Introduction
Hypertension is a risk factor for the development of diabetic microvascular and macrovascular complications. In the UK diuretics are recommended as possible second line therapy after an ACE-inhibitor or angiotensin-II receptor blocker in patients with diabetes and hypertension. Bendroflumethiazide is the most commonly prescribed diuretic, but there are concerns about side effects such as hypokalaemia, glucose intolerance, dyslipidaemia and hyperuricaemia. Indapamide was synthesised by Servier Laboratories in 1969 as part of a programme to produce a sulphonamide that would dissociate the thiazide-like antihypertensive effects from the diuretic effects, with the intention of creating a drug with less side effects.

Pharmacology
Figure 1 outlines the pharmacological action of indapamide. Indapamide is a 2-methyl indoline derivative of 4-chloro-3-sulfamoyl benzamide. It is referred to as a thiazide-like diuretic as it lacks the benzothiadiazine heterocycle seen with the thiazide group of drugs, although it retains a sulphonamide moiety. The molecular mechanism of action is similar to the thiazide diuretics. It inhibits sodium and chloride reabsorption from the distal convoluted tubule by blocking the sodium/chloride co-transporter (symporter). Dose response studies have shown that indapamide lowers blood pressure (BP) at doses below that needed to elicit a diuresis, and appears to have antihypertensive effects other than diuresis, though this may also hold true in the mechanism of action of thiazide diuretics. It is also thought to have effects on vascular smooth muscle by decreasing inward calcium currents and decreasing vascular reactivity to vasoactive substances such as norepinephrine and angiotension II.

Indapamide is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations are seen 1–2 hours after dosing. Because of its long half-life it is effective in once-daily dosing. Indapamide is extensively metabolised, with only about 7% of the total dose administered recovered in the urine as unchanged drug during the first 48 hours after administration. It is usually 10–12 weeks before treatment effect is seen. It is commercially available as indapamide 2.5mg (non-proprietary); Natrilix 2.5mg (Servier), Natrilix SR 1.5 mg, or in combination with perindopril as Coversyl Plus (perindopril 4mg and indapamide 1.25mg, Servier).

Specific evidence for use in diabetes
Indapamide has been used in trials examining the effect on microvascular and macrovascular complications in people with diabetes and hypertension. These trials have tended to use indapamide in combination with perindopril, and have generally shown positive results.

Trials of safety and efficacy
Several studies in the late 1970s demonstrated that indapamide was an effective antihypertensive drug, which was well tolerated and free of significant side effects. A very small (20 patients) randomised trial comparing indapamide and bendroflumethiazide found significant reductions in BP in both groups but no difference between the groups. Both groups had small but significant decreases in potassium.
Regression (PREMIER) study compared diabetes and hypertension over 52 weeks. The combination arm had a reduction in BP of 6/2 mmHg and a relative risk reduction of 9% in total macrovascular and microvascular events, but there was no significant difference for macrovascular or microvascular events separately. Significant reductions were seen in total mortality and cardiovascular mortality, and in the development of microalbuminuria. There was no statistical difference in cerebrovascular or eye events. It is noteworthy that greater than 50% of the patients in the control group were taking open-label perindopril by the end of the study, making the major difference in treatment between the two arms being the use of indapamide (or, put another way, combination treatment vs perindopril on its own).

Discussion
These trials raise a number of interesting issues regarding indapamide, but their design means many questions are left unanswered. In each of the studies the reduction in BP was greater in the study group compared to the control groups. In PREMIER, there was a greater reduction in microalbuminuria with perindopril + indapamide compared to enalapril, but the authors claim that these differences persisted after correction for BP differences. In NESTOR, indapamide alone was more effective at lowering BP than low-dose enalapril, leading to the same reduction in microalbuminuria. In PROGRESS, perindopril + indapamide reduced strokes compared to placebo, and in ADVANCE, perindopril + indapamide reduced mortality compared to placebo. In each of these studies the BP differences may be sufficient to explain the benefits demonstrated. Small but significant deteriorations in HbA1c % and lipid profiles were observed with indapamide in some of these studies, and it is uncertain if this would have a significant adverse effect on long-term cardiovascular prognosis. Despite the favourable outcomes in these trials there is not enough evidence to support indapamide as the diuretic drug of choice in managing hypertension in patients with diabetes when there are no comparative trials with other diuretics.

Conflict of interest statement
Glasgow Royal Infirmary was a centre in the ADVANCE study, and Dr Fisher was the principal investigator for the centre. Dr McKay was a co-investigator in the ADVANCE study when he previously worked as a Consultant Physician at Monklands Hospital, Airdrie.

References