
HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events): A randomized trial of the long-term clinical effects of raising HDL cholesterol with niacin and MK-0524

PROTOCOL SUMMARY

Does niacin combined with MK-0524 prevent vascular events in high-risk patients who are receiving intensive LDL-lowering treatment?

Large-scale randomized trials have demonstrated that lowering LDL cholesterol by about 1 mmol/L for 4-5 years reduces the risks of coronary events and of strokes by about one quarter. Furthermore, recent trials assessing more intensive versus standard statin regimens suggest further benefit with more intensive lowering of LDL cholesterol. Nevertheless, cardiovascular risk remains elevated even after some years of intensive LDL-lowering treatment. For example, in 2 recent trials, over 10% of CHD patients still suffered a major cardiovascular event during 4-5 years of intensive statin therapy. There is limited scope with current agents for much greater reductions in LDL cholesterol, but manipulating other aspects of lipid metabolism may well produce worthwhile reductions in occlusive vascular disease risk.

HDL cholesterol has long been known to have a strong inverse correlation with CHD risk. But, randomized trial evidence for beneficial effects from raising HDL cholesterol is limited. Most previous trials have been performed using fibrates, which raise HDL cholesterol only modestly, and those studies produced mixed results. One of the most effective HDL-raising agents is niacin, but the only previous large randomized trial of niacin was performed before the introduction of effective LDL-lowering treatments. Moreover, the tolerability of niacin has been limited by flushing and cutaneous side-effects, which appear to be mediated largely by prostaglandin D. MK-0524 is a selective prostaglandin D receptor antagonist that substantially reduces the frequency and intensity of niacin-induced flushing. Daily oral doses of extended release (ER) niacin 2 g plus MK-0524 40 mg have been well tolerated in early studies.

A streamlined international trial

The present study aims to assess the clinical effects of a combined daily tablet of niacin 2 g plus MK-0524 40 mg (MK-0524A) versus placebo in 20,000 patients with pre-existing atherosclerotic vascular disease who are all receiving simvastatin 40 mg daily (plus, if indicated, ezetimibe 10 mg daily). Such large-scale recruitment will allow reliable assessment of the effects of raising blood HDL cholesterol on the risk of major vascular events among patients receiving effective LDL-lowering therapy (i.e. LDL cholesterol typically below 2 mmol/L [77 mg/dL]). An international collaboration, with a Central Coordinating Office in Oxford and 3 Regional Coordinating Centres in the UK, China and Scandinavia, will conduct the trial in about 200 hospitals. The study design is "streamlined": extra work for collaborating doctors and hospitals has been kept to a minimum, and only essential data will be collected directly using computer-based systems.

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SUMMARY OF PRACTICAL PROCEDURES

POTENTIALLY ELIGIBLE	
↓	<ul style="list-style-type: none"> • Aged 50 to 80 years • History of myocardial infarction; peripheral or cerebrovascular atherosclerotic disease; or diabetes with evidence of atherosclerotic vascular disease (including angina) • No indication for, or contraindication to, niacin or MK-0524 • No contraindication to simvastatin or ezetimibe
IDENTIFICATION AND INVITATION	
↓	<ul style="list-style-type: none"> • Potentially eligible patients identified from medical records • Patient invited to attend Screening clinic appointment in local study clinic
SCREENING VISIT	
↓	<ul style="list-style-type: none"> • Medical history, relevant current treatment and other eligibility factors recorded • Blood pressure measured • Written informed consent sought from eligible and willing individuals • Non-fasting blood sample taken for dry chemistry assay of ALT, CK and creatinine • Consenting patients given simvastatin 40 mg daily (or, if already on ezetimibe or more potent statin dose, ezetimibe/simvastatin 10/40 mg). Any prescribed non-study statin or ezetimibe stopped • Run-in visit appointment scheduled for 4 weeks later
INITIAL RUN-IN VISIT; only for patients on simvastatin alone since Screening	
↓	<ul style="list-style-type: none"> • Compliance with simvastatin assessed • Any serious adverse events and any new or unexplained muscle symptoms recorded • Fasting blood sample taken for dry chemistry total/HDL cholesterol • If non-HDL cholesterol >2.5 mmol/L, combined ezetimibe/simvastatin 10/40 mg daily substituted for simvastatin and appointment scheduled for full Run-in assessment in 4 weeks • If non-HDL cholesterol ≤2.5 mmol/L, patient proceeds immediately to full Run-in assessment
FULL RUN-IN VISIT (-8 WEEKS); all patients	
↓	<ul style="list-style-type: none"> • Compliance with simvastatin or ezetimibe/simvastatin assessed • Relevant non-study treatments recorded and eligibility reconfirmed • Any serious adverse events and any new or unexplained muscle symptoms recorded • Fasting blood sample taken for dry chemistry total/HDL cholesterol, TG & ALT, and for central laboratory creatinine, glucose, HbA1c, lipid assays and frozen storage • Urine collected for albumin/creatinine ratio and frozen storage • Run-in treatment provided to eligible and consenting patients: Active MK-0524A 1 g: 1 tablet daily for 4 wks then 2 tablets daily for 4 wks • Simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg daily (as required) continued • Randomization visit appointment scheduled for 8 weeks later • Participant's doctor (and/or investigator) sent lipid profile, and asked to consider appropriateness of patient's randomization
RANDOMIZATION VISIT (0 MONTHS)	
↓	<ul style="list-style-type: none"> • All non-study treatments and serious adverse events during Run-in recorded • Final check of compliance and eligibility • Height, weight, and waist circumference recorded • Non-fasting blood sample taken for dry chemistry ALT, and for central lipid assay and frozen storage • Randomization via study clinic computer • Randomly allocated calendar-packed treatment provided to patient: Active MK-0524A 1 g or matching placebo: 2 tablets daily • Simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg daily continued • Follow-up visit appointment scheduled for 3 months' time • Participant's doctor informed of patient's randomization
FOLLOW-UP VISITS AT 3 and 6 MONTHS, THEN 6-MONTHLY	
↓	<ul style="list-style-type: none"> • Serious adverse events, compliance, and changes to non-study medication recorded (plus blood pressure measured at 1 year and final visit) • Reasons for non-compliance and any non-serious adverse events attributed to treatment recorded • Non-fasting blood sample and urine for safety assays (and, in 5% of participants annually and all participants at 1 year and at final visit, for lipid assays and frozen storage) • Follow-up treatment pack dispensed, and next Follow-up visit scheduled
MONITORING OF SAFETY AND EFFICACY	
↓	<ul style="list-style-type: none"> • Central monitoring of blood results and adverse events (with Early Recall visits to monitor any problems) • Further details on relevant outcomes sought from participant's doctor (and, if necessary, other sources) • Relevant events confirmed centrally blind to treatment allocation

