

# Ezetimibe

## (A Drug of Doubtful Value)

Ezetimibe is a cholesterol-lowering drug. It was assumed that a drug that reduced cholesterol would reduce deaths from heart disease and strokes. The question is: was this true?

But let's look at the history of cholesterol-reducing drugs. Except for statins, none of these drugs have ever been found to reduce deaths from heart disease and a long list have been tried. In fact, ezetimibe is an updated version of another drug cholestyramine. This has been investigated before and found to have no cardiovascular benefit.

The first trial to look ezetimibe was called the ENHANCE trial. The results were not promising. It was not an outcome trial but looked at whether those on the drug had less arterial thickening or atherosclerosis. **Arterial thickening developed twice as fast on those taking the drug.** Not surprisingly publication of the results was delayed for 20 months, until pressure from the US congress forced publication.

A similar trial has been done on patients with familial hypercholesterolaemia and again those on ezetimibe had more arterial thickening.

However, the proof of the pudding is an outcome trial. Did ezetimibe reduce cardiovascular deaths? The IMPROVE-IT trial was designed to answer just that question. It compared ezetimibe with ezetimibe combined with simvastatin. Those on ezetimibe plus simvastatin had much greater reductions of both cholesterol and LDL (sometimes caused bad cholesterol) which in theory should help. But did it?

You might wonder why they didn't just compare it with placebo. The reason was it was thought unethical not to give a statin.

IMPROVE-IT was a big expensive trial with 9000 subjects tested over 7.4 years. The result was that there were 537 deaths from cardiovascular disease for those using ezetimibe + simvastatin and 538 deaths for those on simvastatin alone. That was one less death in 66,000 years of treatment and this was not significant. **Basically, the trial showed that the drug had no benefit.** Despite the negative results this

didn't stop ezetimibe becoming a best-selling drug. You might wonder why?

The other outcome trial was the SHARP trial in chronic kidney disease but here simvastatin + ezetimibe was compared to placebo. There were less CV deaths in those taking the drug but it was impossible to say which drug had made a difference.

A trial of 1871 patients with ezetimibe and simvastatin in aortic stenosis revealed no benefit but a **60% increase in cancer**.

Adverse effects include fatigue, abdominal pain and diarrhoea. Given this drug has not been shown to have any cardiovascular benefit it has little to recommend it.