similarly, there may be differences in how interventions affect urinary AER versus GFR. In patients with diabetes, there appear to be differences in the rate of GFR decline that are related to the presence or absence of increased AER.[7,8]

Studies in both type 1 DM (T1DM) and T2DM have shown that glycemic control can decrease the initial development of

microalbuminuria and macroalbuminuria,[9–12] but data documenting an effect on GFR are sparse.[13–16] Recent data suggest that perhaps there should be different hemoglobin A1c (HbA1c) targets for CKD and CVD, as HbA1c levels below 7% (53 mmol/mol) continue to show benefit in preventing the development of microalbuminuria,[17–19] but show no benefit[17–19] and perhaps harm[20] with respect to CVD. Although there may be only a minimal effect of lower HbA1c levels on CKD as it progresses toward end-stage renal disease (ESRD), other complications of diabetes such as retinopathy and neuropathy may benefit from such control.

Similarly, the blood pressure (BP) targets for CKD and CVD may be different. While it is recognized that BP control is very important in slowing the rate of fall of GFR,[21] the optimal BP to benefit all outcomes is controversial. Similar to the effects of glycemic control, a systolic BP lower than 120 mm Hg may be of further benefit for CKD progression,[22] but could be associated with worsened CVD outcomes.[22–24]

The role of RAAS blockade in the development and progression of diabetic CKD over and above BP control needs re-evaluation. Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) are not able to prevent the development of microalbuminuria in normotensive individuals with either T1DM or T2DM[25,26] and their role in normotensive individuals with low levels of microalbuminuria is unclear. The relative benefits of ACE-Is versus ARBs versus direct renin inhibitors (DRIs) in T1DM and T2DM patients with hypertension and albuminuria remain to be determined. Similarly, the role of combinations of drugs acting in the RAAS remains controversial. Finally, whether RAAS-blocking drugs have an effect over and above BP reduction in decreasing the rate of CKD progression in those without increased AER is not clear.

Many other controversies exist in the management of diabetic CKD. Although statins likely decrease CVD in those with CKD before needing dialysis,[27,28] the proof that they are effective in patients on dialysis is lacking.[29–31] Should statins be stopped when patients go on dialysis? Are there any efficacy data for other cholesterol-lowering medications in patients with diabetic CKD? Another controversial issue is the use of metformin to control hyperglycemia in patients with decreased GFR. Although lactic acidosis is a potential problem in such patients, the risk appears to be small.[32–34] Whether the current guidelines are too strict deserves a reanalysis.

To address these and other issues, Kidney Disease: Improving Global Outcomes (KDIGO) held a Controversies Conference on Diabetic Kidney Disease on 16–18th March 2012 in New Delhi, India. Drs Carl Erik Mogensen and Mark E Molitch cochaired this conference with the aim to define the current state of knowledge in the management of diabetic kidney disease (DKD). Topic areas related to DKD included: (1) epidemiology, (2) albuminuria, (3) glycemic control, (4) RAAS blockade, (5) management of hypertension, and (6) role of statins.

Invited participants and speakers consisted of leading worldwide experts on these topic areas, including nephrologists and diabetologists, who gave the broadest views possible on the subject. Their task was to summarize the existing knowledge, develop recommendations on what can be done to optimize the prognosis of patients with DKD based on this knowledge, and to formulate and prioritize research questions. This position statement is the resultant output from the conference.

SCREENING AND EVALUATION OF DKD
The role of albuminuria
Testing for albuminuria—either for screening or for diagnosing—uses the same test for two purposes: to identify people at high risk of subsequent complications (including renal disease, CVD, and death), and to offer treatment. Treatment decisions may depend only on the presence or absence of microalbuminuria (defined either using albumin-to-creatinine ratio or a urinary AER) or on the degree of albuminuria. Microalbuminuria identifies diabetic individuals at higher risk of overt proteinuria and of ESRD[35] relative to those with normoalbuminuria while acknowledging that albuminuria can regress.[36] Currently, the magnitude of increase in the risk of ESRD for patients with T1DM or T2DM and microalbuminuria is four- to fivefold. Further reductions in CVD, a 'competing' cause of death, may translate to more patients with microalbuminuria living longer and developing ESRD. Microalbuminuria approximately doubles the risk of death from CVD and independently increases the chance that patients die earlier than they would in the absence of albuminuria.[36] Albuminuria may reflect a more general damage to the vascular endothelium. When including albuminuria as a component of overall risk, one can calculate the risk of CVD and death in T2DM.[37]

Existing evidence supports therapies proven to reduce the incidence of CVD, namely BP-lowering drugs (notably those that inhibit the renin–angiotensin system) and statins. Angiotensin blockade lowers the risk of subsequent renal decline, although there is an absence of such evidence in normoalbuminuric, normotensive patients. The beneficial effect of statins in prolonging survival is currently limited to patients without ESRD.[38] With respect to the frequency of testing, the conference work group was aware that annual testing for albuminuria among normoalbuminuric patients has been recommended in diabetes by numerous bodies.[39–43]

The work group considered the following controversies related to testing for albuminuria:

Frequency of screening: The ideal frequency of screening remains undetermined. The work group acknowledged that less frequent screening may result in missed diagnoses but may improve cost-effectiveness.[44]

Albuminuria versus other predictors of further diabetic complications: The work group acknowledged that uncertainty remains about the marginal predictive utility of measuring albuminuria over other CV risk factors.

Ongoing measurement of albuminuria: The work group discussed whether retesting for albuminuria provides benefits when this is unlikely to change clinical practice (e.g., when patients have few options for further treatment or when patients meet current standards for BP and glycemic control).

Albuminuria as a treatment target: The work group acknowledged that because microalbuminuria *per se* did not lead to symptoms that worsened health-related quality of life for patients, there is uncertainty in the benefits for treating albuminuria alone.

'Clinically significant' albuminuria: If albuminuria is a target for treatment, the work group acknowledged the importance, and also the uncertainty, related to the magnitude of change in albuminuria that would be considered 'clinically significant'. This issue also applied to defining outcomes for clinical trials of diabetic nephropathy.

ACE-I or ARB versus general BP lowering: The work group acknowledged that controversy remains about whether patients with microalbuminuria derive benefit by using an ACE-I or ARB above that of other BP-lowering drugs[45] and that this benefit may not relate to the degree of albuminuria.[36]

Efficient use of health-care resources: Few studies have addressed the cost-effectiveness of testing for microalbuminuria. The work group acknowledged the need to model, under different scenarios and in different populations with different costs and valuations of quality of life, the cost-effectiveness of testing for albuminuria in groups with and without established disease.

The work group concluded that testing for albuminuria among people with diabetes identifies people at higher risk of subsequent complications and identifies people to whom to offer treatment. The work group also concluded that uncertainties remain about the frequency of testing and the role of ongoing periodic testing, particularly for patients in whom treatment options are few. Further, the cost-effectiveness of testing for albuminuria likely varies across populations defined by different clinical or geographical characteristics. Uncertainty also remains regarding what constitutes a clinically significant change in albuminuria, which complicates how meaningful outcomes are defined in clinical trials.

Is albuminuria an acceptable surrogate marker for diabetic CKD?

Albuminuria reflects glomerulopathy along with measures of glomerular filtration. People with diabetes may develop only albuminuria, only decreased glomerular filtration, or both.[8,46,47] Independent of albuminuria and diabetes, measures of glomerular filtration predict CKD.[48] Both measures independently increase the risk of mortality.[49,50] Unlike for albuminuria, the relationship between glomerular filtration and mortality is 'U' shaped, reflecting an increased risk of death associated with hyperfiltration.[51] CKD, as estimated by estimated glomerular filtration rate (eGFR), increases the risk of death equivalent to that of having existing CVD.[50]

Results of systematic reviews and process-driven guidelines advocate screening for reduced glomerular filtration in all people with diabetes regardless of concurrent risk factors,[40–42] generally using an equation that incorporates serum creatinine. Although serum cystatin C may better predict death and progression to kidney failure than does GFR estimated from creatinine-based equations,[52] the modest increase in accuracy has not been shown to merit the increased cost. Furthermore, cystatin C may reflect non-GFR determinants of these health outcomes, as it is known that cystatin C is increased in smoking and other states that increase the risk of CVD.[53] Currently, testing for serum cystatin C is unlikely to have a significant role in clinical practice. The work group acknowledged that other markers of renal tubular injury, such as neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 may identify patients without other markers of nephropathy (e.g. albuminuria), but that these have not been sufficiently tested to incorporate into clinical practice. Studies of markers of renal function should be held to the same reporting recommendations as those developed for tumor markers.[54]

The work group concluded that albuminuria both reflects and results from nephropathy. Measures of reduced eGFR both identify CKD in people without albuminuria and those at increased risk of cardiorenal complications independent of albuminuria.

GLYCEMIC CONTROL
Glycemic control to minimize DKD

The work group evaluated the role of glycemic control in preventing initiation and slowing progression of DKD in various clinical settings, and focused on management issues for which the evidence is conflicting, incomplete, or unavailable.

Lowering glycated HbA1c to about 7% (53 mmol/mol) reduces the development of the microvascular complications of T1DM and T2DM.[39,55] More intensive glycemic control further reduces the development of these complications, but the added benefit is accompanied by a substantial increase in the risk of severe hypoglycemia and a potential increase in all-cause mortality.[17–19] The evidence for a beneficial effect of glycemic control on DKD is based almost exclusively on prevention of microalbuminuria and reduction of progression to macroalbuminuria. Evidence for an effect on other intermediate DKD outcomes, such as doubling of the serum creatinine concentration or decline in eGFR, is limited,[10,56] and there is no direct evidence that intensive glycemic control reduces the frequency of ESRD.

Intensive glycemic control has less impact on CVD than on the microvascular complications of diabetes, unless treatment is initiated soon after the diagnosis of diabetes.[57,58] Among patients with diabetes of longer duration, intensive glycemic control is not associated with significant reductions in CVD outcomes,[17–19] except among those without known CVD at baseline.[59]

Target HbA1c level may need to be modified in patients with more advanced DKD because the risk of severe

hypoglycemia and death increase with declining kidney function. There are few data on the relationship between HbA1c levels and these health outcomes in this sub-population, and there are no prospective randomized clinical trials (RCTs) to identify the optimum level of glycemic control among patients with diabetes and eGFR <60 ml/min per1.73 m². An observational study of non-dialyzing CKD patients with diabetes and eGFR <60 ml/min per 1.73 m² found a U-shaped relationship between HbA1c level and mortality, with HbA1c levels above 9% (75 mmol/mol) and below 6.5% (48 mmol/mol) associated with increased mortality.[60] A similar U-shaped relationship was also reported in patients with diabetes receiving maintenance hemodialysis[61,62] or peritoneal dialysis.[63] Among dialysis patients, the mortality risk associated with a given HbA1c level was determined in part by nutritional status,[61–63] reflecting a need to individualize the intensity of glycemic control according to the overall health of the patient.

The use of immunosuppressive medicines in patients with diabetes who receive kidney transplants can also affect glycemic control, and they may also lead to new-onset diabetes after transplantation.[64] Although the presence of diabetes posttransplantation is associated with increased morbidity and mortality attributable largely to CVD, there are no prospective RCTs to define the optimum level of glycemic control in this patient group. However, pre-transplant HbA1c $\geqslant 8\%$ (64 mmol/mol) is associated with higher all-cause and CVD mortality posttransplantation;[65] therefore, management of glycemia before kidney transplant is also important.

In addition to identifying appropriate HbA1c targets in various subgroups of diabetic patients, simply achieving glycemic control may present a formidable challenge in some patient groups. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study illustrates the challenges faced in effectively managing glycemic control in the rapidly growing population of youth with T2DM.[66]

The work group considered the following controversies related to glycemic control:

- How can durable glycemic control be achieved?
- What is the HbA1c target for DKD versus CVD?
- Should the HbA1c target or the antidiabetic medicines used to achieve this target vary by severity of CKD or duration of diabetes?
- What is the HbA1c target in patients receiving maintenance hemodialysis or peritoneal dialysis and which antidiabetic medicines should be used to achieve these targets?
- What is the HbA1c target in kidney transplant recipients with diabetes and which antidiabetic medicines should be used to achieve these targets?

The work group concluded that multiple factors, including age, body weight, duration of diabetes, severity of CKD, and other comorbidities should be considered when determining the risks and benefits of intensive glycemic control. The work group noted that the risk of severe hypoglycemia

increases with advancing CKD, and ameliorating this risk may require modifying both the treatment approach and the target HbA1c, or perhaps other measures of glycemic control that more accurately reflects glycemic control in this patient population such as glycated albumin. Few data are available to guide the management of glycemic control in patients with advanced CKD, and the shortage of data is particularly acute in kidney transplant recipients who receive immunosuppressive therapy that further intensifies the challenges of glycemic control. Accordingly, the work group proposed a series of research recommendations to address these gaps in knowledge. Among the recommendations are those designed to expand our knowledge of CKD in young people with T2DM who are expected to have an increasing burden of CKD in the future. Little is known about the course of CKD in these patients or their response to therapy.

Specific interventions

Use of metformin in DKD. The work group evaluated the use of metformin in the management of patients with diabetes in the setting of CKD, focusing in particular on settings in which current US Food and Drug Administration guidelines advise against its use.

Lactic acidosis is a rare but serious side effect of metformin that can occur when metformin accumulates to toxic levels. The mean plasma elimination half-life of metformin after oral administration is 4.0–8.7 h, and since it is cleared almost exclusively by the kidneys, its elimination is prolonged in persons with CKD.[67] Accordingly, the use of metformin in CKD is restricted by Food and Drug Administration guidelines, which specify that it should not be used in men with a serum creatinine concentration $\geqslant 1.5$ mg/dl (133 μmol/l) or in women with a concentration $\geqslant 1.4$ mg/dl (124 μmol/l). Restrictions based on eGFR may be more clinically useful, however, as serum creatinine concentration may reflect factors such as age, weight, or race that are unrelated to the level of metformin clearance. Much of the concern about use of metformin in patients with diabetes and CKD is theoretical and not supported by evidence from clinical practice.[32,33] A Cochrane review[68] that pooled data from 347 comparative trials and cohort studies found no cases of lactic acidosis, and nearly half of the studies included patients with CKD. Another review concluded, based on the available evidence, that metformin use should not be restricted at eGFR $\geqslant 45$ ml/min per 1.73 m², but its use should be re-evaluated when eGFR <45 ml/min per 1.73 m² and stopped when eGFR <30 ml/min per 1.73 m²;[69] this approach was adopted by the British National Formulary,[70] the Japanese Society of Nephrology,[71] and KDIGO.[72]

The work group reviewed the evidence at what level of kidney function should treatment with metformin be stopped and concluded that there was little evidence to support the relationship between metformin use and development of lactic acidosis in patients with CKD. Nevertheless, the occurrence of lactic acidosis is more frequent than previously thought. The major precipitating factor for lactic acidosis in

persons receiving metformin is an abrupt loss of tubular secretion. Such a loss does not occur in stable CKD, but is a characteristic feature of acute kidney injury or rapid volume depletion associated with an intercurrent illness. Hence, patients with CKD should be advised on safety issues related to metformin so that they are alert to the potential side effects and they should be provided with written instructions on when to withhold metformin if they experience inter-current illness that could lead to rapid volume depletion. In addition, the work group concluded that the current Food and Drug Administration guidelines governing the use of metformin should be changed. The available evidence suggests that the dose of metformin should be reduced to a maximum of 1000 mg per day when the eGFR reaches 45 ml/min per 1.73 m^2, and should generally be discontinued when the eGFR reaches 30 ml/min per 1.73 m^2. The use of metformin may be appropriate in patients with even more advanced CKD (eGFR 15–29 ml/min per 1.73 m^2) if the kidney disease is stable and if alternative treatments to manage glycemia are unavailable or produce significant side effects. The work group proposed that pharmacokinetic studies should be performed in patients with diabetes and CKD to provide the evidence to support the proposed change in usage.

Role of pancreas or islet cell transplants. The work group evaluated the impact of pancreas or islet cell transplantation on the risk of CKD in patients with diabetes.

Progressive kidney damage is a significant contributor to ESRD in transplant recipients receiving liver, heart, lung, heart–lung, and intestinal transplants, with up to 21% of recipients developing ESRD within 5 years.[73] Immuno-suppressive therapy, particularly with calcineurin inhibitors, appears to be largely responsible for this transplant-associated nephrotoxicity, but other risk factors, including age, sex, the presence of postoperative acute renal failure, and diabetes may also be involved.[73] These findings suggest that recipients of whole pancreas or islet cell transplants may have potential long-term risks related to transplantation, despite the benefits of improved glycemic control. Indeed, survival among isolated pancreas transplant recipients is significantly worse than in similar patients awaiting a pancreas transplant who are receiving conventional glycemic therapy.[74] Moreover, pancreas transplantation has been linked to an increased risk of kidney failure,[75,76] despite a report suggesting that diabetic glomerulosclerosis may be reversed in native kidneys follow-ing pancreas transplantation.[77] The presence of CKD before transplant may further increase the risk of nephrotoxicity.[75] The choice of calcineurin inhibitor was thought to influence the degree of nephrotoxicity in native kidneys of pancreas transplant recipients, but a recent study suggests that the nephrotoxic potential of tacrolimus and cyclosporine are equivalent, as reflected by similarities in GFR decline and the increase in interstitial fractional volume, tubular atrophy, and percent of globally sclerotic glomeruli.[78] Taken together, these findings suggest that efforts to ameliorate the complications of diabetes through aggressive management of glycemic control with pancreas or islet cell transplantation may actually increase the risk of CKD in some patients. As such, is pancreas or islet cell transplantation nephrotoxic in patients with diabetes?

The work group concluded that progressive kidney damage is a consequence of pancreas or islet cell transplantation, and that the level of GFR should be considered in the selection of transplant recipients because of the increased risk of progressive kidney disease in those with CKD. The work group also recommended that for recipients with eGFR <60 ml/min per 1.73 m^2, close monitoring of kidney function is required.

THERAPEUTIC MANAGEMENT
Lipid management
The work group evaluated the role of lipid lowering in preventing initiation of atherosclerotic disease and slowing progression of DKD. Several trials and *post hoc* analyses examining lipid-lowering therapies and clinical outcomes in CKD have been published in the past few years. Although these trials were not exclusively focused on atherosclerotic disease in persons with DM or DKD, they always had significant numbers of DM patients included in the trials. The work group mainly focused on RCTs and *post hoc* analysis of large statin trials with respect to DKD.

Although several different medications lower LDL-C, only regimens including a statin (including statin/ezetimibe) have convincingly reduced the risk of adverse CV events in CKD populations. At the time this work group discussed specific recommendations, two systematic reviews were published summarizing the studies that examined the effects of lipid-lowering treatment on CV and kidney outcomes and adverse events in adults and children with CKD.[38,79]

LDL-C is strongly and independently associated with risk of atherosclerotic events in the general population.[80] The relative risk reduction associated with statin use is relatively constant across a broad range of baseline LDL-C levels, suggesting that absolute benefit from statin treatment is proportional to baseline coronary risk rather than baseline LDL-C. Similarly, meta-analysis among people with diabetes on statin therapy revealed that the beneficial effects of statin therapy were similar irrespective of whether there was a prior history of vascular disease and other baseline characteris-tics.[81] A 9% proportional reduction in all-cause mortality per mmol/l reduction in LDL-C (rate ratio 0.91; 99% confidence interval (CI): 0.82–1.01; $P = 0.02$) was paralleled by a significant reduction in vascular mortality (rate ratio 0.87; 99% CI: 0.76–1.00; $P = 0.008$). There was a significant 21% proportional reduction in major vascular events per mmol/l reduction in LDL-C in people with diabetes (rate ratio 0.79; 99% CI: 0.72–0.86; $P < 0.0001$). In diabetic participants there were reductions in myocardial infarction or coronary death (rate ratio 0.78; 99% CI: 0.69–0.87; $P < 0.0001$), coronary revascularization (rate ratio 0.75; 99% CI: 0.64–0.88; $P < 0.0001$), and stroke (rate ratio 0.79; 99% CI: 0.67–0.93; $P = 0.0002$). Based on this existing knowledge from the

general population, the work group only focused on the use of statins (with or without ezetimibe) in people with DKD and at risk of future CV events.

Non-dialysis patients. Most patients with DKD and GFR >60 ml/min per $1.73\,m^2$ have albuminuria, but many such patients would have been included but not recognized in randomized trials of statins carried out in the general population. *Post hoc* analysis extracted such patients by eGFR. Data from CARDS (Collaborative Atorvastatin Diabetes Study) and CARE (Cholesterol and Recurrent Events) trials found significant reductions in CV events, but did not detect an interaction between the presence of albuminuria and the effect of statin treatment, suggesting that the benefit of statins is similar in people with and without albuminuria.[82,83]

Data on the effects of statins and statin/ezetimibe combination in adults with CKD and eGFR <60 ml/min per $1.73\,m^2$ non-dialysis patients are available from The Study of Heart and Renal Protection (SHARP) trial, which included 9270 participants.[29] Thirty-three percent of participants ($n=3023$) were receiving dialysis at randomization and 23% ($n=2094$) had diabetes. Statin plus ezetimibe therapy led to a significant 17% relative risk reduction of the primary outcome of major atherosclerotic events (coronary death, myocardial infraction, non-hemorrhagic stroke, or any revascularization) compared with placebo (hazard ratio HR 0.83; 95% CI: 0.74–0.94). Among the 6247 patients with CKD (mean eGFR of 27 ml/min per $1.73\,m^2$) treatment with simvastatin plus ezetimibe did not reduce the risk of progression to ESRD. Other data are supported by *post hoc* analyses of randomized trials of statin versus placebo that focus on the subset of participants with DKD and CKD at baseline. In general, these analyses suggest that statins reduce the relative risk of CV events to a similar extent among patients with and without DKD—but that the absolute benefit of treatment is larger in diabetic patients owing to their higher baseline risk.[38] However, most of the participants with DKD in these analyses had eGFR 45–59.9 ml/min per $1.73\,m^2$ and very few had eGFR <30 ml/min per $1.73\,m^2$ (TNT—Treating to New Targets; ALLIANCE—Aggressive Lipid Lowering Initiation Abates New Cardiac Events; PREVEND IT—Prevention of REnal and Vascular ENdstage Disease Intervention Trial; PPP—Pravastatin Pooling Project).[38,79,84]

Dialysis patients. There are three large-scale RCTs of statin treatment that enrolled dialysis patients. The 4D Study (Die Deutsche Diabetes Dialyse Studie) demonstrated an 8% relative risk reduction (95% CI: 0.77–1.10; $P=0.37$) of the primary end point in 1255 T2DM patients on dialysis, but combined cardiac events (secondary end points) were reduced by 18% (95% CI: 0.68–0.99; $P=0.03$).[31] The AURORA Study (A study to evaluate the Use of Rosuvastatin in subjects On Regular Dialysis: an Assessment of survival and CV events) also did not show a reduction in the risk of individual components of the primary end point (HR 0.96; 95% CI: 0.86–1.07, $P=0.51$).[30] In contrast, a *post hoc* analysis of AURORA among the 731 patients with T2DM found that

rosuvastatin reduced the risk of fatal and nonfatal cardiac events significantly.[85] In the SHARP trial combination treatment did not significantly reduce the risk of the primary outcome in the subgroup of over 3000 patients treated with dialysis at baseline. The smaller reduction of end points in the SHARP trial could be due to lower compliance to study drug in the subgroup of dialysis patients. Dialysis patients showed on an average a 23 mg/dl (0.60 mmol/l) LDL-C reduction in comparison with the non-dialysis CKD group that had a 37 mg/dl (0.96 mmol/l) LDL-C decrease.

When findings from SHARP, 4D and AURORA are considered together, the clinical benefit of statins (alone or in combination with ezetimibe) in prevalent dialysis patients is uncertain.[38]

Guidelines for the general population recommend that (among patients receiving statin treatment) the dose of statin is titrated to achieve the target level of LDL-C, which in turn is determined by each patient's presumed coronary risk.[85] Higher statin doses produce greater clinical benefits, but at the expense of an increased risk of adverse events. DKD patients are at high risk of medication-related adverse events and reduced doses of statins are generally recommended. The work group suggests that prescription of statins in people with DKD with eGFR <60 ml/min per $1.73\,m^2$ should be based on regimens and doses that have been shown to be beneficial in randomized trials carried out specifically in this population. The doses tested were simvastatin/ezetimibe 20/10 mg per day in non-dialysis patients, atorvastatin 20 mg per day, rosuvastatin 10 mg per day, simvastin/ezetimibe 20/10 mg per day in dialysis patients, and fluvastatin 80 mg per day in patients after kidney transplantation. Given the potential for toxicity with higher doses of statins and the relative lack of safety data, a definite target LDL-C is not recommended in DKD patients. There is a lack of studies designed to decide definite target LDL-C levels in such patients. Furthermore, this approach of using maximally tolerated statins rather than targeting specific LDL-C levels has recently been put forward for all patients at risk for CVD by the American Heart Association and the American College of Cardiology.[86] Patients with eGFR >60 ml/min per $1.73\,m^2$ should be considered as general population patients. This approach is consistent with the recently published KDIGO guideline on lipid management in CKD.[87]

The work group considered the following controversies related to lipid management:
- When should statins be started?
- Should statins be stopped when patients go on to dialysis?
- Should we treat risk or treat LDL-C? What is the LDL-C target for various levels of severity of DKD or on dialysis?

The work group concluded that statins lower mortality and CV events in persons with early DKD and have little or no effect in persons on dialysis. Thus, the work group felt that treatment effects differ depending on severity of DKD. Patients with DKD on dialysis should not be initiated on statin or statin/ezetimibe treatment, given the lack of

evidence that such treatment is beneficial. However, statin or statin/ezetimibe treatment should not necessarily be discontinued when dialysis treatment is initiated. The work group noted that few data are available to guide the management of dyslipidemia in kidney transplant recipients and based its recommendation mainly on the ALERT trial and its *post hoc* analysis.[88] It was felt that statin therapy has uncertain effects in kidney transplant recipients, but treatment may be warranted if patients placed relatively high value on a small absolute reduction in the risk of CV events, and relatively less value on the risks of polypharmacy and drug toxicity. Accordingly, the work group proposed a series of research recommendations to address these gaps in knowledge. Among the recommendations are those designed to expand our knowledge on whether lipid-lowering is safe and effective in patients with DKD.

BP management

The work group evaluated the controversies around management of BP in patients with CKD and diabetes. Two guideline groups had recently discussed or updated previous guidelines for the treatment of patients with diabetes.[39,89,90] Our work group focused on some of the issues that were part of these guideline discussions.

Diabetes is a disease that affects multiple organ systems. The risk factors are multifactorial, thus standard practice guidelines advise us to use multiple strategies to prevent or halt disease progression, such as lifestyle changes (including physical activities, dietary measures, and smoking cessation) and pharmacological interventions. With these strategies we aim to manage: glucose, BP, lipids, body weight, urine albumin, etc. Control of BP is considered one of the key factors in slowing or even halting progressive renal function loss, as well as CV morbidity and mortality in diabetes.

Although it is well known that we should control BP in diabetes, many issues about the best way to 'apply' this treatment are still debated. We will focus on the following: first, what is the optimal BP target level? And second, which drugs should be chosen, and what should be the appropriate dietary sodium intake?

Optimal BP level. Recent guidelines suggest that patients with diabetes deserve special attention and a lower BP target

Table 1 | Future research agenda

- Determine the appropriate frequency for screening for eGFR and microalbuminuria among patients with diabetes.
- Assess whether screening for reduced eGFR would lead to better outcomes for patients. Are these benefits above and beyond those achieved by screening for albuminuria?
- Determine if identifying diabetic patients with reduced eGFR is a good use of limited health-care resources and whether this differs by setting.
- Assess the value added from albuminuria to the prediction of complications above and beyond other routinely measured modifiable risk factors.
- Assess whether a strategy of testing for albuminuria and treatment with angiotensin blockade is more or less cost-effective than a strategy of universal treatment in the absence of testing.
- Ascertain if repeated testing of albuminuria among albuminuric individuals represents a cost-effective use of health-care resources related to available treatment options.
- Observational studies are needed in emerging populations of interest, such as young people with T2DM, to further define the course and determinants of CKD in these populations.
- Health-care delivery needs to be evaluated in patients with diabetes and CKD to identify approaches to care that enhance compliance with prescribed glycemic management.
- Other measures of glycemia (e.g., glycated albumin) need to be identified that more accurately reflect the actual level of glycemic control in persons with ESRD. These measures of glycemia need to be evaluated in relation to health outcomes to identify appropriate target levels for glycemic control.
- Existing transplant registry databases need to be reviewed to ensure they collect relevant information required to assess the effect of glycemic control on health outcomes in transplant recipients.
- Analysis of the relationship between HbA1c and mortality is needed in transplant recipients, similar to what has already been done in dialysis patients, using available registry data.
- RCTs are needed to assess the role of continuous glucose monitoring to improve health outcomes in patients with diabetes and CKD.
- RCTs are needed to identify appropriate choices of antidiabetic medicines used to achieve glycemic control in patients with diabetes and CKD, including ESRD as it may be possible to achieve the benefits of glycemic control with less risk than with current treatment regimens.
- RCTs are needed to identify approaches to immunosuppressive therapy that minimize the hyperglycemic effects of immunosuppression.
- Pharmacokinetic and pharmacodynamic studies of metformin are needed in patients with CKD and GFR <30 ml/min per $1.73\,m^2$ and regulatory approval should be sought to broaden the use of metformin in patients with diabetes and CKD.
- Observational studies are needed to identify immunosuppressive regimens that are less nephrotoxic in patients receiving islet cell transplant.
- As multiple mechanisms for CVD are in play in advanced DKD, research is needed to delineate subgroups of patients in this population who are likely to benefit most from lipid-lowering treatments, especially with combination therapy. No preference was placed to investigate higher doses of statins for the prevention of atherosclerosis-mediated CV outcomes.
- A trial studying the optimal target BP levels in patients with diabetes and CKD is needed for both CV and renal outcomes. This trial may also evaluate the relative contribution of a diastolic versus a systolic target.
- Although RAAS blockers appear to be the drugs of choice, additional investigation should be conducted in patients with DKD who do not respond to this therapy.
- Combination (dual or triple) RAAS blocking therapies should be tested cautiously in lower doses that optimize for the balance between wanted and unwanted effects.
- The effect of dietary sodium intake on surrogate markers such as BP and in particular on CV and renal outcomes should be examined in diabetic patients with CKD.
- The effect of reduction in dietary sodium intake on renal and CV risk management with RAAS blockers should be studied prospectively.

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GFR, glomerular filtration rate; RAAS, renin–angiotensin–aldosterone system; RCT, randomized clinical trial; T2DM, type 2 diabetes mellitus.

than patients without diabetes, the recommended goal being 130/80 mm Hg. The work group recognized that most clinical trials in diabetic patients with CKD show that this is not only a goal that is hard to achieve, but that there is also a question whether such low BPs are actually beneficial.[91] Surprisingly, both KDOQI[92] and KDIGO[89] still support this low BP target for patients with DM and CKD (albeit with weak evidence levels). The only new trial on this issue is the SPRINT trial,[93] examining the effect of the ambitious low target of 120 vs. 140 mm Hg, although this trial is not specifically aimed at patients with diabetes. There are no trials specifically studying an optimal BP target on renal outcomes. This could be of importance as decrease in renal function is associated with increased CV risk.

Drug choice. The use of antihypertensive drugs that intervene in the RAAS is preferred in patients with diabetes and CKD as these drugs show CV and renal protection beyond BP control compared with other antihypertensive drug classes. ACE-Is and ARBs are the drugs of choice since CV protection has been demonstrated for ARBs[94–96] and ACE-Is for patients with T2DM even without CKD.[97,98] No studies in patients with diabetes have directly compared ACE-I versus ARB therapy. This has been studied in non-diabetic disease[99] showing no difference between these two mechanisms of blocking the RAAS. For mineralocorticoid receptor blockers, CV protection was shown in a non-diabetes study,[100] and no renal outcome studies are available. For DRIs, no CV or renal outcome studies have been performed.

Studies of combination therapies of RAAS-blocking agents to date have been unsuccessful and such treatment could even be harmful. ONTARGET, although not specifically designed to look at diabetes, showed no clear benefit of combining ACE-I and ARB for either CV or renal outcome.[101,102] Recently, ALTITUDE showed that a combination of either ACE-I or ARB with a DRI in diabetes did not show any appreciable renal or CV protection, and may in fact be harmful.[103] Finally, one trial (VA NEPHRON D) looking at combining ACE-I and ARB was prematurely stopped owing to safety concerns.[104] Despite improvements in surrogate parameters such as BP and albuminuria from dual RAAS therapies shown in some studies, VA NEPHRON-D demonstrated that combined angiotensin inhibition resulted in increased risk for hyperkalemia and acute kidney injury and provided no overall clinical benefit.[105]

Treating early CKD. Several trials have shown that RAAS blockade is not only effective in late-stage renal disease in diabetes but also in early CKD. The IRMA-2, INNOVATION, BENEDICT, and ROADMAP studies showed that RAAS blockade can prevent transition from microalbuminuria to macroalbuminuria, as well as from normoalbuminuria to microalbuminuria in hypertensive diabetic patients.[106–109] Whether this observation can be translated to normotensive individuals remains questionable as the DIRECT study did not show a clear benefit of RAAS intervention in normotensive T1DM or T2DM on transition from normo- to microalbuminuria (although the study was not powered for a renal outcome).[25] Both KDIGO and the updated KDOQI guidelines thus suggest an ARB or ACE-I in normotensive diabetic patients with albuminuria >30 mg per day.[39,89,90]

Sodium restriction. The KDIGO guideline recommends lowering salt intake to <90 mmol (<2 g) per day of sodium (5 g of sodium chloride), unless contraindicated. This lifestyle modification is meant to lower BP and improve CV and other outcomes. The work group noticed that there is a high level of evidence for high dietary sodium intake to be associated with many adverse outcomes. However, two recent publications fueled a debate whether this is true in diabetes.[110,111] The impact of these studies has to be further evaluated.

The work group established that sodium restriction may also influence the effect of drugs such as RAAS blockers on surrogate markers such as BP and albuminuria, and low sodium intake enhances the antihypertensive and antialbuminuric effects of ACE-I/ARB. Recently, *post hoc* analysis of a non-diabetic[112] and two diabetic studies[113] showed that lower sodium intake improves the renal protective effect of RAAS blockade compared with higher sodium intake.

CONCLUSIONS

Although we have gained a great deal of knowledge on how to diagnose and manage patients with DKD, there are still a large number of areas that need clarification (Table 1).
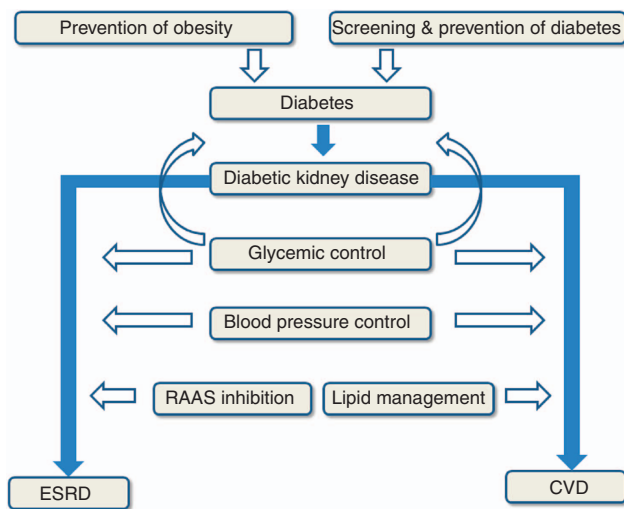

Figure 1 | Approaches to improving outcomes related to diabetic kidney disease. The best approach to prevent diabetic kidney disease is to prevent diabetes itself. However, once diabetes occurs glycemic control may prevent/delay the development of diabetic kidney disease. In those patients who develop diabetic kidney disease, glycemic control, blood pressure control, and RAAS inhibition are all important in delaying/decreasing progression to ESRD and glycemic control, blood pressure control, and lipid management are all important in delaying/decreasing the development of CVD. CVD, cardiovascular disease; ESRD, end-stage renal disease; RAAS, renin–angiotensin–aldosterone system. White arrows denote potential preventive measures.

Although increased urinary albumin levels are markers of both DKD and CVD, the frequency of screening for it in the context of other CVD and CKD risk factors remains uncertain. The relationship of albuminuria to GFR remains an interesting one and how various factors such as glycemic and BP control and RAS blocker use affect them are research questions that remain to be investigated. Additional questions include the roles of glycemic and BP control on the progression of DKD as its severity increases. There is a paucity of knowledge regarding the benefits of glycemic control in dialysis and transplant patients and even how it should be assessed. Controlled clinical trials on the best ways to manage hyperglycemia in the patient with GFR < 30 ml/min per $1.73 \, m^2$ or on dialysis are needed. Of specific interest is a need to reassess the safety and efficacy of metformin in patients with GFR < 60 ml/min per $1.73 \, m^2$ and a careful assessment of the effects of mammalian target of rapamycin inhibitors and calcineurin inhibitors on kidney function in patients receiving islet cell and pancreas transplants. The efficacy of LDL-C reduction by statins has been well assessed in patients with all levels of DKD with the surprising, but reproducible finding of lack of efficacy in dialysis patients. However, there is a need to identify and obtain data on possible subgroups that might benefit most from lipid-lowering treatments, including those who have had kidney transplants. BP control remains a very important area but controversy exists as to the optimal BP to be achieved in those with DKD from both renal and CV outcome perspectives. Although RAAS blockers remain the cornerstone of therapy, how to manage patients who do not respond to them remains an issue. Combination RAAS blockade has not lived up to its promise, especially the combination of DRIs and ACE-Is or ARBs. How these drugs interact with sodium balance is also an interesting area that needs further exploration.

As this conference clearly demonstrated, the aim of improving outcomes related to DKD involves a coordinated and multipronged approach to tackle its comorbidities (Figure 1). The optimal management of DKD has proved challenging but we have made great strides, with the number of patients developing ESRD per 100,000 patients with DM expected to decline considerably over the next decade. New drugs continue to be developed with novel mechanisms of action so that a continued exploration of the basic pathophysiology of DKD becomes ever more important. It may well be that some subgroups of patients respond better to one drug than another and better methods of identifying such subgroups will be of clinical benefit and provide us with a better understanding of the pathophysiology.

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