before trastuzumab deruxtecan. There were numerically more patients with left ventricular dysfunction in the trastuzumab deruxtecan group than in the treatment of physician's choice group (18 [4%] *vs* three [2%]). Nevertheless, the treatment discontinuation rate due to left ventricular dysfunction was less than 1% in both groups.

Another key side-effect of trastuzumab deruxtecan is interstitial lung disease. Similar to the rate observed with trastuzumab deruxtecan,[5,10,11] interstitial lung disease occurred in 42 (10%) patients receiving trastuzumab deruxtecan; most (37 [88%]) events were grades 1 and 2, but there were two grade 5 treatment-related deaths due to interstitial lung disease. Thus, following the established guidelines on managing interstitial lung disease is imperative in patients receiving this drug with early implementation of corticosteroids and permanent discontinuation if interstitial lung disease of grade 2 or higher occurs. Patients should be followed up for an extended period because the median time to onset of interstitial lung disease was more than 6 months after the initiation of trastuzumab deruxtecan (29·9 weeks [IQR 12·3–48·0]).

In summary, the DESTINY Breast-02 trial showed robust activity of trastuzumab deruxtecan in patients with metastatic HER2-positive breast cancer who previously received trastuzumab emtansine. Proper management, particularly with the treatment of interstitial lung disease and prophylactic antiemetics, is crucial to ensure patient safety and allow patients to continue this remarkable treatment. Further research is ongoing to expand the benefit of this treatment in patients with low HER2 expression and in earlier disease settings.

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Saranya Chumsri
chumsri.saranya@mayo.edu

Division of Hematology and Medical Oncology, Mayo Clinic, Jacksonville, FL 32224, USA

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Bariatric–metabolic surgery versus lifestyle intervention in non-alcoholic steatohepatitis

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Non-alcoholic fatty liver disease (NAFLD) is a growing public health issue, set to be the major cause of liver transplantation and liver cancer, with increasing socioeconomic costs.[1] NAFLD is strongly associated with obesity (BMI ≥30 kg/m^2) and metabolic syndrome, with an increased standardised mortality ratio of 1·34 compared with the general population.[2] Despite progress being made regarding our understanding of the cause and pathophysiology of NAFLD, there are no approved treatments for NAFLD. Physical activity and weight-loss strategies are the mainstay for the treatment of non-alcoholic steatohepatitis (NASH), with aerobic and resistance training having been shown to reduce hepatic steatosis and NAFLD-associated cardiovascular risks.[3] Bodyweight loss of more than 10% has been shown to improve fibrosis,[4] but this level of weight loss is seldom reached with lifestyle change, let alone maintained in the longer term. Moreover, in an open-label study, Pais and colleagues showed that despite substantial weight loss after bariatric surgery,


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47% of patients still had advanced fibrosis, although many more had improvements in fibrosis.[5]

In *The Lancet* Ornella Verrastro and colleagues[6] present the first multicentre, open-label, randomised trial randomly assigning 288 patients with biopsy-proven NASH to either an intensive lifestyle intervention with best medical care (n=96 [33%]), Roux-en-Y gastric bypass (n=96 [33%]), or sleeve gastrectomy (n=96 [33%]). The study was done at three hospitals in Rome, Italy. 153 (53%) patients were male, 135 (47%) were female, all were White, and they had a BMI of 30–55 kg/m². 236 (81%) patients completed the trial. In the intention-to-treat analysis, 54 (56%) patients who had Roux-en-Y gastric bypass and 55 (57%) in the sleeve gastrectomy group met the industry-standard primary endpoint, which was histological resolution of NASH with no worsening of fibrosis at 1 year, compared with 15 (16%) patients in the lifestyle modification group (p<0·0001). Those who met the primary endpoint lost more bodyweight, had higher rates of diabetes remission, and better glycaemic control compared with non-responders.

In the per-protocol analysis, improvement of fibrosis score by at least one stage without worsening of NASH was higher in the surgical groups: 35 (46%) of 76 patients in the Roux-en-Y gastric bypass group and 37 (47%) of 78 patients in the sleeve gastrectomy group, compared with 22 (28%) of 80 patients in the lifestyle modification group (p=0·017). Diabetes remission was also significantly higher in the surgical groups than in the lifestyle modification group (p<0·0001). There were no serious adverse events reported, with expected common surgical complications being managed endoscopically or medically. The 1-year mean weight loss in the study was 5·5% in the lifestyle modification group, with only 27·2% having weight loss of 10% or more. This is the first study to show that there is little incremental benefit on liver histology of weight loss of more than 20%, suggesting the role of other factors in sustaining disease activity.

This is the first randomised trial studying the effects of bariatric surgery with the conventional industry-standard primary endpoint of NASH resolution using liver histology. As in any study there are some limitations meriting consideration. First, the study was done in three Italian centres and, as all patients were White, the trial participants probably do not reflect the multiethnic diversity of people with NAFLD worldwide. Second, more effective pharmacological interventions for the management of obesity, including incretin hormone analogues such as semaglutide,[7,8] tirzepatide,[9] and BI 456906,[10] are being investigated for patients with NASH. In this study, mean baseline BMI in the lifestyle modification group was 41·2 (SD 6·4), which means that patients were also eligible for the higher dose of liraglutide at 3·0 mg rather than the 1·8 mg daily dosing used in this study. Thus, a potentially suboptimal lower dose of GLP-1 agonist was used in a third of the eligible cohort. Third, most patients (n=139 [48%]) enrolled had minimal (F1) fibrosis, with only 32 (11%) having advanced (F3) fibrosis. Because stages F3 and F4 fibrosis, rather than F1 and F2 fibrosis, are associated with increased rates of major adverse liver outcomes and major adverse cardiac events,[11] it would be important to establish whether bariatric surgery was effective in these patients with more advanced liver disease. Not only are interventions likely to be limited to patients with advanced fibrosis, such patients might also be more refractory to therapies, hence the need to show effectiveness in this group.

In summary, although this study clearly shows the value of bariatric surgery in patients with NASH, questions remain about the effectiveness in those with advanced fibrosis. Although both surgical approaches were effective, further guidance is needed to inform which procedure should be recommended for specific patient groups. Finally, there is value in considering the potential utility of combining bariatric surgery with pharmacotherapy to enhance efficacy.

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*Sara Mahgoub, *Philip N Newsome*
p.n.newsome@bham.ac.uk

Centre for Liver and Gastrointestinal Research, Institute of Biomedical Research, Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham B15 2TT, UK

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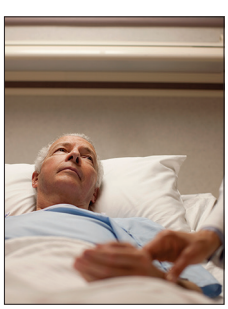
Endovascular reperfusion strategy for infra-popliteal chronic limb threatening ischaemia

Atherosclerotic lower extremity peripheral artery disease affects more than 230 million people worldwide, with prevalence increasing over the past decade.[1] Chronic limb threatening ischaemia is a severe form of peripheral artery disease that affects 11% of patients with peripheral artery disease and is associated with significant cardiovascular morbidity and death.[2] Furthermore, amputation rates of 10–40% during a 6-month follow-up in patients with non-revascularisable chronic limb threatening ischaemia have been reported, highlighting the severity of atherosclerotic burden and need for improved treatment strategies.[2] In this disease setting, two randomised clinical trials have compared surgical bypass using vein graft with endovascular treatment: the Bypass versus Angioplasty in Severe Ischaemia of the Leg Trial (BASIL) trial[3] and the Best Surgical Therapy in Patients with Chronic Limb threatening Ischaemia (BEST-CLI) trial.[4]

In the BASIL trial,[3] 452 patients with infra-inguinal disease chronic limb threatening ischaemia were randomly assigned to receive vein bypass or best endovascular treatment. Although the interim analysis reported similar short-term outcomes and increased morbidity in patients who received vein bypass, vein bypass was associated with improved overall survival and amputation-free survival in patients who survived at least 2 years after random assignment.[3] The BEST-CLI trial[4] also reported 32% lower risk of a composite of major adverse limb events or death in patients with chronic limb threatening ischaemia undergoing a surgery-first strategy compared with endovascular therapy, mostly in patients with suitable single segment of great saphenous vein. Considering the technical challenges with infra-popliteal lesions-associated chronic limb threatening ischaemia, more evidence for patients with the disease is needed.

In *The Lancet*, Andrew Bradbury and colleagues[5] report the BASIL-2 trial, a comparison of vein bypass (vein bypass group) or best endovascular treatment (best endovascular treatment group) for patients with chronic limb threatening ischaemia who required an infra-popliteal revascularisation with or without an additional proximal infra-inguinal revascularisation procedure to restore limb perfusion. 345 patients (65 [19%] women and 280 [81%] men; median age 72·5 years [IQR 62·7–79·3]) were randomly assigned to the vein bypass group (n=172) or the best endovascular treatment group (n=173). More than 60% of patients across both groups had both rest pain and tissue loss at random assignment. The authors concluded that in patients with chronic limb threatening ischaemia due to atherosclerotic disease and those who required infra-popliteal revascularisation with or without an additional proximal infra-inguinal procedure, best endovascular treatment was associated with better amputation-free survival (primary outcome; defined as time to first major amputation [amputation above the ankle] or death from any cause) compared with vein bypass surgery (adjusted hazard ratio [HR] 1·35 [95% CI 1·02–1·80]; p=0·037).



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