

UPDATE ARTICLE

Glycemic Control in Patients with Diabetic Kidney Disease; Time to Recognize Perils of Iatrogenic Hypoglycemia? Moving away from Intensive Glycemic Control

Puneeta Gupta¹, Rajesh Gupta², Anil K Gupta³

Abstract

The chronic complications of Diabetes Mellitus (DM), which may be present in as many as 50% of the patients at the time of diagnosis, are a major burden for both individuals with the disease and health systems and it has been estimated that as much as 60–70% of healthcare expenditure related to diabetes (about 670 billion dollars a year) is currently attributable to chronic complications of the disease. These high prevalence rates are widely acknowledged to further rise as poor lifestyle choices and their consequences continue to rise. Adding to that is an aging population and urbanization that together will make situation even more challenging. Type 2 diabetes affects about 90–95% of newly diagnosed patients of diabetes and accounts for majority of cases of Chronic Kidney Disease (CKD). In other words, CKD affects about 20–40% of individuals with diabetes making it one of the most common complication related to the disease. The risk of renal failure is 25 times higher in diabetic patients than in the non-diabetic population. Thus patients with diabetes and renal failure represent a special risk group as they have higher morbidity and mortality and are at a higher risk of hypoglycaemia than diabetic individuals with normal renal function. In addition, for all the physicians who are taking care of patients of diabetes and kidney disease, formulation of comprehensive plan of management directed at modification of risk factors of cardiovascular disease (CVD) is of utmost importance as majority of patients with CKD die as a result of cardiovascular complications rather than progression to ESRD, (accounting for about 70% of deaths over the age of 65). The contrasting results available from clinical trials in recent years have generated perplexity amid concerns that glucose-lowering therapies, under certain circumstances, might even be detrimental; in light of the fact that intensive glycemic control increased the risk for death by 22% in the ACCORD trial. Moreover it should be pooled data of some extensive reviews which has been carried in last one and half year have demonstrated that intensive glycemic control significantly increases the risk of cardiovascular and all-cause mortality in patients of CKD. So it is increasingly problematic for clinicians to continue aggressive glycemic control for the treatment of renal outcome in patients of advanced renal insufficiency with multiple co-morbidities. Thus, a lower survival benefit due to multiple co-morbidities combined with general lower life expectancy necessitates a balanced approach. Suggesting the need for revised and extended target of HBA1C in this patient population.

population growth and changing lifestyles, the first part of the statement is no longer relevant as incidence of diabetes has doubled every 20 years since 1945. The figures available in 7th world diabetes atlas released by International Diabetes Federation (IDF) showed that approximately 415 million adults were living with diabetes in 2015. Further, five million people died because of diabetes related causes, accounting for more mortality than that resulted from malaria, tuberculosis, and HIV combined together.² The World Health Organization estimates that prevalence of diabetes (DM) will increase from 415 million to 642 million in 2040; with two countries, China and India accounting for largest numbers of patients with diabetes.³ The second part of our introducing statement is as true today as it was almost 2000 years ago, as approximately 44% of patients with type 2 diabetes are likely to succumb to their disease within 10 years of diagnosis. The chronic complications of diabetes, which may be present in as many as 50% of the patients at the time of diagnosis, are a major burden for both individuals with the disease and health systems and it has been estimated that as much as 60–70% of healthcare expenditure related to diabetes (about 670 billion dollars a year) is currently attributable to chronic complications of the disease.⁴ These high prevalence rates are widely acknowledged to increase further as poor lifestyle choices and their consequences continue to rise. Adding to that is an aging population and urbanization that together will make situation even more challenging.

Introduction

Diabetes was first recognized 3500 years ago by the Ancient Egyptians. One of the first clinical description was given by Aretaeus, who practiced in the city of Cappadocia around 120 AD. He wrote that the condition was 'fortunately rare', but 'short will be

the life of the man in whom the disease is fully developed".¹ Now in 21st century, as we struggle with explosive

¹Professor, Department of Medicine, Acharya Shri Chander College of Medical Sciences and Hospital, Jammu, Jammu and Kashmir;

²Consultant, Department of Medicine, Government Medical College, Jammu, Jammu and Kashmir; ³Professor and HOD, Department of Medicine, Acharya Shri Chander College of Medical Sciences and Hospital, Jammu, Jammu and Kashmir

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About 90-95% of those afflicted with DM are diagnosed with type 2 diabetics and Type 2DM is the main cause of chronic kidney diseases (CKD) affecting about 20-40% of individuals with diabetes, making it one of the most common complication related to the diabetes.⁵ The risk of renal failure is 25 times higher in diabetic patients than in the non-diabetic population. Thus patients with diabetes and renal failure represent a special risk group as they have higher morbidity and mortality and are at a higher risk of hypoglycaemia than diabetic individuals with normal renal function. In addition, for all the physicians who are taking care of patients of diabetes and kidney disease, formulation of comprehensive plan of management directed at modification of risk factors for cardiovascular disease (CVD) is of utmost importance as majority of patients with CKD die as a result of cardiovascular complications rather than progression to ESRD (End Stage Renal Disease),⁶⁻⁸ (about 70% of people over the age of 65). Also there is graded inverse relationship between CVD risk and glomerular filtration rate (GFR) that is independent of age, sex and other risk factors, thus making CKD an independent risk factor for CVD events.⁶ Altogether, knowledge regarding the prevention and management of diabetic nephropathy, along with other aspects of diabetes care, is part of the comprehensive care of any patient with diabetes and nephropathy.

Discussion

Intensive versus conventional glycemic control and long term complications of the diabetes.

It has been recognized for quite some time now that uncontrolled hyperglycemia has pathogenic role in micro- and macrovascular complications of the diabetes. Still debated, however, is the level of glucose lowering necessary to reduce complications, balanced by the risk and costs of the means used.⁸ There have been numerous studies over the past 20 years or so that have attempted to clearly address the benefits, risks, and complications of intensive versus standard glycemic control. The core data for target setting of blood glucose in type 1 and type 2 diabetes initially came from two landmark trials published in the last decade of

20th century; the Diabetes Control and Complications Trial (DCCT, 1993)^{9,10} and the United Kingdom Prospective Diabetes Study^{9,11} (UKPDS, published in 1999) which aimed to prove the benefit of tight glucose control in terms of diabetic complications. Although tight glucose control was already suspected to be beneficial in terms of chronic complications, these two studies formally demonstrated such a hypothesis. Since then, the evidence provided by these studies has guided clinical practice and medical decisions for several years. Thus, based on the trials results, the American Diabetes Association (ADA) recommended a target HbA1C < 7.0% for prevention of renal disease and other microvascular complications which was also endorsed by National Kidney Foundation Kidney Disease Outcome Quality Initiative (KDOQI) Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease.¹² Although both DCCT and UKPDS studies showed a trend toward an improvement in cardiovascular complications with intensive glycemic control, as, yet this debate between intensive versus conventional control refused to die as this difference was not statistically significant. So, several long-term trials were started in the past decade to compare the effects of intensive versus standard glycemic control on chronic complications especially the cardiovascular mortality. These trials were expected to show more favorable results in reducing the chronic complications of the diabetes with intensive glucose control as participants here were relatively high risk with established type 2 diabetes. In both DCCT and UKPDS studies enrolled patients were younger or recently diagnosed with diabetes with no history of cardiovascular events and absence of other cardiovascular risk factors apart from diabetes. With those differing characteristics of selected population in both trials were believed to be main reason for less desirable result seen as far as cardiovascular mortality was concerned.⁹

In 2008, two of these trials, Action in Diabetes and Vascular Disease—PreterAx and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Veterans Affairs Diabetes Trial (VADT), were completed but both trials failed to demonstrate

conclusively that intensive glycemic control was associated with decreased morbidity and mortality. A third trial, Action to Control Cardiovascular Risk in Diabetes (ACCORD), terminated its glycemic control study early due to the finding of increased mortality in participants randomized to a strategy of very intensive glycemic control with a target A1C of <6.^{13,14} Thus this unexpected outcome and results of other two trials reduced the enthusiasm generated by the aforementioned studies and forced the representatives of the American Heart Association (AHA) and the American College of Cardiology (ACC), to reexamine the recommendations for glycemic targets in patients with diabetes, the majority of whom have type 2 diabetes.¹⁵

Simultaneously, when this point about intensive glycemic control and cardiovascular mortality was being actively debated, many researchers also started questioning the actual benefit of intensive glycemic control in preventing clinical renal endpoints (e.g., progressive loss in glomerular filtration rate) beyond albuminuria in type 2 diabetics. In a significant paper, which reviewed data from 7 trials involving 28,065 adults and encompassing 163,828 patient-years of follow up, between January 1, 1950, and December 31, 2010; conventional and intensive glycemic control in patients with T2DM and its effect on renal outcome was evaluated. The points evaluated by the researchers were the development of micro- or macroalbuminuria, and the clinical endpoints were doubling of serum creatinine level, ESRD, and renal related deaths suggesting that intensive glycemic control reduces albuminuria (referred to as surrogate end point by these and many researchers) but evidence was lacking that it prevented clinically meaningful renal outcome in patients with T2DM measured during the 3.5 to 10.7 years of the published trials.¹⁶

Thus various questions remain to be answered as far as glycemic management of patients of diabetic kidney disease is concerned.¹⁷

1. Should we aim to lower HbA1C by tighter glycaemic control in patients with diabetes and advanced stages of CKD (eGFR <45 mL/min)? (estimated Glomerular Filtration Rate).

2. Is an aggressive treatment strategy (in number of injections and controls and follow-up) superior to a more relaxed treatment strategy in patients with diabetes and CKD?
3. Is any oral drug superior to another in terms of mortality/ complications/glycaemic control in patients with diabetes type 2 in advanced CKD (GFR <45 mL/min/1.73 m²)?
4. In patients with diabetes type 2 and CKD (GFR <45 mL/min/1.73 m²), is maximal oral therapy better than starting/adding insulin at an earlier stage?
5. Are there better alternatives than HbA1c to estimate glycaemic control in patients with diabetes and CKD stage 3b or higher (GFR <45 mL/min/1.73 m²)?¹⁶ Before discussing these points with available evidence from clinical trials; in following paragraph, the anti-diabetic drugs use in chronic kidney disease is reviewed

Metformin

Metformin which is recommended as the initial pretermed pharmacological agent for type 2 diabetes is eliminated via the kidneys and its clearance decreases 75% when the GFR falls to less than 60; without any further change when the GFR declines to 30 mL/min/1.73 m². Thus to minimize the risk of lactic acidosis, various guidelines have advised against using this compound in men with serum creatine more than or equal to 1.5 and women with serum creatinine of more than or equal to 1.4 mg/dl.¹⁸⁻²⁰

Sulfonylureas (SUs) are drugs that stimulate endogenous insulin secretion by pancreatic β cells. The first-generation SU are almost exclusively excreted by the kidney and can accumulate in CKD patients and are contraindicated. Second-generation SU (glipizide, glimepiride, glyburide, gliclazide) are metabolized in the liver and active metabolites are excreted in the urine. They should be used with caution in patients with mild CKD (eGFR 60- 90 ml/min/1.73 m²) and normally aren't recommended in patients with GFR <60. However, certain individual variation in metabolism and clearance of these molecules can be effectively used when prescribing these drugs for CKD patients. Glipizide is metabolized by the liver into several

inactive metabolites and its clearance and elimination half-life are not affected by a reduction in GFR so can be used in almost all the patients of CKD in whom sulfonylureas are under consideration.^{18,19}

Glitazones

These are potent insulin sensitizers which have been available for the management of type 2 diabetes for over a decade. The pharmacokinetics of pioglitazone is not altered by renal impairment, and there is no need for dose adjustment in this setting. Despite this advantage also lack of hypoglycemia as side effect, the drug should still be used with caution in CKD because of the risk of water and sodium retention and heart failure. Data regarding its safety in dialysis patients is as yet very limited.^{19,20}

Glinides

Out of two available drugs repaglinide has been used in CKD. Although renal impairment may slightly prolong its half-life, the use of repaglinide is not contraindicated in patients with renal impairment or in dialysis patients. A preprandial dose of 0.5-4 mg should be titrated according to the postprandial blood glucose response.^{19,20}

Glucagon like peptide-1 (GLP-1) analogue

Incretin mimetics include glucagon-like peptide 1 (GLP1) analogs and agonists (exenatide, lixisenatide and liraglutide), which are injectable and increase insulin secretion and suppress glucagon secretion in a glucose-dependent manner, with reduced risk of hypoglycemia. These drugs show diuretic effect via GLP-1 receptors expressed in renal tubules and may aggravate renal impairment, especially in patients treated with renin-angiotensin system inhibitors or diuretics.¹⁸⁻²⁰

The DPP-4 inhibitors

The commonly used DPP-4 inhibitors, also known as "gliptins", despite their common mechanism of action have structural heterogeneity that translates into different pharmacological properties and different metabolism and excretion pathways. Sitagliptin is mostly eliminated unchanged in the urine and can be used with appropriate dose reduction in all chronic kidney stages. The usual dose of 100 mg

once per day is reduced to 50 mg/day for patients with moderate renal impairment (GFR 30-50 mL/min), which is further reduced to 25 mg once a day in end-stage renal disease (ESRD) requiring dialysis. The Vildagliptin dose is reduced by half (to 50 mg/day) for both moderate and severe CKD. The dose of Saxagliptin (5 mg once daily) should be reduced to 2.5 mg once daily in patients with moderate or severe renal impairment (GFR 30-50ml/mt) and is not recommended for patients with ESRD requiring dialysis. Presently, linagliptin is the only DPP-4 inhibitor that is eliminated nearly entirely via the bile, thus making this agent a possible treatment choice for patients in all stages of CKD, and even stage 5 (GFR <15 mL/min/1.73 m²), without dose adjustments. The safety of this therapeutic class has been questioned after the release of a phase 4 trial showing increase in hospitalization for HF. Certain risk factors are associated with this higher HF rate, such as previous HF, a GFR of <60 mL/min and increased levels of N-terminal pro-B-type natriuretic peptide (BNP).^{21,22}

Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors (canagliflozin, dapagliflozin, empagliflozin) are novel hypoglycemic agents³.

SGLT2 Inhibitors

The kidney plays an important role in glucose homeostasis, mostly by the reabsorption of filtered glucose. In the kidney, filtered glucose is actively reabsorbed by specific transporters located on the apical (brush-border) membrane of proximal tubular cells. A new generation of drugs called SGLT2 inhibitors, decreases the capacity for renal glucose reabsorption and reduces the renal threshold at which glucose is excreted resulting in net loss of excess glucose in the urine thus directly reducing plasma glucose concentrations in patients with hyperglycemia. This therapeutic class has been approved for the treatment of patients with T2DM with an GFR of ≥ 45 mL/min/1.73 m², but only one drug canagliflozin has been evaluated in this setting, however use of canagliflozin in patients with moderate CKD is less effective in improving glycemic control and is associated with a higher occurrence of adverse reactions compared to patients with mild renal impairment or normal renal function. The SGLT-2

inhibitors are only effective with some degree of kidney function and are not recommended in dialysis patients.²³

Insulin Treatment

Regardless of the fact that insulin is considered as the best choice to improve glycemic control in patients with renal failure, specific information about dose adjustment and differences in insulin profiles in this population is still limited because of few studies carried out in patients with advanced renal insufficiency.¹⁷⁻²⁰ There is no a consensus about the choice of various preparation of insulin in patients with CKD. However the principles of insulin therapy for CKD patients are not different from general diabetic patients. When GFR is 10-50 mL/min/1.73 m², the total insulin dose should be reduced by 25% and by 50% if GFR <10 mL/min/1.73 m², with no dose adjustment if the GFR is > 50 mL/min. As renal failure progresses, insulin clearance decreases and this situation is compensated with an increment in insulin uptake by proximal tubule. Although all the available acting insulin analogue preparations can be used, insulin analogues are generally preferred over regular and NPH insulin because they are less likely to cause hypoglycemia. The rapid-acting insulin analogs aspart, lispro and glulisine are the quickly absorbed and are ideal for rapid correction of elevated blood sugars or for prandial insulin needs as renal impairment does not affect the pharmacokinetics of insulin analogs in a clinically significant manner. Patients with Stage 4-5 CKD and those on dialysis often have some delayed gastric emptying; giving rapid-acting insulin *after* the meal may be helpful for matching the insulin peak with the time of the postprandial blood glucose peak. In patients with nausea who may not know how much they will eat, postprandial rapid-acting insulin dosing may be worth trying. Similarly, patients on peritoneal dialysis obtain large amounts of calories from their dialysis fluid and often have variable appetite, so that postprandial dosing maybe helpful for them also. Because of its pharmacokinetics and stable half-life, insulin glargine has a time-action profile of approximately 24 hours and has been found to be safe to use in some of the studies, but data is quite limited.^{18,19,20,24}

Thus various recommendations on

management of diabetes in CKD can be summarised as:

1. In type 2 diabetic subjects with the early stage of CKD, all hypoglycaemic agents can be applicable. Once the estimated glomerular filtration rate (eGFR) falls below 60 ml/min, a subject's antidiabetic therapy needs to be re-evaluated as some oral antidiabetic drugs are formally contraindicated and others require dose reduction.
2. As in CKD stage 3b or higher, the risk of hypoglycaemia is enhanced and hypoglycemia from antidiabetic drug therapy is among the four leading causes of hospitalization for adverse drug reactions in the elderly and the survival benefit is probably lower due to the general lower life expectancy; therefore, a balanced approach, taking into account the specific condition of these patient is needed suggesting that the target of HbA1c can be extended above 7.0% in this patient population. Hypoglycemia triggers a cascade of physiologic effects, inducing adrenergic activation, oxidative stress, and cardiac arrhythmias, and may contribute to sudden death and ischemic cerebral damage²⁵
3. In an extensive review²⁶ of adults with type 2 diabetes using various hypoglycemic therapy, reviewers observed no significant differences in the associations between any of available classes of glucose-lowering drugs (alone or in combination) and the risk of cardiovascular or all-cause mortality or in terms of nephro-protection²⁶ thus the first concern on the part of prescribing practitioner should always be not to increase the risk for severe hypoglycaemia. As a consequence, preference should go to drugs with a low risk for hypoglycaemia and risk was reported to be low with metformin, glipizide, acarbose, DPP-IV inhibitors and the SGLT2 inhibitors. Sulfonylureas and glinides are associated with an increased risk of hypoglycaemia and when sulfonylureas are combined with insulin, the risk of hypoglycaemia may increase more than 14-fold.^{24,26}
4. For CKD patients with type 2 diabetes, many physicians are of the opinion that initial treatment with an oral agent rather than insulin is appropriate because of the lack of pharmacokinetic studies for the various types of insulin in patients with different degrees of renal insufficiency and the absence of therapeutic guidelines that define insulin adjustments based on GFR making it difficult to advocate ideal insulin therapies in these patients. Moreover, because intensive insulin therapy is associated with more episodes of hypoglycaemia and weight gain indirectly raising blood pressure. However, the patients who fail therapy with oral agents or have frequent episodes of hypoglycemia are treated with insulin.
5. After the publication of various encouraging reports on safety of metformin in patients of chronic kidney disease, it was concluded that although metformin is mainly cleared by the kidneys, the drug levels generally remain within the therapeutic range and lactate concentrations are not substantially increased when used in patients with mild to moderate renal insufficiency (estimated glomerular filtration rates, 30-60 mL/min) thus making overall incidence of lactic acidosis in metformin users generally indistinguishable from the background rate in the population with diabetes. Observational studies suggest a potential benefit from metformin on macrovascular outcome, even in patients with prevalent renal contraindications for its use. So many experts are of the opinion that metformin use can be considered in patients with GFR of upto 30 mL/min/1.73 m², with dose reduction advised at 45 mL/min/^{27,28} However, there is indirect evidence that a rapid drop of GFR can lead to a sudden accumulation of metformin. Therefore, patients should be instructed to reduce or stop metformin in conditions with enhanced risk of acute kidney injury, e.g. severe bouts of diarrhoea, dehydration or fever.
6. In patients with a GFR >45 ml/min, in whom the glycaemic target has not been achieved with

metformin, it can be combined, either with a DPP4 inhibitor or repaglinade. However, when cost is an issue, a short-acting second-generation sulphonylurea, with no active metabolites could be considered, as these drugs are commonly cheaper than other drugs. If the control is still not adequate, basal insulin should be added as a third agent. There is little experience with triple oral therapy in CKD and also combination of insulin with secretagogue drugs increases the risk of hypoglycaemic episodes, and therefore, should be avoided.

7. In patients with a GFR <30ml/min/1.73m² or who are on dialysis, the experience with non-insulin anti-diabetic drugs has been very limited, and as such the treatment of choice should be insulin. However, some clinicians prefer to continue oral agents which are approved in this setting rather than switching to insulin, in patients who have already achieved acceptable glycemic control on these agent and both repaglinade and DPP4 inhibitors are alternatives to be assessed.
8. As renal clearances of different agents might differ, combining drugs in a one pill formulation can lead to overdosing of one of the constituents in patients with CKD these formulations should be avoided in patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m²), as the two components may have different dose adaptation requirements.
9. Glycated hemoglobin may not be as accurate among ESRD patients as in the general population due to biological and patient-specific factors. HbA1c values may be falsely elevated or decreased in those with CKD. The factors associated with a lower than expected HbA1c are decreased red blood cell survival and increased red blood cell formation (use of iron, erythropoietin). The accumulation of uraemic toxins may be responsible for a higher than expected HbA1c values. The fructosamine level and glycated albumin level are proposed as a better measure of glycemic control in patients with CKD in future.²⁹

9. The presence of albuminuria in patients with T2DM is a predictor of chronic renal failure, with the mean time from the start of proteinuria until end-stage kidney disease being 7 years. Therefore, a strategy to detect diabetic kidney disease earlier by screening for albuminuria and reduced glomerular filtration rate is important to prevent progression of diabetic nephropathy.

Conclusion

The assumption that treatment of hyperglycemia can prevent all diabetes complications, including CVD, has been an "act of faith" in the medical fraternity for many decades. The contrasting results available from clinical trials in recent years have generated perplexity amid concerns that glucose-lowering therapies, under certain circumstances, might even be detrimental; in light of the fact that intensive glycemic control increased the risk for death by 22% in the ACCORD trial. Moreover, pooling the data from all these studies did not produce the expected outcome of decreased cardiovascular-related death or all-cause mortality in many high risk cohorts. The reasons for the lack of clinical benefits are unclear. The possible explanation for this are many like, intensive control may have been initiated too late in the course of the disease (the legacy effect), there may have been insufficient duration of glycemic treatment, or once HbA1c levels reach a certain point (e.g <7%), further reduction does not result in greater benefits. A recent study demonstrated that despite substantial increases in the use of glucose-lowering medications (and inhibitors of the renin-angiotensin-aldosterone system) from 1988 to 2008, the prevalence of CKD in patients of diabetes has actually increased. So it is increasingly problematic for clinicians to continue aggressive glycemic control for the treatment of renal outcome in patients of advanced renal insufficiency with multiple co-morbidities. Thus it can be concluded that the selection of a glycemic goal in a person with diabetes is a compromise between the documented upside of glycemic control—the partial prevention or delay of microvascular complications—and the documented downside of glycemic control—the recurrent morbidity and potential mortality of iatrogenic

hypoglycemia causing harmful effects on the patient's safety. Some extensive reviews which have been carried out in last one and half year have reported that intensive glycemic control significantly increases the risk of cardiovascular and all-cause mortality in patients of CKD.^{30,31} In other words, the goal should be to keep the blood glucose within the narrow range to reduce the progression of the disease and improve quality of life, minimizing comorbidities and cardiovascular risks. However, to date, the real benefits and impact of tight glycemic control in patients with long-standing diabetes and advanced CKD in particular are not yet fully known. Patients with type 2 diabetes are heterogeneous for age, duration of disease, comorbidity, and genetic background. Glucose-lowering therapy should be adapted to this complexity, with an attempt at improving, or at least avoidance of worsening of associated cardiovascular risk factors and thus HbA1c goal between 7% and 8% is perhaps more appropriate. The latest guidelines of ADA¹⁵ advises less stringent HbA1c goals in patients with long duration of disease, limited life expectancy, presence of important comorbidities and established vascular complication. It further states that patient attitude and expected treatment efforts, available resources and support system should also be taken into consideration while setting glycemic targets.

Suggestions for further research

1. More studies are required to evaluate whether it is glycaemic variability and specifically the recurrent episodes of hypoglycaemia, that contribute to increased cardiovascular risk, rather than the average blood glucose level.
2. A study of intensive versus standard control (HbA1c <53 mmol/mol versus <69 mmol/mol), specifically in patients with diabetes and CKD stage 3–5 using drugs with very low risk of inducing hypoglycaemia, is warranted.

Conflict of interest

The all three authors declare that there is no conflict of interest.

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