RESEARCH LETTER

Coeliac Artery Release or Sham Operation in Patients Suspected of Having Median Arcuate Ligament Syndrome: The CARoSO study

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In patients with median arcuate ligament (MAL) syndrome (MALS), external compression of the coeliac artery (CA) by the MAL causes chronic disabling postprandial abdominal pain, weight loss, and, consequently, lethargy and social deprivation.[1,2] The majority of patients with MALS will experience a long medical journey before a diagnosis of MALS is considered, resulting in a substantial burden of disease and high healthcare and societal costs.

By eliminating external compression of the CA by endoscopic retroperitoneal CA release (eCAR), patients may be relieved of their complaints and may potentially be able to return to normal life.[3] Although several systematic reviews have shown a long term benefit of CA release, in terms of a significant and durable improvement of quality of life, in more than the 70% of patients with suspected MALS, there remains no consensus on the existence and treatment of MALS.[4,5] Two recent sets of guidelines concluded that patients with MALS might be considered for surgical CA release.[1,2] To end the ongoing debate and to enable the development of evidence based guidelines for the management of MALS, both guideline committees recommended that a blinded, randomised controlled trial (RCT) be conducted comparing a CA release with a sham operation: the Coeliac Artery Release or Sham Operation (CARoSO) study. The diagnostic and therapeutic dilemma meets the criteria established for performing a blinded RCT, including a sham operation.[6](Figure 1)

The sham operation consists of making four incisions up to the fascia, similar to eCAR. After 60 to 75 minutes of general anaesthesia, in accordance with the average operating time of eCAR, the sham operation is ended. To ensure a blinded trial in this Dutch nationwide collaboration and to rule out operator dependencies, learning curves, and procedural variation in eCAR, all procedures will be performed by two experienced eCAR surgeons in one hospital. All procedures will be filmed. The surgeon that performs the operation will not be involved in patient follow up.

The members of the Dutch Mesenteric Ischaemia Study Group (DMIS) and patient representatives unanimously recommend a disease specific composite endpoint measured with a daily visual analogue scale for abdominal pain and/or the Patient Global Impression of Improvement as a primary endpoint for the CARoSO study. This clinical outcome parameter can be assessed reliably within six months after CA release. A two year follow up is suggested to extinguish the positive effect of attention in the diagnostic phase.

The CARoSO is a superiority study in which the expected success rate for the CA release group of 0.7, based on two systematic reviews in which sustained symptom relief is reported in 69% to 78% of patients with MALS treated by CA release.[4,5] For the sham operation, the expected success rate of 0.3 is based on five previous RCTs that included sham operations.

To be eligible for participation in this study, patients aged $>$ 18 years must have a consensus diagnosis of MALS based on a multidisciplinary discussion at both Dutch expert centres for mesenteric ischaemia. The multidisciplinary teams consist of a vascular surgeon, gastroenterologist, and radiologist, and the diagnosis is based on symptoms fitting MALS: at a minimum, postprandial pain, and at least two of dietary modification, unexplained weight loss, and unexplained diarrhoea. Patients should have an eccentric CA stenosis of $\geq$ 70% at the MAL, demonstrated by two imaging techniques (duplex, digital subtraction angiography, magnetic resonance angiography, or computed tomography angiography [CTA]), including at least an inspiration and expiration CTA with 1 mm sections. Other plausible abdominal abnormalities should be excluded by abdominal ultrasound and a gastroduodenoscopy. The CARoSO study is registered with ClinicalTrials.gov (NCT05468580).

The proposed CARoSO study will either underline the usefulness of eCAR as a minimal invasive (cost) effective

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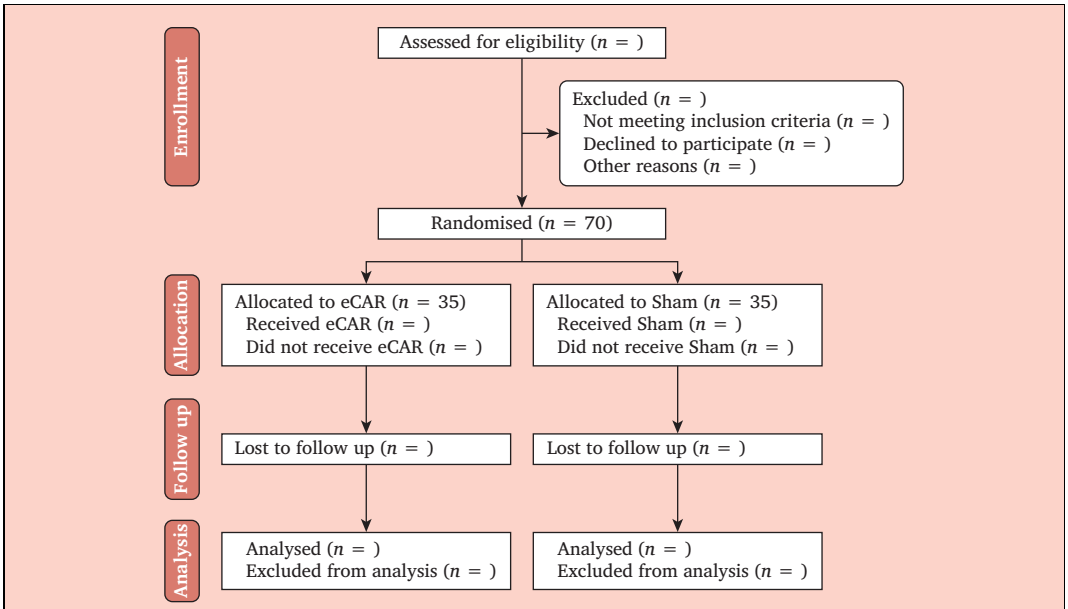

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) study flow diagram of the planned and registered Coeliac Artery Release or Sham Operation (CARoSO) study. eCAR = endoscopic retroperitoneal coeliac artery release.

treatment for MALS or it will prohibit a meaningless intervention in patients with disabling abdominal symptoms. If the CARoSO study proves that treatment of MALS by eCAR is effective, it is estimated that, in the Netherlands, up to 490 patients with chronic disabling abdominal symptoms per year can be treated. These patients are mostly in the second and third decade of their lives. Effective treatment of MALS is therefore expected to result in a mean health gain of 6.05 quality adjusted life years per patient, and to reduce the substantial productivity loss and healthcare consumption caused by MALS, resulting in a saving of up to €4.3 million annually. If the CARoSO study provides evidence that the supposed relief from eCAR is only a placebo effect, an estimated 20 to 100 annual CA release procedures will no longer be charged to the healthcare budget, resulting in a saving of €25 000 to €125 000 per year.

The outcome of the CARoSO study will be translated into strong recommendations in relevant (inter)national multidisciplinary guideline updates, and will be adopted into daily practice.

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