Prevention of diabetes? Dream on!

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For more information on the DREAM study, see page 156.

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'Superpill will save millions', screamed the headline in the tabloid on the newsstand. Intrigued, I took a closer look and was amazed to find that 'diabetes can be prevented' by a 'new pill unveiled today'. The reference, it turned out, was to the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) study, the results of which were announced at the *42nd Annual Meeting of the European Association for the Study of Diabetes*, in Copenhagen.

The DREAM study was seeking to plug a hole in our knowledge with regard to the therapeutic efficacy of two commonly used drug classes, angiotensin-converting enzyme (ACE) inhibitors and glitazones, with respect to their effects on progression from impaired glucose metabolism to type 2 diabetes.

A number of studies over the past few years have confirmed the primary importance of diet and exercise in reducing progression to type 2 diabetes (58% relative risk reduction in both the Diabetes Prevention Program [DPP; Knowler et al, 2002] and the Finnish Diabetes Prevention Study [Tuomilehto et al, 2001]). Studies have also suggested that agents used conventionally for treating diagnosed type 2 diabetes may have a role to play in diabetes prevention (31% relative risk reduction with metformin in the DPP [Knowler et al, 2002] and 25% relative risk reduction with acarbose in the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus [STOP-NIDDM; Chiasson et al, 2002] for progression to type 2 diabetes). Finally, studies have hinted at a promise of reduction in incidence of type 2 diabetes with the use of ACE inhibitors (34% relative risk reduction in a post-hoc analysis of the Heart Outcomes Prevention Evaluation [HOPE] study [Yusuf et al, 2001]) and glitazones (55% relative risk reduction in a very high-risk population seen in the Troglitazone in Prevention of Diabetes [TRIPOD] study [Buchanan et al, 2002]), but we have lacked definitive trial evidence to support their potential use until now.

The DREAM study, therefore, hoped to provide the definitive evidence to support the efficacy of ramipril, rosiglitazone or both in preventing type 2 diabetes.

The DREAM study: Design and major findings

In this massive study, 5269 people were enrolled and followed for a period of around 3 years. In a 2-by-2 factorial study design, they were treated with rosiglitazone, ramipril, rosiglitazone and ramipril, or placebo. The primary outcome measure was progression to type 2 diabetes; a combined cardio-renal endpoint relating to complications was also measured.

For rosiglitazone-containing regimens, relative risk reduction in progression to diabetes was a significant 62%; for ramipril-containing regimens it was a non-significant 9%. The results for ramipril were slightly disappointing; however, the trend suggested that if the study had continued beyond 3 years, then significance would have been reached.

The rosiglitazone result was less surprising. It had been widely expected, and some people, myself included, had forecast even larger reductions in progression to diabetes.

The DREAM study: Potential impact on practice

So what does this study add to our knowledge? Certainly, the safety data were impressive, although, once again, the spectre of heart failure was lurking in the background. Overall, the cardiovascular events did not reach significance, and data from the wash-out part of the study will be useful.

But will it change practice? Will we develop strategies to seek out the estimated 14% of the population who have impaired glucose metabolism and put them all on medication to prevent two-thirds from progressing to diabetes? I think not. This would require, in the first instance, a cohesive screening policy – this is notably absent. It would also seek to ignore the almost equivalent benefit from intensive lifestyle change, demonstrated in previous studies. After the DPP, did metformin have a new licensed indication for prevention of diabetes?

Prevention of diabetes is a problem for governments to tackle – it will require a different approach from policies on education, on nutrition, on transport, on working conditions, on housing, or on commerce.

The impact of DREAM on clinical practice will be to underline the safety of this class of drugs, and to suggest that the drugs have a mode of action which might place them higher up the treatment algorithm to second line after metformin, or even first line.

Concluding remarks

Like the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), this study asks more questions than it answers. Further work is needed to establish whether the insulin sensitisers will lead to a reduction in the cardiovascular diseases which kill up to 75% of people with type 2 diabetes.

A Diabetes Outcome Progression Trial (ADOPT) will be presented in December at the *19th World Diabetes Congress* in Cape Town. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study will report in 2008. Perhaps then we will have the answers we need. Until then, DREAM on. ■