Niacin causes serious unexpected side-effects, but no worthwhile benefits, for patients who are at increased risk of heart attacks and strokes

Adding extended-release (ER) niacin to statins does not reduce the chances of high risk patients having a heart attack or stroke, Oxford University scientists leading the HPS2-THRIVE study have revealed at the ACC conference in San Francisco today.

In addition, the researchers report that the use of ER niacin causes a significant number of different types of serious side effect. Some of these side effects were already known to be caused by niacin, but some of them were unexpected.

Niacin has been used for many years to modify cholesterol levels in people at high risk of heart attacks and strokes. It is particularly widely used in the United States, although there is limited evidence that it reduces the risk of cardiovascular outcomes (e.g. heart attacks and strokes), especially when added to current cholesterol-lowering therapy. Flushing is a common side effect that reduces compliance with niacin therapy. In HPS2-THRIVE, the ER niacin was combined with a new drug called laropiprant (which is a prostaglandin receptor blocker) in order to reduce problems due to flushing.

Over 25,000 patients with pre-existing cardiovascular disease from the UK, Scandinavia and China were recruited into HPS2-THRIVE. They were all given simvastatin (plus, when required, another cholesterol-lowering drug called ezetimibe) as background treatment to reduce their initial cholesterol level. They were then assigned at random to receive either the ER niacin with laropiprant or a dummy (placebo) treatment for about 4 years. HPS2-THRIVE is, by far, the biggest study of niacin ever undertaken. The use of randomised treatment assignment, and the large size and long duration, make the findings very reliable.

The primary aim of the HPS2-THRIVE trial was to find out whether adding niacin to currently standard treatments (including effective statin-based cholesterol-lowering therapy) would produce worthwhile reductions in the risks of heart attacks, strokes or other cardiovascular outcomes. Among those who took the ER niacin combination 13.2% suffered a heart attack, stroke or had an arterial procedure compared with 13.7% in those who took the dummy (placebo) tablets – a small but not clearly significant difference.

Side effects previously found with niacin, which were also seen in HPS2-THRIVE, included skin rashes, gastro-intestinal (stomach) problems, complications with the management of pre-existing diabetes and increased risk of developing diabetes. The newly identified side effects were infections and bleeding (particularly in the gut and brain), neither of which had been clearly demonstrated with niacin previously.
The results in HPS2-THRIVE are consistent with the results from other trials of ER niacin. For example, the AIM-HIGH trial of ER niacin alone (i.e. without the addition of laropiprant) in 3,400 high-risk patients was stopped prematurely after 3 years because no beneficial effects on heart attacks and strokes were seen. The known side effects of ER niacin were also seen in AIM-HIGH. Further analyses of AIM-HIGH should be able to show if there are similar trends on bleeding and infections to those in HPS2-THRIVE.

The HPS2-THRIVE findings have resulted in the suspension by Merck & Co/MSD of the ER-niacin and laropiprant combination therapy from Europe and other countries where it had been approved for use. Although the combination therapy was not licensed in the US, regulatory authorities are now considering the implications of these results for the use of other forms of extended release niacin.

Principal Investigator Professor Jane Armitage, from Oxford University’s CTSU, said: “The use of niacin for the prevention of cardiovascular events should now be reconsidered. The HPS2-THRIVE trial shows that niacin causes significant hazards and does not reduce the number of people suffering heart attacks and strokes when added to treatments, such as cholesterol-lowering statin therapy, which are known to be safe and effective.”

With regard to the bleeding and infection, it seems likely that earlier studies of niacin were too small to detect these new side effects reliably. “The lack of benefit with niacin in HPS2-THRIVE is consistent with the result in AIM-HIGH. Similarly the risks of the known side-effects of niacin are consistent between HPS2-THRIVE and the other trials. Although it is a possibility that these new side effects are due to laropiprant rather than to niacin, we consider this to be unlikely,” Professor Armitage said.

Oxford University’s Dr Martin Landray, one of the other lead investigators, said: “We are disappointed that we have not been able to find a drug that helps patients further. However, it is just as important to find out about the hazards of a treatment, particularly for a drug as widely used as niacin.”

THRIVE also reported last month in the European Heart Journal that there was an increased risk of myopathy in Chinese participants, which was seen particularly in patients who took niacin as well as simvastatin.

Professor Armitage expressed her gratitude to all of the participants in the study. “Without their help we would not have been able to make this progress towards improving the care of people who have had, or are at risk of having, a heart attack or stroke,” she said.

HPS2-THRIVE was funded by a grant to Oxford University from Merck & Co, who also provided the ER niacin/laropiprant and matching placebo tablets, as well as background simvastatin or ezetimibe/simvastatin combination. However, the study was designed, conducted, analysed and interpreted independently by the investigators at Oxford University and the independent members of the study Steering Committee.