Diabetes mellitus: effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on cardiovascular events and mortality

A meta-analysis has reported that angiotensin-converting enzyme (ACE) inhibitor therapy reduced the risk of death from any cause or cardiovascular death in people with type 1 or type 2 diabetes. Angiotensin receptor blocker (ARB) therapy did not reduce these risks. This study has limitations and should not influence clinical practice. Clinicians should continue to follow NICE guidance for the use of renin-angiotensin system drugs as outlined below.

Overview and current advice

Diabetes mellitus is a group of metabolic disorders in which blood glucose is persistently raised. People with type 1 and type 2 diabetes mellitus are at increased risk of developing microvascular and macrovascular complications, including renal disease, retinopathy, cardiovascular and cerebrovascular disease.

The renin-angiotensin system is a major regulatory system of cardiovascular and renal function, and the renin-angiotensin system drugs, ACE inhibitors or ARBs, are used in a wide range of indications including hypertension, heart failure, treatment after a myocardial infarction, chronic kidney disease and type 1 and type 2 diabetes.

NICE clinical guideline 15 (July 2004) Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults, (currently being updated, publication expected August 2015) recommends that ACE inhibitors should be started and, with the usual precautions, titrated to full dose in all adults with confirmed nephropathy (including those with microalbuminuria alone) and type 1 diabetes. If ACE inhibitors are not tolerated, ARBs should be substituted. Combination therapy with an ACE inhibitor and an ARB is not recommended in people with type 1 diabetes.

NICE clinical guideline 87 (May 2009) Type 2 diabetes: The management of type 2 diabetes (currently being updated; publication expected August 2015) recommends that first-line blood-pressure-lowering therapy should be a once-daily, generic ACE inhibitor. Exceptions to this are people of African-Caribbean descent or women for whom there is a possibility of becoming pregnant. If the person has continuing intolerance to an ACE inhibitor (other than renal deterioration or hyperkalaemia), then change to an ARB. The guideline makes no recommendation on dual blockade with renin-angiotensin drugs however more recent guidance from the Medicines and Healthcare
products Regulatory Agency (MHRA) states that dual therapy with an ACE inhibitor plus an ARB is not recommended in people with type 2 diabetes. See the Medicines Evidence Commentary Efficacy and safety of dual blockade of the renin angiotensin system for more information.

‘Renin-angiotensin system drugs’ is included in NICE Key therapeutic topics - Medicines management options for local implementation.

The NICE Pathway: diabetes brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

**New evidence**

A meta-analysis has assessed the effects of ACE inhibitors and ARBs on all-cause mortality and cardiovascular outcomes in people with type 1 and type 2 diabetes (Cheng et al. 2014)\(^1\). It included 35 randomised controlled trials (RCTs), including 56,444 people, with study follow-up ranging from 12 months to 9 years. The meta-analysis included studies in both type 1 and type 2 diabetes (or mixed populations) and no stratification by type of diabetes mellitus was conducted.

Control therapy included placebo and active treatments; in 1 study ACE inhibitors and ARBs were compared directly. There was a wide variation in the studied populations, including different ACE inhibitors, ARBs and dosages; different defined parameters (for example HbA\(_1c\), and blood pressure targets); different lengths of studies, use of background therapies and baseline risk. For example, more people with established cardiovascular disease were included in the ACE inhibitor trials than the ARB trials, and the ACE inhibitor group included a larger number of studies (23 compared with 13) and people (32,827 compared with 23,867).

For the primary outcome of all-cause mortality, there was a statistically significant reduction in risk with ACE inhibitors compared with control therapy (relative risk [RR] 0.87, 95% confidence interval [CI] 0.78 to 0.98; \(p=0.02\); 20 RCTs, \(n=25,544\)). There was no statistically significant reduction in the risk of all-cause mortality with ARBs compared with control therapy (RR 0.94, 95% CI 0.82 to 1.08; \(p=0.39\); 11 RCTs, \(n=17,334\)).

For the primary outcome of cardiovascular death, ACE inhibitor therapy produced a statistically significant reduction in risk compared with control therapy (RR 0.83, 95% CI 0.70 to 0.99; \(p=0.04\); 13 RCTs, \(n=24,334\)). ARB therapy did not reduce this risk compared with control therapy (RR 1.21, 95% CI 0.81 to 1.80; \(p=0.35\); 7 RCTs, \(n=10,801\)). Heterogeneity was moderate in the ACE inhibitor trials, but was significant in the ARB trials.

For the primary outcomes of all-cause mortality and cardiovascular death, the results were similar when ACE inhibitors and ARBs were compared with placebo or active treatment, and there was no evidence of publication bias.

Secondary outcomes of the effects of ACE inhibitors and ARBs on the occurrence of major cardiovascular events (composite of cardiovascular death, non-fatal myocardial infarction, stroke, congestive heart failure and coronary artery bypass grafting or percutaneous coronary intervention) and cause-specific cardiovascular outcomes were also included in the analysis. Compared with control therapy, ACE inhibitors statistically significantly reduced the risk of major cardiovascular events, myocardial infarction and heart failure, but not stroke. ARB therapy did not statistically significantly reduce the risk of major cardiovascular events; myocardial infarction or stroke compared with control therapy, but did statistically significantly reduce the risk of heart failure.
Commentary

Commentary provided by Professor Philip Home. Professor of Diabetes Medicine, Newcastle University

There are a number of limitations with this paper. Whilst data are presented for ACE inhibitors compared with control therapy and ARBs compared with control therapy, the data presented do not support any differences between ACE inhibitors and ARBs on all-cause mortality, cardiovascular deaths or cardiovascular events for people with diabetes. The authors do not test any hypothesis that ACE inhibitors differ from ARBs. For example the results for all-cause mortality with ACE inhibitors compared with active treatment (RR 0.80, 95% CI 0.60 to 1.08) are very similar and not statistically significantly different from ARBs compared with active treatment (RR 0.82, 95% CI 0.62 to 1.09).

The investigators appear to make errors. The intervention in the ADVANCE study was not perindopril but perindopril plus indapamide. If this largest weighted study was removed from the mortality meta-analysis, the reductions in all-cause mortality with ACE inhibitors compared with placebo or compared with all control therapy may no longer be statistically significant. They also included UKPDS data from the UKPDS 39 paper (captopril vs atenolol), not the UKPDS 38 study which had the primary randomisation (captopril or atenolol vs lifestyle only) and which had very positive clinical outcomes; this may be expected to have biased their findings.

Issues also arise over the clinical heterogeneity of the included studies. It is not correct to combine data from populations of people with type 1 and type 2 diabetes. These are different conditions with very different cardiovascular profiles. Type 1 diabetes is a hormone deficiency disease with high HDL-cholesterol levels and cardiovascular disease in association with renal disease. On the other hand, type 2 diabetes is a metabolic condition with low HDL-cholesterol levels and endemic cardiovascular disease. The indications for renin-angiotensin system drug use are different for the most part (microvascular protection in type 1 diabetes and antihypertensive in type 2 diabetes).

The study populations are different in the included studies, and can be expected to respond differently to secondary prevention drugs. This should caution against combining the data. ADVANCE, for example, was a study in people with late stage type 2 diabetes with extant cardiovascular disease or a high risk of cardiovascular disease, while UKPDS was a study in people with newly diagnosed type 2 diabetes.

Renin-angiotensin system drugs are prescribed in type 2 diabetes primarily to reduce blood pressure for renal protection and stroke protection. Findings in regard of all-cause mortality, cardiovascular mortality, and MI would really be only of interest if there were a large protective effect, or an adverse effect, which is not the case here. In type 1 diabetes, the indications for renin-angiotensin system blockade are diabetic nephropathy (including hypertension in diabetic nephropathy). The results of this meta-analysis should not influence clinical practice, and clinicians should continue to follow NICE guidance for the use of renin-angiotensin system drugs as outlined above.

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References

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