EFFECTS OF TIGHT GLUCOSE CONTROL ON ONSET AND PROGRESSION OF KIDNEY DISEASE IN ADULTS WITH DIABETES: A META-ANALYSIS OF RANDOMIZED TRIALS

M Ruospo[1], V Saglimbene[1,2], SC Palmer[3,4], S De Cosmo[5], A Pacilli[5], O Lamacchia[6], M Cignarelli[6], P Fioretto[7], M Vecchio[8], JC Craig[2], GFM Strippoli[1,2,4,9]

[1]Diaverum Medical Scientific Office, [2]University of Sydney, [3]University of Otago, [4]Cochrane Kidney and Transplant, [5]Scientific Institute CSS, [6]University of Foggia, [7]University of Padova, [8]Danone Research and [9]University of Bari

Background

Diabetes is the leading cause of end-stage kidney disease (ESKD) around the world. Blood pressure lowering and glucose control treatments are used to prevent diabetes-associated disability including kidney failure. However there is a lack of an overall evidence summary of the optimal target range for blood glucose control to prevent kidney failure. We aimed to evaluate the benefits and harms of intensive (HbA1C below 7% of fasting glucose levels <120 mg/dl [6.7 mmol/l]) versus standard glycemic control (HbA1C 7% or higher or fasting glucose levels 120 mg/dl [6.7 mmol/l] or higher) for preventing the onset and progression of kidney disease for adults with diabetes.

Methods

Using standard Cochrane methods, we did a systematic review and meta-analysis of randomized controlled trials that evaluated intensive versus standard glycemic control administered to adults and children with type 1 or type 2 diabetes with or at risk of kidney disease. Intensive glycemic control was defined by a treatment targeting an HbA1c below 7% or fasting glucose levels <120 mg/dL. Summary estimates of effect were calculated using a random-effects model. Confidence in the evidence was assessed using GRADE.

Results

Fourteen studies involving 29,319 people with diabetes were included and 11 studies involving 29,141 people were included in our meta-analyses. Treatment duration was 56.7 months on average (range 6 months to 10 years). Studies included people with a range of kidney function. Incomplete reporting of key methodological details resulted in uncertain risks of bias in many studies. Using GRADE assessment, we had moderate confidence in the effects of glucose lowering strategies on ESKD, all-cause mortality, myocardial infarction, and progressive protein leakage by kidney disease and low or very low confidence in effects of treatment on death related to cardiovascular complications and doubling of serum creatinine (SCr).

For the primary outcomes, tight glycemic control may make little or no difference to doubling of SCr compared with standard control (4 studies, 26,874 participants: RR 0.84, 95% CI 0.64 to 1.11; I2= 73%, low certainty evidence), development of ESKD (4 studies, 23,332 participants: RR 0.62, 95% CI 0.34 to 1.12; I2= 52%; low certainty evidence) **(Figure 1)**, all-cause mortality (9 studies, 29,094 participants: RR 0.99, 95% CI 0.86 to 1.13; I2= 50%; moderate certainty evidence), cardiovascular mortality (6 studies, 23,673 participants: RR 1.19, 95% CI 0.73 to 1.92; I2= 85%; low certainty evidence), or sudden death (4 studies, 5,913 participants: RR 0.82, 95% CI 0.26 to 2.57; I2= 85%; very low certainty evidence) **(Table 1)**. People who received treatment to achieve tighter glycemic control probably experienced lower risks of non-fatal myocardial infarction (5 studies, 25,596 participants: RR 0.82, 95% CI 0.67 to 0.99; I2= 46%, moderate certainty evidence), onset of microalbuminuria (4 studies, 19,846 participants: RR 0.82, 95% CI 0.71 to 0.93; I2= 61%, moderate certainty evidence), and progression of microalbuminuria (5 studies, 13,266 participants: RR 0.59, 95% CI 0.38 to 0.93; I2= 75%, moderate certainty evidence). In absolute terms, tight versus standard glucose control treatment in 1,000 adults would lead to between zero and two people avoiding non-fatal myocardial infarction, while seven adults would avoid experiencing new-onset albuminuria and two would avoid worsening albuminuria.

Figure 1. Doubling of serum creatinine and development of ESKD

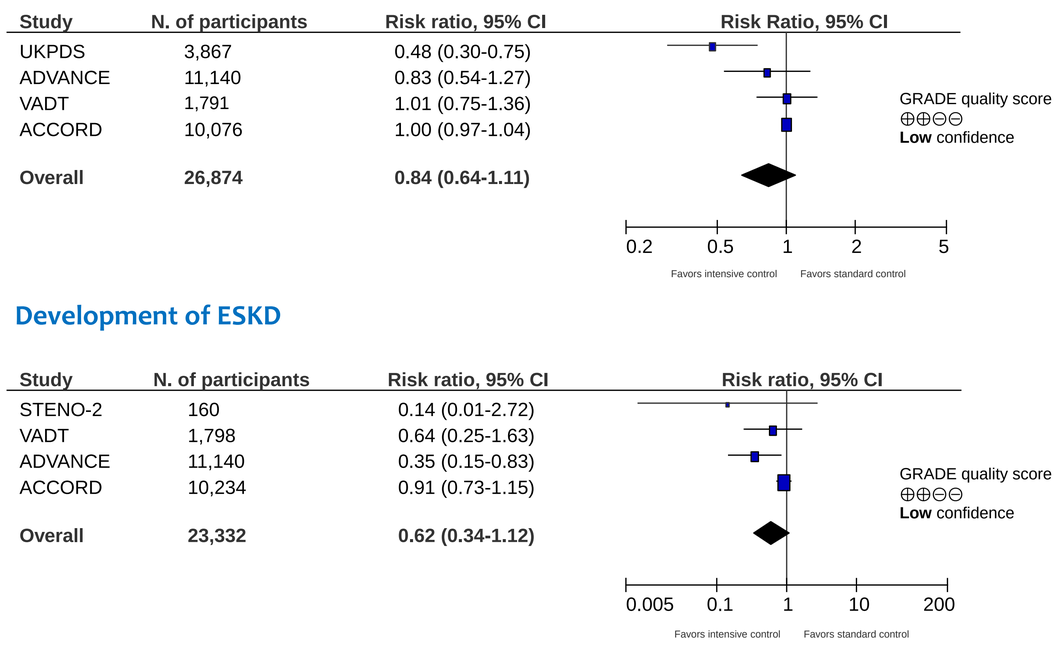

Table 1. Cardiovascular outcomes

Outcomes	No. of studies	No. of participants	No. of events	Risk ratio (95% CI)
All-cause mortality	9	29,094	2,748	0.99 (0.86, 1.13)
Cardiovascular mortality	6	23,673	930	1.19 (0.73, 1.92)
Sudden death	4	5,913	60	0.82 (0.26, 2.57)
Fatal myocardial infarction	3	14,220	339	1.11 (0.76, 1.62)
Fatal stroke	3	15,909	88	1.11 (0.71, 1.75)
Non-fatal myocardial infarction	**5**	**25,596**	**1,051**	**0.82 (0.67, 0.99)**
Non-fatal stroke	5	25,596	733	0.94 (0.68, 1.31)

Conclusion

This review suggests that people who receive intensive glycemic control for treatment of diabetes had comparable risks of kidney failure, death and major cardiovascular events as people who received less stringent blood glucose control, while experiencing small clinical benefits on the onset and progression of microalbuminuria and myocardial infarction. The adverse effects of glycemic management are uncertain. Based on absolute treatment effects, the clinical impact of targeting an HbA1c < 7% or blood glucose < 6.6 mmol/L is unclear and the potential harms of this treatment approach are largely unmeasured.

W kidneyandtransplant.cochrane.org
T @CochraneKidney
E gfmstrippoli@gmail.com
DOI 10.1002/14651858.CD010137.pub2