a third of participants with a previous insufficient response to biologic therapy, thereby reflecting real-world treatment patterns in axial spondyloarthritis. As a result of these findings, the European Medicines Agency Committee for Medicinal Products for Human Use recommended approval of upadacitinib for the treatment of non-radiographic axial spondyloarthritis, and an application for an indication in non-radiographic axial spondyloarthritis has been submitted to the US Food and Drug Administration.[11] Notably, the most recent revision of the The European Alliance of Associations for Rheumatology recommendations for the management of axial spondyloarthritis (including radiographic and non-radiographic forms) recommend JAK inhibitors as second-line pharmacotherapy following inadequate response to NSAIDs.[12]

The SELECT-AXIS 2 trial, in combination with earlier trials of JAK inhibitors in radiographic axial spondyloarthritis, represents a turning point in axial spondyloarthritis management, in which patients will now have an option of a targeted, highly effective and oral medication for the treatment of all forms of axial spondyloarthritis. Furthermore, these data provide additional evidence that treatment response does not differ substantially between radiographic axial spondyloarthritis and non-radiographic axial spondyloarthritis. This might serve as rationale toward removing a distinction between these two phenotypes within the axial spondyloarthritis spectrum within guidelines and clinical practice.

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Lowering LDL cholesterol in clinical practice: time for change?

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Atherosclerotic cardiovascular disease (ASCVD) events are associated with cumulative exposure to LDL cholesterol. Clinical guidelines for blood cholesterol management in people with ASCVD recommend monotherapy with the highest tolerated dose of statin before consideration of additional non-statin therapy to reach the LDL cholesterol goal.[1,2] Combination lipid-lowering therapy (LLT) reduces LDL cholesterol concentrations to a greater extent than doubling the statin dose.[3] However, until now, no randomised clinical trial had compared the long-term clinical event outcomes of high-intensity statin monotherapy versus lower-intensity statin with ezetimibe.

In *The Lancet*, in a randomised, open-label, non-inferiority trial done in 26 clinical centres in South Korea, Byeong-Keuk Kim and colleagues[4] randomly assigned 3780 patients (75% male, 25% female, mean [SD] age 64 [10] years) with ASCVD on a 1:1 basis to receive rosuvastatin 10 mg with ezetimibe 10 mg versus rosuvastatin 20 mg. The primary endpoint of

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cardiovascular death, major cardiovascular event, or stroke occurred in 172 patients (9·1%) in the combination-therapy group versus 186 (9·9%) in the high-intensity-statin group, which met the prespecified non-inferiority endpoint. The combination-therapy group had a significantly lower mean LDL cholesterol concentration (58 mg/dL) than the high-intensity statin group (66 mg/dL) and had fewer discontinuations of therapy (88 patients [4·8%] *vs* 150 patients [8·2%], respectively).

The overall event rate for the primary endpoint was lower than predicted in the sample size calculation (13% expected *vs* 9·1% actual events in the combination-therapy group; 14% expected *vs* 9·9% actual events in the high-intensity statin monotherapy group), with remarkably few myocardial infarctions occurring in either group over 3 years. Additionally, this trial used a pragmatic open-label design, which poses a risk of bias in patients' reporting of symptoms and physicians' discretionary discontinuation of high-intensity statins, which are generally perceived to have more side-effects. Objective muscle side-effects, such as myonecrosis, which is associated with elevated creatinine kinase concentrations, showed little difference between the groups (11 in the combination-therapy group, 13 in the high-intensity statin monotherapy group). However, subjective side-effects, such as myalgia, showed a greater difference between groups (17 in the combination-therapy group, 29 in the high-intensity statin monotherapy group). Additionally, there were significant differences in discontinuation or dose reduction of medication owing to intolerance. These findings might have been influenced by the nocebo effect,[5] which has been reported with statin therapy, as myalgias are a common non-specific complaint among those eligible for statin therapy.[6] However, these results might better reflect real-world scenarios in regard to adherence, as patients are often hesitant to take high-intensity statins because of concern about potential side-effects.

Although greater LDL cholesterol reductions with combination LLT were expected on the basis of previous comparative trials, the comparison of efficacy on clinical endpoints is long overdue, considering that ezetimibe was approved in 2002, a combination ezetimibe–statin formulation was approved in 2004, and ezetimibe has been the most widely used adjunctive therapy with statins for most of the last two decades. Additionally, despite the advent of new and effective LLT, real-world data from DA VINCI[7] and the GOULD registry[8] show low implementation of guideline-recommended intensity and intensification of LLT; in DA VINCI, high-intensity statin monotherapy was used for secondary prevention in 38% of patients at very-high risk and moderate-intensity or high-intensity statin–ezetimibe combination was used in 9%, although 62% were above the LDL cholesterol goal, and in GOULD, only 17·1% of patients with ASCVD and LDL cholesterol above the goal had their medications intensified: 5·8% with statin intensification and 5·3% with addition of ezetimibe. This therapeutic inertia might be overcome through early initiation of combination LLT, leading to a greater proportion of patients with ASCVD meeting the LDL cholesterol goal.[9]

Treatment of blood pressure and LDL cholesterol with behaviour change and drug therapy is foundational to ASCVD prevention, yet dramatically different approaches are taken for reduction of these major risk factors. Historically, the recommended treatment of hypertension began with monotherapy, which was increased to the maximum dose before adding a second agent. However, the hypertension guidelines changed in 2003, with initial consideration of combination therapy for more severe elevations of blood pressure.[10] Combination therapies for blood pressure, including fixed-dose formulations, are now widely used in clinical practice and advocated more broadly as initial therapy in the guidelines for hypertension management.[11,12] Is it time for a paradigm shift in the management of lipids toward an approach with combination therapy

as an initial treatment option that is more similar to the treatment of hypertension?

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The Health and Care Act 2022: challenges and priorities for embedding research in the NHS

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The Health and Care Bill received Royal Assent and became an Act of the UK Parliament on April 28, 2022.[1] Aimed at rebuilding the National Health Service (NHS) in the context of the continuing impacts of the COVID-19 pandemic, the Health and Care Act 2022 incorporates a valuable lesson learnt from the pandemic: the extraordinary value a research-active NHS can deliver. Embedding research in the NHS to improve outcomes for patients is now on a statutory footing. Yet whether the Act will address other challenges for the UK's health system is uncertain. The absence of commitment to regular workforce forecasts within the Act will be problematic because of existing NHS staff shortages, which will leave the UK Government struggling to deliver across its ambitions, including for research.[2] A key challenge is the pressure for an overstretched and exhausted workforce of dealing with the rising demand for NHS services after the acute stages of the COVID-19 pandemic, which will leave little room to do more despite the opportunity that research brings to improve patient outcomes and reduce inequalities.

Even before COVID-19, there was growing evidence of the benefits of embedding research in the NHS. Research-active NHS trusts delivered improved survival rates, provided better care experiences, and found it easier to recruit and retain staff.[3,4] Patients report added satisfaction when involved in research studies aligned with their clinical care.[5] Clinicians value research as important to their job satisfaction, but are hampered by time pressures, an NHS culture that disregards research as core business despite research being a key part of the NHS Constitution, and an increasing research skills gap.[6] These barriers are acute for women, staff who work part time, and those in non-teaching hospitals.[6] What will not work is simply adding research to an already