We appreciate Andrew Redd’s suggestion to offer the full HIV prevention package to all study participants, but recognise that in doing so, the study’s ability to detect an effect could be reduced, an issue that has affected previous trials and one which might be particularly salient given that the effect estimate in the general population might not exceed 1·5.1

All those involved in this debate have the best interests of women in mind; we simply differ on the path forward. As the recent pre-exposure prophylaxis trials have shown, it is possible to spend tremendous resources on a trial that yields results that, given low adherence, leave lingering questions on underlying effects and are thus difficult to translate into practice or policy. In this situation, perhaps an effectiveness study with randomisation at the community or group level might prove more informative. The reality is that resources are limited and continued efforts to broaden women’s contraceptive options and increase demand and supply for existing Tier 1 methods must not be overshadowed by the proposed trial.

We declare that we have no conflicts of interest.

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1 Ralph LJ, McCoy SI, Hallett T, Padian N. Next steps for research on hormonal contraception and HIV. Lancet 2013; 382: 1467–69.


Linagliptin for elderly patients with type 2 diabetes

I read with great interest the report by Anthony Barnett and colleagues (Oct 26, p 1413) about their randomised controlled trial of linagliptin in elderly patients with type 2 diabetes. They concluded that linagliptin was effective for lowering glucose with similar safety to placebo. However, I have some concerns.

First, there is a risk of hypoglycaemia. Although there was no significant difference for hypoglycaemia between linagliptin and placebo (24·1% vs 16·5%), they studied a small patient population and the follow-up period was only 24 weeks.

Dementia is also a concern, although it is unclear whether patients with dementia were excluded. A recent meta-analysis of 0·9 million individuals by Goto and colleagues showed that severe hypoglycaemia is strongly associated with a higher risk of cardiovascular disease (relative risk 2·05), and Yaffe and colleagues reported that patients experiencing hypoglycaemia had a two-times higher risk of developing dementia than had those without hypoglycaemia.

Older adults with diabetes who developed dementia had a greater risk of subsequent hypoglycaemic events than had those who did not (hazard ratio 3·1). Accordingly, avoidance of severe hypoglycaemia is important. Furthermore, the American Diabetes Association stated that glycaemic targets must be individualised and less stringent glycated haemoglobin A1c goals (eg, 7·5–8·0% or higher) are acceptable for older adults (>65–70 years) who often have atherosclerotic disease, reduced renal function, and various comorbidities.

In my opinion, physicians should carefully consider the risks and benefits of treatment, rather than focusing on glycated haemoglobin A1c levels. I declare that I have no conflicts of interest.

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The conclusion by Anthony Barnett and colleagues that in elderly patients with type 2 diabetes the safety profile of linagliptin is similar to placebo, is misleading. As shown in table 3, drug-related adverse events, serious adverse events, hospital admission, and adverse events leading to discontinuation of the drug were higher in the linagliptin group than in the placebo group. Barnett and colleagues suggested that these adverse events were not related to the drug under study. However, in randomised trials, all intervention groups are treated identically except for the experimental treatment. Therefore, all the adverse events should be due to the study treatment, which might be a known or an unknown effect of the study treatment.

In addition, it is not clear how many patients discontinued the study drug due to adverse events. According to table 3, eight patients discontinued the study drug due to adverse events,
but in the results section, it seems that only one patient discontinued because of side-effects.

I declare that I have no conflicts of interest.

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Anthony Barnett and colleagues recently reported the results of a trial comparing linagliptin with placebo in elderly patients with type 2 diabetes. They note that the higher incidence of hypoglycaemia with linagliptin, although not statistically significant, was mainly recorded in patients receiving sulfonylureas; hypoglycaemia was much the same between groups in patients not receiving sulfonylureas. The authors conclude that hypoglycaemia in patients receiving linagliptin is driven by sulfonylureas. However, it could similarly be argued that an excess of hypoglycaemia in patients receiving sulfonylureas is driven by linagliptin, because this excess is observed when both drugs are associated. This can be seen in Barnett and colleagues’ figure S5, and more easily if we present the same data as shown in our figure.

It is expected that drugs stimulating insulin secretion induce hypoglycaemia and that giving two of these drugs increases the risk. Barnett and colleagues’ safety results confirm that giving both linagliptin and sulfonylureas has an increased risk of hypoglycaemia that should be considered carefully in elderly patients. This finding should not be minimised because of statistical interpretation, but should be emphasised because it is of clinical importance.

FS is a consultant for YOLORx Consultants. NM has received honoraria from Pfizer, Servier, Pierre Fabre, Roche, Merck Serono, Novartis, AstraZeneca, Abbott, Acton, Bristol-Myers Squibb, Celgene, Cephalon, Vivatec, Lundbeck, GlaxoSmithKline, Leo Pharma, Helsinn Healthcare, Onion, Genevieve, Takeda, Sanofi, and Johnson and Johnson. AP declares that he has no conflicts of interest.

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Authors’ reply

We read with interest the Comment by Alan Sinclair and John Morley, and the Correspondences from Tomohide Yamada, Rahman Shah, and Francesco Salvo and colleagues on our Article describing a randomised study of linagliptin, a dipeptidyl peptidase-4 (DPP4) inhibitor, in elderly patients (≥70 years) with type 2 diabetes.

Although we largely agree with Sinclair and Morley’s comments, we would like to offer the following observations. They challenge the necessity of lowering glycated haemoglobin (HbA₁c) levels towards 7-0% and indicate that such attempts might lead to harmful overall outcomes in elderly patients. This argument reflects the current debate regarding the appropriate target for glycaemic control in older adults. There is general consensus that hyperglycaemia leading to symptoms or risk of acute hyperglycaemic complications should be avoided in all patients. Beyond this concept, however, the scarcity of clinical studies in elderly patients means that guideline recommendations remain vague. Thus, recommendations are based on individualised assessments of the likely benefit to risk profile of the intervention. These assessments should consider factors such as susceptibility to hypoglycaemia, ability to self-manage, presence or absence of other disorders, cognitive status, and life expectancy of the patient.

Recent evidence, however, has linked hyperglycaemia to an increased risk of dementia, an observation that might argue against generally higher targets for HbA₁c in elderly people. Moreover, the general concern about stricter HbA₁c control is largely based on studies that used glucose-lowering drugs with relatively high risk of hypoglycaemia. Thus, hypoglycaemia might outweigh the benefits of intensive glycaemic control, particularly in patients of older age and frail. This illustrates the dilemma of poor health outcomes with either hyperglycaemia or hypoglycaemia in older adults with diabetes. This burden, however, might be alleviated by using pharmacotherapies that could improve glycaemic control with low risk of hypoglycaemia or other adverse effects. We thus concur with Sinclair and Morley that...