

Editorial

Surrogate v clinical: what's the outcome?

Recently published findings from the ENHANCE trial,^[1] which investigated the effect on atherosclerotic progression of adding ezetimibe to simvastatin, have highlighted the potential complexities of using surrogate outcomes as biomarkers for clinical events.

There is evidence that combining ezetimibe with a statin leads to a greater reduction in low-density lipoprotein (LDL) cholesterol levels compared with a statin alone.^{[2] [3][4]} The ENHANCE trial investigators reasoned that the greater reduction in LDL achieved with ezetimibe plus simvastatin should translate to a slower progression of atherosclerosis compared with simvastatin alone. They measured the change from baseline in carotid-artery intima-media thickness, a commonly used surrogate outcome for vascular disease, as a primary outcome. Unexpectedly, the trial found that, in people with familial hypercholesterolaemia, adding ezetimibe to simvastatin conferred no additional benefit — there was no significant difference in carotid-artery intima-media thickness between simvastatin plus ezetimibe and simvastatin alone 24 months after treatment.^[1] However, although not measured as a specified outcome of interest, the trial did find a significantly greater reduction in LDL cholesterol with combined therapy compared with simvastatin alone.

Controversy surrounding some aspects of the study prompted the drafting of a detailed assessment of the trial data by an independent panel as an adjunct to the trial results.^[5] One element discussed in this report, and in an accompanying editorial,^[6] was the validity of using rate of change of intima-media thickness as a surrogate outcome for clinical cardiovascular events. Associations between intima-media thickness and rate of stroke, angina pectoris, and MI have been reported,^[1] as has a strong correlation between change in intima-media thickness and change in LDL levels.^[7] In the case of trials assessing statins, change in intima-media thickness has been purported to meet clinically based criteria for a surrogate marker of cardiovascular outcome,^[8] and LDL cholesterol is routinely used as a key measure of atherosclerotic progression. It would therefore seem reasonable to infer that intima-media thickness and LDL cholesterol levels complement each other as surrogate outcomes for CVD.

So, how do we reconcile the findings from the ENHANCE trial with the predicted correlation of LDL cholesterol and intima-media thickness? Ezetimibe functions by blocking absorption of LDL cholesterol rather than by increasing LDL cholesterol clearance. So, ezetimibe might affect biological pathways, distinct from those affected by statins, which might not translate to changes in intima-media thickness. This is a key problem when interpreting the results of surrogate outcomes — their potential for generating false positive and false negative results. If the intervention has a beneficial effect on the surrogate outcome but a detrimental effect on another biological process, then the outcome measured would appear to show a positive effect, and the negative effect would not be detected. Conversely, a positive effect on an outcome not being measured could be overlooked. However, it may be that either LDL cholesterol levels or intima-media thickness, or both, are clinically meaningless outcomes for the specific population and comparison addressed by the ENHANCE trial.

Should biomarkers ever be used as surrogate outcomes? Ideally, if a laboratory measurement is to be substituted for a clinically meaningful response, the association between the surrogate outcome and clinical endpoint of interest should be a true indicator of disease, or risk of disease, and be underscored by a biological explanation of effect. Furthermore, for the surrogate to be clinically valid, its association with the clinical end point should have been consistently observed across trials: that is, the effect should be the same for drugs of different classes, as well as for those of the same class. It is recommended that surrogate outcomes are also, for example, highly sensitive and specific, reproducible, and exhibit a

rapid response that accurately reflects treatment response (that is, levels should normalise when the patient has recovered or is in remission), with a specified range of normal and abnormal values.[\[9\]](#)

In addition to raising questions as to the effectiveness of using intima-media thickness as a biological marker, do the results of the ENHANCE trial cast doubt on the validity of LDL cholesterol as a surrogate outcome? One study specifically designed to assess the effect of reducing LDL cholesterol with simvastatin on the clinical outcome of mortality and morbidity was the 4S study.[\[10\]](#) This was the first large trial (4444 people) to find a significant beneficial effect for simvastatin compared with placebo on reducing cholesterol, which translated to a beneficial effect in survival rates in people with CHD. Subsequently, other large RCTs assessing various statins found the same result, establishing change in LDL cholesterol as a viable surrogate outcome for CVD.[\[11\]\[12\]\[13\]](#) However, there is some controversy about the effects of statins on lipid-independent outcomes, and trials are ongoing to address these issues. Another issue is whether the effectiveness of LDL as a clinically valid surrogate for cardiovascular events is limited to studies of statins.

A large trial conducted by The Women's Health Initiative assessed the effects of oestrogen plus progestin in healthy postmenopausal women, using a clinical primary outcome measure (CHD, defined as non-fatal MI and CHD death). The trial reported changes in LDL cholesterol at 1 year as an interim cardiovascular marker.[\[14\]](#) It found greater reductions in LDL cholesterol with oestrogen plus progestin compared with placebo, which, on the basis of the results of trials in statins, would be expected to lead to a decreased risk of cardiovascular events. However, the trial investigators found that the rate of women experiencing a cardiovascular event was 29% higher for those women taking oestrogen/progestin compared with those taking placebo.

Does focusing on one biological marker, even if that marker has been found to be valid, give the complete picture of a drug's effects? An example of the importance of measuring long-term clinical outcomes can also be found in the statin family. After publication of the large trials showing the effectiveness of simvastatin and pravastatin in reducing MI and death, other statins were marketed based on findings that they reduced LDL cholesterol to the same degree, with the assumption that they would also reduce clinical outcomes. One such statin was cerivastatin. However, cerivastatin was subsequently withdrawn because of the high rates of deaths attributed to drug-related rhabdomyolysis.[\[15\]](#)

Physiological outcomes could perhaps be considered more reliable surrogate outcomes than biomarkers. But this is not always the case. Flecainide was found to be effective in the treatment of a wide range of mild ventricular and atrial arrhythmias and tachycardias. Because it corrected arrhythmia in some people, it was assumed that flecainide would prevent fatal cardiac events, and so results on clinical cardiovascular outcomes were not investigated. However, questions were raised about the long-term effects of flecainide, and it soon became clear from a subsequent trial assessing mortality and morbidity (the trial was discontinued prematurely) that flecainide exacerbated the condition it was prescribed to treat, with the risk of death from a cardiovascular event being three times higher with flecainide and encainide than with placebo.[\[16\]](#) It has been estimated that 50,000 people died as a result of taking flecainide.[\[17\]](#) It is now recommended that its use be limited to patients with life-threatening forms of ventricular arrhythmia.

As the data from several trials highlight, using a surrogate outcome can raise more questions than answers. If using surrogate outcomes can lead to confusion and controversy, why are they measured rather than clinical outcomes? Using a surrogate outcome often enables trials to be conducted over a shorter period and with fewer people to determine a measureable clinical effect — which is particularly useful if the condition under investigation is rare and the number of expected events is small. Surrogate

outcomes are typically biochemical markers, and so can be measured more quickly and more easily, and with higher precision and objectivity, than clinical outcomes. Also, for conditions for which prognosis is poor, if a drug under investigation seemed likely to improve a clinical outcome based on a surrogate outcome, investigators may feel that it might not be appropriate to wait until clinical outcomes had been measured. Surrogate outcomes do have their role in assessing drug effects, and they can give insights into the pathophysiology of a condition when considered in the context of the condition being treated.

When assessing the benefits and harms of interventions, *BMJ Clinical Evidence* prefers to use clinical outcomes — such as symptom severity, quality of life, and survival — for all the reasons highlighted above. However, surrogate outcomes, such as blood pressure and ovulation rates, are frequently the primary outcome, and sometimes the only outcome, measured in the evidence we appraise. In our assessment of the evidence surrounding treatment choices, we try to minimise their limitations.

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