Port J Nephrol Hypert 2015; 29(1): 10-14
Advance Access publication 3 March 2015

Mind the gap. Which are the evidences in the treatment of diabetic kidney disease?

Mind the gap. Quais são as evidências no tratamento da doença renal diabética?

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Received for publication: 04/01/2015
Accepted: 7/01/2015

INTRODUCTION

Diabetes is a strong risk factor not only for cardiovascular disease (CVD) but also for the development of chronic kidney disease (CKD). In Portugal, 3300 diabetic patients are submitted to hemodialysis and peritoneal dialysis, it means 27.7% of end-stage renal disease (ESRD) patients. Furthermore in the last six years there was a trend to increased incidence of diabetic patients (29% to 32.2%) in patients with ESRD.

Additionally, about 30% of patients with myocardial infarction are diabetics, as well as 30% of patients with stroke. Despite the higher risk of CVD in diabetic patients, the mortality rate by myocardial infarction or stroke in Portuguese patients, with or without diabetes, does not differ significantly[1]. In fact, in the absence of nephropathy the mortality of diabetics is similar to that of the general population[2,3]. The excess mortality among diabetics appears to be largely limited to the subgroup with kidney disease and explained by their high burden of CVD. For patients with CKD Stage 3, the risk of death is over 10 times higher than the risk of progression to ESRD[4]. It should also be pointed out that older patients with diabetic kidney disease (DKD) tend to progress to ESRD less commonly than younger patients, largely due to the competing risk of death from CVD.

The mainstays of prevention and treatment for DKD and CVD address shared risk factors and therapeutic approach, including control of hyperglycaemia, hypertension, and dyslipidemia. However, the evidence of the use of drugs lowering those conditions does not show that they always contribute to the reduction of the diabetic complications. The exaggerated advice and claims of causal effect or unjustified inferences or extrapolations of drugs used in the treatment of diabetes should be identified and discarded. The need to be familiar with the risk of using these drugs is so critical as to know the expected benefits, in particular to reduce the diabetic complications.

DOES INTENSIVE GLYCAEMIC CONTROL REDUCE CVD?

The evidence for a cardiovascular benefit of intensive glycaemic control primarily rests on long-term follow-up of study cohorts treated early in the course of T1DM and T2DM (DCCT/EDCI and UKPDS). The

long-term follow-up of DCCT in EDCI cohort confirmed a persistently reduced complications rate, although the large differences in HbA1c between the 2 treatment groups that existed during the study had dissipated within a year of completion of the DCCT and by the 5th year of the EDIC study, the difference in A1C between groups was no longer significant[24]. In the UKPDS cohort during ten years similar benefits were shown, with similar dissipation of HbA1c in intensively and the conventionally treated groups. To explain the follow-up findings of both clinical trials with periods of good and bad glycaemic control, the concept of ''metabolic memory'' or ''legacy effect", respectively to T1DM and T2DM was raised[24,25]. It has been argued that the legacy effect is no more than (advanced) lead time, such that a brief period of hyperglycaemia advances patients closer to complications. Much like any machine, no matter how long you have purchased but more or less use to warranty their future reliability. Is this memory or simply the delay of their inevitable fate?[5]

Because of ongoing uncertainty regarding whether intensive glycaemic control can reduce the increased risk of CVD in people with T2DM, three trials were launched (ACCORD, ADVANCE and VADT) to compare the effects of intensive *versus* standard glycaemic. Findings from those trials showed that medium-term trials of intensive glucose lowering, in participants with long-established diabetes (8-11 years) and with a history of CVD, have failed to demonstrate a reduction in major CV events by aggressively reducing HbA1c levels to less than 7 %[26].

The findings observed in these trials have changed the perception that intensive control of hyperglycaemia should be tailored to all diabetic patients. Theirs clinical outcomes contributed to establish the goals of HbA1c in older adults. The care of older adults with diabetes is complicated by their clinical and functional heterogeneity. Some older adults with diabetes are frail and have other underlying chronic conditions, substantial diabetes-related comorbidity, or limited physical or cognitive functioning. Other older individuals with diabetes have little comorbidity and are active. Providers caring for older adults with diabetes must take this heterogeneity into consideration when setting and prioritizing treatment goals. Intensive glycaemic control can be a risky business because it is associated with more harm than benefit. Thus, the ADA considers 3 levels of older patients according to "Patient characteristics/health status" and recommended different goals to HbA1c: ‹ 7.5 %, ‹8 % and ‹ 8.5 %[6].

Of note is that no prospective randomized clinical trials have evaluated the effect of glycemic control on health outcomes in patients with CKD Stages 3 to 5. Although aggressive glycemic control has been shown to alter the clinical course of early DKD, data supporting the benefits of tight glycaemic control on clinical outcomes in patients with advanced CKD, including ESRD, are lacking.[7]

DOES LIPID-LOWERING DRUG THERAPY SLOW DOWN PROGRESSION OF CKD AND PREVENT CVD?

Patients with DKD present with several lipoprotein abnormalities, such as higher plasma levels of LDL-C and triglycerides[27].

Although some conflicting data previously existed suggesting that lipid-lowering therapy might hamper progression of CKD, this was not demonstrated in the much larger SHARP trial with a combination of simvastatin and ezetimibe. Subgroup analyses did not demonstrate any differences among patients with and without diabetes[8].

Regarding CVD prevention, statin therapy should be considered in nearly all patients with diabetes and CKD stages 1 to 4 given their high risk of CVD. Specific LDL-C treatment targets were removed from recent recommendations on managing lipids in patients with CKD in the KDIGO 2013 Clinical Practice Guidelines[9]. These recommendations align with those in the recent prevention guidelines by the AHA/ACC[10] and American Diabetes Associaton that advised that the decision to initiate statin therapy should be based on the absolute risk of coronary events. Testing for LDL-C may be considered on an individual basis to, for example, monitor adherence and efficacy.

Whether patients on statins should discontinue their use once dialysis commences remains unclear. Moreover, several studies have shown a paradoxical effect of low serum cholesterol in CKD and dialysis populations to be an adverse predictor of mortality[11].

This might reflect an adverse outcome of chronic inflammation and malnutrition that results in risk reversal.

WHICH ARE THE BENEFITS TO LOWER HYPERTRIGLYCERIDEMIA WITH FENOFIBRATE?

The independence of hypertriglyceridemia as a causal factor in promoting CVD remains debatable. Rather, triglyceride levels appear to provide unique information as a biomarker of risk, especially when combined with low HDL-C and elevated LDL-C. These lipoprotein abnormalities are commonly present in T2DM and stages 3 to 5 of CKD[12].

The present mainstay of treatment of hypertriglyceridemia focuses on intensive therapeutic lifestyle change and glycaemic control[12]. When these measures are not sufficient the use of drugs to lower hypertriglyceridaemia is recommended. However, there is a diversion between the recommendation of the European and American guidelines regarding the triglycerides level, › 200 mg/dL *versus* › 500 mg/dL, respectively[10,13].

Nevertheless, both guidelines are in agreement in several clinical trials that did not show cardiovascular benefit from drugs that lowered triglyceride levels or increased HDL cholesterol levels. In fact, in the ACCORD study, in patients with T2DM who were at high risk for CVD, the combination of fenofibrate and simvastatin moderately reduced triglycerides (23 mg/dL or 14%), but did not reduce the rate of fatal cardiovascular events, non-fatal MI, or non-fatal stroke, as compared with simvastatin alone[28].

Behind the lack of evidence of reduction of CVD with added fenofibrate to statin therapy, it should be consider the potential risk for adverse effects of this combination, namely more likely to increased risk for abnormal transaminase levels, myositis, rhabdomyolysis and creatinine serum level[10]. Furthermore, it is recommended evaluating of serum creatinine level before fenofibrate initiation, within 3 months after initiation, and every 6 months thereafter. If eGFR is between 30 and 59 mL/min, the dose of fenofibrate should not exceed 54 mg/day, and should be discontinued or not used if eGFR ‹30 mL/min. Thus, combination therapy of statin plus fenofibrate has not been shown to provide additional cardiovascular benefit above statin therapy alone and is not generally recommended[10,13].

ARE ACEI OR ARB RECOMMENDED FOR THE PRIMARY PREVENTION OF DIABETIC KIDNEY DISEASE?

In determining the initial choice of antihypertensive treatment, multiple trials powered for kidney outcomes demonstrate an advantage of renin-angiotensin system inhibition for slowing progression of CKD and reducing proteinuria in patients with diabetes. All of the appropriately powered trials that demonstrate this effect are in individuals with advanced Stage 3 CKD who also had proteinuria above 500 mg/day[5], The role of specific interruption of the renin-angiotensin system in the prevention and management of early diabetic nephropathy remains controversial with disappointing results[14,15]. To further puzzle this failure to outcomes the relationship between macroalbuminuria and progression of CKD is not always very obvious. For example, in the DCCT/EDIC cohort, the risk of progression from macroalbuminuria to impaired GFR was not absolute: the majority of people with incident macroalbuminuria maintained an eGFR≥60 ml/min through 15 years of follow-up, suggesting that macroalbuminuria does not represent an intractable course to GFR loss. Reductions in AER were also common, with more than one half of participants who developed macroalbuminuria regressing to persistent AER ‹300 mg/d 10 years after macroalbuminuria diagnosis 16. Not all patients with albuminuria will undergo progressive kidney dysfunction, and not all diabetic patients with progressive kidney impairment will develop albuminuria. Albuminuria in T2DM, as in T1DM, may regress, persist, or progress (respectively 31%, 38%, and 31%) as exhibited in the Steno-2 study[17].

Some of the albuminuria reduction can occur during treatment with renin-angiotensin inhibitors, through haemodynamic mechanisms without improving underlying pathology[16]. Further, the combined use of an ACEI and ARB did not show additive benefits in reducing progression of diabetic nephropathy. The ONTARGET trial, which included patients with and without diabetes, demonstrated that

although a combination of ramipril and telmisartan decreased proteinuria compared with monotherapy with either agent, a worsening of CKD progression with the combination of an ARB and an ACEI was observed[18]. The VA NEPHRON-D trial, which compared therapy with losartan and lisinopril to losartan alone in patients with T2DM and macroalbuminuria (›300 mg/day), also failed to demonstrate benefit from combination therapy in slowing CKD progression or death[19]. Therefore, the assessment of albuminuria has limitations with respect to its specificity for diabetic nephropathy and prognostic value for kidney outcomes, and cannot be a validated surrogate for slowing nephropathy progression[20]. Thus, the use of renin-angiotensin inhibitors in diabetic patients without hypertension and albuminuria is not recommended[21].

WHICH OF THE DRUGS IS MORE EFFECTIVE, ACEIS OR ARBS?

Adequately powered head-to-head trials comparing the effectiveness of ACEIs with ARBs in the reduction of vascular diabetic complications are limited. A Cochrane review demonstrated in patients with diabetes mellitus and normoalbuminuria that ACEIs prevent new onset DKD and death, while more data are needed to clarify the role of ARBs in preventing DKD[22]. In another recent meta-analysis, ACEIs significantly reduced the risk of all-cause mortality by 13%, cardiovascular deaths by 17%, and major cardiovascular events by 14%, including myocardial infarction by 21% and heart failure by 19%, whereas ARBs had no benefits on these outcomes. Both ACEIs and ARBs were not associated with a decrease in the risk for stroke in patients with diabetes[23]. Thus, the most benefit of ACEIs, compared with ARBs, in cardiovascular and renal outcomes suggest that they should be considered as first-line therapy in diabetic patients.

In conclusion, more research is necessary to understand the pathogenesis of diabetes to address the root causes. Until then we must focus on implementing evidence-based prevention and treatment approaches in determining how to best use the currently available tools.

Conflict of interest statement: None declared.

Key points

- The DKD risk is reduced by the control of hypertension and hyperglicaemia
- In T2DM, the prevention of CVD, a major cause of death in DKD, centres upon management of hypertension and dyslipidaemia.
- In elderly and/or frail people intensive and thigh glycaemic control regimens may be harmful.
- Add fenofibrate to statin do not reduce CVD and can increase creatinine serum.
- ACEis or ARBs are not recommended for the primary prevention of DKD in diabetics who have normal blood pressure and normoalbuminuria.
- ACEIs seem to reduce more CVD and DKD than ARBs.
- The combined use of an ACEI and ARB did not show additive benefits in reducing progression of diabetic nephropathy and may be harmful.

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