Diabetes

# ROADMAP – fact and fallacy in one paper

**Prof Eoin O'Brien** takes a close look at findings of the ROADMAP study, which has recently been published

The Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study has recently been published in the prestigious *New England Journal of Medicine*. ROADMAP was a multicentre, multinational trial, in which nearly 4,500 patients with type II diabetes without microalbuminuria were randomly assigned to receive 40mg of olmesartan, an angiotensin receptor antagonist (ARB), once daily, or placebo.

It is indeed interesting that reputable scientific investigators and a journal of the such international standing can incorporate in one article a scientific finding of major importance, while at the same time failing to explore what is likely to be a a blatant scientific fallacy.

Patients with either type I or type II diabetes mellitus are at high risk for chronic kidney disease, which is usually first evident with the onset of microalbuminuria. There is convincing epidemiologic evidence that in patients with diabetes who also have microalbuminuria, renal impairment and cardiovascular events occur earlier than they do in patients with diabetes who do not have microalbuminuria.

Diabetes patients are at high risk for chronic kidney disease

In ROADMAP, patients with diabetes who were given olmesartan 40mg daily had a delayed onset of microalbuminuria, even though blood pressure (BP) control in both groups was excellent according to conventional BP measurement. The important conclusion, therefore, is that olmesartan protects diabetic patients from developing renovascular disease.

This finding is not unexpected, but it is important confirmatory evidence in a large, well-conducted trial that now firmly establishes that patients with diabetes, especially those with hypertension, should be treated with the ARB, olmesartan, so as to protect them from the structural renal damage that is an almost inevitable consequence of diabetes.

## Scientific fallacy

So far, so good. The ROADMAP study then goes on to state: "The higher rate of fatal cardiovascular events with olmesartan among patients with pre-existing coronary heart disease is of concern." This statement is based on the fact that although non-fatal cardiovascular mortality was decreased, the occurrence of fatal cardiovascular events was increased in a small number of patients – 15 patients in the treatment arm versus three in the placebo arm – from the study cohort of 4,447 patients.

The authors admit that the study was hopelessly underpowered to draw any conclusions from this perplexing observation, which is all the more difficult to explain given the reduction in non-fatal cardiovascular events.

They state: "Owing to the very small number of affected patients, it is difficult to interpret this unexpected finding, and it may simply be related to chance. Nevertheless, because of its potential significance, several exploratory analyses were performed."

Surprisingly, these exploratory analyses do not include analysis of a sub-study cohort of 568 patients in whom ambulatory blood pressure measurement (ABPM) was performed. If indeed there is an explanation for the small excess of cardiovascular deaths in the treated patients, it will most likely be found in an excessive reduction in nocturnal BP in the treated patients, 35 per cent of whom had pre-existing cardiovascular disease and were therefore likely to have had a compromised coronary or cerebrovascular circulation, rendering them susceptible to nocturnal hypotension that the high dose of olmesartan may have induced.

## 24-hour monitoring

In this regard, one is put in mind of the HOPE (Heart Outcomes Prevention Evaluation) study, in which the importance of 24-hour BP coverage was well illustrated. In the main study, the group receiving ramipril had approximately 35 per cent fewer cardiovascular events, despite an insignificant reduction in BP of 3/2 mmHg; the outcome benefit was attributed to ACE inhibition, which was recommended in all high-risk patients regardless of baseline BP.

However, it became evident from a later analysis of the ABPM substudy that ramipril was actually taken in the evening, with clinic BP measured some 10-to-14 hours later the following day. The reported insignificant change in BP reported in the main study gave no indication of a whopping 17/8 mmHg reduction in BP during the night-time period, which translated into a 10/4 mmHg average reduction in BP over the entire 24-hour period.

This lesson in scientific bungling should be taken to heart by both the investigators of ROADMAP and the FDA, which is now investigating the excess of cardiovascular deaths in the study.*

However, the lesson for us practising physicians is that even if olmesartan did carry a small cardiovascular risk, the conferring of renal protection by olmesartan in diabetic patients is such that the benefit far outweighs the small and disputed risk that in all likelihood is due to chance.

**Since this paper was submitted for publication, the FDA has completed its assessment of olmesartan and stated in an alert: "After reviewing the results of the ROADMAP and ORIENT trials, the benefits of olmesartan continue to outweigh its potential risks when used for the treatment of patients with high blood pressure according to the drug label." Therefore, treatment with olmesartan should not be stopped or modified because of the spurious findings in the ROADMAP study.*

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