Hypertension and dyslipidaemia frequently co-exist. It is not surprising, therefore, that the majority of hypertensive patients warrant consideration for concomitant lipid-lowering therapy. The most recent meta-analyses published by the Cholesterol Treatment Trialists Collaboration, reported that the lowering of LDL-cholesterol by approximately 1mmol/L, was associated with a reduction in vascular events of about one quarter. This meta-analysis demonstrated that in virtually all subgroups of patients studied, the relative risk reductions were consistent, including patients with hypertension.

Two hypertension trials specifically evaluated the effects of lipid-lowering with statins in patients with hypertension. In the Anglo-Scandinavian Cardiac Outcomes Trial, over 10,000 hypertensive patients with a total cholesterol less than 6.5mmol/L, were randomised to atorvastatin 10mg or placebo. The primary endpoint of fatal and non-fatal myocardial infarction was reduced by 36% in those assigned a statin, and there was a reduction in a composite secondary endpoint of combined cardiovascular events. In the Antihypertensive and Lipid-Lowering Heart Attack Prevention Trial, a subgroup of hypertensive patients were randomised to pravastatin 40mg or “usual care”. In this study there was a non-significant (9%) reduction in myocardial infarction - a reduction that was compromised by the fact that statin treatment was common in those assigned “usual care”- and the difference achieved in cholesterol between the two treatment groups (9%) was therefore minimised. However, based on the CTTC meta-analysis, it can be concluded from the substantial evidence base, that statin treatment is effective in hypertensive patients and, for those at high absolute risk, the concomitant use of statins should be considered mandatory.

I wrote about the FOURIER trial in one of my earlier commentaries to the ISH Hypertension News and the trial has now completed. The first report was presented at the American College of Cardiology in March this year, and published simultaneously in the New England Journal of Medicine. The identification of proprotein convertase subtilisin/kinase type 9 was first reported in 2003 and within 14 years, the first major morbidity and mortality trial has been completed.

FOURIER was a randomised, double-blind, placebo controlled trial of over 27,500 patients with established cardiovascular disease and an LDL-cholesterol level of less than 1.8mmol/L. All patients were receiving concomitant statin therapy in optimal or best tolerated doses. Patients were randomly assigned either evolocumab or placebo, which was administered as a subcutaneous injection. The primary endpoint was a composite of cardiovascular (CV) death, myocardial infarction, stroke and hospitalisation for unstable angina or coronary revascularisation. The key secondary endpoint was a composite of CV death, non-fatal myocardial infarction or non-fatal stroke. The study was concluded after a median follow-up period of 2.2 years.

During the trial, LDL-cholesterol levels were reduced by almost 60% from a baseline of 2.4mmol/L to 0.78mmol/L. Active treatment reduced the primary endpoint by 15% and the key secondary endpoint by 20%. Both of these relative risk reductions were highly significant and were consistent across all key subgroups. Importantly, 80% of the patients recruited into FOURIER had a history of hypertension, and benefited to the same extent as the total trial population. There were no differences between evolocumab and placebo in any adverse events.

A further analysis of the endpoints revealed that, whilst there were clear reductions in myocardial infarction and stroke, there were no reductions in either CV death or all-cause mortality. It is, however, important to point out that the trial was stopped, as pre-specified, when 1,630 key secondary endpoints had been reported. It was not expected that, with this duration of follow-up, a reduction...
in CV death would have occurred and, in previous trials comparing more versus less lipid-lowering treatment, there was also no reduction in CV mortality.\(^5\)

A time-dependent analysis of the results of FOURIER suggested that there was a delay in the achievement of the maximal benefit from lipid-lowering, with approximately half the risk reduction observed in year 1 compared with year 2. Whether a longer duration of trial would have demonstrated a reduction in CV mortality is conjectural.

These are important results, which are in line with predictions based on the CTT meta-analyses, and confirm the benefits of adding evolocumab to statins in the prevention of further CV events in patients with established vascular disease.

In an important sub-study of FOURIER, the EBBINGHAUS Trial, the effect of evolocumab compared with placebo was assessed using a battery of tests of cognitive function. Concern had previously been expressed, based on some observational studies, that statins adversely affected cognitive function. This was highlighted by the MHRA (2009) and the FDA (2012) and led to an addition to the statin label of potential adverse effects on cognitive function. However, in double blind, randomised controlled clinical trials, no such adverse effects on cognitive function had been reported. In some short term trials with monoclonal antibodies to PCSK9, there were reports of adverse effects of these drugs on cognitive function. This stimulated the need for a more comprehensive evaluation of these drugs on cognitive function. EBBINGHAUS incorporated a highly sophisticated range of cognitive function tests (CANTAB, http://cambridgecognition.com). Almost 2,000 patients were randomised and followed-up for an average of just over 2 years. In a non-inferiority analysis, there were no differences in any of the outcome assessments for cognitive function.

Committees formulating new guidelines, and healthcare providers, will now assess the place of evolocumab and other monoclonal antibodies to PCSK9 in future treatment strategies. The SPIRE trial of bococizumab,\(^6\) another monoclonal antibody to PCSK9, was stopped prematurely on account of the development of antidrug antibodies, and an attrition of the effects of the drug on lowering cholesterol. For those assigned to SPIRE 2 - the sub study that recruited patients with prior vascular disease - a reduction in CV events was also seen with active treatment versus placebo. Thus these findings support the results of FOURIER. Importantly, these studies also demonstrated that achieving very low levels of LDL-cholesterol was not associated with the emergence of any untoward adverse events.

Cost effectiveness studies will provide guidance on the future use of evolocumab in high risk patients with CV disease and, more specifically, in those who have not reached target levels of LDL-cholesterol with statin treatment. Costs for the drug vary enormously, from around $14,000 per year per patient in the USA to around £2,000 per year, the discounted price to the NHS, in the UK. Cost effectiveness analyses will therefore be substantially influenced by the annual cost of the drug.

It is worth noting that the potential patient population for whom evolocumab would be advantageous is large. In the latest EUROSPIRE programme (2016), approximately 80% of patients with a previous history of myocardial infarction had an LDL-cholesterol of greater than 1.8mmol/L on existing statin treatment, with 40-50% having an LDL-cholesterol of greater than 2.5mmol/L. Many of these patients would not have been on optimal statin treatment, however.

Perhaps one of the most important implications from the results of FOURIER is that there are real benefits of achieving much lower levels of LDL-cholesterol and that these are safe and not associated with any untoward side effects. This should stimulate clinicians to ensure their existing patients are treated with optimal doses of the more effective statins (which is not the case in clinical practice).

Many will argue that the numbers needed to treat (NNT) are high. Approximately 50 patients have to be treated for 3 years to prevent one major CV event. The critics highlight the other 49 who do not benefit! Many will recall similar arguments being levelled at treating mild hypertension.

The final decision must await the outcome of cost effectiveness studies, but for many patients, particularly those with high residual levels of LDL-cholesterol on optimal doses of statins – particularly those with familial hyperlipidaemias - the benefits are real, and the outcome of the FOURIER trial is a major advance in our knowledge of the benefits and safety of a new form of lipid-lowering treatment.

REFERENCES:


Introduction: Is adherence to medication the elephant in the room?

Most medications act best when patients take them; and this appears to be the case also for antihypertensive drugs. Unfortunately, there is evidence that patients stop taking treatment that is intended to be taken lifelong. This is unfortunate and will reduce the potential preventive effects of their medication. Thus, adherence to antihypertensive medication is inversely related to cardiovascular outcomes [1]. Similar findings have been demonstrated in other chronic disease conditions with high cardiovascular risk, such as diabetes [2] and coronary heart disease [3]. Adherence to medication is generally greater in secondary prevention of cardiovascular disease (approximately two thirds adherent) than in primary prevention (approximately one half adherent) [4]. Of note, adherence to cardiovascular preventive medication is generally not related to drug class, suggesting that other factors than side effects are important [4].

There are several ways to assess adherence in clinical practice. They all have their advantages and disadvantages, and no way is perfect. Tablet counts, often used in clinical studies, and questionnaires, such as the commonly use Morisky adherence questionnaire, are often used but of limited value. Other methods, which appear to provide better information, include the combined use of electronic health records, data registries, and data on dispensed drug prescriptions; electronic pill containers recording opening and closing of the container; observed therapy units; and monitoring of drug concentrations in blood or urine. However, there are important ethical considerations to the assessment of adherence to treatment that should be considered.

Lack of adherence to medication is the elephant in the room. In order to improve blood pressure control we need to pay more attention to patient adherence to antihypertensive medication. The essays presented below will hopefully contribute to this.

REFERENCES:


- Thomas Kahan