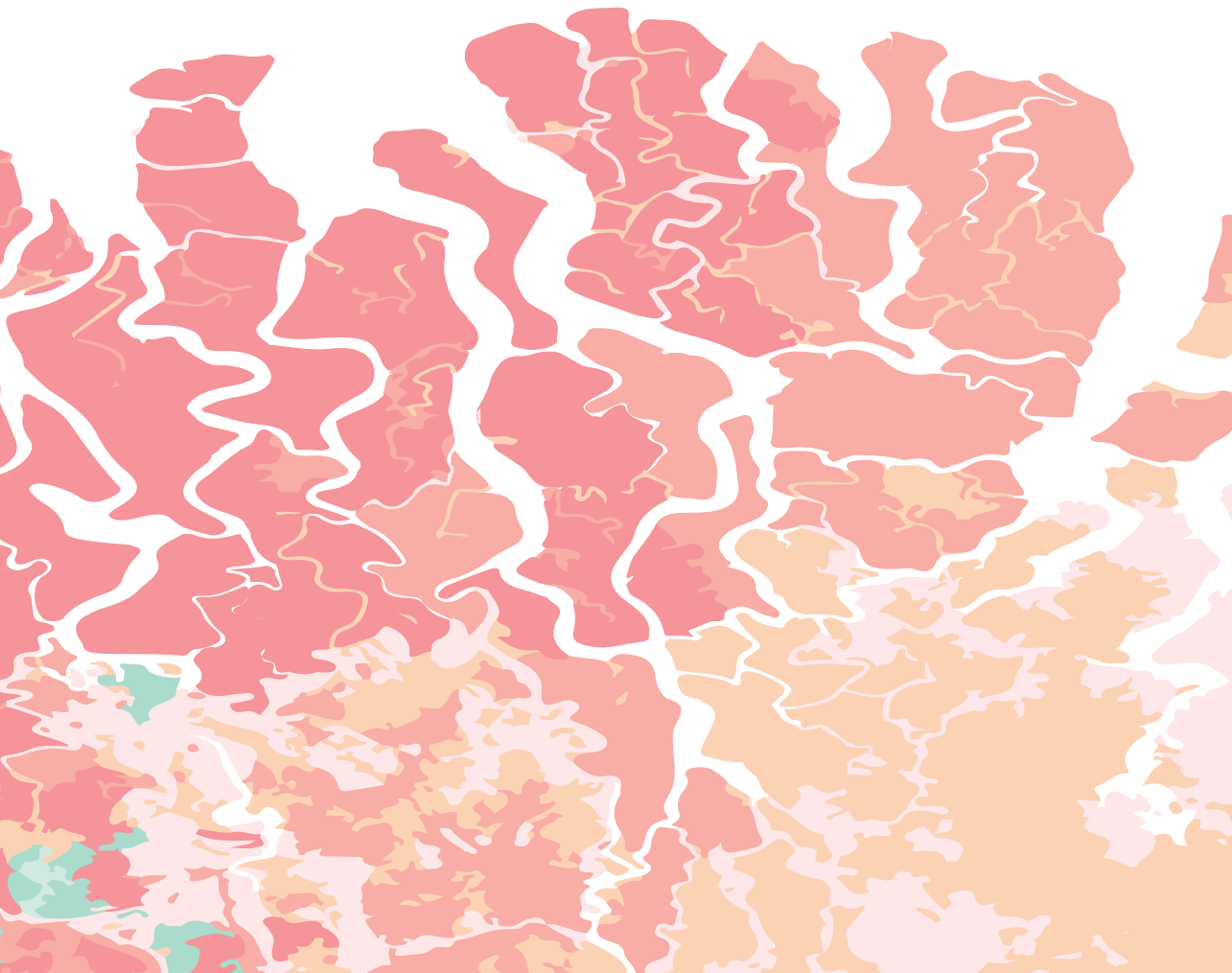
OPTIMIZING OUTCOME AND QUALITY OF LIFE

FOR MESENTERIC ISCHEMIA PATIENTS BY IMPROVING DIAGNOSTIC AND TREATMENT STRATEGIES

Juliëtte Theresia Maria Blauw



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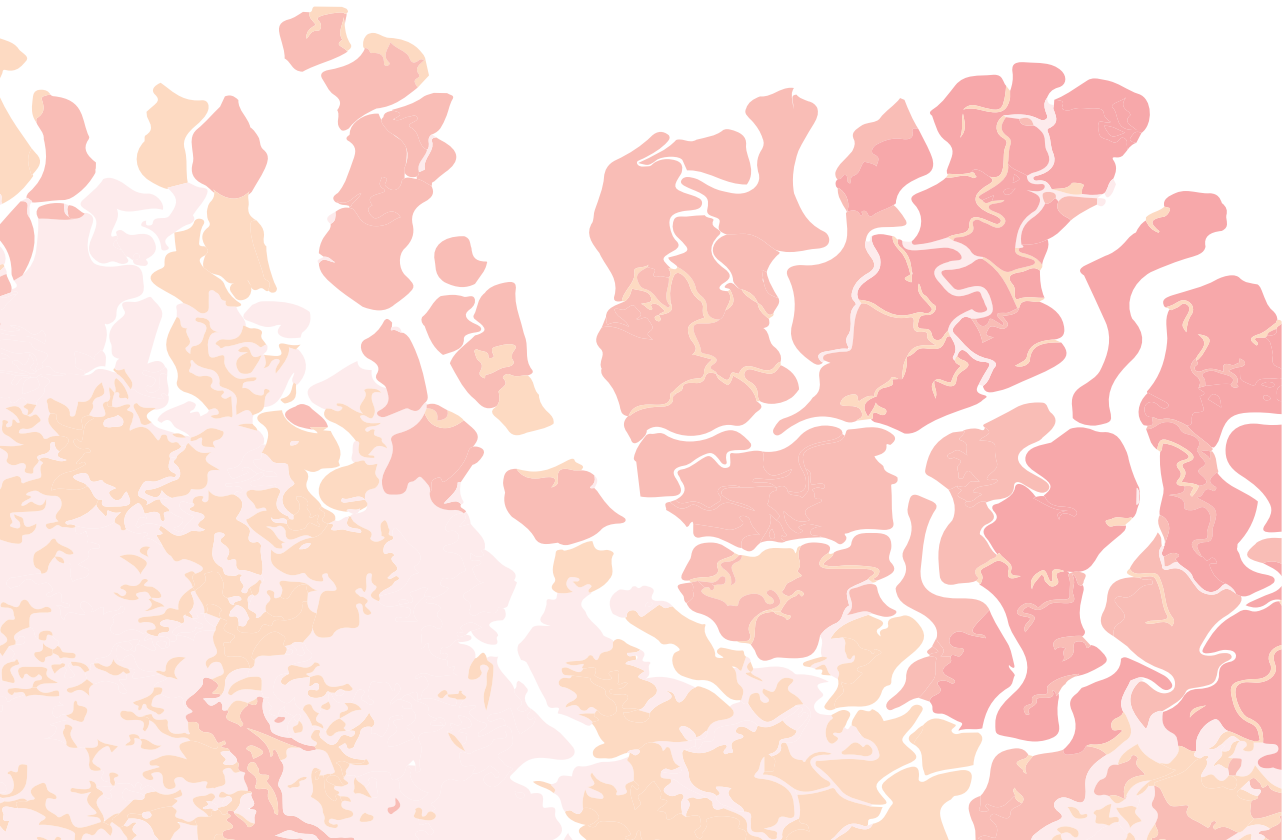


Chapter 1

General introduction
and Outline of this thesis

We have all heard our mothers tell us not to go swimming the first 30 minutes after lunch to avoid stomach ache. And if you're a runner like me, somewhere in your career you sprinted to the bathroom with a squeezed buttock. Or perhaps you remember Tom Dumoulin getting of his bike in the queen stage of the Giro d'Italia in 2017 because of intestinal problems. Although for many years, doctors have thought that symptomatic mesenteric vascular diseases were relatively uncommon, I dare to say that, like Christmas, they are all around us. But where our experiences were mild and harmless, our patients are at great risk of a significant reduction in quality of life (QoL) and in the absence of treatment have a high mortality in the end stage of mesenteric ischemia. They experience chronic abdominal pain on a daily basis with a crescendo character over time and are therefore unable to eat sufficiently. They are less able to participate in family life and fulfil their socioeconomic roles, and they increasingly experience mental problems. Altogether, mesenteric ischemia results in an unrecognized high societal burden.

Mesenteric ischemia occurs after more than 70% reduction of the basal blood flow when metabolic requirements are not met.(1) After only ten minutes increased mucosal ischemia occurs, which is still reversible. If left untreated, (irreversible) transmural ischemia occurs after 8 hours leading to a bowel infarction with a mortality up to 90%.(1) But, although everybody can develop some form of mesenteric ischemia on different occasions, the difficult job healthcare professionals have, is to diagnose those who are at risk of organ damage in an early stage. This allows them to provide adequate treatment and save bowel, which positively affects QoL and decreases societal burden.

The aim of this thesis is to improve outcome and quality of life of patients with mesenteric ischemia by improving diagnosis and treatment strategies.

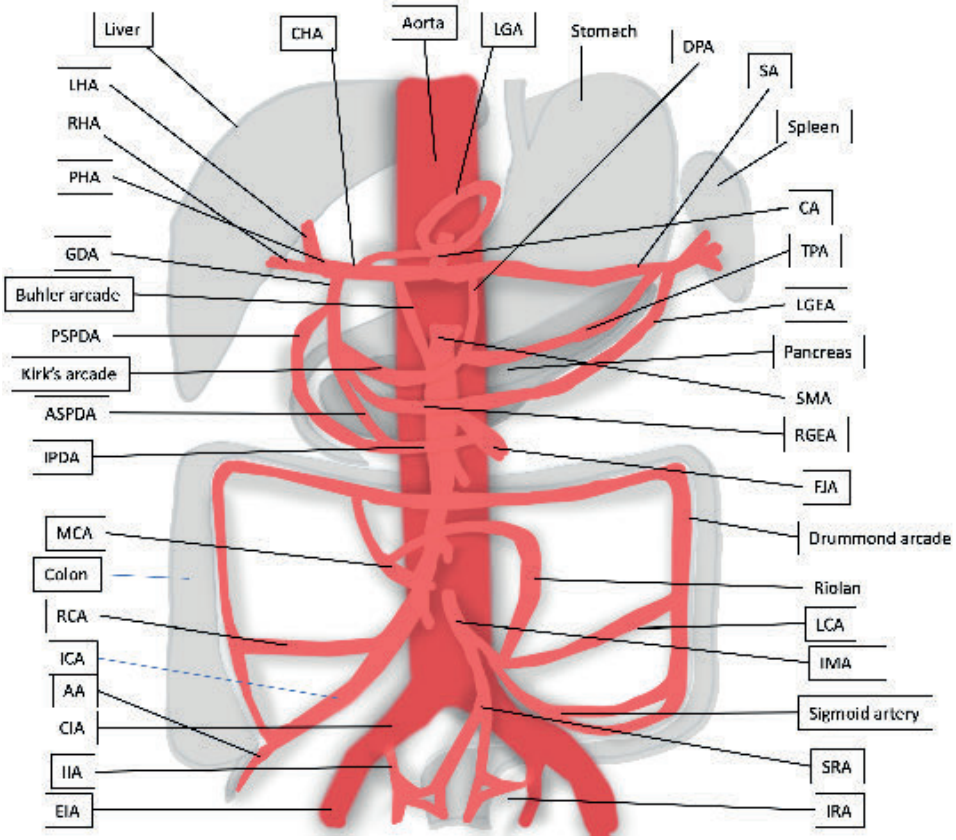
Anatomy

Over the years many different synonyms were used in the literature, like "splanchnic", "visceral" and "gastrointestinal", but “mesenteric” is preferred and now used in the ESVS Guideline since 2017 to describe the arterial supply, capillaries and venous discharge of the stomach, duodenum, small and large intestine, bile ducts, liver, pancreas and spleen.(2)

There are three major mesenteric arteries. The coeliac artery (CA), which splits directly into three major branches, the left gastric artery, the common hepatic artery and the splenic artery and supplying associated organs. The superior mesenteric artery (SMA), providing the entire length of the small intestine, except for the proximal part of the duodenum, up to about halfway up the transverse colon. And finally, the inferior mesenteric artery (IMA),

supplying the left half of the colon and most of the rectum.(2) The normal diameters and grade of stenosis of these vessels are highly relevant when judging the risk of ischaemia. The CA and SMA have a diameter of 6 and 7 mm, whereas the IMA normally measures 1 mm. Consequently, a significant IMA occlusion would reduce the total mesenteric flow by only 4%, whereas a significant CA or SMA stenosis would reduce this by 87% (1).

Figure 1 Mesenteric anatomy and most common collaterals.



AA = appendiceal artery, ASPDA = anterior superior pancreaticoduodenal artery, CA = coeliac artery, CHA = common hepatic artery, CIA = common iliac artery, DPA = dorsal pancreatic artery, EIA = External iliac artery, FJA = first jejunal artery, GDA = gastroduodenal artery, ICA = ileocolic artery, IIA = internal iliac artery, IMA = inferior mesenteric artery, IPDA = inferior pancreaticoduodenal artery, IRA = inferior rectal artery, LCA = left colic artery, LGA = left gastric artery, LGEA = left gastroepiploic artery, LHA = left hepatic artery, MCA = medial colic artery, PHA = proper hepatic artery, PSPDA = posterior superior pancreaticoduodenal artery, RCA = right colic artery, RGEA = right gastroepiploic artery, RHA = right hepatic artery, SA = splenic artery, SMA = superior mesenteric artery, SRA = superior rectal artery, TPA = transverse pancreatic artery.

The mesenteric vascular bed is characterized by an abundant collateral circulation, Figure 1. Between the CA and the SMA the gastroduodenal artery (GDA) is the main collateral, connecting the common hepatic artery with branches of the inferior pancreatic duodenal artery, coming from the SMA. Via the splenic artery, the dorsal pancreatic artery (DPA) anastomoses with the anterior and posterior pancreaticoduodenal arcades via a right transverse branch of the DPA (Kirk's arcade).(6) And lastly and probably the best known is the arc of Bühler. An embryological remnant, estimated to be present in less than 3% of population, anastomosing the CA and middle colic artery.(7)

The SMA and the IMA are connected by Drummond's marginal artery, which is a vascular capillary bed from the left colic artery along the descending colon towards the middle colic artery. Not to be confused with the more centrally located Riolan arcade, which is a direct anastomosis between the left colic artery and the middle colic artery. And an extensive collateral network through the hemorrhoidal branches of the inferior rectal artery out of the internal iliac artery anastomosis with the superior rectal artery emerging from the IMA.(8) Less well-known collateral circulations are the arc of Barkow for example. It anastomoses the right gastroepiploic, a side branch of the gastroduodenal artery, and left gastroepiploic, a side branch of the splenic artery, arteries, supplying the transverse colon via multiple ascending branches.(6, 8, 9) Also, the left and right internal mammary or thoracic artery (LIMA and RIMA, or LITA and RITA) can anastomose the CA via the superior epigastric arteries or the IMA via the inferior epigastric arteries. The lower oesophageal arteries and the phrenic arteries can anastomose the CA via the left gastric artery.

The small intestine starts at the pylorus, running from the duodenum to the ileum, ending at the ileocecal valve, facilitating the breakdown of macronutrients,(10, 11) the absorption of a number of micronutrients, the production of various gastrointestinal hormones to regulate the autonomic nervous system(10), the absorption of carbohydrates, proteins, bile salts and vitamins(12, 13) and the in- and outflow of water and sodium.(13-15) The colon has an essential role in the reabsorption of fluids and electrolytes, the absorption of poorly absorbed carbohydrates and storage and propelling of intestinal contents.(10, 16, 17)

Pathophysiology of mesenteric ischemia

Mesenteric blood flow is dynamic with large fluctuations regulated on multiple levels to preserve metabolism.(18) In a resting state, normal mesenteric blood flow is 20-30% of cardiac output, raising an additional 10-20% in 30 minutes after caloric intake.(19-21) Increased CA flow can last for approximately one hour, but increased SMA flow can last for 3 hours.(2, 22) The mucosal and submucosal layers receive more than two-thirds of

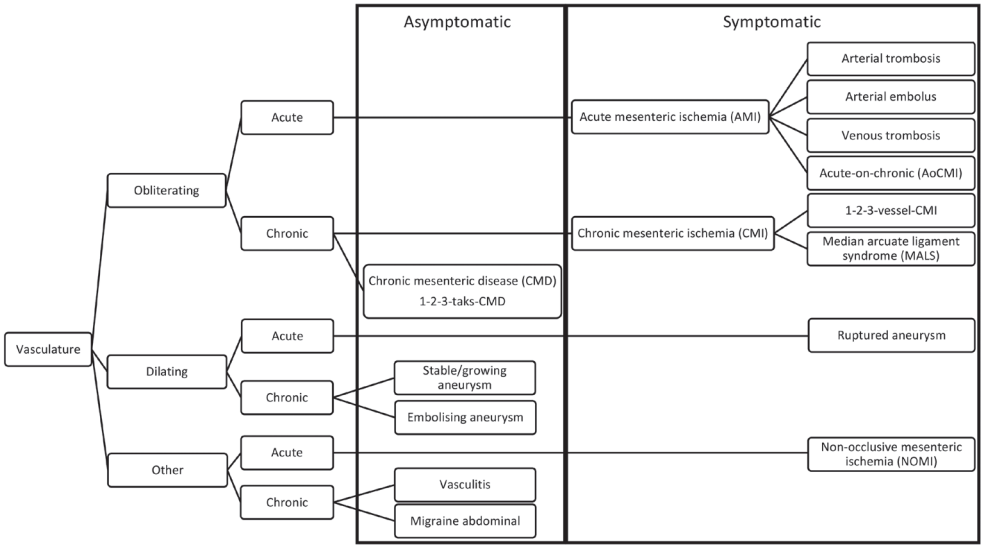
blood flow to facilitate nutrient exchange, meaning that the mucosal layer is predominantly affected with impaired perfusion and ischemia.(19, 20, 22, 23) But the mesenteric vascular bed also serves as a reserve if there is an increased need in blood flow elsewhere in the body, like in a hypovolemic situation with a threatened deprivation of normal blood flow of vital organs such as heart, lungs and the brain, or during exercise.(2, 18, 21) The sympathetic nervous system (SNS) is activated and increases the mesenteric vascular resistance, which leads to a reduction of mesenteric blood flow and a decrease in flow to the distal villus causing a relative mucosal atrophy and reversable superficial ischemia because of arterial shunting in the top of the villus.(21, 24) Because of the significant collateral circulation, the intestines can tolerate a 70-80% reduction in blood flow for up to 12 hours and varies according to the conditions the patient is in.(21, 25-27)

To perform its tasks, the bowel needs oxygen (O2). Normal oxygen extraction by the tissues of the distal villous is 10–20% which raises with increased metabolic demand after eating, but will decline with ongoing ischemia.(18, 24, 28) Oxygen exchange is dependent on the ability of the villi to increase oxygen uptake and recruit additional capillary beds to maintain circulatory homeostasis. To ensure a constant level of intestinal oxygen uptake, Mother Nature has created one of the most beautiful forms of anatomy to regulate mesenteric flow: the villi Countercurrent system.(19, 20) With decreasing blood flow, countercurrent shunting increases to maintain O2 uptake by prolonging transit time in the villi.(24, 29, 30) If this compensatory mechanism does not suffice to maintain aerobic metabolism, the tissue switches to anaerobic metabolism. But this leads to cellular swelling, electrolyte imbalances and the production of toxic oxygen free radicals, causing direct damage to cell membranes and endogenous inflammatory cascades leading to capillary leakage and widespread tissue damage. Although, revascularisation is the main treatment in this situation, one should be aware that with the restoration of blood supply, outflow of the free oxygen radicals and ischemic products into the systemic circulation leads to systemic injury and responses. This is called reperfusion injury.(1, 18, 22, 24, 28)

Etiology

The classical syndrome "angina abdominalis" was first described in the early twentieth century.(28) Since then, our knowledge has expanded and we speak of a spectrum of mesenteric circulatory disorders with a variety of complaints. Mesenteric vessel pathology can be divided into occlusive and non-occlusive abnormalities, presentation in asymptomatic and symptomatic and onset can be acute (acute mesenteric ischemia, AMI) or chronic (chronic mesenteric ischemia, CMI). Figure 2 shows the spectrum of mesenteric disorders.

Figure 2 Spectrum of mesenteric disorders.



Epidemiology

AMI is thought to be rare and accounting for one in 1000 patients presenting to emergency rooms and approximately 1% of acute abdomen hospitalizations, but experts believe that this is an underestimation with its incidence of 7.3-12.9/100.000 persons per year which increases with the aging population and unhealthy lifestyle.(2, 31-34) In general, women are affected three times more often than men, ages are typically between 60 and 70 and most patients have an extensive (vascular) history.(2, 28) About 20% of the AMI patients previously had chronic complaints. This is called acute-on-chronic mesenteric ischemia (AoCMI).(3)

Acute arterial occlusion causes 70% to 80% of AMI. A cardiac embolism in the first branch of the SMA accounts for 40-50% of cases and incidence rises significantly with age, up to more than 200 per 100,000 persons per year over the age of 85 years.(1, 2, 35) In 20-30% acute arterial thrombosis is seen, often as a manifestation of progressive (premature) atherosclerosis, vasculitis and hereditary coagulation disorders. Acute venous mesenteric thrombosis is seen in 5-15% of cases, with 90% related to thrombophilia, trauma or local inflammatory changes.(1) In the other cases, the cause is often unknown or a combination of factors.

In 5-15% AMI can also occur in the absence of anatomical deformities, like in severe shock from multi-trauma or cardiac surgery, called non-occlusive mesenteric ischemia (NOMI). It is

a hypoperfusion syndrome that occurs as a result of selective mesenteric vasoconstriction, one of the earliest compensatory mechanisms for systemic shock, mediated by catecholamines.(1, 2, 36)

The incidence of CMI has always been estimated at 2 to 3 per 100,000. But recently, Terlouw et al. showed that incidence is at least 9,2 per 100,000 per year, making CMI anything but a rare disease, approximating Crohn's disease (10,9 per 100,000) and topping ruptured abdominal aortic aneurysms (7,0 per 100.000) and gastric (7,3 per 100.000) and oesophageal cancer (9,1 per 100.000).(37-39)

A distinction is made between symptomatic stenoses in one, two or all three mesenteric arteries, also described as one-vessel, two-vessel or three-vessel CMI, with varying degrees of severity of the disease. The median arcuate ligament syndrome (MALS), also referred to as Dunbar's syndrome or the coeliac artery compression syndrome (CACS), is a special entity of 1-vessel CMI in which chronic abdominal pain occurs due to respiratory-related alternating compression of the coeliac artery by the median arcuate ligament (MAL). The existence of this syndrome has been discussed since 1972.(2, 3, 40) Incidence and prevalence are a great unknown, but CA compression by the MAL can be found at 3.4-7.3% in asymptomatic patients undergoing imaging for other reasons.(3) More than 90% of chronic stenoses and occlusions in the mesenteric arteries are caused by atherosclerosis with accompanying risk factors, such as smoking, hypertension and dyslipidaemia.(1)

Clinical presentation

Diagnosing both AMI and CMI is based on a "high index of suspicion" in patients with (acute) nonspecific abdominal symptoms.(2, 3)

AMI should be considered for acute abdominal complaints lasting for more than two hours, after exclusion of much more common causes such as acute cholecystitis, intestinal perforation or obstruction and acute pancreatitis. In all forms of AMI, the discrepancy between the patient's complaints, the abdominal examination and the routine blood test is striking. In the first hours there are severe abdominal pains, while physical examination is mostly reassuring. After that there is a relatively quiet period in which the severe abdominal pains diminish, peristalsis subsides and the abdomen becomes more diffusely painful. When the intestinal infarction becomes transmural, all the symptoms of peritonitis occur with the accompanying rapidly deteriorating prognosis.(2, 18, 28)

Be aware of progression to acute-on-chronic mesenteric ischemia (AoCMI) in patients with longstanding abdominal complaints and a history of two-vessel CMI. If they develop

persistent abdominal pain for more than two hours in a fasting state - vascular abdominal resting pain – they have a high risk of imminent transmural infarction.(2, 32)

Classic presentation of CMI patients is a postprandial pain. The pain, which can be indicated throughout the abdomen, starts within 30 minutes of the meal, is whining, nagging or gnawing and may be accompanied by bloating or a "brick" feeling in the upper abdomen. One or two hours after the meal, the pain subsides. Due to the pain attributed to the meal, patients develop a fear of eating, although they do like to eat.(3) As a result, they will increasingly omit different foods from their diet, especially fats and proteins. Finally, they eat in small portions 6-8 times a day, causing unintentional weight loss in 61–94% of patients and malnutrition.(3) The abdominal pain may also be related to physical exercise, for instance in cycling, but also in household chores like vacuuming. Long lasting gastritis, peptic ulcers or recurrent mild diarrhea may also be signalling symptoms.(3)

The physical examination hardly contributes to the diagnosis of CMI. The abdominal souffle is a highly non-specific sign and cannot predict the presence or absence of any significant stenosis in an intestinal artery. Weight and body-mass index (BMI in kg / m2) will only be reduced in the final stage of CMI.(3)

Diagnosis

Delayed recognition is the biggest problem, but ever so common in diagnosing mesenteric ischemia, because clinical presentation is vague and non-specific. Only a high index of suspicion and expeditious exclusion of other causes may lead to the timely diagnosis of AMI or CMI, but there is still not a single test or combination of tests that is easily accessible, non-invasive, low in costs and has a high positive and negative predictive value for determining AMI or CMI. It’s good to realize that in CMI the classic triad of chronic postprandial pain, an upper abdominal souffle and weight loss, along with significant stenoses in two or three intestinal arteries is present in only 22% of the patients.(3, 41) The negative predictive value of this triad is 15% and the positive predictive value is 62 %.(3, 42)

Historically, *digital subtraction angiography (DSA)* was considered the gold standard for diagnosing mesenteric ischemia. It provides excellent imaging of the mesenteric vasculature and gives direct access for endovascular intervention. In addition, and in contrast to the computer tomographic angiography (CTA) and magnetic resonance angiography (MRA), DSA is the only imaging technique that offers the possibility to give meaning about the clinical relevance of mesenteric macrovascular abnormalities.(5) Namely, the presence of a grade 2 collateral, a collateral that is visible on non-selective angiography, is indicative for a

significant mesenteric stenosis. In addition, the presence of a Riolan collateral is indicative for multivessel disease.(5) It is, however, an invasive procedure with a high radiation load and concomitant potential complications. Also, CTA became more accessible over the last decades. This led to the replacement of DSA by *Computer Tomographic Angiography (CTA)*. (2, 3, 42) It offers good possibilities for assessing the degree of stenosis or occlusion and revascularization possibilities. And for AMI also, the presence of ominous pathological features such as pneumatosis intestinalis, intra-abdominal free air and portal pneumatosis. With an accuracy of 95 - 100% an acute three-phase contrast-enhanced CTA with a maximum section thickness of 1 mm in the arterial phase is the first choice in AMI and second in CMI, operated according to the ALARA-principal for doses, in other words "as low as reasonably achievable, economic and social factors taken into account".(2, 3, 43) It can give insight in both all macrovascular anatomical abnormalities of the mesenteric arteries and veins and possible perfusion problems of the mucosa with the important advantage that other causes of the abdominal complaints can be examined as well.(2, 3)

Transabdominal doppler ultrasonography (Duplex) aids visualizing the anatomy and measuring flow rates in the mesenteric arteries. It has an accuracy of 90% in trained hands. In the fasted patient, the flow rates during in- and expiration are measured at the location of the origins of the mesenteric arteries. An absent flow pattern, an increased peak systolic flow rate, or an increased end-diastolic flow rate is indicative of significant stenoses.(2, 3, 44) The verdict is still out on the role of duplex after endovascular treatment, as a stent could cause haemodynamic changes, possibly leading to overestimation of in-stent stenosis.(45)

Magnetic resonance angiography (MRA) has a sensitivity of 100% and a specificity of 91–100% and can also be used to visualize the mesenteric vessels in three dimensions, making it a good alternative to the CTA in case of, for example, contrast allergy. Although, both the CTA and the MRA can show collateral vascularisation, both modalities are not suitable to assess the clinical relevance of these collaterals.(2, 3)

Much research has been done to develop an accurate, minimally invasive and widely applicable function test for the determination of intestinal wall blood flow. Stomach exercise tonometry, 24-hour gastrojejunotonometry (78% and 92%, sensitivity and specificity, respectively) and visual light spectroscopy (VLS, 90% and 60%, sensitivity and specificity, respectively) are the only validated function tests for gastric and intestinal blood flow. (3) However, these tests are operator-dependent and invasive and the mechanism of the tonometry apparatus is vulnerable and no longer in production.

In an attempt to achieve more timely diagnosis, much research has been done in recent years into the diagnostic value of biomarkers in AMI and CMI. This is based on the idea that blood is taken from all patients and biomarkers are already assessed, causing no additional burden to the patient and may reduce time between onset of symptoms and undergoing a CTA. Because of conflicting data and low quality of studies in literature, the international Guidelines on AMI and CMI have stated that up until now there is not a valid biomarker test for AMI and CMI.(2, 3) Nonetheless, biomarkers like lactate, leucocytes and CRP are continually used in daily practice. Whether there is sufficient evidence for biomarkers to have a role in the diagnostic process of AMI patients will be substantiated in **Chapter 2**.

Treatment strategies for AMI and CMI

If there is only one thing you take away from this thesis, it will have to be that the number one rule in AMI treatment is to first restore vascularisation before any resection can take place, if still necessary, stated in **Chapters 3, 4 and 5**.

Historically, big surgeons made big incisions. Nothing less could be said for dinosaur vascular surgeons operating on mesenteric ischemia patients. But, with the uprise and broad acceptance of the minimally invasive intervention doctrine, also patients with AMI and CMI are preferably treated with percutaneous mesenteric artery stenting (PMAS). In **Chapter 3 and 5** we will show that outcome is improved and bowel and lives are being saved, with less morbidity and better quality of life. So nowadays, endovascular treatment is first choice in both AMI and CMI patients, Figure 3.(2, 3)

Due to the emergence of the hybrid operating theatre, the possibility of multimodal treatment arose with the ultimate development of retrograde open mesenteric stenting (ROMS). In ROMS, retrograde stenting can be performed via a small laparotomy and bowel vitality can be assessed in the same procedure. Combining the best of both techniques and is now the second choice in the treatment of AMI, as described in **Chapter 4**.(2, 3)

And last choice is antegrade autologous reconstruction of both the origin of the AC and the SMA. It has the best primary patency (90% versus 50% in PMAS), but as we will show in **Chapter 3 and 5**, it is reserved for relatively young patients in good condition, with little co-morbidity, because morbidity is higher and hospital stay including IC stay is longer after open surgical treatment than endovascular treatment. Furthermore, most AMI and 3-vessel CMI patients are not in the right condition to undergo this extensive bypass surgery.(2, 3)

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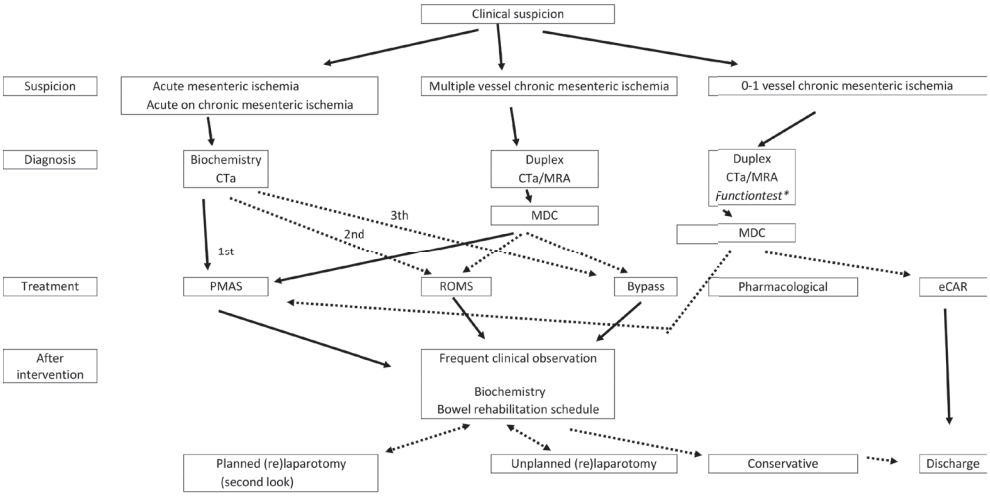
Figure 3 Flow diagram for the diagnosis and treatment of mesenteric ischemia.



CTa = contrast enhanced multislice Computer Tomographic Angiography, MRA = Magnetic Resonance Angiography, MDC = Multidisciplinary consultation, PMAS = Percutaneous Mesenteric Antegrade Stenting, ROMS = Retrograde Open Mesenteric Stenting, eCAR = endoscopic Coeliac Artery Release

The main reason to perform revascularization first is to stop the ischemia and thereby prevent the progression of the disease. Although reperfusion injury can also contribute to transmural ischemia, this effect is smaller than ongoing ischemia, which occurs when a laparotomy is performed to assess the bowel vitality and to resect any necrotic segments before restoration of blood flow. However, if there are signs of peritonitis or if transmural ischemia is suspected after revascularization, a laparotomy is necessary to assess bowel vitality.

Assessment of bowel vitality

The assessment of bowel vitality, also described in **Chapter 5**, is first done by the visual assessment of intestinal wall for signs of necrosis and whether this is still reversible or not. In addition, palpation and the use of Doppler of arteries and veins gives information whether there is blood flow to the inspected bowel segment, both performed in the mesentery and on the transition from mesentery to the intestinal wall. It is essential to assess the entire

intestinal package in this way. To ensure this, laparotomy is recommended over laparoscopy. Intestinal segments with evident transmural ischemia are resected.(2)

It is often difficult to distinguish dubiously vital from non-vital intestines. A severely ischemic bowel, especially if there is an acute venous ischemia, can fully recover after aggressive support of the local and systemic circulation. Furthermore, reperfusion injury can also cause transmural ischemia and lead to necrotic bowel, which should be resected. Therefore, planned relaparotomy, second look, is advised to reassess vitality.

If the remaining bowel appears vital, a primary anastomosis of the bowel is recommended, as performing ostomy leads to more morbidity.(2, 46) If a primary anastomosis is not possible or desirable due to questionable bowel vitality, it is recommended to leave the stapled bowel in the abdomen and also perform a planned, second look after 24 to 48 hours. When possible, a postponed primary anastomosis can be performed.(2)

Supportive measurements and additional treatments

Although revascularisation stops the viscous downward spiral of (localized) severe vasoconstriction and systemic shock caused by toxins, fluid resuscitation and administering low dose of positive inotropes (preferably no dopamine or adrenaline) and vasodilators can help with the reversal of the reactive vasoconstriction.(2, 18, 47) Additionally, systemic heparinization is recommended to inhibit (progressive) thrombosis, but be aware of severe bleeding from the ischemic mucosa.(2) Due to the possibility of fast reversibility, we opt for unfractionated heparin and striving for an antiXa between 0.4 and 0.7.

In the absence of signs of peritonitis and with an angiographically proven NOMI or venous thrombosis, a laparotomy can be omitted. Frequent clinical observation is requirement. Antibiotic therapy in the acute phase is strongly recommended to minimize the systemic consequences of bacterial translocation through the damaged mucosa.(2)

Caution should be exercised with oral and parenteral nutrition of patients with (suspected) imminent intestinal infarction to prevent further infarction, both before and after revascularization. Increasing the metabolic intake will actually lead to an increased demand in mesenteric blood circulation which cannot be met and exacerbates ischemia. Parenteral nutrition can further aggravate ischemia by hepatic steal. Intestinal blood flow will decrease ultimately resulting in ileocoecal infarction, because blood is “diverted” towards the liver as a result of increased demand, because the liver metabolizes the parenteral nutrition.(2)

After revascularization, the extension of the oral diet should be adjusted according to the severity of the patient's ischemia prior to revascularization. A specially developed bowel rehabilitation schedule is essential, see Table 1 and **Chapter 5**. Progression through the diet is based on the monitoring of complaints and the course of leucocytosis and CRP. After elective reconstruction, patients can be fully mobilized quicker. Due to the occurrence of reperfusion damage or revascularization oedema, the functional recovery of the bowel may take longer in severe multivessel CMI and AMI, requiring long-term support with total parenteral nutrition (TPN). In patients in whom enteral nutrition is not expected soon, tube feeding in minimal amounts can prevent severe villi atrophy.

Table 1 Intestinal rehabilitation schedule (9 steps) after revascularization of AMI or end-stage 2-3 vessel CMI

Step		Oral intake
1	*Day 0*	No oral intake
2	*Day 1*	One sip of water or tea every half hour
3		Up to 75 ml (one glass) of clear drinks every two hours
4	*Day 2-3*	75 ml clear drinks every 2 hours + 1 slice of bread spread over six portions per day
5		1 to 2 sandwiches throughout the day + unlimited clear fluids
6	*Day 3-5*	1 to 2 sandwiches throughout the day + unlimited clear fluids + ¼ bright hot meal
7	*Day 4-6*	2 sandwiches throughout the day + unlimited clear fluids + possibly a hot meal divided in several portions of ¼ or ½
8	*Day 5-7*	Normal diet throughout the day in ¼ or ½ servings + unlimited fluids
9	*Day 6-8*	Normal nutrition. If necessary, expand 6 smaller portions spread over the day to normal amounts 3 times a day, depending on the patient's diet

Secondary prevention is essential, both before and after revascularization. Lifestyle rules should be advised, such as a transition to use smaller meals more frequent and spread throughout the day, to reduce the metabolic load per meal. In addition, patients should be advised on the importance of healthy nutrition, little or no alcohol consumption, frequent exercise and weight monitoring. And of course, the importance of smoking cessation should be stressed, as nicotine is a strong mesenteric vasoconstrictor. Furthermore, attention should be paid to optimizing treatment of additional diseases, like hypertension and hyperlipidaemia. Also, the use of proton pump inhibitors could be considered to balance gastric energy-consuming activity and gastric mucosal blood flow by strongly inhibiting gastric acid secretion.(2, 3) For optimum results, patients should preferably be guided by professionals.

No specific guidelines or studies are available for the anticoagulation policy after PMAS, ROMS or open vascular reconstructions in mesenteric ischemia. Based on a literature review the Dutch Mesenteric Ischemia StudyGroup (DMIS) recommends six months of double platelet aggregation inhibitor (TAR) (clopidogrel 1dd 75mg + ascal 1dd 80/100mg), followed by lifelong clopidogrel in atherosclerotic cases. If there is an indication for Vitamin K-antagonists or direct thrombin inhibition, three months direct oral anticoagulantion (DOAC) or coumarin + ascal, after which DOAC or coumarin is continued is postulated. (www.dmisg.nl)

Outcome

As mentioned before, end stage AMI is a deadly disease, with a mortality up to 90% if left untreated.(1, 2) Unfortunately, there is no data on morbidity and mortality before treatment of CMI available and the 2017 ESVS Guidelines encouraged research in this field.(2) The in-hospital mortality and morbidity rates after revascularisation for AMI are 60 to 80% and 39%, respectively. For CMI in-hospital mortality and morbidity rates after revascularisation are 1 to 17% and 38%, respectively.(1, 48-50) These numbers are still substantial and improvement is vital. By centralizing care and treating patients in dedicated teams, outcome can be improved. Looking at the outcome data of the Dutch Expert Centre of Gastro-Intestinal Ischemia in the MST for the past 5 years, hospital mortality for acutely or urgently treated patients was mean 21.1% and for elective patients 1.2%. For the entire population, the probability of a reintervention was mean 9.5% and of a complication was 25.1%.

Authors' perspectives

It is what we all want. A long and happy life. Interestingly, if you look at outcome measures in mesenteric ischemia studies, the number of studies reporting on QoL, socioeconomic burden and costs is dramatically low. In exaggerated terms, all studies focus on technical outcomes. Don't get me wrong, good technical results are very important. However, anno 2022 we find ourselves in a new era of patient centered care with much more emphasis on minimally invasive and organ-preserving treatment and improvement of QoL, as we focus more on life after the illness. Therefore, in **Chapter 8 and 9** we described the impact of treatment for CMI patients on their QoL and the impact of being taken serious on QoL.

Stomach-ache belongs to everyone and everyone has had it from time to time. Mainly because of very obvious and innocent reasons. And, yes, public opinion portraits someone

complaining of a stomach ache from eating an apple as a little crazy. Stomach aches will pass with time. So, stop whining, pull yourself together and get on with it. Not infrequently, we see that our patients have suffered for years with misunderstood abdominal complaints. They have visited countless different doctors without the desired result and ended up semi-voluntarily, semi-forced going to the psychiatrist or exploring alternative medicine, because the cause of the complaints will probably be a matter of the mind or the soul. This is very true for MALS patients, for example. Not in the least because to this day there is a discussion amongst healthcare professionals whether this disease even exists and whether endoscopic coeliac artery release ((e)CAR) is a (cost)effective treatment. Therefore, in **Chapter 6** we will give more inside on these questions, leading up to the study protocol in **Chapter 7** with which we hope to answer both questions for once and for all.

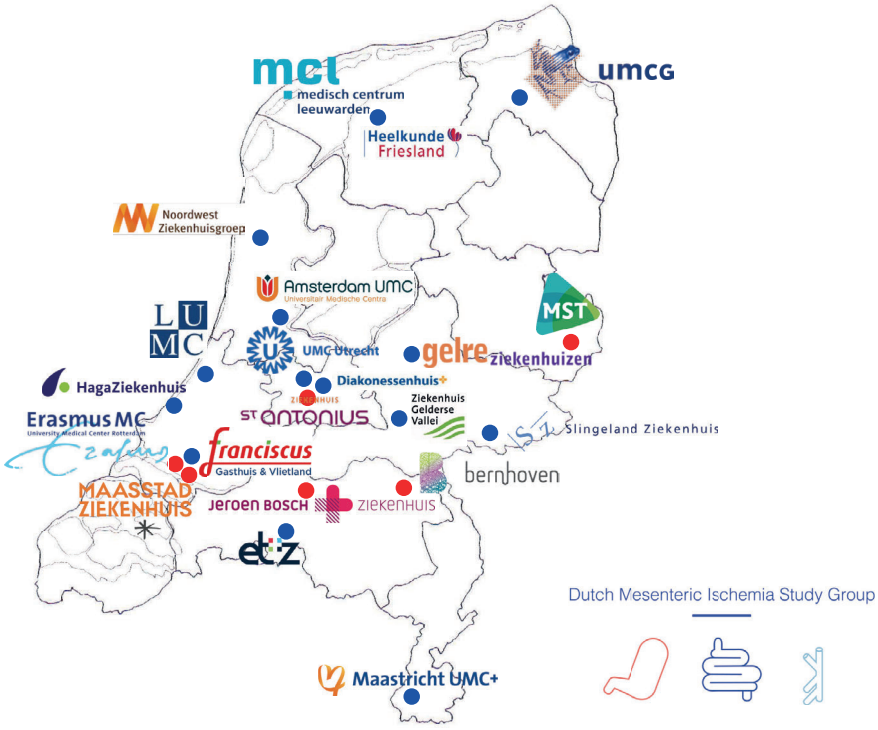
So, can we do more? Can we save more patients? Can we help doctors by providing more awareness and better tools? Can we silence the dinosaurs and make minimally invasive treatment option number one all over the world? Because those who were treated, what kind of life do they get to lead? We saved their life, but did we save enough? Did we leave them with enough bowel? Did we leave them without one or more ostomies? Did we leave them with a closed abdomen? Are they able to eat normally or do they need parenteral nutrition?

What measures can we take to prevent further harm? First, we should listen to our mothers. Second, we must follow a good training plan for the marathon and not get ahead of ourselves. But third, and most importantly, we must enhance awareness of this disease and enable more doctors to recognise, diagnose and treat this debilitating illness properly in order to save bowel and patients.

Since 2015, DMIS was founded by a multidisciplinary group of experts in The Netherlands and has been working hard to expand knowledge and create more awareness among doctors and investigate better options for diagnosis and treatment, Figure 4. With worldwide collaborations and papers covering all fields of the disease, we have contributed to the acceleration of exposure of mesenteric ischemia on the global playing field of vascular and gastrointestinal diseases.

And, although we have hit many obstacles along the way, we will continue to work and grow and help patients.

Figure 4 Collaborating Hospitals of the Dutch Mesenteric Ischemia Study Group (DMIS) November 2021



Outline of this thesis

The general objective of this thesis is to broaden insight in diagnostic and therapeutic developments in mesenteric ischemia and to raise awareness for more modern approaches in bowel saving practices. In Part I we will show what the possibilities are to prevent or reduce morbidity and mortality for AMI patients. We will discuss the present status of diagnostic developments in occlusive AMI patients and focus on possibilities to improve the diagnostic process. Furthermore, we will focus on the evolution of treatment strategies. We will describe the historical route to contemporary practice and end with the new insights. In Part II we will focus on QoL. We will share with you the impact of treatment on QoL for CMI and in particular MALS and the protocol of the ground breaking new DMIS study on treatment of MALS.

In the General Discussion we will look to the future and express expectations and address those topics in which we feel further research is necessary.

Part I Developments in Diagnostics and the evolution of Treatment

In the search for a better diagnostic tool, biomarkers are thought to be the solution to our problems. The aim of **Chapter 2** was to this review is to assess the potential diagnostic value of biomarkers for AMI.

In addition to the importance of early diagnosis on QoL, optimal treatment is key in aiming for the best QoL. But which treatment do you choose? In an era in which endovascular treatment enjoys it heydays, what can be expected of open surgical mesenteric artery repair and which patients benefit the most at what time? This is investigated in **Chapter 3**.

Modern times need modern solutions for modern problems. What to do when daily practice does not suit the patient or the problem? You adapt. **Chapter 4** shows the reader that there is an alternative for major surgery or doing nothing when antegrade endovascular treatment is not an option.

To get a better understanding of what to expect of the outcome of the different treatment options, **Chapter 5** paints the full picture of treating patients with mesenteric ischemia by describing current insights. In order to help make the best decisions.

Part II: Life after mesenteric ischemia

Does the Median Arcuate Ligament Syndrome (MALS) exist? It's literally a million-dollar question. To answer the question, we performed a systematic review in **Chapter** 6 to give an overview of current literature. This review serves as a scientific basis for our application to the National Health Care Institute for a subsidy from the "Promising Care" project with which we can answer this important question. Building on that, in **Chapter 7** we aimed to answer the question whether patients with disabling abdominal symptoms benefit from being treated with endoscopic Coeliac Artery Release ((e)CAR). Which would mean that MALS does exist. And furthermore, if (e)CAR is useful as a minimal invasive (cost)effective treatment for MALS.

The big question is, are we actually helping our patients? We know our primary outcome measures and we know that we are technically doing excellent work. But never before have we looked at the patient's perspective. **Chapter 8** evaluates the impact of revascularisation on quality of life.

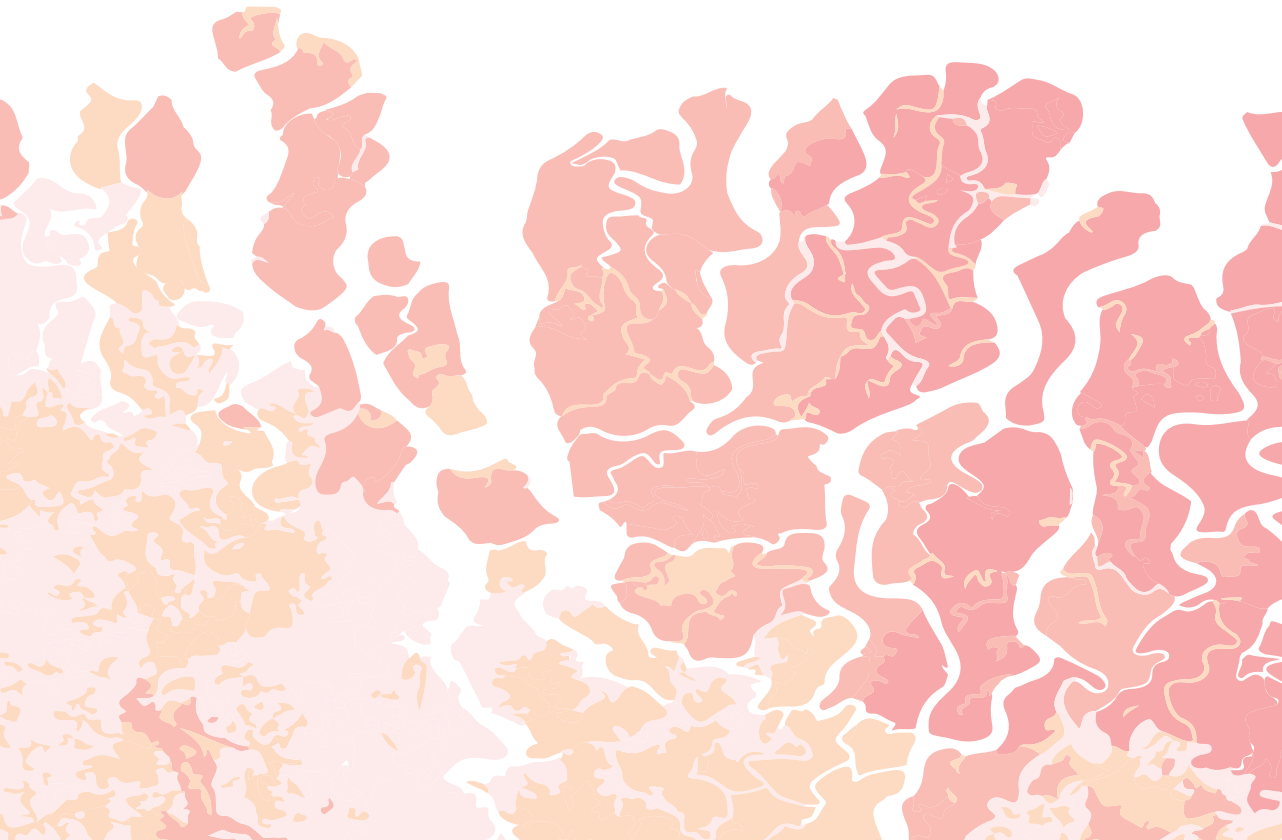
And last, but not least, **Chapter 9** evaluates the quality of life of patients referred to our hospital but not diagnosed and treated for mesenteric ischemia. Is there any influence of the thoroughly diagnostic process including shared decision making on the experienced QoL of individuals referred to an expert centre of gastro-intestinal ischemia?

References

1. Clair DG, Beach JM. Mesenteric Ischemia. N Engl J Med. 2016;374(10):959-68.
2. Björck M, Koelemay M, Acosta S, Bastos Goncalves F, Kölbel T, Kolkman JJ, et al. Editor's Choice - Management of the Diseases of Mesenteric Arteries and Veins: Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2017;53(4):460-510.
3. Terlouw LG, Moelker A, Abrahamsen J, Acosta S, Bakker OJ, Baumgartner I, et al. European guidelines on chronic mesenteric ischaemia - joint United European Gastroenterology, European Association for Gastroenterology, Endoscopy and Nutrition, European Society of Gastrointestinal and Abdominal Radiology, Netherlands Association of Hepatogastroenterologists, Hellenic Society of Gastroenterology, Cardiovascular and Interventional Radiological Society of Europe, and Dutch Mesenteric Ischemia Study group clinical guidelines on the diagnosis and treatment of patients with chronic mesenteric ischaemia. United European Gastroenterol J. 2020;8(4):371-95.
4. Wilson DB, Mostafavi K, Craven TE, Ayerdi J, Edwards MS, Hansen KJ. Clinical course of mesenteric artery stenosis in elderly americans. Arch Intern Med. 2006;166(19):2095-100.
5. van Petersen AS, Kolkman JJ, Meerwaldt R, Huisman AB, van der Palen J, Zeebregts CJ, et al. Mesenteric stenosis, collaterals, and compensatory blood flow. J Vasc Surg. 2014;60(1):111-9, 9.e1-2.
6. McNulty JG, Hickey N, Khosa F, O'Brien P, O'Callaghan JP. Surgical and radiological significance of variants of Buhler's anastomotic artery: a report of three cases. Surg Radiol Anat. 2001;23(4):277-80.
7. Michalinos A, Schizas D, Ntourakis D, Filippou D, Troupis T. Arc of Buhler: the surgical significance of a rare anatomical variation. Surg Radiol Anat. 2019;41(5):575-81.
8. Walker TG. Mesenteric vasculature and collateral pathways. Semin Intervent Radiol. 2009;26(3):167-74.
9. Saad WE, Davies MG, Sahler L, Lee D, Patel N, Kitanosono T, et al. Arc of buhler: incidence and diameter in asymptomatic individuals. Vasc Endovascular Surg. 2005;39(4):347-9.
10. DiBaise JK, Young RJ, Vanderhoof JA. Intestinal rehabilitation and the short bowel syndrome: part 1. The American journal of gastroenterology. 2004;99(7):1386-95.
11. Nightingale J SR. Normal intestinal anatomy and physiology. In: Nightingale J, ed. Intestinal Failure. London.: Greenwich Medical Media Limited,; 2001.
12. Borgstrom B, Dahlqvist A, Lundh G, Sjovall J. Studies of intestinal digestion and absorption in the human. J Clin Invest. 1957;36(10):1521-36.
13. Levitan R, Goulston K. Water and electrolyte content of human ileostomy fluid after d-aldosterone administration. Gastroenterology. 1967;52(3):510-2.
14. Davis GR, Santa Ana CA, Morawski SG, Fordtran JS. Permeability characteristics of human jejunum, ileum, proximal colon and distal colon: results of potential difference measurements and unidirectional fluxes. Gastroenterology. 1982;83(4):844-50.
15. Fordtran JS, Rector FC, Jr., Ewton MF, Soter N, Kinney J. Permeability characteristics of the human small intestine. J Clin Invest. 1965;44(12):1935-44.
16. Debongnie JC, Phillips SF. Capacity of the human colon to absorb fluid. Gastroenterology. 1978;74(4):698-703.
17. Jorgensen JR, Fitch MD, Mortensen PB, Fleming SE. In vivo absorption of medium-chain fatty acids by the rat colon exceeds that of short-chain fatty acids. Gastroenterology. 2001;120(5):1152-61.
18. Oldenburg WA, Lau LL, Rodenberg TJ, Edmonds HJ, Burger CD. Acute mesenteric ischemia: a clinical review. Arch Intern Med. 2004;164(10):1054-62.

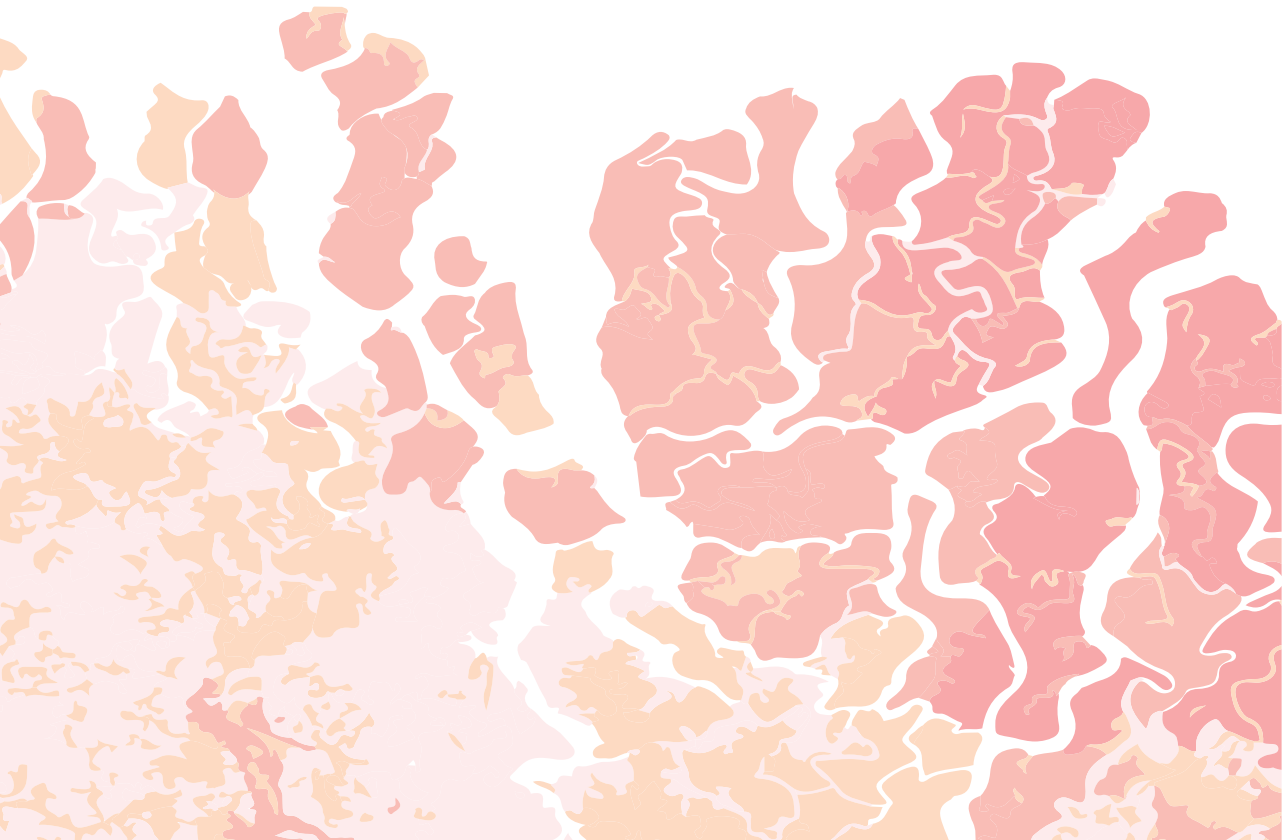
19. Marston A CJ, Garcia Garcia J. Intestinal function and intestinal blood supply: a 20-year surgical study. Gut 1985;26:656–66. 1985.
20. Granger DN RP, Kvietys PR, Mortillaro NA. Intestinal Blood Flow. Gastroenterology 1980 Apr;78(4):837-63. 1980.
21. ter Steege RW, Kolkman JJ. Review article: the pathophysiology and management of gastrointestinal symptoms during physical exercise, and the role of splanchnic blood flow. Aliment Pharmacol Ther. 2012;35(5):516-28.
22. van Noord D, Kolkman JJ. Functional testing in the diagnosis of chronic mesenteric ischemia. Best practice & research Clinical gastroenterology. 2017;31(1):59-68.
23. Kvietys P. The Gastrointestinal Circulation. Chapter 2, Anatomy. San Rafael (CA): Morgan & Claypool Life Sciences; 2010.
24. Powell A, Armstrong P. Plasma biomarkers for early diagnosis of acute intestinal ischemia. Semin Vasc Surg. 2014;27(3-4):170-5.
25. Boley SJ, Sprayregan S, Siegelman SS, Veith FJ. Initial results from an agressive roentgenological and surgical approach to acute mesenteric ischemia. Surgery. 1977;82(6):848-55.
26. Eltarawy IG, Etman YM, Zenati M, Simmons RL, Rosengart MR. Acute mesenteric ischemia: the importance of early surgical consultation. Am Surg. 2009;75(3):212-9.
27. Cudnik MT, Darbha S, Jones J, Macedo J, Stockton SW, Hiestand BC. The diagnosis of acute mesenteric ischemia: A systematic review and meta-analysis. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 2013;20(11):1087-100.
28. Wyers MC. Acute mesenteric ischemia: diagnostic approach and surgical treatment. Semin Vasc Surg. 2010;23(1):9-20.
29. Levitt DG, Bond JH, Levitt MD. Use of a model of small bowel mucosa to predict passive absorption. The American journal of physiology. 1980;239(1):G23-9.
30. Shepherd AP, Kiel JW. A model of countercurrent shunting of oxygen in the intestinal villus. The American journal of physiology. 1992;262(4 Pt 2):H1136-42.
31. Acosta S. Epidemiology of mesenteric vascular disease: clinical implications. Semin Vasc Surg. 2010;23(1):4-8.
32. Karkkainen JM, Acosta S. Acute mesenteric ischemia (part I) - Incidence, etiologies, and how to improve early diagnosis. Best practice & research Clinical gastroenterology. 2017;31(1):15-25.
33. Karkkainen JM, Lehtimaki TT, Manninen H, Paajanen H. Acute Mesenteric Ischemia Is a More Common Cause than Expected of Acute Abdomen in the Elderly. J Gastrointest Surg. 2015;19(8):1407-14.
34. Acosta S, Ogren M, Sternby NH, Bergqvist D, Bjorck M. Clinical implications for the management of acute thromboembolic occlusion of the superior mesenteric artery: autopsy findings in 213 patients. Annals of surgery. 2005;241(3):516-22.
35. Brown DJ, Schermerhorn ML, Powell RJ, Fillinger MF, Rzucidlo EM, Walsh DB, et al. Mesenteric stenting for chronic mesenteric ischemia. J Vasc Surg. 2005;42(2):268-74.
36. Kolkman JJ, Mensink PB. Non-occlusive mesenteric ischaemia: a common disorder in gastroenterology and intensive care. Best practice & research Clinical gastroenterology. 2003;17(3):457-73.
37. Terlouw LG, Verbeten M, van Noord D, Brusse-Keizer M, Beumer RR, Geelkerken RH, et al. The Incidence of Chronic Mesenteric Ischemia in the Well-Defined Region of a Dutch Mesenteric Ischemia Expert Center. Clin Transl Gastroenterol. 2020;11(8):e00200.

38. IntegraalKankercentrumNederland. Slokdarm- en maagcarcinoom2021.
39. FederatieMedischSpecialisten. Richtlijn Maagcarcinoom2017.
40. Szilagyi DE, Rian RL, Elliott JP, Smith RF. The celiac artery compression syndrome: does it exist? Surgery. 1972;72(6):849-63.
41. Mensink PB, Moons LM, Kuipers EJ. Chronic gastrointestinal ischaemia: shifting paradigms. Gut. 2011;60(5):722-37.
42. Kolkman JJ, Bargeman M, Huisman AB, Geelkerken RH. Diagnosis and management of splanchnic ischemia. World J Gastroenterol. 2008;14(48):7309-20.
43. https://www.eu-alara.net/.
44. AbuRahma AF, Scott Dean L. Duplex ultrasound interpretation criteria for inferior mesenteric arteries. Vascular. 2012;20(3):145-9.
45. van Dijk LJ, van Petersen AS, Moelker A. Vascular imaging of the mesenteric vasculature. Best practice & research Clinical gastroenterology. 2017;31(1):3-14.
46. Gooszen AW, Geelkerken RH, Hermans J, Lagaay MB, Gooszen HG. Quality of life with a temporary stoma: ileostomy vs. colostomy. Diseases of the colon and rectum. 2000;43(5):650-5.
47. Montagnana M, Danese E, Lippi G. Biochemical markers of acute intestinal ischemia: possibilities and limitations. Annals of translational medicine. 2018;6(17):341.
48. Kougias P, Lau D, El Sayed HF, Zhou W, Huynh TT, Lin PH. Determinants of mortality and treatment outcome following surgical interventions for acute mesenteric ischemia. J Vasc Surg. 2007;46(3):467-74.
49. Lejay A, Georg Y, Tartaglia E, Creton O, Lucereau B, Thaveau F, et al. Chronic mesenteric ischemia: 20 year experience of open surgical treatment. Eur J Vasc Endovasc Surg. 2015;49(5):587-92.
50. Schermerhorn ML, Giles KA, Hamdan AD, Wyers MC, Pomposelli FB. Mesenteric revascularization: management and outcomes in the United States, 1988-2006. J Vasc Surg. 2009;50(2):341-8 e1.



PART I

Developments in Diagnostics
and the evolution of Treatment



Chapter 2

The diagnostic value of biomarkers in mesenteric ischemia is insufficiently substantiated, a systematic review

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Submitted.

Abstract

Background In recent years, there has been a growing interest in the diagnostic value of biomarkers to support timely diagnosis of acute mesenteric ischemia (AMI) and thereby improve clinical outcome. With this review we aim to substantiate the potential diagnostic value of biomarkers for AMI.

Methods We have conducted a systematic review of the literature to define the potential diagnostic value of biomarkers for AMI. All studies including ≥10 patients describing biomarkers for macrovascular occlusive AMI between 1950 and May 15th 2021 were identified within the Pubmed, Embase and the Cochrane Library electronic databases. The QUADAS-2 tool was used for the critical appraisal of quality. The study protocol was registered on Prospero (CRD42021254970).

Results There were 49 of 3663 studies eligible for this review describing 60 different biomarkers. The heterogeneity of the studies was high, with endless differences in in- and exclusion criteria, study populations and controls, normal values and cut-off values. The overall quality of the studies was low.

Discussion Biomarkers have the potential to improve outcome of AMI by shortening diagnostic delay. With this systematic review, we have shown that no conclusions can be drawn on the diagnostic value of any biomarker or combination of biomarkers for AMI. Due to the high heterogeneity and low quality of the available evidence on biomarkers for AMI, we advise caution when rejecting or determining AMI solely based on biomarkers.

Introduction

Acute mesenteric ischemia (AMI) is not a rare disease. Although incidence is thought to be 7.3-12.9/100.000 person years, accounting for one in 1000 patients presenting to emergency rooms and approximately 1% of acute abdomen hospitalizations, experts still believe these numbers represent an underestimation.(1-5) Despite significant advances in imaging and treatment options over the past decades, mortality rates remain high, respectively 60 to 80%.(1, 6-12) The single most important reason for this is a delay in diagnosis, because symptoms are non-specific and diagnosis relies on a high index of suspicion.(1, 6, 8, 10, 11, 13-15)

Currently, the gold standard for patients suspected of AMI is to undergo a 1-mm multiphase computer tomography angiography (CTA) scan, with a sensitivity and specificity of 73% to 100% and 90% to 100%, respectively for diagnosing acute superior mesenteric artery (SMA) occlusion.(1) However, in almost all studies that have focused on the diagnostic value of the CT in AMI, the diagnosis was known in advance.(5) In real life, however, clinical suspicion is only mentioned in 31% of the CT referrals.(16, 17) In fact, the critical point lies in 'the suspicion'. Without clinical suspicion, the CT has significantly less diagnostic value (sensitivity of 94% with clinical suspicion versus 81% without clinical suspicion, $p = 0.04$). (5, 18) Accurate triage seems to be the key for timely diagnosis of AMI patients.(19) Lemma et al.(19) showed important differences between presentation at surgical (SER) and non-surgical (SER) emergency departments.(19) Time to CT, diagnosis and operations (10 vs 15 hours) were all shorter with SER presentation compared to non-SER presentation, which also led to shorter hospital stays (7 vs 11 days), fewer bowel resections and less 90-day death rate (50% vs. 75%).(5, 18, 19) If we take in consideration that we only have a 6-8 hours window before transmural ischemia occurs, it is clear patients need a solution to get diagnosed earlier.(20)

In recent years, research has been focussing on biomarkers in the hopes of finding a highly accurate, non-invasive, rapid, 24/7 available and cost-effective diagnostic marker that can solve the diagnostic dilemma and reduce the time to diagnosis.(6, 13, 15, 21) Besides traditional biomarkers like lactate, C-reactive protein (CRP), leucocytes, D-dimer, phosphate and creatine kinase (CK), new biomarkers like Intestinal-Fatty Acid Binding Protein (I-FABP), Ischemia Modified Albumin (IMA) and D-lactate are increasingly investigated. But the holy grail of a single or combination of markers has not been found.(1)

Many systematic reviews and even meta-analyses have been performed on this topic and despite a general very low quality of articles, still diagnostic value has been given to different

biomarkers.(6, 10, 15, 22-24) We wondered what the scientific value of these conclusions was. Furthermore, these reviews included non-homogeneous patient populations and investigated only one or a couple of biomarkers. With this systematic review, we aimed to give a reappraisal of the available literature on the diagnostic value of biomarkers for occlusive AMI, to evaluate if there is any substantial evidence to indicate a leading place for biomarkers in the diagnostic process. By including all biomarkers investigated we aimed to give a more complete overview of the current state of affairs. In addition, we have formulated stricter in- and exclusion criteria striving for a more heterogeneous patient population.

Methods

Search strategy

The literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.(25) Eligible studies describing a biomarker to determine arterial occlusive AMI in humans published between 1950 up until May 15th 2021 were included. A systematic search in Pubmed, Embase and the Cochrane Library was performed to identify all relevant studies published. Secondly, the references of the included studies were checked for additional citations (JB). The protocol for this systematic review was registered on PROSPERO (CRD42021254970).

Study selection

Duplicates were removed. One author (FE) performed the electronic searches. Titles and abstracts of the studies were independently reviewed by two authors (JB and AN), blinded from each other. A first selection was made by screening the titles and abstracts of all studies using pre-defined inclusion and exclusion criteria (Table 1). Next, full text articles were read to make a final selection, and consensus was reached for inclusion. A third screener (RHG) resolved disagreements by adjudication. Full texts were obtained via PubMed, through national and international library requests, and if necessary, by contacting the primary author. If full texts could not be retrieved via these methods, the study was excluded.

To improve the homogeneity of the study population, we decided to include purely macrovascular occlusive mesenteric ischemia. As a result, studies purely describing patients with non-occlusive mesenteric schemia (NOMI), mesenteric ischemia after major surgery or in Intensive Care Unit (ICU) patients and ischemic bowel secondary to other diseases, such as strangulation and obstruction, have been excluded. If the results of macrovascular occlusive AMI patients could be distracted separately from the other subgroups, a study was included.

Table 1 In- and exclusion criteria

Inclusion:	Exclusion:
• Biomarkers in arterial occlusive AMI, defined as arterial atherosclerotic and/or thromboembolic events • Adults • RCT, cohort, retro- and prospective • English, Dutch, German, French • Between 1950 and May 15th 2021	• No arterial occlusive AMI • No data specific for the subgroup of AMI patients included • NOMI, venous thrombosis or bowel ischemia secondarily to other diseases like strangulation • No biomarkers or prognostic use of biomarkers • Children, animals • Duplicate • No abstract or full text available • Others than inclusion languages • Microdialysis • Comments, letter to editor or other forms of own opinions without scientific substantiation • <10 patients included

AMI = Acute mesenteric ischemia, NOMI = non-occlusive mesenteric ischemia, RCT = Randomized Controlled Trial

Assessment of methodological quality

The QUADAS-2 tool was used by two authors (JB and FM) to, independently and blinded from each other, critically appraise the selected studies for risk of bias and applicability. (26) The individual assessments were discussed (JB, FM and RG) after which consensus was reached. Criteria used are available in Appendix 1.

Data extraction and statistical analysis

Two authors (JB, FM) independently extracted data from the included studies. Data extraction included clinical setting, study design, study population, number of patients, reference standard employed, disease prevalence, properties of the respective diagnostic tests and the cut-off level used for each biomarker. Due to the expected heterogeneity in used normal and cut-off values and patient cohorts, no meta-analysis was planned.

Continuous variables were presented as means (standard deviation, SD) or median (interquartile range, IQR) for parametric and nonparametric, respectively. Categorical variables were presented as numbers (percentages).

Results

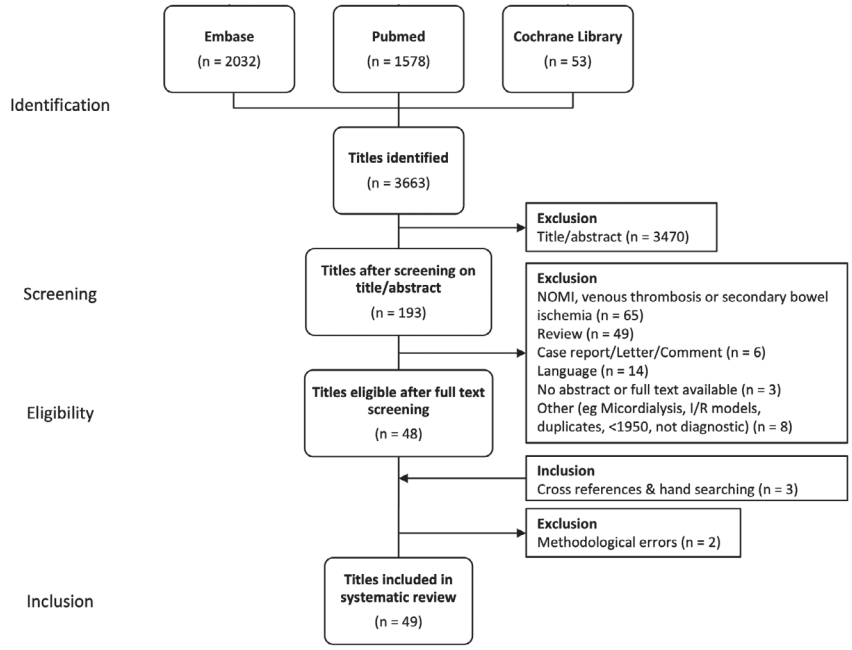
Search and selection criteria

The flowchart according to PRISMA is shown in Figure 1. The terms used for the literature searches are shown as supplementary contents online. A total of 3663 papers were identified

of which 193 were retrieved for full-text review. A total of 49 papers were ultimately selected for final critical appraisal. See Table 2 for the characteristics of the included articles, with prospective articles in grey and retrospective articles in white.

We also excluded 2 studies in which patient data was inconsistent.(27, 28) Both studies showed conflicts in outcomes presented in tables versus what was stated on these outcomes in the text. To the best of our knowledge, one study(27) has been cited 3 times so far, including two systematic reviews(24, 29, 30) and the second study(28) has been cited 4 times so far.(31-34) We have asked both the corresponding authors and the journals concerned for a response, but unfortunately they have not been forthcoming.

Figure 1 Flowchart of search strategy for screening, eligibility and inclusion of included articles describing biomarkers for diagnosing AMI.



NOMI = non-occlusive mesenteric ischemia

Critical appraisal

Results of the critical appraisal are shown in the last column of Table 2. The full QUADAS-2 data is shown in Appendix 2. Overall quality of studies is low, because overall risk of bias and applicability is high. There is only one(35) study with 'low' risk of bias and applicability, and

three studies(36-38) with 'moderate' risk. Of the 49 studies, 34 (69%) were retrospective analysis. Moreover, there was a great variance in used in- and exclusion criteria, leading to great differences in selected AMI patients and control groups, possible exclusion of eligible patients and risks of missing or questionable data. The exact intervals between the index test and the reference standard and whether the investigators were blinded to the outcomes were also not reported in the vast majority of studies. No studies were excluded based on the QUADAS-2 appraisal.

Table 2 Characteristics of included articles describing biomarkers for diagnosing AMI

Author	Marker(s)	Period	Study population	No. of pts (AMI prevalence in %)	Reference test	Quadas – 2 risk of bias
Acosta (36)	D-dimer	1999 - 2000	Clinical suspicion of AMI	6/14 (43%)	Laparotomy	Moderate
Acosta (37)	APTT, Antithrombin, Creatinine, CRP, D-dimer, Fibrinogen, Hb, PT, WBC	2000 - 2003	Acute abdominal pain	9/101 (9%)	Clinical, ECG, endoscopy, lab, laparotomy, radiology, pathology	Moderate
Acosta (39)	Amylase, ALT, AST, INR, Lactate, Troponin 1	2005 - 2009	Acute abdominal pain and vascular treatment of AMI referral	55 (100%)	Laparotomy, radiology	High
Aktimur (40)	MPV, NLR, RDW, WBC	2009 - 2014	AMI patients for laparotomy and/or bowel resection	70/193 (36%)	Laparotomy, pathology	High
Akyildiz (41)	D-dimer	2005 - 2007	Clinical suspicion of AMI	28/47 (60%)	CT, laparotomy	High
Altintoprak (42)	Albumin, ALP, ALT, Amylase, AST, Ca, Cl, Creatinine, GGT, Hb, Ht, K, MPV, Na, Bilirubin, PC, Urea, WBC	2008 - 2012	Surgical intervention for AMI	30 (100%)	Laparotomy	High
Ambe (43)	L-lactate	2009 - 2014	Laparotomy for suspected AMI	64/75 (85%)	Laparotomy	High
Arnalich (44)	Amylase, Bicarbonate, Cell-free plasma DNA, Creatinine, Glucose, LDH	2004 - 2007	Laparotomy for suspected AMI	99/130 (76%)	Laparotomy	High
Beng Fuh (45)	Blood gas, Lactate, WBC	1990-1999	Acute abdomen with suspected AMI	62/116 (53%)	Laparotomy, radiology	High
Bilgiç (46)	LDH, RDW, Urea, WBC	2008 - 2011	Laparotomy for suspected AMI	61 (100%)	Laparotomy	High

Author	Marker(s)	Period	Study population	No. of pts (AMI prevalence in %)	Reference test	Quadas – 2 risk of bias
Bilgiç (47)	ALP, ALT, Amylase, AST, Creatinine, GGT, Hb, Ht, LDH, MPV, PC, Urea, WBC	2005 - 2011	Patients operated with a diagnosis of AMI	61 (100%)	Laparotomy	High
Brillantino (38)	Lactate	2014 - 2015	Acute abdomen	48/284 (17%)	CTA	Moderate
Canfora (48)	CRP, Lactate, LDH, WBC	2010 - 2016	Laparotomy for suspected ITIN	36/55 (65%)	Laparotomy, radiology	High
Chiu (49)	D-dimer	2007 - 2009	Acute abdominal pain and clinical suspicion of AMI	23/67 (34%)	CT	High
Czerny (50)	Lactate	1970 - 1996	Diagnosis of AMI	145 (100%)	Autopsy, clinic, laparotomy, radiology	High
Degerli (51)	MPV, PC	2008 - 2014	Patients operated with a diagnosis of AMI and pathological confirmation	41/123 (33%)	Laparotomy, pathology	High
Destek (52)	CRP, D-dimer, L-lactate, NLR, WBC	2015 - 2019	Laparotomy for suspected AMI	44/51 (86%)	CT, laparotomy or laparoscopy	High
Elthes (53)	ALT, AST, CK, creatinine, Glucose, INR, K, LDH, Na, QT, Urea, WBC	2014 - 2016	Diagnosed with AMI	50 (100%)	Laparotomy	High
Emile (54)	Albumin, Amylase, Creatinine, Electrolytes, Hb, Lactate, pH, PT, WBC	2013 - 2017	Acute abdomen	101 (100%)	Clinic, histology, laparotomy	High
Fried (55)	CK-MB, CK-BB, Total CK		Acute abdomen, suspicion of intra-abdominal catastrophe or admitted with unexplained symptoms	8/50 (16%)	Autopsy, laparotomy, radiology	High
Gaddam (56)	ADH, GGT		AMI	32/125 (26%)		High
Gün (57)	CK, D-dimer, WBC	2012	Abdominal pain, suspected of AMI	13/676 (2%)	CT, laparotomy	High
Gunduz (58)	IMA	2006 - 2007	ED patients with thromboembolic SMA occlusion	7/14 (50%)	Clinic, laparotomy, radiology	High
Güzel (59)	D-dimer, IFABP, WBC	2007 - 2008	AMI, Acute abdomen and controls	30/77 (39%)	Clinic, laparotomy, radiology	High

Author	Marker(s)	Period	Study population	No. of pts (AMI prevalence in %)	Reference test	Quadas – 2 risk of bias
Jamieson (60)	Phosphate	5-year period	Abdominal symptoms and massive gut ischaemia	20 (100%)	Laparotomy	High
Janda (61)	Lactate	1979 - 1983	Acute abdomen, final diagnosis of AMI	18/132 (14%)	Laparotomy	High
Kim (62)	CRP, WBC	2001 - 2016	Consecutive patients diagnosed with acute SMAE	66 (100%)	Clinic, laparotomy, radiology	High
Kisaoglu (63)	Albumin, BUN, CBC, Creatinine, Glucose, LDH, RDW, WBC	2005 - 2013	Patients with AMI, AA patients without urgent surgery required	49/159 (31%)	CTA, laparotomy	High
Lange (64)	Amylase, Lactate	1985 - 1992	Acute abdomen	20/90 (22%)	Clinic, laparotomy	High
Leo (65)	Phosphate	1990 - 1994	Acute abdomen, final diagnosis of AMI or infarction	23/50 (46%)	Laparotomy	High
Lieberman (66)	I-FABP		Clinical suspicion of AMI	7/19 (36%)	Laparotomy	High
Matsumoto (35)	AST, Base deficit, CK, CRP, D-dimer, I-FABP, Lactate, LDH, WBC	2009 - 2010	Acute abdomen	24/208 (12%)	Autopsy, clinic, laparotomy	Low
Meyer (67)	Lactate, WBC	1988 - 1994	AMI	35 (100%)	Clinic, laparotomy, radiology	High
Murray (68)	D-lactate		Laparotomy for acute abdominal emergencies including suspected AMI	9/41 (22%)	Laparotomy	High
Rivera Nunez (69)	LDH, Neutrophils, NLR, WBC	2013 - 2016	Acute abdomen	32/61 (52%)	Radiology, pathology	High
Sachs (70)	CPK, LDH, SGOT, WBC	1965 -1980	Intestinal ischemia treated on medical and surgical departments	49 (100%)	Laparotomy	High
Schoeffel (71)	C3a, EarPI, Endotoxin, FibA, Lactate, PGE2, TNFa		Ischemic bowel wall damage during laparotomy	15/19 (79%)	Laparotomy, angiography	High
Sgourakis (72)	ALP, ALT, AST, BUN, Creatinine, GGT, IL6, IL-8, Lactate acidosis, Neurotensin	2011 - 2012	Acute abdomen	8/53 (15%)	Histology, laparotomy	High
Shi (73)	CPK, CRP, D-lactate, I-FABP, LDH, WBC	2011 - 2014	Severe abdominal pain requiring surgery	7/272 (3%)	Autopsy, endoscopy, laparotomy, CT	High

Author	Marker(s)	Period	Study population	No. of pts (AMI prevalence in %)	Reference test	Quadas – 2 risk of bias
Struder (74)	CRP, Lactate, pH, WBC	2006 - 2012	AMI	91 (100%)	Histology, laparotomy	High
Takis (75)	Blood metabolic fingerprint		Acute abdomen	9/64 (14%)		High
Tanrıkulu (76)	CBC, CRP, MPV, NLR, RDW, WBC	2010 - 2015	Laparotomy or resection for AMI and NVBN patients	58/182 (32%)	Laparotomy	High
Thuijls (77)	BE, Lactate, Plasma and urinary IFABP, L-FABP, I-BABP, WBC	2007 - 2009	Consecutive patients with clinical suspicion of AMI	22/46 (48%)	Autopsy, histology, laparotomy	High
Toptas (78)	CBC, CRP, Lymphocytes, Neutrophils, WBC	2009 - 2013	Patients with AMI	46/92 (50%)		High
Tsai (79)	Amylase, Lactate, Phosphate, WBC	1981 - 1988	Acute intestinal ischemia	43 (100%)	Angiography, histology, laparotomy	High
Türkoglu (80)	Hb, MPV, PC, WBC	2006 - 2011	Laparotomy for AMI	95/185 (51%)	Clinic, laparotomy	High
Uzun (81)	I-FABP	2009 - 2010	Acute abdomen	7/171 (4%)	Clinic, laparotomy, radiology	High
Wang (82)	NLR, PLR	2008 - 2015	Patients with AMEA or AMAT	137 (100%)	Laparotomy, radiology	High
Yilmaz (83)	PLR	2014 - 2016	Operation for AMI	34 (100%)	Laparotomy	High

Prospective studies are presented in grey, retrospective studies in white. If field is left blank, no data was available

Abbreviations: A. = Artery, AA = Acute Abdomen, AAA = Acute Abdominal Aorta, ADH = Alcohol Dehydrogenase, AMI = Acute Mesenteric Ischemia, AMEA = Acute Mesenteric Arterial Embolism, AMAT = Acute Mesenteric Arterial Thrombosis, AP = Abdominal Pain, APTT = Activated Partial Thromboplastin Time, AST = Aspartate Aminotransferase, ALT = Alanine Transaminase, ALP = Alkaline Phosphatase, BE = Base Excess, BUN = Blood Urea Nitrogen, C3a = complement factor 3 split product, Ca = Calcium, CBC = Complete Blood Count, CK = Creatine Kinase, CK-BB = Creatine Kinase isoenzyme BB, Cl = Chloride, CPK = Creatine Phosphokinase, CRP = C-reactive Protein, CT = Computed Tomography, CTA = Computed Tomography Angiography, CU = Colitis Ulcerosa, DNA = Deoxyribonucleic Acid, EarPI = Elastase-a1 Proteinase Inhibitor-complex , ECG = Electrocardiography, FibA = Fibrinopeptide A, GGT = γ - Glutamyl Transpeptidase, Hb = Hemoglobin, Ht = Hematocrit, ICU = Intensive Care Unit, I-FABP = Intestinal Fatty-acid Binding Protein, I-BABP = Ileal Bile Acid-binding Protein, IBD = Inflammatory Bowel Disease, IMA = Ischemia Modified Albumin, INR = International Normalized Ratio, K = Kalium, LDH = Lactate Dehydrogenase, L-FABP = Liver-type Fatty Acid-binding Protein, MPV = Mean Platelet Volume, Na = Natrium, NA = Not Appendix, NLR = Neutrophil to Lymphocyte Ratio, NOMI = Nonocclusive Mesenteric Ischemia, NVBN = Non-vascular Bowel Necrosis, NVI = Non-vascular Ischemia, PC = Platelet Count, PGE2 = Prostaglandin E2, pH = Potential of Hydrogen, PLR = platelet-to-lymphocyte ratio, PT = Prothrombin Time, Ptn. = Patients, QT = Quick Time, RAAA = Ruptured Acute Abdominal Aorta, RDW = Red Cell Distribution Width, SBI = Small Bowel Ischemia, SGOT = Serum Glutamate-Oxaloacetate Transaminase, SMA = Superior Mesenteric Artery, SMAE = Superior Mesenteric Artery Embolus, SMV(T) = Superior Mesenteric Venous Thrombosis, TE = Thrombo-Embolic, TNFa = Tumor Necrosis Factor alpha, WBC = White Blood Cell Count

Biomarkers

A total of 60 biomarkers were identified, shown in Table 3. Fifteen biomarkers were described in 5 or more studies and 20 biomarkers were described in 2 or more studies. Twenty-five biomarkers were described in only one study for which data is not shown. These 25 biomarkers were Antithrombin(37), ADH(56), APTT(37), Bicarbonate(44), Bilirubin(42), Cell-free DNA(44), Chloride(42), CK-MB(55), Complement Factor 3(71), Elastase-a1 Proteinase Inhibitor-complex (71), Endotoxin(71), Fibrinogen(37), Fibrinopeptide A(71), Ileal Bile Acid-binding Protein (77), IL-6(72), IL-8(72), IMA(58), Liver-type Fatty Acid-binding Protein (77), MCH(63), MCV(63), Net-CK BB(55), Neurotensin(72), pH(54), Troponin(39) and TQ(53).

Table 4-6, show the data of the 5 most described biomarkers and the 3 deemed promising by the ESVS Guideline, IFABP, D-dimer and D-lactate. There were no diagnostic outcome parameters on Amylase. The data of the other biomarkers will be shown as supplementary contents online. Reviewing the individual biomarkers, a wide variety in units, normal values and cut-off values was observed. Furthermore, as mentioned before, a great variety of included patient groups was observed, making it difficult to pool data into comparable subgroups. Although many studies presented descriptive data on the researched biomarkers, there were not a lot of studies portraying diagnostic outcome parameters per individual biomarker.

Table 3 Overview of biomarkers for diagnosing AMI described in 2 or more articles

	Prospective articles			**Retrospective articles**		
Marker	**Number**	**References**	**No. pts (AMI%)**	**Number**	**References**	**No. pts (AMI%)**
WBC	5	(35, 37, 49, 59, 71)	101/472 (21%)	19	(40, 42, 45, 47, 48, 52, 53, 57, 62, 63, 67, 69, 70, 73, 76-80)	881/2442 (36%)
Lactate	5	(35, 38, 49, 54, 64)	216/750 (29%)	9	(39, 45, 48, 61, 64, 67, 74, 77, 79)	362/628 (58%)
Amylase	4	(44, 49, 54, 64)	243/388 (63%)	6	(39, 42, 47, 52, 54, 79)	233/240 (97%)
LDH	2	(35,Z 44)	123/338 (36%)	8	(47, 48, 52, 53, 63, 69, 70, 73)	356/680 (52%)
CRP	2	(35, 37)	33/309 (11%)	8	(39, 48, 52, 62, 73, 76, 78, 79)	384/945 (41%)
D-dimer	6	(35-37, 41, 49, 59)	120/514 (23%)	2	(52, 57)	57/727 (8%)
Hb	2	(44, 54)	200/231 (87%)	5	(42, 47, 63, 78, 80)	281/527 (53%)
I-FABP	4	(35, 59, 66, 81)	68/475 (14%)	2	(73, 77)	29/318 (9%)
Creatinine	2	(44, 54)	200/231 (87%)	4	(42, 47, 53, 63)	190/300 (63%)
CPK	1	(35)	24/208 (12%)	5	(53, 55, 57, 70, 73)	127/1097 (12%)
Platelet	1	(54)	101 (100%)	5	(42, 47, 51, 78, 82)	315/443 (71%)

	Prospective articles			Retrospective articles		
Marker	**Number**	**References**	**No. pts (AMI%)**	**Number**	**References**	**No. pts (AMI%)**
NLR	-	-	-	6	(40, 52, 69, 76, 78, 82)	387/716 (54%)
MPV	-	-	-	6	(40, 42, 47, 51, 76, 80)	355/774 (46%)
AST	1	(35)	24/208 (12%)	4	(39, 42, 47, 53)	196 (100%)
RDW	-	-	-	5	(40, 46, 63, 76, 78)	284/687 (41%)
Neutrophil	1	(44)	99/130 (76%)	3	(69, 78, 82)	215/290 (74%)
Albumin	1	(54)	101 (100%)	2	(63)	49/159 (31%)
Glucose	1	(44)	99/130 (76%)	2	(53, 63)	99/209 (47%)
PLR	-	-	-	3	(78, 82, 83)	217/263 (83%)
Lymphocyte	-	-	-	3	(69, 78, 82)	215/290 (74%)
ALT	-	-	-	3	(39, 47, 53)	166 (100%)
Phosphate	-	-	-	3	(60, 65, 79)	88/113 (78%)
Urea	-	-	-	3	(42, 47, 53)	141 (100%)
PT	2	(37, 54)	193	-	-	-
D-lactate	1	(68)	9/41 (22%)	1	(73)	7/272 (3%)
BE	1	(35)	24/208 (12%)	1	(77)	22/46 (48%)
INR	1	(54)	101 (100%)	1	(53)	50 (100%)
BUN	1	(44)	99/130 (76%)	1	(63)	49/159 (31%)
L-lactate	-	-	-	2	(43, 52)	108/126 (86%)
GGT	-	-	-	2	(47, 56)	93/186 (50%)
Ht	-	-	-	2	(42, 47)	91 (100%)
ALP	-	-	-	2	(42, 47)	91 (100%)
Calcium	-	-	-	2	(42, 65)	53/80 (66%)
Kalium	-	-	-	2	(42, 53)	80 (100%)
Natrium	-	-	-	2	(42, 53)	80 (100%)

- = No data available
AST = Aspartate Aminotransferase, ALT = Alanine Transaminase, ALP = Alkaline Phosphatase, BE = Base Excess, BUN = Blood Urea Nitrogen, CBC = Complete Blood Count, CK = Creatine Kinase, CK-BB = Creatine Kinase isoenzyme BB, CPK = Creatine Phosphokinase, CRP = C-reactive Protein, DNA = Deoxyribonucleic Acid, GGT = γ - Glutamyl Transpeptidase, Hb = Hemoglobin, Ht = Hematocrit, I-FABP = Intestinal Fatty-acid Binding Protein, INR = International Normalized Ratio, LDH = Lactate Dehydrogenase, MPV = Mean Platelet Volume, NLR = Neutrophil to Lymphocyte Ratio, PC = Platelet Count, PLR = Platelet to Lymphocytes Ratio, PT = Prothrombin Time, RDW = Red Cell Distribution Width, TNFa = Tumor Necrosis Factor alpha, TQ = Quick Time, WBC = White Blood Cell Count

Table 4 Statistical data on biomarkers

Biomarker	Design	Study	No. pts (AMI%)	Cut-off values	Sens	Spec	+LR	- LR	PPV	NPV	OR	AUC
WBC	Prospective	Güzel(59)	30/77 (39%)	>11042 mm3	90%	100%			100%	87%		
		Matsumoto(35)	24/208 (12%)									0.54 (95% CI 0.39 - 0.70)
	Retrospective	Aktimur(40)	70/193 (36%)	14.4 /µL	57.1%	69.3%						0.623 (95% CI 0.53 –0.71)
		Beng Fuh(45)	62/116 (53%)	> 9000 /µL	93.6%	26.2%						
		Gün(57)	13/676 (2%)		92.3%							
		Kisaoglu(63)	49/159 (31%)	10.05 /µL	81.6%	55.2%	1.82	0.33				
				12.90/µL	71.4%	81.2%	3.80	0.35				
				15.05/µL	55.1%	92.7%	7.55	0.48				
		Shi(73)	7/272 (3%)	> 8.50 x10*9/L	61.1% (50.6-78.4)	36.5% (28.7-40.5)	0.86 (0.71-1.17)	1.12 (0.69-1.58)	13.3% (9.1-17.8)	79.8% (72.4-87.5)		0.47
		Tanrıkulu(76)	58/182 (32%)	10.99 x10*9/L	86.21%	95.16%			94.30%	88.10%		0.814
Lactate	Prospective	Brillantino(38)	48/284 (17%)	≥ 2.050	64%	90%						0.85
		Lange(64)	20/90 (22%)	> 2.4	100%	42%						
		Matsumoto(35)	24/208 (12%)									0.72 (95% CI 0.58 - 0.86)
	Retrospective	Beng Fuh(45)	62/116 (53%)		92%	42.9%						
		Canfora(48)	36/55 (65%)	>2mmol/l							49.66, p = 0.0021	
Amylase	No data available											
LDH	Prospective	Matsumoto(35)	24/208 (12%)	>211 U/L								0.78 (95% CI 0.68 - 0.88)
	Retrospective	Kisaoglu(63)	49/159 (31%)	>249 U/L	91.8%	49.0%	1.80	0.17				
				>299.5 U/L	87.8%	76.0%	3.66	0.16				
				>407 U/L	71.4%	88.5%	6.21	0.32				
		Shi(73)	36/55 (65%)	>211 U/L	61.6% (49.3-72.1)	77.3% (70.4-83.6)	2.61 (2.04-3.81)	0.54 (0.31-0.73)	36.7% (23.2-42.7)	72.3% (67.5-86.4)		0.62
CRP	Prospective	Matsumoto(35)	24/208 (12%)	< 0.5 mg/dL								0.74 (95% CI 0.64 - 0.84)
	Retrospective	Shi(73)	36/55 (65%)		68.9% (54.1-80.6)	34.2% (28.8-47.2)	1.21 (0.93-1.55)	0.71 (0.44-1.08)	13.8% (10.9-20.4)	81.6% (79.5-91.3)		0.53
		Tanrıkulu(42)	58/182 (32%)	2.10 mg/dL	100%	100%			100%	100%		1.00

Biomarker	Design	Study	No. pts (AMI%)	Cut-off values	Sens	Spec	+LR	- LR	PPV	NPV	OR	AUC
D-dimer	Prospective	Acosta(36)	6/14 (43%)		100%	35%						
		Acosta(37)	9/101 (9%)	> 0.3 mg/l	100%	36%	1.6		100%	13%		
				> 0.8 mg/l			2.4					
				> 1.5 mg/l			3.9					
		Akyildiz(41)	28/47 (60%)	> 3.17 µg FEU/mL	95%	79%			75.0	95.7		0.93 (95% CI 0.81–0.98) (P<0.001)
		Chiu(49)	23/67 (34%)	> 1.0 µg FEU/ mL	96%	18%	1.17	0.24				
		Güzel(59)	30/77 (39%)	>130 µg/L	93%	100%			100%	91%		
		Matsumoto(35)	24/208 (12%)									0.74 (95% CI 0.63 - 0.85)
	Retrospective	Gün(57)	13/676 (2%)	>1000 ng/ml	85%	48%						
I-FABP	Prospective	Güzel(59)	30/77 (39%)	> 90 pg/mL	90%	100%			100%	87%		
		Matsumoto(35)	24/208 (12%)	> 9.1 ng/ml	83.3	89.1			97.6%	50.0%		0.88 (95% CI 0.79 - 0.96)
		Uzun(81)	7/171 (4%)	> 145 pg/ml	71.4%	94.6%			41.7%	98.4%		0.755
	Retrospective	Shi(73)	7/272 (3%)	> 82.4 ng/mL	76.2% (67.4-91.5)	74.8% (68.7-82.4)	3.25 (2.41-3.92)	0.24 (0.15-0.47)	32.1% (24.7-41.4)	96.3% (91.6-98.4)		0.85
		Thuijls(77)	22/46 (48%)	> 268 pg/mL	68%	71%	2.34 (95% CI 1.18–4.67)	0.45 (95% CI 0.23–0.87)	68% (95% CI 52–81)	29% (95% CI 18–45)		0.70 (95% CI 0.53–0.86) p = 0.02
D-lactate	Prospective	Murray(68)	9/41 (22%)	>20 µg/ml	90%	87%			70%%	96%		
	Retrospective	Shi(73)	7/272 (3%)	> 31.8 µg/ml	66.7% (52.8-84.2)	85.9% (77.8—92.6)	2.82 (2.07-3.61)	0.31 (0.17-0.57)	86.3% (79.8-90.7)	72.6% (65.3-88.2)		0.69

Amylase no data available.
Sens = Sensitivity, Spec = Specificity, +LR = Positive likelihood ratio, -LR = Negative likelihood ratio, PPV = Positive predictive value, NPV = Negative predictive value, OR = Odds ratio, AUC = Area under the Receiver Operating Characteristic Curve.

Table 5 Data on biomarkers of AMI patients versus controls

Biomarker	Design	Study	No. pts	Normal values	Subgroups	Ischemic patients	Control	P-value
WBC	Prospective	Acosta(37)	9/101 (9%)	4.0 – 10.0	SMA occl (n = 9), No SMA occl (n = 92)	28.3 (9.6–60)	11.2 (1.3–98.0)	P = 0.001
		Chiu(49)	23/67 (34%)		AMI (n = 23), No-AMI (n = 44)	15.2 ± 6.7	13.1 ± 7.4	P = 0.200
		Güzel(59)	30/77 (39%)		AMI (n = 30), Control (n = 20)	18.50 (3.73–40.89)	6.99 (3.55–11.04)	P < 0.001
		Matsumoto(35)	24/208 (12%)	3.50 – 8.50	AMI (n = 24), NID (n = 122)	11.7 ± 7.7	10.3 ± 4.8	Not sign.
	Retrospective	Aktimur(40)	70/193 (36%)		AMI (n = 70), Total (n = 193)	15.2 (2.8–34.2)	13.0 (2.8–39.9)	P = 0.002
		Beng Fuh(45)	62/116 (53%)	4.0 – 9.0	AMI (n = 62), No-AMI (n = 42)	19.40	12.90	
					AMI (n = 62)	Elevated in 58 of 62 (93.54%)		
					No-AMI (n = 42)	Elevated in 31 of 42 (73.81%)		
		Gün(57)	13/676 (2%)	4.30 - 10.30	AMI (n = 13), No-AMI (n = 629)	Elevated in 12 of 13 (92.3%)		P < 0.05
						20.38 ± 7.18	10.28 ± 5.32	P = 0.001
		Kisaoglu(63)	49/159 (31%)		AMI (n = 49), Control (n = 110)	16.63 ± 6.84	9.83 ± 3.46	P < 0.0001
		Rivera Nunez(69)	32/61 (52%)		AMI (n = 32), Control (n = 29)	1.18 (0.54–2.07)	2.2 (7.95–2.01)	P < 0.05
		Tanrıkulu(76)	58/182 (32%)	4.0 – 10.0	AMI (n= 58), Control (n = 62)	16.38 (4.48–38.20)	8.28 (4.15–12.23)	P = 0.002
		Thuijls(77)	22/46 (48%)		AMI (n = 22), Control (n = 24)	13.9 [1.7– 28.0]	12.7 [3.3–33.7]	P = 0.89
		Toptas(78)	46/92 (50%)		AMI (n = 42), Control (n = 42)	17.6 ± 7.8	8.8 ± 4.6	P < 0.001
		Tsai(79)	43 (100%)		SMA occl (n = 22)	Elevated in 22 of 22 (100%)		
		Türkoglu(80)	95/185 (51%)	4.0 – 10.0	AMI (n = 95), Control (n = 90)	20.4 ± 8.3	7.4 ± 2.1	P < 0.001
Lactate	Prospective	Brillantino(38)	48/284 (17%)	0.5–1.8	AMI (n = 48), NID (n = 201)	2.3 (1.1–5.2)	1.2 (0.2–5.1)	p < 0.0001
		Chiu(49)	23/67 (34%)		AMI (n = 23), non-AMI (n = 44)	3.56 (0.62-32.69)	3.66 (0.75-14.05)	p = 0.884
		Matsumoto(35)	24/208 (12%)	0.44 - 1.78	AMI (n = 24), NID (n = 122)	4.22 (0.78 - 13.88)	1.89 (0 – 6.55)	p < 0.010
		Lange(64)	20/90 (22%)	0.6 - 2.4	AMI = 20, Acute abdomen other = 30	5.4 (± 2.3)	1.5 (± 0.8)	
				0.6 - 2.4	AMI	Elevated in 20 (100%)	0	
	Retrospective	Acosta(39)	55 (100%)	0.5–2.2		2.4 (1.6 – 4.5)		
					Only available in 27 AMI patients	Elevated in 14 of 27 (52%)		
		Beng Fuh(45)	62/116 (53%)		AMI (n = 62), Control (n = 42)	5.5	2.6	
					AMI	Elevated in 57 of 62 (91.93%)		
					Non-AMI	Elevated in 24 of 42 (57.14%)		
		Meyer(67)	35 (100%)	5-20 U/L		53 (15 - 156) U/L		
					Only available in 26 AMI patients	Elevated in 24 of 26 (92.30%)		
		Thuijls(77)	22/46 (48%)		AMI = 22, control = 24	2.5 [0.4–23.1]	2.3 (1.0–5.2)	p = 0.56

Biomarker	Design	Study	No. pts	Normal values	Subgroups	Ischemic patients	Control	P-value
Amylase	Prospective	Arnalich(44)	99/130 (76%)		AMI (n = 63), Non-AMI (n = 31)	258 (136–438)	148 (122–183)	p < 0.05
		Chiu(49)	23/67 (34%)		AMI (n = 23), Non-AMI (n = 44)	215 (38-875)	109 (18-2850)	p = 0.078
		Emile(54)	101 (100%)			103.7 ± 133.5 U/L (26–422)		
		Lange(64)	20/90 (22%)			Elevated in 3 of 10 (30%)		
	Retrospective	Acosta(39)	55 (100%)	0.15–1.10 mkat/L		Elevated in 12 of 45 (27%)		
						0.69mkat/L (IQR 0.32–1.19)		
		Destek(52)	44/51 (86%)	25–125 U/L				
		Tsai(79)	43 (100%)		SMA occl (n = 18), Overall (n = 32)	Elevated in 8 of 18 (44%)	Elevated in 15 of 32 (47%)	
LDH	Prospective	Arnalich(44)	99/130 (76%)		AMI (n = 63), No AMI (n = 31)	414 (345–470)	316 (278–372)	NS
	Retrospective	Bilgiç(47)	61 (100%)			381.4 (124–1779)		
		Destek(52)	44/51 (86%)	125–220 U/L	Embolic (n = 14)	277.50 (218–832)		
					Trombotic (n = 13)	267 (175–524)		
		Kisaoglu(63)	49/159 (31%)		AMI (n = 49), Control (n = 110)	700 ± 450	283 ± 120	<0.0001
		Rivera Nunez(69)	32/61 (52%)		AMI (n = 32), Control (n = 29)	311 (258–422)	213 (182.25–239)	p < 0.05
		Sachs(70)	49 (100%)	100 - 225 IU/L	Arterial embolus (n = 3)	257		
						Elevated in 2 (67%)		
					Arterial thrombosis (n = 5)	334		
						Elevated in 4 (80%)		
CRP	Prospective	Matsumoto(35)	24/208 (12%)	< 0.5 mg/dl	AMI (n = 24), No AMI (n = 122)	3.5 (1–37.0)	0.4 (0–34.5)	P < 0.010
		Acosta(37)	9/101 (9%)	? 5 mg/L	SMA occl (n = 9), No SMA occl (n = 92)	117 (5–446)	23 (5–393)	p = 0.015
	Retrospective	Acosta(39)	55 (100%)	0.15–1.10 mkat/L	Only available in 45 AMI patients	0.69mkat/L (IQR 0.32–1.19)		
						Elevated in 12 of 45 (27%)		
		Kim(62)	66 (100%)			7.32 (0.08-35.39)		
		Tanrıkulu(42)	58/182 (32%)	< 0.5 mg/dl	AMI (n = 58), Control (n = 62)	16.60 (3.20–63.20)	0.20 (0–2.10)	p < 0.001
		Tsai(79)	43 (100%)		AMI (n = 42), Control (n = 42)	2.1 ± 3.02	1.3 ± 1.22	P = 0.01

Biomarker	Design	Study	No. pts	Normal values	Subgroups	Ischemic patients	Control	P-value
D-dimer	Prospective	Acosta(36)	6/14 (43%)	< 0.3 mg/L	AMI (n = 6), No AMI (n = 8)	4.7 (3.3) mg/L	1,38 (1.7) mg/L	p < 0.05
		Acosta(37)	9/101 (9%)	< 0.3 mg/L	SMA occl (n = 9), No SMA occl (n = 92)	1.6 (0.4–5.6) mg/L	0.5 (0.1–7.7) mg/L	p = 0.009
							Elevated in 33 of 92 (36%)	
		Chiu(49)	23/67 (34%)		AMI (n = 23), No AMI (n = 44)	6.24 (0.96-53.48) µg FEU/mL	3.45 (0.50-44.69) µg FEU/mL	p = 0.064
		Matsumoto(35)	24/208 (12%)	< 1.0 µg/ml	VII (n = 19), NID (n = 122)	11.0 (1.3–47.2)	2.0 (0.5–53.8)	P < 0.010
	Retrospective	Destek(52)	44/51 (86%)	0 – 0.5 µg/mL FEU	Embolic	2.90 (1.30–7.10)		
					Thrombotic	2.1 (0.4–5.9)		
		Gün(57)	13/676 (2%)	< 470 ng/ml	AMI (n = 13), No-AMI (n = 217)	Elevated in 11/13 (84.6%)		p < 0.05
						1177.77 ± 710.4	744.89 ± 1752.4	p = 0.003
I-FABP	Prospective	Güzel(59)	30/77 (39%)		AMI (n = 30), Acute abdomen (n = 27)	421 (40–5000)	80 (1–200)	p < 0.001
		Liebermann(66)	7/19 (36%)	< 1.87 ng/ml	AMI (n = 7), Control (n = 12)	50 ± 72 ng/ml (5.4 - 100)		
						Elevated in 7 of 7 (100%)	Elevated in 1 of 12 (8,3%)	
		Matsumoto(35)	24/208 (12%)	1.1(0.9) (0.1–5.5) ng/ml	AMI (n = 24), NID (n = 122)	31.0 (1.1–498.4)	2.5 (0.2–56.7)	P < 0.010
		Uzun(81)	7/171 (4%)		AMI (n = 7), Control (n = 130)	708.6 ± 669.1	61.4 ± 47.4	p < 0.05
	Retrospective	Shi(73)	7/272 (3%)	8.33 ± 6.25 ng/mL	AMI (n = 7), Controls (n = 37)	125.8 ± 39.8	8.33 ± 6.25	P < 0.05
		Thuijls(77)	22/46 (48%)		AMI (n = 22), Control (n = 24)	653 pg/mL (40–74,711)	109 pg/mL (40–1,691)	P = 0.02
D-lactate	Prospective	Murray(68)	9/41 (22%)	< 20 µg/ml	AMI (n = 9), Controls (n = 10)	32.37 ± 4.0 µg/ml	4.89 ± 0.9 µg/ml	P < 0.00005
						Elevated in 8 of 9	Elevated in 0 of 10	
	Retrospective	Shi(73)	7/272 (3%)	5.47 ± 1.64 ug/mL	AMI (n = 7), Controls (n = 37)	78.4 ± 27.6 ug/mL	5.47 ± 3.64	P < 0.05

AA = Acute abdomen, ITIN = Irreversible transmural intestinal necrosis, II = Intestinal Ischemia, VII = Vascular irreversible ischaemia, BR = Bowel resection, Occl = Occlusion, NID = non-ischaemic disease, SBI = Small bowel ischemia, SLBI = Small & Large bowel ischemia. Not sign = not significant

Table 6 Data on biomarkers in different subgroups

Biomarker	Design	Study	No. pts	Normal values	Subgroups	Ischemic patients	Control	P-value
WBC	Prospective	Güzel(59)	30/77 (39%)		AMI = 30, AA = 27	18.50 (3.73–40.89)	14.56 (4.44–32.00)	P < 0.001
		Matsumoto(35)	24/208 (12%)	3.5–8.5	VII (n=19), No-VII (n=122)	13.0 ± 8.1	10.3 ± 4.8	Not significant
					AMI (n = 24), Non-vascular (n = 62)	11.7 ± 7.7	10.4 ± 3.7	Not significant
					VII (n=19), Non-VII (n=26)	13.0 ± 8.1	11.1 ± 3.9	Not significant
		Schoeffel(71)	15/19 (79%)		SMA occlusion (n = 9)	7.4 ± 8.97		
	Retrospective	Acosta(39)	55 (100%)	3.5–8.8	Embolic (n = 24), Thrombotic (n = 27)	18.9 (14.8 –24.1)	14.5 (11.4 –23.4)	
					Embolic (n = 24)	Elevated in 1 of 24 (4%)		
					Thrombotic (n = 27)	Elevated in 1 of 27 (2%)		
		Aktimur(40)	70/193 (36%)		AMI (n = 70), AA (n = 62)	15.2 (2.8–34.2)	13.7 (3.7–24.5)	P = 0.111
					AMI (n = 70), NA (n = 61)	15.2 (2.8–34.2)	11 (3.4–39.9),	P = 0.001
		Altintoprak(42)	30 (100%)		Death (n = 15), Survival (n = 15)	18.05	14.04	P > 0.05
		Beng Fuh(45)	62/116 (53%)		Total necrosis = ?, vital bowel = ?	22.36	18.10	
					Partial necrosis = ?, vital bowel = ?	19.40	18.10	
		Bilgiç(47)	61 (100%)			16.47 (6.20 –52.20)		
		Canfora(48)	36/55 (65%)	< 10*4/ml	ITIN (n = 36), No-ITIN (n = 19)	Elevated in 28 of 36 (78%)	Elevated in 16 of 19 (84%)	P = 0.57
		Destek(52)	44/51 (86%)	4.6–10.2	SBI (n = 37), SLBI (n = 7)	18.51 (4.21–50.67)	20 (10.80–42.10)	P = 0.730
					Embolic (n = 14)	19.10 (6.75–42.10)		
					Trombotic (n = 13)	18.51 (7.51–50.67)		
		Elthes(53)	50 (100%)		Deceased (n = 37), Survivors (n = 13)	16.69	18.55	P = 0.3679
		Kim(62)	66 (100%)		BR (n = 31), No-BR (n = 31)	17.91 (5.45-54.51)	16.09 (1.47-42.39)	P = 0.450
						16.83 (1.47-54.51)		
						Elevated in 32 of 35 (91.42%)		
		Sachs(70)	49 (100%)		Arterial thrombosis (n = 12)	21,20		
					Arterial embolization (n = 14)	22,10		
					Emboli secondary to angio (n = 4)	18,50		

Biomarker	Design	Study	No. pts	Normal values	Subgroups	Ischemic patients	Control	P-value
Lactate	Prospective	Emile(54)	101 (100%)			19.2 ± 9 (11.3–44) mg/dL		
					Bowel necrosis (n = 73), VB (n = 28)	27.8 ± 12.8 mg/dL	15.5 ± 2.7 mg/dL	P < 0.0001
		Lange(64)	20/90 (22%)	0.6 - 2.4	Peritonitis (n = 15)	3.9 (± 0.8)		
						Elevated in 15 (100%)		
					Intestinal obstruction (n = 20)	2.7 (± 1.6)		
						Elevated in 10 of 20 (50%)		
		Matsumoto(35)	24/208 (12%)	0.44 - 1.78	VII (n = 19), NID (n = 122)	4.55 (0.78 –13.87)	1.89 (0 – 6.55)	P < 0.010
	Retrospective	Beng Fuh(45)	62/116 (53%)	< 2.2	Total necrosis = ?, vital bowel = ?	7.6	3.8	
		Canfora(48)	36/55 (65%)	< 2.0	ITIN = 36, No-ITIN = 19	Elevated in 30 of 36 (83%)	Elevated in 1 of 19 (5%)	P = 0.00001
		Janda(61)	18/132 (14%)	1 - 2	AMI = 18, Occl a Fem = 10	7.45 ± 2.86	1.72 ± 0.85	? = 0.02
		Struder(74)	91 (100%)		Non-survivor (n=39), Survivor (n=52)	5.6 ± 4.8	3.0 ± 2.2	p = 0.024
		Tsai (79)	43 (100%)		SMA occl = 21, Total group = 35	Elevated in 9 of 21	Elevated in 31 of 35	
Amylase	Prospective	Emile(54)	101 (100%)		Bowel necrosis (n = 73), VB (n = 28)	218.7 ± 191.5	46.2 ± 20.7	p < 0.0001
	Retrospective	Altintoprak(42)	30 (100%)		Death (n = 15), Survival (n = 15)	214.0	73.0	p = 0.022
		Bilgiç(47)	61 (100%)		Death (n = 35), Survivor (n = 26)	108 (4–471)	57 (11–329)	P < 0.01
		Destek(52)	44/51 (86%)	25–125 U/L	Embolic	72.50 (22–593)		
					Trombotic	122 (41–902)		
					SBI (n = 37), SLBI (n = 7)	96 (19–902)	71 (22–464)	0.615
LDH	Prospective	Matsumoto(35)	24/208 (12%)	106 – 211 U/L	VII (n=19), NID (n=122)	398 (186–1048)	228 (138–613)	P < 0.010
	Retrospective	Canfora(48)	36/55 (65%)		ITIN (n = 36), No-ITIN (n = 19)	33/36 (92%)	17/19 (89%)	0.788
		Destek(52)	44/51 (86%)	125–220 U/L	SBI (n = 37), SLBI (n = 7)	263 (162–832)	330 (223–400)	0.134
		Elthes(53)	50 (100%)		Deceased (n = 37), Survivors (n = 13)	392.92 U/L	249.13 U/L	p = 0.0440

Biomarker	Design	Study	No. pts	Normal values	Subgroups	Ischemic patients	Control	P-value
CRP	Prospective	Matsumoto(35)	24/208 (12%)	< 0.5 mg/dl	VII (n = 19), NID (n = 122)	7.5 (0.3–37.0)	0.4 (0–34.5)	P < 0.010
	Retrospective	Acosta(39)	55 (100%)	? 5 mg/L	Embolic	Elevated in 7 of 28 (25%)		
						49 mg/L (IQR 3.8–167)		
					Thrombotic	Elevated in 6 of 24 (25%)		
						123 mg/L (IQR 11.5–245.2)		
		Canfora(48)	36/55 (65%)	<50	ITIN (n = 36), No-ITIN (n = 19)	Elevated in 25 of 36 (69%)	Elevated in 15 of 19 (79%)	0.452
		Destek(52)	44/51 (86%)	< 0.5 mg/dl	Embolic	30.29 (16–412)		
					Thrombotic	18.53 (1.1–50)		
					SBI (n = 37), SLBI (n = 7)	23 (1.9–412)	9 (1.1–22)	0.018
		Toptas(78)	46/92 (50%)		AMI (n = 42), Control (n = 42)	2.1 ± 3.02	1.3 ± 1.22	P = 0.01
D-dimer	Prospective	Güzel(59)	30/77 (39%)		AMI (n = 30), AA (n = 27)	675 (50–6403)	435 (76–1290)	p < 0.001
	Retrospective	Destek(52)	44/51 (86%)	0 – 0.5 µg/mL FEU	SBI (n = 37), SLBI= 7	2.30 (0.30–7.80)	0.70 (0.20–2.80)	0.029
I-FABP	Prospective	Matsumoto(35)	24/208 (12%)	1.1 (0.1–5.5) ng/ml	VII (n = 19), NID (n = 122)	38.2 (1.1–498.4)	2.5 (0.2–56.7)	P < 0.010
	Retrospective	Shi(73)	7/272 (3%)	8.33 ± 6.25	Death (n = 14), survival (n = 25)	108 ± 40.6 ng/mL	104 ± 58.2 ng/mL	P > 0.05
D-lactate	Prospective	Murray(68)	9/41 (22%)	< 20 µg/ml	AMI (n = 9), AA (n = 17)	32.37 ± 4.0 µg/ml	10.61 ± 3.2 µg/ml	P < 0.00005
					AMI (n = 9), SBO (n = 5)	32.37 ± 4.0 µg/ml	10.65 ± 1.6 µg/ml	P < 0.0005
	Retrospective	Shi(73)	7/272 (3%)	5.47 ± 1.64 ug/mL	Ischemic deceased (n = 14), Ischemic survived (n = 25)	76.7 ± 34.5 ug/mL	23.7 ± 14.3 ug/mL	P < 0.01
					Ischemia (n = 39), No-ischemia (n = 233)	59.7 ±24.5 ug/mL	13.2 ± 5.7 ug/mL	P < 0.001
					Ischemia (n = 39), Controls (n = 37)	59.7 ±24.5 ug/mL	5.47 ± _3.64 ug/mL	P < 0.001

Angio = angiography, AA = Acute Abdomen, ITIN = Irreversible transmural intestinal necrosis, II = Intestinal Ischemia, VII = Vascular irreversible ischemia, BR = Bowel resection, Occl = Occlusion, SBI = Small bowel ischemia, SLBI = Small & Large bowel ischemia, SBO = Small Bowel Obstruction, VB = Viable bowel

Discussion

With this systematic review we presented the results of 49 studies on the diagnostic value of 60 biomarkers in AMI patients. We observed a great methodological variety in the studies, and there is a huge variation in the studied patient populations. Furthermore, there are large differences in terms of units used and normal values between studies, if any are even given. Subsequently, different cut-off values are used per study. Altogether, this makes it impossible to compare outcomes. We concluded that the quality of the studies was low after risk of bias and applicability assessment using the QUADAS-2 tool. The main reasons for this are the high number of retrospective studies and the use of laparotomy as the reference test. For these reasons, no conclusions can be drawn on the diagnostic value of any of these biomarkers or combination of biomarkers in the diagnostic pathway of AMI patients. Therefore, biomarkers are not yet suitable for use in daily practice.

While almost all systematic reviews on this topic have indicated that better quality research is needed to answer this question, many still have performed meta-analyses and assigned a diagnostic accuracy to various biomarkers despite the aforementioned methodological errors.(1, 6, 10, 15, 22-24) We believe that by doing this, researchers uphold the clinical problem at hand. By giving an insufficiently substantiated qualitative measure to a certain biomarker, clinicians may be tempted to use such biomarkers in daily practices without knowing the full scope and limitations of the underlying data.

A highly accurate, minimally invasive, rapid, 24/7 available and cost-effective tool that can be deployed between presentation and the CTA to shorten the delay and eliminate the uncertainty of 'having a suspicion' on AMI is needed. So, the warning sign of elevated biomarkers has the potential to increase the index of suspicion of AMI, which can lower the threshold for and speed up the deployment of additional diagnostic modalities. Ideally, the biomarker has both a high sensitivity and specificity to diagnose AMI. In the clinical setting, however, the positive predictive value (PPV) and negative predicted value (NPV) are more commonly used, which are influenced by the prevalence of the disease. In case of a high PPV, patients are more prone to actual have AMI and a targeted CTA can be performed with optimal use of its high sensitivity and specificity.(1) However, this will probably be a disease-specific biomarker which will only be determined if AMI is already considered by the healthcare professional. In that case, the time gain is minimal. If a biomarker has a high NPV, it offers the possibility to rule out the diagnosis and a CTA can possibly be omitted.

Currently, only D-dimer is considered by the 2017 ESVS Guideline as a biomarker that can be used to exclude the diagnosis of AMI due to its high sensitivity of 100% 100% and

therefore a NPV of 100%.(1) However, D-dimer is suggested to aid in the diagnostic process of AMI alongside a 'clinical suspicion' and the CTA,(37, 41) and will therefore not result in earlier diagnosis, because the timing of the 'clinical suspicion' will determine the time to diagnosis. Furthermore, although the quality of the studies that formed the basis for this recommendation is relatively good, again there is a wide variety in units used and normal and cut-off values in these small patient groups studies (9-28 patients).(35, 37, 41, 49) Therefore, we wonder whether using D-dimer in daily practice as an exclusion biomarker for AMI is sensible given the brief underlying scientific substantiation.

High quality research is needed using uniform standards and pre-set thresholds, normal and cut-off values and used units in order to perform meta-analysis and validate biomarkers. Clearer frameworks need to be established for future studies performed through national and international collaborations instead of individual institutions to create a clearer overview on this topic and to prevent anymore blurring of data. As a result, outcomes can be reproduced, finally giving statements and guidelines more depth, value and content, with our patients ultimately benefitting the most.

In conclusion, this systematic review underlines the conclusion of the 2017 European Guideline on Treatment of Mesenteric Ischemia that no individual biomarker or combination of biomarkers are yet suitable to aid in the diagnostic process of AMI, based on the lack of high-quality and homogenic evidence.(1) In fact, we believe that it is justifiable to argue that clinicians should stop ascribing any diagnostic value to any biomarker in daily practice, even lactate, leukocytes and D-dimer. The diagnosis of AMI can currently only be made on the basis of a high index of suspicion followed by a multislice CTA.(1) This index of suspicion should be defined in more detail, and disease specific biomarkers may eventually aid in the process of earlier diagnosis.

Appendices

Appendix 1 Criteria for the QUADAS-2 tool

- A retrospective analysis was marked as “high risk of bias”, because eligible patients could have been missed, not included in the first place or inappropriately been excluded, unless explicit details were given.
- A pre-specified threshold was defined as the description of normal values in the methods. If not available, this was marked as “high risk”.
- If an article did not explicitly state that investigators were blinded to the index test and/or the reference standard, then these portions of the QUADAS-2 were marked as “unclear”.
- Laparotomy alone was marked a “unclear” to define the target condition as a reference standard.
- If all domains are ‘low’, the overall risk is deemed ‘low’.
- In case of maximum two ‘moderate” domains or one ‘high’ domain, overall risk is deemed ‘moderate’.
- All other combinations will be deemed ‘high’ risk.

Appendix 2 Appraisal of the methodologic quality of the studies reviewed based on the QUADAS-2 tool.

	Risk of bias				Applicability		
First author, year of publication	Patient selection	Index test	Reference test	Patient flow and timing	Patient selection	Index test	Reference test
Acosta 2001(36)	Low	Low	?	Low	Low	Low	?
Acosta 2004(37)	Low	Low	Low	High	Low	Low	Low
Acosta 2012(39)	High	?	?	High	Low	Low	?
Aktimur 2015(40)	High	High	High	Low	Low	Low	?
Akyildiz 2009(41)	High	?	?	Low	Low	Low	Low
Altintoprak 2013(42)	High	High	High	?	Low	Low	?
Ambe 2017(43)	High	High	High	Low	Low	Low	?
Arnalich 2010(44)	High	High	High	Low	Low	Low	?
Beng Fuh 2004(84)	High	?	High	High	Low	Low	?
Bilgiç(46)	High	?	High	?	Low	Low	?
Bilgiç(47)	High	High	High	?	Low	Low	?
Brillantino 2018(38)	?	Low	?	Low	Low	Low	Low
Canfora 2019(48)	High	High	?	?	Low	Low	?
Chiu 2009(49)	Low	?	?	Low	Low	Low	Low
Czerny 1997(50)	High	High	High	High	Low	Low	?
Degerli 2016(51)	High	?	High	?	Low	Low	?
Destek 2020(52)	High	?	High	High	Low	Low	?
Elthes 2018(53)	High	High	High	High	Low	Low	?
Emile 2018(54)	Low	High	?	High	Low	Low	Low
Fried 1991(55)	High	?	High	High	Low	Low	?
Gaddam 2011(56)	High	High	High	High	?	?	High
Gun 2014(57)	?	?	High	High	Low	Low	?
Gunduz 2008(58)	High	High	?	?	Low	Low	Low
Güzel 2014(59)	?	High	?	High	Low	Low	Low
Jamieson 1982(60)	High	High	High	High	Low	Low	High
Janda 1984(61)	High	?	High	?	Low	Low	?
Kim 2017(62)	Low	High	?	High	Low	Low	Low
Kisaoglu 2014(63)	High	High	?	High	Low	Low	?
Lange 1994(64)	High	?	High	?	Low	Low	?
Leo 1996(65)	High	?	High	Low	Low	Low	?
Lieberman 1997(66)	High	?	High	?	Low	Low	?
Matsumoto 2014(35)	Low	Low	Low	Low	Low	Low	Low
Meyer 1998(67)	High	?	High	High	Low	Low	?
Murray 1994(68)	High	?	High	?	Low	Low	?

	Risk of bias				Applicability		
First author, year of publication	**Patient selection**	**Index test**	**Reference test**	**Patient flow and timing**	**Patient selection**	**Index test**	**Reference test**
Rivera Nunez 2019(69)	High	High	High	High	Low	Low	?
Sachs 1982(70)	High	?	High	High	Low	Low	?
Schoeffel 1997(71)	Low	High	?	?	Low	Low	?
Sgourakis 2013(72)	High	High	High	High	Low	Low	?
Shi 2015(73)	?	High	?	High	Low	Low	?
Studer 2014(74)	High	High	High	?	Low	Low	?
Takis 2018(75)	?	High	High	High	Low	Low	High
Tanrıkulu 2016(76)	?	?	High	High	Low	Low	?
Thuijls 2011(77)	Low	High	High	High	Low	Low	?
Toptas 2016(78)	High	High	High	High	Low	Low	High
Tsai 1990(79)	High	High	High	?	Low	Low	?
Türkoglu 2015(80)	High	?	High	?	Low	Low	?
Uzun 2014(81)	?	High	?	?	Low	Low	Low
Wang 2018(82)	High	High	High	?	Low	Low	?
Yilmaz 2017(83)	High	High	High	?	Low	Low	?

References

1. Björck M, Koelemay M, Acosta S, Bastos Goncalves F, Kölbel T, Kolkman JJ, et al. Editor's Choice - Management of the Diseases of Mesenteric Arteries and Veins: Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2017;53(4):460-510.
2. Karkkainen JM, Lehtimaki TT, Manninen H, Paajanen H. Acute Mesenteric Ischemia Is a More Common Cause than Expected of Acute Abdomen in the Elderly. J Gastrointest Surg. 2015;19(8):1407-14.
3. Acosta S, Ogren M, Sternby NH, Bergqvist D, Bjorck M. Clinical implications for the management of acute thromboembolic occlusion of the superior mesenteric artery: autopsy findings in 213 patients. Annals of surgery. 2005;241(3):516-22.
4. Acosta S. Epidemiology of mesenteric vascular disease: clinical implications. Semin Vasc Surg. 2010;23(1):4-8.
5. Karkkainen JM, Acosta S. Acute mesenteric ischemia (part I) - Incidence, etiologies, and how to improve early diagnosis. Best practice & research Clinical gastroenterology. 2017;31(1):15-25.
6. Derikx JP, Schellekens DH, Acosta S. Serological markers for human intestinal ischemia: A systematic review. Best practice & research Clinical gastroenterology. 2017;31(1):69-74.
7. Clair DG, Beach JM. Mesenteric Ischemia. N Engl J Med. 2016;374(10):959-68.
8. Acosta S, Björck M. Acute thrombo-embolic occlusion of the superior mesenteric artery: a prospective study in a well defined population. Eur J Vasc Endovasc Surg. 2003;26(2):179-83.
9. Acosta S. Mesenteric ischemia. Current Opinion in Critical Care. 2015;21(2):171-8.
10. Cudnik MT, Darbha S, Jones J, Macedo J, Stockton SW, Hiestand BC. The diagnosis of acute mesenteric ischemia: A systematic review and meta-analysis. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 2013;20(11):1087-100.
11. Kassahun WT, Schulz T, Richter O, Hauss J. Unchanged high mortality rates from acute occlusive intestinal ischemia: six year review. Langenbecks Arch Surg. 2008;393(2):163-71.
12. Menke J. Diagnostic accuracy of multidetector CT in acute mesenteric ischemia: systematic review and meta-analysis. Radiology. 2010;256(1):93-101.
13. Oldenburg WA, Lau LL, Rodenberg TJ, Edmonds HJ, Burger CD. Acute mesenteric ischemia: a clinical review. Arch Intern Med. 2004;164(10):1054-62.
14. Tilsed JV, Casamassima A, Kurihara H, Mariani D, Martinez I, Pereira J, et al. ESTES guidelines: acute mesenteric ischaemia. European journal of trauma and emergency surgery : official publication of the European Trauma Society. 2016;42(2):253-70.
15. Acosta S, Nilsson T. Current status on plasma biomarkers for acute mesenteric ischemia. Journal of thrombosis and thrombolysis. 2012;33(4):355-61.
16. Lehtimaki TT, Karkkainen JM, Saari P, Manninen H, Paajanen H, Vanninen R. Detecting acute mesenteric ischemia in CT of the acute abdomen is dependent on clinical suspicion: Review of 95 consecutive patients. European journal of radiology. 2015;84(12):2444-53.
17. Karkkainen JM. Acute Mesenteric Ischemia: A Challenge for the Acute Care Surgeon. Scandinavian journal of surgery : SJS : official organ for the Finnish Surgical Society and the Scandinavian Surgical Society. 2021;110(2):150-8.
18. Wiesner W, Khurana B, Ji H, Ros PR. CT of acute bowel ischemia. Radiology. 2003;226(3):635-50.
19. Lemma AN, Tolonen M, Vikatmaa P, Mentula P, Vikatmaa L, Kantonen I, et al. Choice of First Emergency Room Affects the Fate of Patients With Acute Mesenteric Ischaemia: The Importance of Referral Patterns and Triage. Eur J Vasc Endovasc Surg. 2019;57(6):842-9.

20. Luther B, Mamopoulos A, Lehmann C, Klar E. The Ongoing Challenge of Acute Mesenteric Ischemia. Visc Med. 2018;34(3):217-23.
21. van den Heijkant TC, Aerts BA, Teijink JA, Buurman WA, Luyer MD. Challenges in diagnosing mesenteric ischemia. World J Gastroenterol. 2013;19(9):1338-41.
22. Evennett NJ, Petrov MS, Mittal A, Windsor JA. Systematic review and pooled estimates for the diagnostic accuracy of serological markers for intestinal ischemia. World J Surg. 2009;33(7):1374-83.
23. Khan SM, Emile SH, Wang Z, Agha MA. Diagnostic accuracy of hematological parameters in Acute mesenteric ischemia-A systematic review. International journal of surgery (London, England). 2019;66:18-27.
24. Treskes N, Persoon AM, van Zanten ARH. Diagnostic accuracy of novel serological biomarkers to detect acute mesenteric ischemia: a systematic review and meta-analysis. Internal and emergency medicine. 2017;12(6):821-36.
25. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-12.
26. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.
27. Kulu R, Akyildiz H, Akcan A, Ozturk A, Sozuer E. Plasma citrulline measurement in the diagnosis of acute mesenteric ischaemia. ANZ J Surg. 2017;87(9):E57-E60.
28. Groteluschen R, Bergmann W, Welte MN, Reeh M, Izbicki JR, Bachmann K. What predicts the outcome in patients with intestinal ischemia? A single center experience. J Visc Surg. 2019;156(5):405-11.
29. Montagnana M, Danese E, Lippi G. Biochemical markers of acute intestinal ischemia: possibilities and limitations. Annals of translational medicine. 2018;6(17):341.
30. Wu C, Zhu X, Ren H, Tan F, Liu X. Intestinal fatty acid-binding protein as a biomarker for the diagnosis of strangulated intestinal obstruction: A meta-analysis. Open medicine (Warsaw, Poland). 2021;16(1):264-73.
31. Pedersoli F, Schonau K, Schulze-Hagen M, Keil S, Isfort P, Gombert A, et al. Endovascular Revascularization with Stent Implantation in Patients with Acute Mesenteric Ischemia due to Acute Arterial Thrombosis: Clinical Outcome and Predictive Factors. Cardiovasc Intervent Radiol. 2021;44(7):1030-8.
32. Tang W, Jin B, Kuang LQ, Zhang J, Li CX, Wang Y. Risk factors of geriatrics index of comorbidity and MDCT findings for predicting mortality in patients with acute mesenteric ischemia due to superior mesenteric artery thromboembolism. The British journal of radiology. 2020;93(1116):20190605.
33. Wu W, Liu J, Zhou Z. Preoperative Risk Factors for Short-Term Postoperative Mortality of Acute Mesenteric Ischemia after Laparotomy: A Systematic Review and Meta-Analysis. Emerg Med Int. 2020;2020:1382475.
34. Wu W, Yang L, Zhou Z. Clinical Features and Factors Affecting Postoperative Mortality for Obstructive Acute Mesenteric Ischemia in China: A Hospital- Based Survey. Vasc Health Risk Manag. 2020;16:479-87.
35. Matsumoto S, Sekine K, Funaoka H, Yamazaki M, Shimizu M, Hayashida K, et al. Diagnostic performance of plasma biomarkers in patients with acute intestinal ischaemia. Br J Surg. 2014;101(3):232-8.

36. Acosta S, Nilsson TK, Björck M. Preliminary study of D-dimer as a possible marker of acute bowel ischaemia. Br J Surg. 2001;88(3):385-8.
37. Acosta S, Nilsson TK, Bjorck M. D-dimer testing in patients with suspected acute thromboembolic occlusion of the superior mesenteric artery. Br J Surg. 2004;91(8):991-4.
38. Brillantino A, Iacobellis F, Renzi A, Nasti R, Saldamarco L, Grillo M, et al. Diagnostic value of arterial blood gas lactate concentration in the different forms of mesenteric ischemia. European journal of trauma and emergency surgery : official publication of the European Trauma Society. 2018;44(2):265-72.
39. Acosta S, Block T, Björnsson S, Resch T, Björck M, Nilsson T. Diagnostic pitfalls at admission in patients with acute superior mesenteric artery occlusion. The Journal of emergency medicine. 2012;42(6):635-41.
40. Aktimur R, Cetinkunar S, Yildirim K, Aktimur SH, Ugurlucan M, Ozlem N. Neutrophil-to-lymphocyte ratio as a diagnostic biomarker for the diagnosis of acute mesenteric ischemia. European journal of trauma and emergency surgery : official publication of the European Trauma Society. 2016;42(3):363-8.
41. Akyildiz H, Akcan A, Oztürk A, Sozuer E, Kucuk C, Karahan I. The correlation of the D-dimer test and biphasic computed tomography with mesenteric computed tomography angiography in the diagnosis of acute mesenteric ischemia. American journal of surgery. 2009;197(4):429-33.
42. Altintoprak F, Arslan Y, Yalkin O, Uzunoglu Y, Ozkan OV. Mean platelet volume as a potential prognostic marker in patients with acute mesenteric ischemia-retrospective study. World J Emerg Surg. 2013;8(1):49.
43. Ambe PC, Kang K, Papadakis M, Zirngibl H. Can the Preoperative Serum Lactate Level Predict the Extent of Bowel Ischemia in Patients Presenting to the Emergency Department with Acute Mesenteric Ischemia? BioMed research international. 2017;2017:8038796.
44. Arnalich F, Maldifassi MC, Ciria E, Quesada A, Codoceo R, Herruzo R, et al. Association of cell-free plasma DNA with perioperative mortality in patients with suspected acute mesenteric ischemia. Clinica chimica acta; international journal of clinical chemistry. 2010;411(17):1269-74.
45. Beng Fuh R, Eisele R. Acute disturbance of the mesenterial circulation. What is the diagnostic value of easily performed preoperative tests?. [German]. Chirurgische Praxis. 2004;63(4):573-83.
46. Bilgic I, Dolu F, Senol K, Tez M. Prognostic significance of red cell distribution width in acute mesenteric ischemia. Perfusion. 2015;30(2):161-5.
47. Bilgic IC, Gelecek S, Ozmen MM, Kasapoglu B. The association of elevated mean platelet volume with the outcome of acute mesenteric ischemia. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2015;26(7):727-30.
48. Canfora A, Ferronetti A, Marte G, Maio VD, Mauriello C, Maida P, et al. Predictive Factors of Intestinal Necrosis in Acute Mesenteric Ischemia. Open medicine (Warsaw, Poland). 2019;14:883-9.
49. Chiu YH, Huang MK, How CK, Hsu TF, Chen JD, Chern CH, et al. D-dimer in patients with suspected acute mesenteric ischemia. The American journal of emergency medicine. 2009;27(8):975-9.
50. Czerny M, Trubel W, Claeys L, Scheuba C, Huk I, Prager M, et al. [Acute mesenteric ischemia]. Zentralblatt fur Chirurgie. 1997;122(7):538-44.
51. Degerli V, Ergin I, Duran FY, Ustuner MA, Duran O. Could Mean Platelet Volume Be a Reliable Indicator for Acute Mesenteric Ischemia Diagnosis? A Case-Control Study. BioMed research international. 2016;2016:9810280.

52. Destek S, Yabacı A, Abik YN, Gül VO, Değer KC. Predictive and prognostic value of L-lactate, D-dimer, leukocyte, C-reactive protein and neutrophil/lymphocyte ratio in patients with acute mesenteric ischemia. Ulusal travma ve acil cerrahi dergisi = Turkish journal of trauma & emergency surgery : TJTES. 2020;26(1):86-94.
53. Elthes EE, Cozlea AL, Torok A. Factors associated with in-hospital death in patients with acute mesenteric artery ischemia. Journal of Cardiovascular Emergencies. 2018;4(3):133-9.
54. Emile SH. Predictive Factors for Intestinal Transmural Necrosis in Patients with Acute Mesenteric Ischemia. World J Surg. 2018;42(8):2364-72.
55. Fried MW, Murthy UK, Hassig SR, Woo J, Oates RP. Creatine kinase isoenzymes in the diagnosis of intestinal infarction. Digestive diseases and sciences. 1991;36(11):1589-93.
56. Gaddam KP, Shaikh AK, Joshi NG, Suryakar AN, Katkam RV. Study of certain biochemical parameters as markers in Intestinal ischemia. Biomedical Research. 2011;22(4):443-7.
57. Gün B, Yolcu S, Değerli V, Elçin G, Tomruk Ö, Erdur B, et al. Multi-detector angio-CT and the use of D-dimer for the diagnosis of acute mesenteric ischemia in geriatric patients. Ulusal travma ve acil cerrahi dergisi = Turkish journal of trauma & emergency surgery : TJTES. 2014;20(5):376-81.
58. Gunduz A, Turkmen S, Turedi S, Mentese A, Yulug E, Ulusoy H, et al. Time-dependent variations in ischemia-modified albumin levels in mesenteric ischemia. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 2009;16(6):539-43.
59. Güzel M, Sözüer EM, Salt Ö, İkizceli İ, Akdur O, Yazıcı C. Value of the serum I-FABP level for diagnosing acute mesenteric ischemia. Surgery today. 2014;44(11):2072-6.
60. Jamieson WG, Marchuk S, Rowsom J, Durand D. The early diagnosis of massive acute intestinal ischaemia. Br J Surg. 1982;69 Suppl:S52-3.
61. Janda A, Hagmüller GW, Denck H. [Lactate in the diagnosis of acute intestinal vascular occlusions]. Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen. 1984;55(7):469-73.
62. Kim HK, Hwang D, Park S, Huh S, Lee JM, Yun WS, et al. Effect of Clinical Suspicion by Referral Physician and Early Outcomes in Patients with Acute Superior Mesenteric Artery Embolism. Vascular specialist international. 2017;33(3):99-107.
63. Kisaoglu A, Bayramoglu A, Ozogul B, Atac K, Emet M, Atamanalp SS. Sensitivity and specificity of red cell distribution width in diagnosing acute mesenteric ischemia in patients with abdominal pain. World J Surg. 2014;38(11):2770-6.
64. Lange H, Jäckel R. Usefulness of plasma lactate concentration in the diagnosis of acute abdominal disease. The European journal of surgery = Acta chirurgica. 1994;160(6-7):381-4.
65. Leo PJ, Simonian HG. The role of serum phosphate level and acute ischemic bowel disease. The American journal of emergency medicine. 1996;14(4):377-9.
66. Lieberman JM, Sacchettini J, Marks C, Marks WH. Human intestinal fatty acid binding protein: report of an assay with studies in normal volunteers and intestinal ischemia. Surgery. 1997;121(3):335-42.
67. Meyer T, Klein P, Schweiger H, Lang W. How can prognosis of acute mesenteric ischemia be improved? Results of a retrospective analysis. [German]. Zentralblatt fur Chirurgie. 1998;123(3):230-4.
68. Murray MJ, Gonze MD, Nowak LR, Cobb CF. Serum D(-)-lactate levels as an aid to diagnosing acute intestinal ischemia. American journal of surgery. 1994;167(6):575-8.
69. Rivera Núñez MA, Rodríguez Gijón L, Tung Chen Y, Martí de Gracia M, Buitrago Weiland G, Díez Tascón A. Neutrophil-to-lymphocyte ratio and mesenteric ischemia: can it predict the etiology of mesenteric ischemic at computed tomography? Emergency radiology. 2019;26(5):515-21.

70. Sachs SM, Morton JH, Schwartz SI. Acute mesenteric ischemia. Surgery. 1982;92(4):646-53.

71. Schoeffel U, Baumgartner U, Imdahl A, Haering R, v Specht BU, Farthmann EH. The influence of ischemic bowel wall damage on translocation, inflammatory response, and clinical course. American journal of surgery. 1997;174(1):39-44.

72. Sgourakis G, Papapanagiotou A, Kontovounisios C, Karamouzis MV, Lanitis S, Konstantinou C, et al. The value of plasma neurotensin and cytokine measurement for the detection of bowel ischaemia in clinically doubtful cases: a prospective study. Experimental biology and medicine (Maywood, NJ). 2013;238(8):874-80.

73. Shi H, Wu B, Wan J, Liu W, Su B. The role of serum intestinal fatty acid binding protein levels and D-lactate levels in the diagnosis of acute intestinal ischemia. Clinics and research in hepatology and gastroenterology. 2015;39(3):373-8.

74. Studer P, Vaucher A, Candinas D, Schnüriger B. The value of serial serum lactate measurements in predicting the extent of ischemic bowel and outcome of patients suffering acute mesenteric ischemia. J Gastrointest Surg. 2015;19(4):751-5.

75. Takis PG, Taddei A, Pini R, Grifoni S, Tarantini F, Bechi P, et al. Fingerprinting Acute Digestive Diseases by Untargeted NMR Based Metabolomics. International journal of molecular sciences. 2018;19(11).

76. Tanrıkulu Y, Şen Tanrıkulu C, Sabuncuoğlu MZ, Temiz A, Köktürk F, Yalçın B. Diagnostic utility of the neutrophil-lymphocyte ratio in patients with acute mesenteric ischemia: A retrospective cohort study. Ulusal travma ve acil cerrahi dergisi = Turkish journal of trauma & emergency surgery : TJTES. 2016;22(4):344-9.

77. Thuijls G, van Wijck K, Grootjans J, Derikx JP, van Bijnen AA, Heineman E, et al. Early diagnosis of intestinal ischemia using urinary and plasma fatty acid binding proteins. Annals of surgery. 2011;253(2):303-8.

78. Toptas M, Akkoc İ, Savas Y, Uzman S, Toptas Y, Can MM. Novel hematologic inflammatory parameters to predict acute mesenteric ischemia. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2016;27(2):127-30.

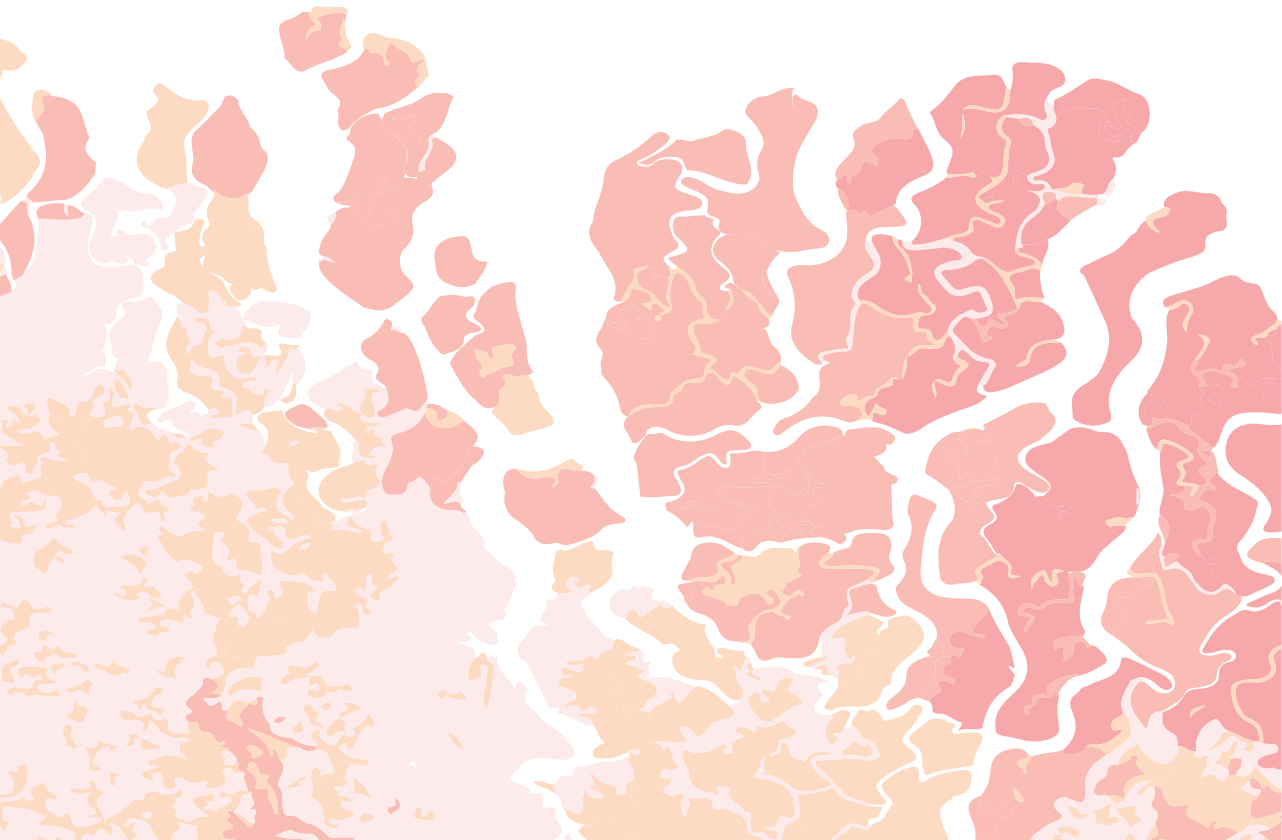
79. Tsai CJ, Kuo YC, Chen PC, Wu CS. The spectrum of acute intestinal vascular failure: a collective review of 43 cases in Taiwan. The British journal of clinical practice. 1990;44(12):603-8.

80. Turkoglu A, Gul M, Oguz A, Bozdag Z, Ulger BV, Yilmaz A, et al. Mean platelet volume: is it a predictive parameter in diagnosis of acute mesenteric ischemia? International surgery. 2015;100(5):962-5.

81. Uzun O, Turkmen S, Eryigit U, Mentese A, Turkyilmaz S, Turedi S, et al. Can Intestinal Fatty Acid Binding Protein (I-FABP) Be A Marker in the Diagnosis of Abdominal Pathology? Turkish journal of emergency medicine. 2014;14(3):99-103.

82. Wang S, Liu H, Wang Q, Cheng Z, Sun S, Zhang Y, et al. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio Are Effective Predictors of Prognosis in Patients with Acute Mesenteric Arterial Embolism and Thrombosis. Ann Vasc Surg. 2018;49:115-22.

83. Yılmaz EM, Cartı EB. Prognostic factors in acute mesenteric ischemia and evaluation with Mannheim Peritonitis Index and platelet-to-lymphocyte ratio. Ulusal travma ve acil cerrahi dergisi = Turkish journal of trauma & emergency surgery : TJTES. 2017;23(4):301-5.



Chapter 3

Chronic mesenteric ischemia: When and how to intervene on patients with coeliac/SMA stenosis

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Abstract

Background Studies that compared open surgical mesenteric artery repair (OSMAR) with percutaneous mesenteric artery stenting (PMAS) in patients with chronic mesenteric ischemia (CMI) are based on merely older studies in which only a minority of patients received PMAS. This does not reflect the current PMAS-first choice treatment paradigm. This article focused on the present opinions and changes in outcomes of OSMAR for CMI in the era of preferred use of PMAS.

Methods Patients who received OSMAR for CMI from 1997 until 2014 in a tertiary referral centre for chronic mesenteric ischemia were included in this report. Patients were divided into two groups, the historical OSMAR preferred group and present PMAS preferred group.

Results Patient characteristics, SVS comorbidity severity score, clinical presentation and number of diseased mesenteric arteries were not significantly changed after the widespread introduction of PMAS. In the present PMAS first era there were trends of less open surgical mesenteric artery multivessel repair, less antegrade situated bypasses, decreased clinical success but improved survival after OSMAR.

Discussion Elective OSMAR should only be used in patients with substantial physiologic reserve and who have unfavourable mesenteric lesions, failed PMAS or multiple recurrences of in-stent stenosis/occlusion. PMAS in CMI patients is evolved from “bridge to surgery” to nowadays first choice treatment and “bridge to repeated PMAS” in almost all patients with CMI.

Introduction

Atherosclerosis is the most common diseases of the vascular tree and the major cause of death in the western world. Atherosclerotic disease occurs in all human arteries and ultimately it can lead to stenosis, occlusions and aneurysms. Among the more uncommon clinical manifestations of atherosclerosis are symptomatic mesenteric diseases. Synonyms of the word "mesenteric" are "splanchnic", "visceral" and "intestinal". Mesenteric is derived from the new Latin word *mesenterium* and indicates "any peritoneal membrane that enfolds an internal vertebrate organ and attaches it to the body wall". Splanchnic is derived from the new Latin word *splanchnicus*, which indicates "pertaining to, or supplying the organs in the cavities of the body". Visceral is derived from Medieval Latin and means "pertaining to, or affecting the organs in the cavities of the body". Intestinal is of new Latin origin and means "pertaining to, being in, or affecting the lower part of the alimentary canal, extending from the pylorus to the anus". Although the word splanchnic is clear, the synonym mesenteric is preferred to indicate the coeliac artery (CA), the superior (SMA) and inferior mesenteric arteries (IMA), and ischemia in that region, since it is used by far most frequent in the literature.

Chronic mesenteric ischemia (CMI) is defined by abdominal symptoms due to inadequate blood supply to the gastrointestinal tract, most frequently caused by atherosclerosis.(1) The majority of patients suffer from abdominal pain and weight loss. Without revascularization of the intestine, CMI can ultimately progress to acute-on-chronic mesenteric ischemia with a high mortality rate up to 90%.(2, 3) Open surgical mesenteric artery repair (OSMAR) has been the gold standard of treatment since 1958 and is associated with excellent long-term patency and symptom relief.(4-6) As an alternative, the use of percutaneous mesenteric artery stenting (PMAS) has increased greatly during the past decades.(7) Advantages include less in-hospital morbidity, shorter hospital stay and availability in patients with high surgical risk. In contrast, primary patency and symptom recurrence rates are traditionally inferior to OSMAR. Furthermore, PMAS can be challenging in heavily calcified osteal lesions. Studies that compared OSMAR and PMAS cohorts showed that patients who received OSMAR had less extensive comorbidity, but more severe mesenteric artery atherosclerosis when compared to patients who received PMAS.(8, 9) Nevertheless indications for treatment with PMAS have broadened in recent years, and now also include patients who would have been candidates for OSMAR in the past. Consequently, the fast majority of patients with CMI now receive PMAS.(9)

One recently published(10) and two shortly published reviews(11, 12) collectively discuss nearby all relevant topics of acute and chronic mesenteric ischemia. In these careful edited

papers outcome of OSMAR and PMAS are based on merely older studies in which only a minority of patients received PMAS. This does not reflect the current PMAS-first choice treatment paradigm. Because of this changed daily practice traditional results of OSMAR may not be applicable nowadays. Therefore, the present study focused on changes in outcomes of open surgical mesenteric artery repair for CMI in the era of preferred use of PMAS.

Methods

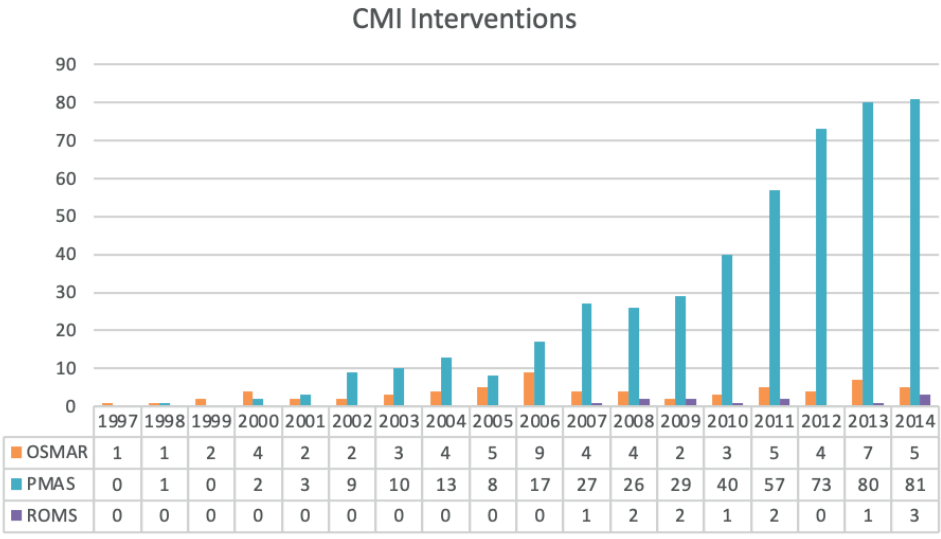
Patient inclusion

Medical Spectrum Twente is a tertiary referral center for mesenteric ischemia in the Netherlands. Starting in 1997 all admitted patients diagnosed with mesenteric ischemia have been prospectively enrolled in our database. Patients who received OSMAR for CMI from 1997 until 2014 were included in this report. Excluded were patients who received OSMAR for acute mesenteric ischemia, acute-on-chronic mesenteric ischemia, coeliac artery compression syndrome, or previous mesenteric artery revascularizations. Patients who received OSMAR were divided into two groups based on date of intervention. PMAS became the preferred treatment for CMI in our centre since 2006, therefore 01-01-2006 was used as a dividing line between the historical OSMAR preferred group and present PMAS preferred group. Annual interventions with OSMAR and PMAS for the treatment of CMI in our clinic are shown in Figure 1. According to institutional regulations, review board individual patient approval was not required for this retrospective study. Therefore, no patient informed consent was obtained. Patient data were analysed anonymously.

Diagnosis

Each patient referred to our center for evaluation of CMI received a standard diagnostic workup as described previously.(13) Complete screening consisted of thorough interviews by a gastroenterologist and a vascular surgeon, mesenteric artery duplex ultrasound, 24-hour CO_2 tonometry and/or gastric exercise tonometry, laboratory studies, and multidisciplinary assessment of diagnostic evidence. When suspicion of CMI was confirmed, mesenteric digital subtraction angiography or computed tomography angiography was performed resulting in the final diagnosis and treatment advice.

Figure 1: Overview of number and type of interventions for Chronic Mesenteric Ischemia in a tertiary referral hospital.



	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
OSMAR	1	1	2	4	2	2	3	4	5	9	4	4	2	3	5	4	7	5
PMAS	0	1	0	2	3	9	10	13	8	17	27	26	29	40	57	73	80	81
ROMS	0	0	0	0	0	0	0	0	0	0	1	2	2	1	2	0	1	3

Treatment

In general, treatment preference was based on life expectancy, vascular anatomy, nutritional status and surgical risk. OSMAR was preferably performed using autologous antegrade revascularization techniques. Retrograde bypass was performed when the supracoeliac anatomy was considered unsuitable for aortic clamping, or the hemodynamic risk of supracoeliac clamping was considered too challenging in the context of patient comorbidities.

Supportive care and follow-up

All patients received proton pump inhibition. Postoperatively all patients were placed on a strict stepwise progressive oral refeeding protocol including daily clinical and haematological assessments to reduce the ischemia reperfusion sequels. Patients were heparinized until oral anticoagulant or antiplatelet therapy was effective. Patients received at that moment state of the art medical treatment for secondary prevention of atherosclerosis. Patients underwent a standardized follow-up schedule, consisting of outpatient visits and duplex ultrasound at 3, 12, 24, and 48 months, followed by once every 2 years.

Data gathering and outcomes

For this report the prospective patient database was supplemented with data from hospital records and referring physician or patient correspondence. Data registered were demographics, presenting symptoms, cardiovascular risk factors according to society for vascular surgery (SVS) reporting standards, SVS comorbidity severity score, previous interventions for mesenteric ischemia, the number of significant stenosed or occluded mesenteric arteries, and treatment details. A vessel lumen diameter reduction of >70% was considered significant.

Primary outcomes were postoperative mortality and complications. Grade 3a or greater complications according to the Dindo-Clavien Classification were recorded. Secondary outcomes were patency rates according to SVS reporting standards and clinical success rates. Clinical success was defined as anatomical success and improvement or continued absence of symptoms. Clinical failure was defined as persistence or recurrence of symptoms caused by residual, recurrent, or additional vessel stenoses or occlusions. Ischemia- or therapy-related death was also recorded as clinical failure.

The Netherlands municipal personal records database was accessed for confirmation of survival. The in-hospital/30-day (IH/30D) follow-up period was defined as the first 30 postoperative days or until discharge when postoperative admittance duration was >30 days. The late follow-up period started at 30 days, or at discharge when postoperative admittance duration was >30 days.

Statistical analysis

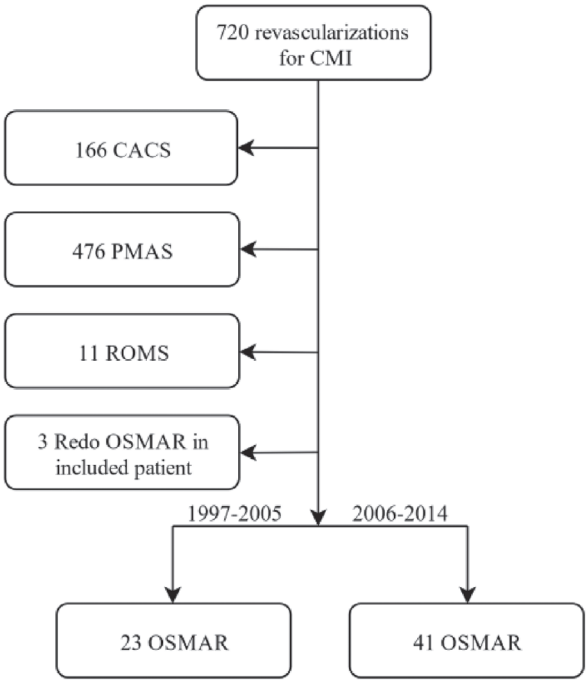
Continuous variables were expressed as mean with standard deviation (SD) when normally distributed or as median with interquartile range (IQR) when not normally distributed. Categorical variables were expressed as counts with percentages. Continuous variables were compared using independent sample t-tests when normally distributed or Mann-Whitney *U* tests when not normally distributed. Categorical variables were compared using Pearson's χ^2 or Fisher's exact tests as appropriate. Survival, patency and clinical success rates were analyzed by Kaplan-Meier plots, using log-rank tests to determine significance. P-values less than 0.05 were considered significant and values between 0.05 and 0.20 were considered a trend. Univariate analysis of survival, patency and clinical success rates was performed using Cox regression. Data was analyzed using SPSS, version 22 (IBM Corp. Armonk, NY, USA).

Results

Patient characteristics

In total 64 patients with OSMAR were included; 23 in the historical group and 41 in the present group (Figure 2). Patient and disease characteristics are shown in Table I. In the historical group, 21 patients received OSMAR for newly diagnosed CMI and 2 patients with previous PMAS for CMI. In the present group 20 patients received OSMAR for newly diagnosed CMI and 21 patients with previous PMAS for CMI (8.7% *vs.* 51.2%; p=0.001). Both groups had similar gender, age and body mass index (BMI). The present group had higher incidences of hypertension (21.7% *vs.* 51.2%; p=0.021) and hyperlipidaemia (26.1% *vs.* 53.7%; p=0.033). Both groups had similar incidences of other comorbidities and median SVS comorbidity severity score. Both groups had similar clinical presentation except for a trend towards greater incidence of adapted eating pattern in the present group (56.5% *vs.* 79.4%; p=0.064). Both groups had equal numbers of diseased vessels per patient.

Figure 2: Flowchart of patient treated for CMI between 1997 and 2014.



CACS = coeliac artery compression syndrome, CMI = chronis mesenteric ischemia, OSMAR = open surgical mesenteric artery repair, PMAS = percutaneous mesenteric artery stenting, ROMS = retrograde open mesenteric stenting.

Table 1 Patient characteristics of 64 patients treated with OSMAR for CMI.

Variable	Historical group (N.=23)	Present group (N.=41)	P-value
Male sex (N., %)	3 (13.0%)	10 (24.4%)	0.227
Age, years (mean, SD)	53.2 (±11.1)	54.2 (±10.9)	0.719
BMI (mean, SD)	21.0 (±3.4)	21.8 (±3.7)	0.405
Risk factors (SVS)			
Diabetes mellitus (N., %)	1 (4.3%)	4 (9.8%)	0.646
Currently smoking (N., %)	18 (78.3%)	26 (63.4%)	0.219
Hypertension (N., %)	5 (21.7%)	21 (51.2%)	**0.021**
Hyperlipidemia (N., %)	6 (26.1%)	22 (53.7%)	**0.033**
Coronary artery disease (N., %)	4 (17.4%)	8 (19.5%)	1.000
Cerebrovascular disease (N., %)	1 (4.3%)	3 (7.3%)	1.000
Renal disease (N., %)	2 (8.7%)	2 (4.9%)	0.614
Pulmonary disease (N., %)	4 (17.4%)	9 (22.0%)	0.755
Peripheral artery disease (N., %)	7 (30.4%)	15 (36.6%)	0.619
SVS comorbidity score (median, IQR)	1 (0-5)	2 (0-5.5)	0.317
Previous treatment for CMI (N., %)			
PTA	1 (4.3%)	1 (2.4%)	1.000
PMAS	1 (4.3%)	15 (36.6%)	**0.004**
ROMS	0 (0.0%)	2 (4.9%)	0.532
OSMAR	0 (0.0%)	4 (9.8%)	0.288
Any	2 (8.7%)	21 (51.2%)	**0.001**
Symptoms among symptomatic patients (N., %)			
Weight loss	22 (95.7%)	30 (88.2%)	0.638
Postprandial pain	22 (95.7%)	28 (82.4%)	0.233
Adapted eating pattern	12 (56.5%)	27 (79.4%)	0.064
Diarrhea	11 (47.8%)	20 (58.8%)	0.413
Nausea	8 (34.8%)	13 (38.2%)	0.791
Vomiting	7 (30.4%)	7 (20.6%)	0.397

CMI = chronis mesenteric ischemia, OSMAR = open surgical mesenteric artery repair.

Treatment

A summary of treatment characteristics is shown in Table II. Multivessel repairs were performed in 73.9% in the historical group and in 56.1% in the present group (p=0.158), 78.9% of bypasses in the historical group and 61.1% in the present group were antegrade (p=0.180). More single SMA bypasses were performed in the present group (p=0.056) and a significant but clinical not relevant decrease in blood loss in the present group was noted (p=0.039). Technical success was achieved in all patients. Simultaneous procedures in the historical group were nephrectomy for renovascular hypertension in one patient and

aortoiliac endarterectomy for claudication in another patient. Simultaneous procedures in the present group were aortobi-iliac bypass for claudication in one patient, combined right sided iliofemoral bypass and left iliac endarterectomy for claudication in one, cicatricial hernia correction in three and liver segment resection for a carcinoid tumour metastasis found incidentally in another one. There were no intraoperative deaths.

Table 2 Operative treatment characteristics of 64 patients treated with OSMAR for CMI.

Variable	Historical group (N.=23)	Present group (N.=41)	P-value
Bypass (N., % of total cases)			
CA and SMA bypass	13 (56.5%)	21 (51.3%)	0.683
Single CA bypass	3 (13.0%)	3 (7.3%)	0.451
Single SMA bypass	2 (8.7%)	12 (29.3%)	0.056
IMA patch angioplasty to SMA bypass	1 (4.3%)	0 (0.0%)	0.359
Any bypass	19 (82.6%)	36 (87.8%)	0.711
Bypass configuration (N., % of all bypasses)			
Antegrade	15 (78.9%)	22 (61.1%)	0.180
Retrograde	4 (21.1%)	14 (38.9%)	0.180
Bypass material (N., % of all bypasses)			
Autologous vein	13 (68.4%)	32 (88.9%)	0.071
Autologous artery	5 (26.3%)	3 (8.3%)	0.124
Synthetic (6-mm Dacron)	1 (5.3%)	0 (0.0%)	0.359
Combined artery and vein	0 (0.0%)	1 (2.8%)	1.000
Endarterectomy (N., % of total cases)	4 (17.4%)	4 (9.8%)	0.443
SMA reimplantation (N., % of all cases)	0 (0.0%)	1 (2.4%)	1.000
Vessels treated (N., % of all cases)			
CA	20 (87.0%)	27 (65.9%)	0.067
SMA	19 (82.6%)	37 (90.2%)	0.443
IMA	1 (4.3%)	1 (2.4%)	1.000
1 vessel treated	6 (26.1%)	18 (43.9%)	0.216
2 vessels treated	17 (73.9%)	22 (53.7%)	0.216
3 vessels treated	0 (0.0%)	1 (2.4%)	0.216
Intraoperative blood loss, mL (median, IQR)	600 (400-1500)	400 (300-700)	**0.039**
Intervention duration, min (mean, SD)	309 (±83)	296 (±87)	0.595

CA = coeliac artery, CMI = chronis mesenteric ischemia, IMA = inferior mesenteric artery, IQR = interquartile range, OSMAR = open surgical mesenteric artery repair, SMA = superior mesenteric artery.

Mortality and complications

Median hospital admission duration was 13 (IQR 10-17) days in the historical group and 16 (IQR 11-31) days in the present group (p=0.139). Median intensive care unit admission was 2 (IQR 1-5) days in the historical group and 1 (IQR 1-2) day in the present group (p=0.059).

Table 3 Complications of 64 patients treated with OSMAR for CMI.

Variables	Historical Group (N.=23)	Present Group (N.=41)	P-value
Early follow-up morbidity, Dindo-Clavien grade >2 (N., %)			
Procedure related			
Bleeding	2 (8.7%)	5 (12.2%)	1.000
Infection	0 (0.0%)	3 (7.3%)	0.547
Occlusion/stenosis	1 (4.3%)	7 (17.1%)	0.241
Other	4 (17.4%)	4 (9.8%)	0.443
Any	6 (26.1%)	12 (29.3%)	0.786
Systemic			
Multiorgan failure	2 (8.7%)	1 (2.4%)	0.291
Pulmonary	2 (8.7%)	3 (7.3%)	1.000
Cardiac	1 (4.3%)	0 (0.0%)	0.359
Cerebrovascular	0 (0.0%)	0 (0.0%)	NA
Renal	0 (0.0%)	0 (0.0%)	NA
Any	4 (17.4%)	4 (9.8%)	0.443
Early follow-up highest Dindo-Clavien grade			0.675
3a	1 (4.3%)	2 (4.9%)	
3b	3 (13.0%)	6 (14.6%)	
4a	1 (4.3%)	3 (7.3%)	
4b	1 (4.3%)	0 (0.0%)	
5	3 (13.0%)	2 (4.9%)	
Late follow-up morbidity, Dindo-Clavien grade >2 (N., %)			
Procedure-related			
Bleeding	0 (0.0%)	0 (0.0%)	NA
Infection	0 (0.0%)	1 (2.4%)	1.000
Occlusion/stenosis	3 (13.0%)	6 (14.6%)	1.000
Other	3 (13.0%)	3 (7.3%)	0.658
Any	5 (21.7%)	10 (24.4%)	0.810

CMI = chronis mesenteric ischemia, NA = not available, OSMAR = open surgical mesenteric artery repair.

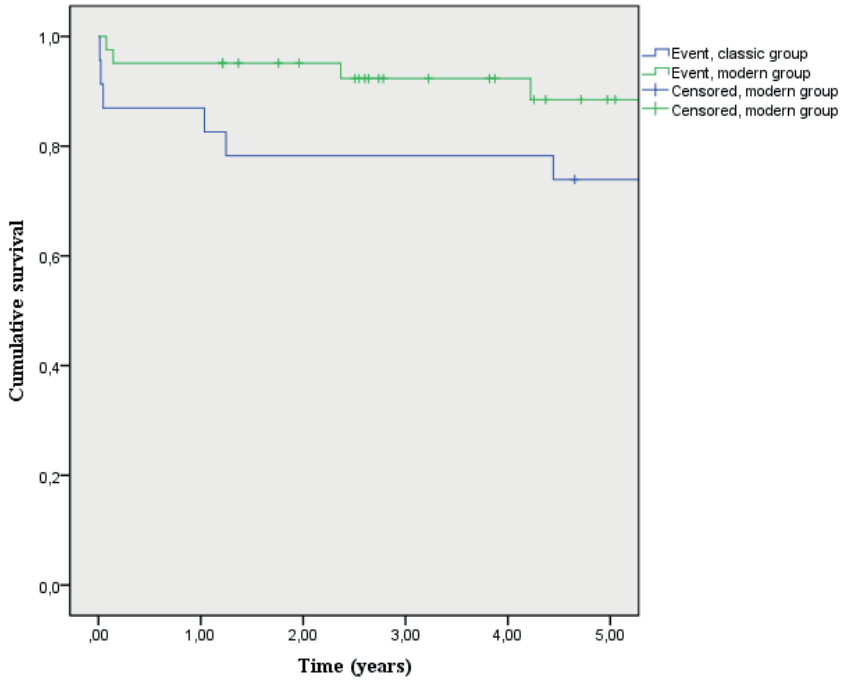
Three patients (13.0%) died during the IH/30D period in the historical group. Causes were small bowel necrosis despite a patent bypass, small bowel necrosis caused by SMA dissection following endarterectomy, and multi-organ failure. Two patients (4.9%; p=0.341) died during the IH/30D period in the present group. One patient died of multi-organ failure following partial resection of necrotic small bowel caused by SMA dissection during antegrade 2-vessel bypass. One patient died of hypovolemic shock caused by a retrograde SMA bypass anastomosis rupture after hospital discharge. The five patients who died during the IH/30D period had a median BMI of 18.0 (IQR 15.9-22.2) compared to 21.5 (IQR 19.7-

23.0) among those who survived (p=0.070). Median SVS comorbidity severity score was 4 (IQR 0-9) compared to 2 (IQR 0-5) among those who survived (p=0.515).

Median follow-up was 92 (IQR 16-123) months in the historical group and 20 (IQR 11-49) months in the present group. Five patients died during follow-up in the historical group. The reasons were congestive heart failure, diabetic foot complicated by sepsis, end-stage chronic obstructive pulmonary disease, stroke and cholangiocarcinoma. Three patients died during follow-up in the present group, the cause of death was unknown but in all these three patients no symptoms consistent with CMI were recorded. For both groups the IH/30D and late complications were demonstrated in Table III.

Kaplan Meier estimates of survival are shown in Figure 3, there was a trend of improved survival in the present group (p=0.134). One-, 3- and 5-year survival in the historical and present group was 87.0% *versus* 95.1%, 78.3% *versus* 92.3% and 73.9% *versus* 88.5% respectively. Factors associated with decreased survival were duration of intensive care unit admittance (p=0.001), age (p=0.007), cardiac disease (p=0.041), conservative treatment of coeliac artery disease (p=0.054), carotid disease (p=0.057) and intraoperative blood loss (p=0.117).

Figure 3: Kaplan Meier estimates of overall survival after OSMAR for the 23 patients with CMI in the historical and 41 patients in the present cohort.



Blue line historical group, green line present group (p=0.134).

Clinical success and patency rates

There was a trend of decreased clinical success in the present group (p= 0.174). One-, 3, and 5-year clinical success rates in the historical and the present group were 82.6% *versus* 72.1%, 82.6% *versus* 60.1% and 70.7% *versus* 53.4% respectively Factors associated with decreased clinical success duration were intensive care admittance duration (p=0.017), carotid disease (p=0.070), cardiac disease (p=0.092) and intraoperative blood loss (p=0.093).

Clinical failure occurred in seven patients (30.4%) in the historical group. In addition to the three in-hospital deaths, four patients experienced a symptomatic recurrence. Of these four patients, one had CA endarterectomy restenosis, one had combined CA endarterectomy re-occlusion and SMA endarterectomy restenosis, one had occlusion of both limbs of an antegrade 2-vessel bypass and one had occlusion of a single vessel CA bypass. Treatment was PMAS of the CA, 2-vessel antegrade bypass, PMAS of the native CA combined with PTA of the native SMA, and conservative respectively.

Clinical failure occurred in 14 patients (34.1%) in the present group. In addition to the two IH/30D deaths, 11 patients had a symptomatic recurrence and one patient received preventive PMAS of the IMA after asymptomatic SMA limb occlusion of a 2-vessel antegrade bypass. Of the 11 patients who experienced a symptomatic recurrence, three had stenosis or occlusion of a single vessel SMA bypass. The other eight had a two-vessel antegrade or retrograde bypass. Of these eight patients, four had occlusions of both bypass limbs, two had stenosis or occlusion of the SMA limb, one had occlusion of the CA limb, and one had bypass origin stenosis. One patient who experienced a symptomatic recurrence was treated conservatively and 10 patients received a reintervention. Reinterventions were PMAS or PTA of the bypass and/or native vessels in five patients, surgical bypass revision in three, and redo retrograde SMA bypass in two patients. One patient who was treated with PMAS of the native SMA also underwent relaparotomy and subsequent drainage of a necrotic gallbladder.

One patient with asymptomatic occlusion of a single vessel CA bypass in the classic group and one patient with asymptomatic double limb occlusion of a 2-vessel antegrade bypass in the modern group were treated conservatively. One-, 3-, and 5-year primary patency of SMA reconstructions in the historical and present group was 94.7% *versus* 71.8%, 88.4% *versus* 53.8% and 88.4% *versus* 47.9% respectively (p=0.024). No factors were associated with decreased primary patency. One-, 3-, and 5-year secondary patency in the historical and present group was 94.7% *versus* 83.1%, 88.4% *versus* 69.8% and 88.4% *versus* 62.5% respectively (p=0.155).

One-, 3-, and 5-year primary patency of CA reconstructions in the historical and present group was 89.4% *versus* 81.2%, 89.4% *versus* 60.9% and 75.0% versus 60.9% respectively ($p \geq 0.222$). Factors associated with decreased primary patency were retrograde bypass (p=0.050), hyperlipidaemia (p=0.054), previous intervention for CMI (p=0.075), carotid disease (p=0.094) and diabetes mellitus (p=0.141). One-, 3-, and 5-year secondary patency in the historical and present group was 89.4% *versus* 88.7%, 89.4% *versus* 75.1%, and 82.5% *versus* 75.1% respectively ($p \geq 0.569$).

Discussion

The present study demonstrated that patient characteristics, SVS comorbidity severity score, clinical presentation and number of diseased mesenteric arteries were not significantly changed after the widespread introduction of PMAS in a cohort of patients with CMI treated with OSMAR. In the present PMAS first era there were trends of less open surgical mesenteric artery multivessel repair, less antegrade situated bypasses, decreased clinical success but improved survival after OSMAR. The most presumable explanation is that with the rise of PMAS, patients with more extensive atherosclerosis of the mesenteric arteries and in a better physical condition now undergo OSMAR. Patient characteristics indicating that advanced generalized atherosclerotic disease was associated with decreased in hospital survival after OSMAR. Morbidity and mortality increased substantially in patients undergoing OSMAR with significant weight loss. BMI below 19.5 kg/m^2 was associated with two to tenfold increased major morbidity and mortality.(4, 14) Also in the present study the five patients who died shortly after OSMAR had a significant lower BMI compared to those who survived, 18.0 versus 21.5 kg/m^2.

One- or two-vessel repair in case of multi-vessel CMI is still a point of debate. An evidence summary report, albeit with a high risk of confounding, supported for both PMAS and OSMAR the statement that long-term relief of symptoms can be achieved best by repair of more than one splanchnic artery.(9)

The level of evidence for convincing advice which material to use in OSMAR is low and local preferences rule the opinion. On the one hand, a couple of reports state the use of polyester grafts.(8, 15, 16) On the other hand, because of observed superb patencies there is support to justify, like in PAD, an autologous vein bypass of the CA and/or the SMA as the preferred technique.(5, 17)

The main priorities in revascularization of CMI are improving quality of life and prevention of bowel infarction. Secondary weight gain is a bonus. PMAS is now the primary treatment

choice.(7) But when analysing available literature there is a clear selection bias, which should be taken in to account in coming to a conclusion. The forthcoming review by Blauw *et al.*(12) underlines that PMAS has lower mortality and morbidity, length of stay and recovery time compared to OSMAR, but the counterpart is that more recurrence of symptoms, restenosis and re-interventions are seen after PMAS. A retrospective analysis of our own data on PMAS(18) between November 2004 and November 2012 showed that PMAS primary patency was 77% at 1 year and 45% after 5 years. But primary assisted, respectively 90% and 69.8%, and secondary patency, respectively 98.3% and 93.6%, were excellent and comparable to those published by centres of excellence after OSMAR. In our experience osteal mesenteric artery occlusions does not exclude successful PMAS.

Although literature is scares, covered stents were associated with less restenosis, a lower clinical symptom recurrence rate, and fewer re-interventions when compared to bare metal stents.(19) A Dutch randomised controlled trial comparing bare metal with covered stents for PMAS in patients with CMI is including patients yet, first result are awaited in 2018.

All patients need life-long anticoagulation to prevent atherosclerosis. There was a clear shift in postoperative thromboprophylaxis from lifelong single antiplatelet therapy to 3-6 months of double antiplatelet therapy followed by lifelong single therapy ($p<0.001$).

As mentioned in the introduction several excellent reviews were recently or will be published soon.(10-12) We assume this review gains strength if two points are added. Firstly, single-vessel CMI can only be diagnosed when a validated functional test indicates mesenteric ischemia. Without such a function test the diagnosis of single vessel CMI is more or less a coin flip. With gastric tonometry in the workup of single vessel CMI a durable relief of symptoms is achievable in 84% of patients.(20) Secondly, the influence of respiration and collateral flow on the normal values of Duplex ultrasonography is not accentuated.(21) Consequently, the degree of stenosis of the CA or the SMA could be easily over or underscored with Duplex ultrasound.

Conclusions

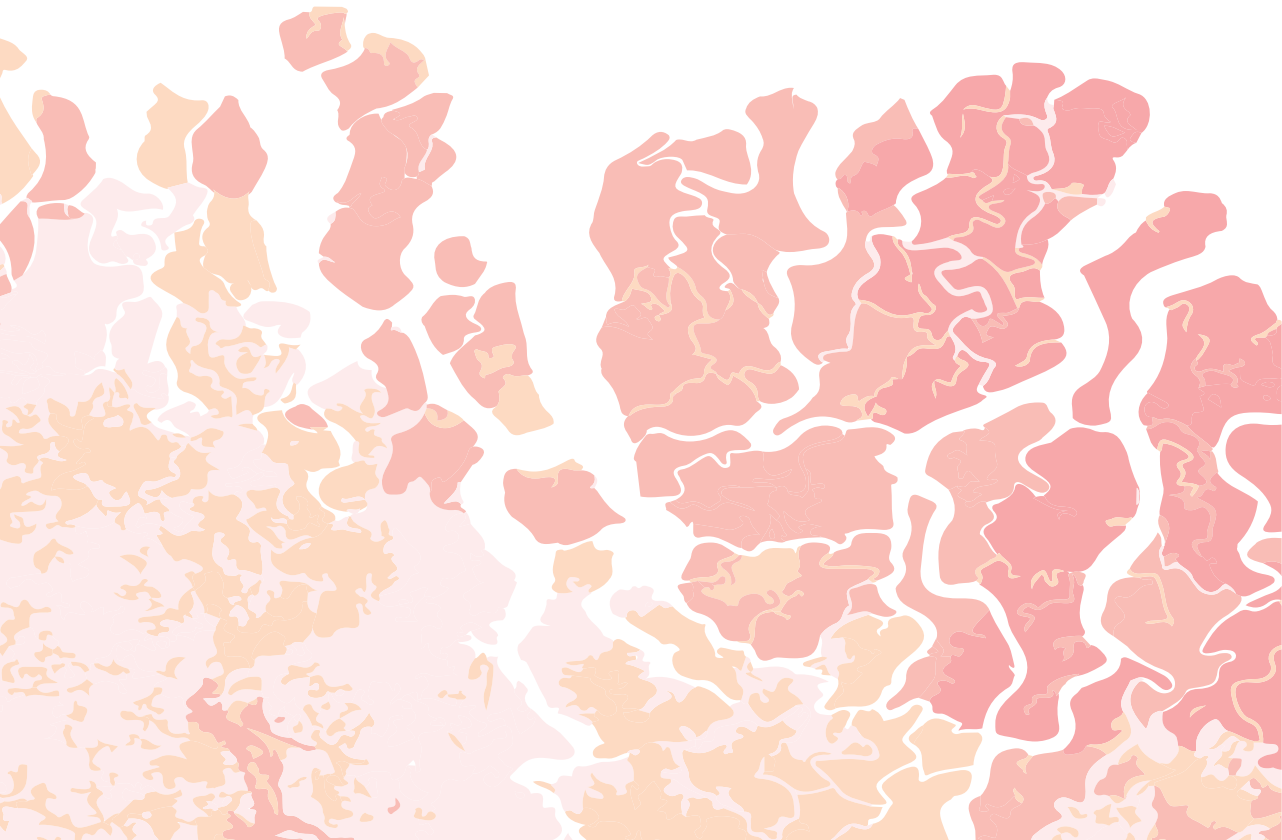
The present study supports that the historical results of OSMAR cannot be extrapolated to the current CMI patient population. There are no randomized controlled trials comparing an endovascular first versus an open surgery first approach and level I evidence is lacking. There is widespread support that long-term primary patency was better after OSMAR, with significantly more and mainly endovascular reinterventions in the PMAS group, secondary patency was not significantly different between PMAS and OSMAR. Nowadays, elective

OSMAR should only be used in patients with substantial physiologic reserve and who have unfavourable mesenteric lesions, failed PMAS or ROMS or multiple recurrences of in-stent stenosis/occlusion.(11, 12, 22, 23) The type of OSMAR should be tailored to the anatomy and the patient's clinical risk assessment. Planning OSMAR involves selection of the type of incision (transperitoneal *vs.* retroperitoneal), conduit (vein *vs.* prosthetic), graft configuration (antegrade *vs.* retrograde), source of inflow (aortic *vs.* iliac) and the number of vessels to be reconstructed (single *vs.* multiple). PMAS in CMI patients is evolved from "bridge to surgery" to nowadays first choice treatment and "bridge to repeated PMAS" in almost all patients with CMI.

References

1. Kolkman JJ, Bargeman M, Huisman AB, Geelkerken RH. Diagnosis and management of splanchnic ischemia. World J Gastroenterol. 2008;14(48):7309-20.
2. Park WM, Gloviczki P, Cherry KJ, Jr., Hallett JW, Jr., Bower TC, Panneton JM, et al. Contemporary management of acute mesenteric ischemia: Factors associated with survival. J Vasc Surg. 2002;35(3):445-52.
3. Schoots IG, Koffeman GI, Legemate DA, Levi M, van Gulik TM. Systematic review of survival after acute mesenteric ischaemia according to disease aetiology. Br J Surg. 2004;91(1):17-27.
4. Cho JS, Carr JA, Jacobsen G, Shepard AD, Nypaver TJ, Reddy DJ. Long-term outcome after mesenteric artery reconstruction: a 37-year experience. J Vasc Surg. 2002;35(3):453-60.
5. Geelkerken RH, van Bockel JH, de Roos WK, Hermans J, Terpstra JL. Chronic mesenteric vascular syndrome. Results of reconstructive surgery. Arch Surg. 1991;126(9):1101-6.
6. Shaw RS, Maynard EP, 3rd. Acute and chronic thrombosis of the mesenteric arteries associated with malabsorption; a report of two cases successfully treated by thromboendarterectomy. N Engl J Med. 1958;258(18):874-8.
7. Schermerhorn ML, Giles KA, Hamdan AD, Wyers MC, Pomposelli FB. Mesenteric revascularization: management and outcomes in the United States, 1988-2006. J Vasc Surg. 2009;50(2):341-8 e1.
8. Oderich GS, Bower TC, Sullivan TM, Bjarnason H, Cha S, Gloviczki P. Open versus endovascular revascularization for chronic mesenteric ischemia: risk-stratified outcomes. J Vasc Surg. 2009;49(6):1472-9 e3.
9. van Petersen AS, Kolkman JJ, Beuk RJ, Huisman AB, Doelman CJ, Geelkerken RH. Open or percutaneous revascularization for chronic splanchnic syndrome. J Vasc Surg. 2010;51(5):1309-16.
10. Clair DG, Beach JM. Mesenteric Ischemia. N Engl J Med. 2016;374(10):959-68.
11. Björck M, Koelemay M, Acosta S, Bastos Goncalves F, Kölbel T, Kolkman JJ, et al. Editor's Choice - Management of the Diseases of Mesenteric Arteries and Veins: Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2017;53(4):460-510.
12. Blauw JT, Bulut T, Oderich GS, Geelkerken BR, Dutch Mesenteric Ischemia Study G. Mesenteric vascular treatment 2016: from open surgical repair to endovascular revascularization. Best practice & research Clinical gastroenterology. 2017;31(1):75-84.
13. Otte JA, Geelkerken RH, Oostveen E, Mensink PB, Huisman AB, Kolkman JJ. Clinical impact of gastric exercise tonometry on diagnosis and management of chronic gastrointestinal ischemia. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2005;3(7):660-6.
14. Kihara TK, Blebea J, Anderson KM, Friedman D, Atnip RG. Risk factors and outcomes following revascularization for chronic mesenteric ischemia. Ann Vasc Surg. 1999;13(1):37-44.
15. Oderich GS, Gloviczki P, Bower TC. Open surgical treatment for chronic mesenteric ischemia in the endovascular era: when it is necessary and what is the preferred technique? Semin Vasc Surg. 2010;23(1):36-46.
16. Wyers MC. Acute mesenteric ischemia: diagnostic approach and surgical treatment. Semin Vasc Surg. 2010;23(1):9-20.
17. Shah AS, Schwartz LB, Moawad J, Gewertz BL. Technique profile: mesenteric reconstructions for occlusive disease. Expert Rev Cardiovasc Ther. 2015;13(12):1445-58.

18. Bulut T, Oosterhof-Berktas R, Geelkerken RH, Brusse-Keizer M, Stassen EJ, Kolkman JJ. Long-Term Results of Endovascular Treatment of Atherosclerotic Stenoses or Occlusions of the Coeliac and Superior Mesenteric Artery in Patients With Mesenteric Ischaemia. Eur J Vasc Endovasc Surg. 2017;53(4):583-90.
19. Oderich GS, Erdoes LS, Lesar C, Mendes BC, Gloviczki P, Cha S, et al. Comparison of covered stents versus bare metal stents for treatment of chronic atherosclerotic mesenteric arterial disease. J Vasc Surg. 2013;58(5):1316-23.
20. Mensink PB, van Petersen AS, Geelkerken RH, Otte JA, Huisman AB, Kolkman JJ. Clinical significance of splanchnic artery stenosis. Br J Surg. 2006;93(11):1377-82.
21. van Petersen AS, Kolkman JJ, Meerwaldt R, Huisman AB, van der Palen J, Zeebregts CJ, et al. Mesenteric stenosis, collaterals, and compensatory blood flow. J Vasc Surg. 2014;60(1):111-9, 9.e1-2.
22. Acosta S. Mesenteric ischemia. Curr Opin Crit Care. 2015;21(2):171-8.
23. Atkins MD, Kwolek CJ, LaMuraglia GM, Brewster DC, Chung TK, Cambria RP. Surgical revascularization versus endovascular therapy for chronic mesenteric ischemia: a comparative experience. J Vasc Surg. 2007;45(6):1162-71.



Chapter 4

Retrograde open mesenteric stenting for acute mesenteric ischemia

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Abstract

Background Acute mesenteric ischemia (AMI) encompasses the sequels of end stage untreated chronic mesenteric ischemia (CMI) and acute mesenteric artery thrombosis. Percutaneous mesenteric artery stenting (PMAS) is the preferred treatment in patients with AMI, but is not always feasible. Retrograde open mesenteric stenting (ROMS) is a hybrid technique that combines the advantages of open surgical and endovascular approaches. Literature on the results of this new technique is scarce. The aim of this study was to evaluate the results of ROMS in a consecutive series of patients with AMI.

Methods All patients with emergent mesenteric revascularization for AMI between January 2007 and September 2011 were entered in our prospective registry. Technical success, mortality, patency, clinical success and complication rate at 30 days, 6 and 12 months were assessed.

Results Sixty-eight patients presented with AMI and 54 underwent PMAS of which 4 were unsuccessful in which ROMS followed. Eleven patients were directly treated with ROMS, making a total of 15 patients. Ten women and five men with median age of 66 (Inter Quartile Range (IQR) 54-73) years. In all patients only the SMA was revascularized. In nine of the 15 patients all three mesenteric arteries were severely stenotic or occluded. Technical success was achieved in 14 patients. At ROMS in 2 patients the small bowel was severely ischemic. One of these patients needed a partial bowel resection due to irreversible transmural ischemia. At 30 days the mortality rate was 20% and the primary patency was 92%. Ten patients underwent unplanned relaparotomy of which one needed resection of a large part of the small bowel. At 12 months the mortality rate was still 20%. The primary patency was 83%. Primary assisted patency was 91% and secondary patency were 100%. Clinical success at 30 days, 6 months and 12 months, respectively, was 73%, 67% and 67%.

Conclusion AMI is still a devastating event. If PMAS is not feasible, ROMS is a reliable alternative and is associated with a relative low mortality and morbidity rate.

Introduction

Acute mesenteric ischemia (AMI) encompasses the sequels of end stage untreated chronic mesenteric ischemia (CMI) and acute mesenteric arterial thrombosis. Transmural bowel ischemia and a full-blown peritonitis will follow without timely restoration of mesenteric blood flow. Over the years, mortality of acute on chronic mesenteric ischemia remained unchanged between 60-90% despite advances in therapeutic intervention.(1-3) Therefore, the most important factors for improvement of survival are a high index suspicion, a proper and timely diagnosis of CMI to the onset of AMI, and immediate restoration of blood flow with minimal collateral damage.

Percutaneous mesenteric artery stenting (PMAS) for CMI is the preferred option in patients with increased operative risk due to local or systemic risk factors.(4) PMAS in case of AMI could also be a bridge to an operative revascularisation in a more stable and improved clinical condition. In our experience PMAS is not possible in nearly 20% of patients with AMI due to extensive aortic wall and mesenteric artery origin atherosclerosis. Furthermore, patients with AMI often need, besides immediate revascularization, a laparotomy for inspection and sometimes resection of nonviable bowel. Retrograde open mesenteric stenting (ROMS) of mesenteric arteries is a hybrid technique that combines open surgical and endovascular approaches. This technique has been described in some case reports, but larger series reporting mid-term outcome are rare.

In this article we describe our experience with ROMS in a cohort of 15 patients with AMI.

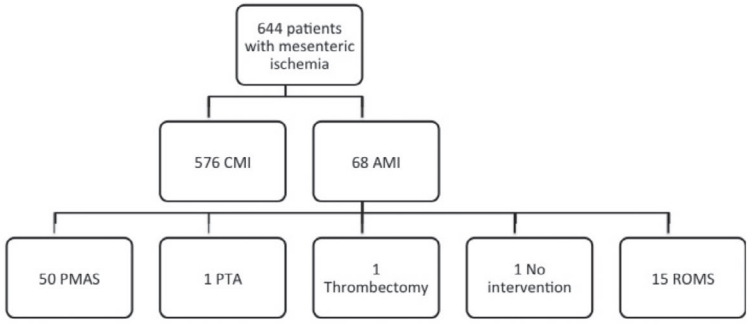
Methods

Patients

Our hospital is a nationwide, tertiary referral centre for evaluation of patients with suspicion of CMI and AMI in The Netherlands. Since 1996 all patients with CMI and AMI were prospectively included in our vascular registry. We started with ROMS in 2007. All 68 patients with AMI presenting between January 2007 and September 2011 were included in this report (Figure 1). The prospectively gathered data were retrospectively analysed.

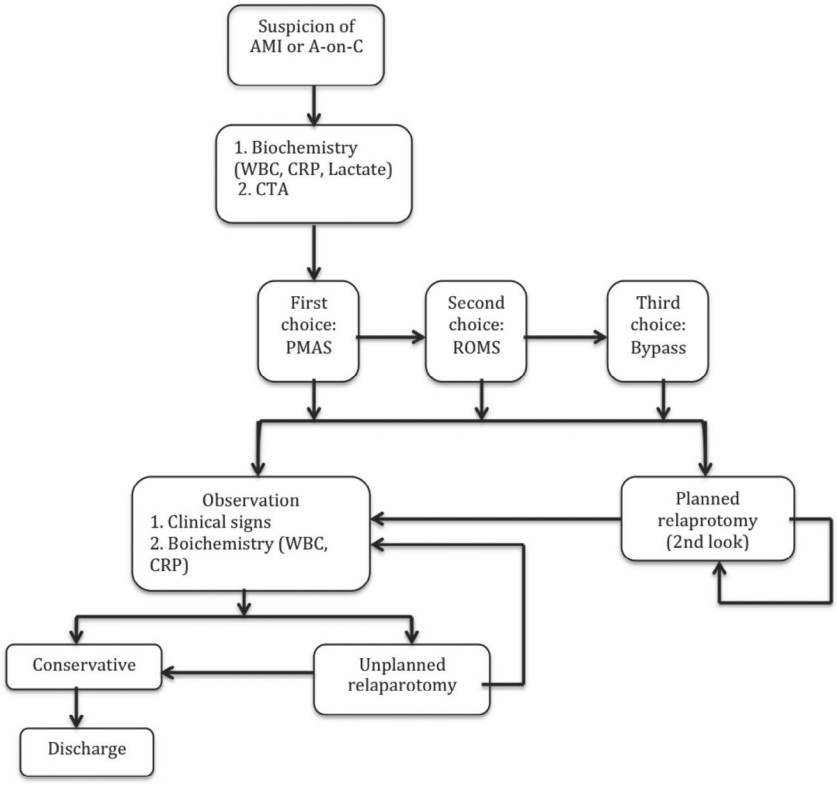
All patients suspected of AMI will undergo a computed tomography angiography (CTA) to confirm significant stenoses or occlusions of the mesenteric arteries and to assess signs of transmural bowel ischemia. PMAS was the preferred option for mesenteric artery revascularisation. Additional urgent laparotomy decision was based upon clear clinical signs of peritonitis. ROMS was second choice if PMAS was not feasible (Figure 2).

Figure 1: Flow chart of final treatment of patients suspected of CMI and/or AMI



Initially 54 patients underwent PMAS, but four patients underwent ROMS afterwards because of the clinical presentation.

Figure 2: Flowchart treatment of patients with suspicion of AMI



AMI = acute mesenteric ischemia, A-o-C = acute on chronic mesenteric ischemia, CRP = C-reactive protein, CTA = computed tomography angiography, PMAS = percutaneous mesenteric artery stenting, ROMS = retrograde open mesenteric stenting, WBC = white blood cell.

Retrograde open mesenteric stenting (ROMS)

A small transverse upper abdominal laparotomy is performed. The superior mesenteric artery (SMA) is exposed and controlled inferior to the transverse colon mesentery. After exposure, the patient is fully heparinised (5000 international units). The SMA is incised distally from the occlusion, a short 0.035 wire is introduced and a 6-Fr flexible sheath is placed in a retrograde fashion. Metallic abdominal retractors are removed or replaced when the sheath is in place and a hand-injected retrograde lateral angiography (Figure 3) is performed. Imaging of the re-entry target may be accessed by a simultaneous flush aortography using a pigtail catheter introduced by femoral access. A 0.035-inch guidewire (Terumo, Somerset, NJ, USA) is used to cross the lesion trans- or subluminally. A short 5-Fr PIER (Cordis, Florida, USA) catheter or an Outback re-entry catheter (Cordis J&J Waterloo, Belgium) is used to reach the aortic lumen. Calcified lesions usually require pre-dilatation. A short 6- or 7-mm balloon-expandable (BE) stent (Express, Boston Scientific, Voisins-le-Bretonneau France) is placed retrograde in the SMA origin. In case of longer occlusions, the stent is extended with a self-expandable stent (Wallstent, Boston Scientific, Voisins-le-Bretonneau France). The exact performance depends on length and calcification of the lesion. The proximal side of the stent is intended to protrude into the aortic lumen. Completion angiography in both antero-posterior and lateral projections to assess the inflow are performed, before the sheath is removed (Figure 4). After sheath removal, the incision in the SMA is closed with Prolene 6-0.

Figure 3: A hand-injected retrograde lateral angiography

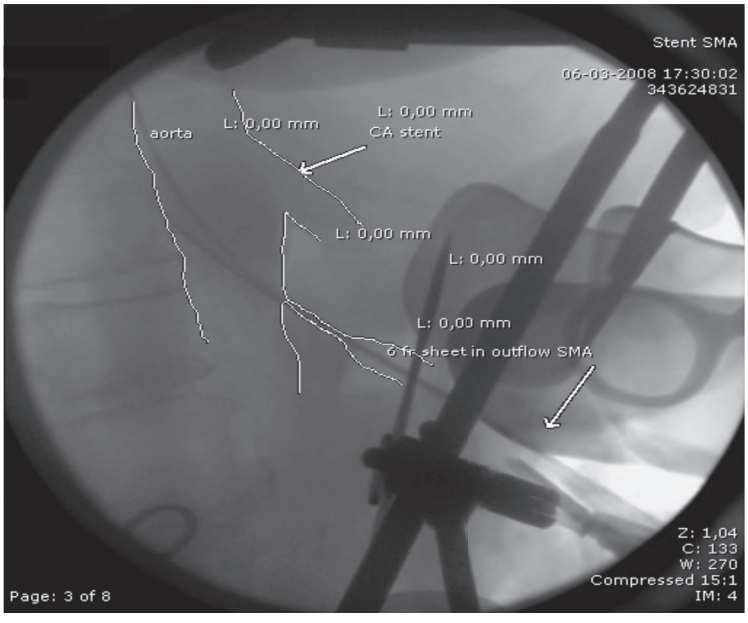
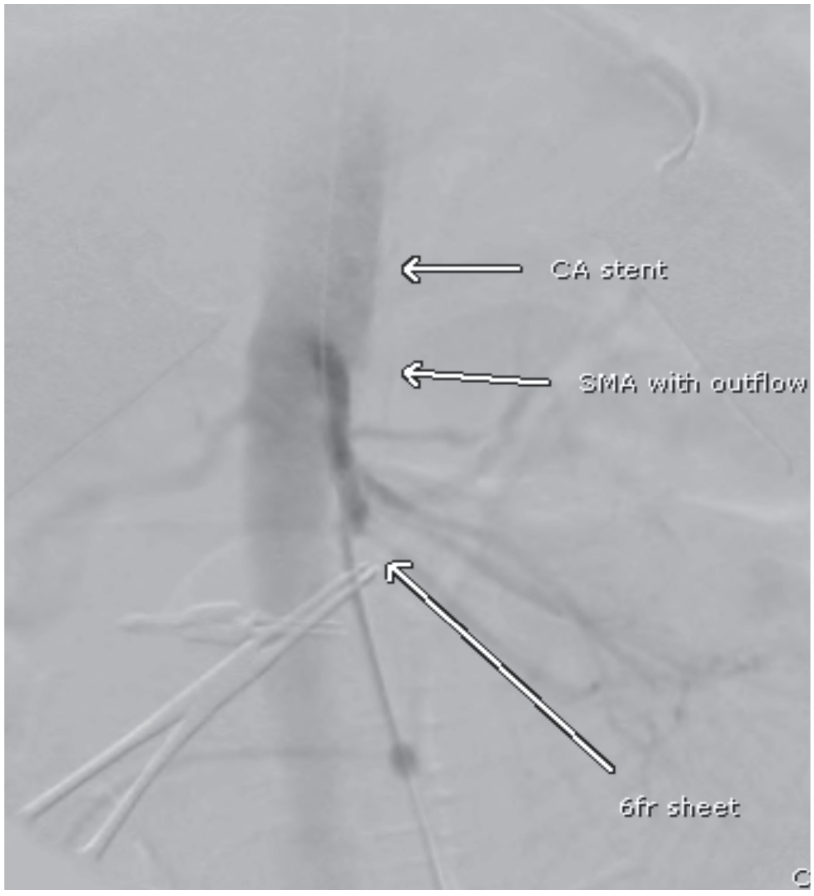


Figure 4: Retrograde completion angiography after placement of a SMA self-expandable stent. During the stay of the 6 french sheat there is no flow distally through the SMA. The coeliac artery (CA) balloon expandable (BE) stent was percutaneous placed.



Postoperative treatment and follow-up

All patients received systemic heparin postoperatively (activated partial thromboplastin time between 40-60 seconds). Enteral intake was gradually restarted according to a strict protocol adjusted upon clinical examination, daily white blood cell (WBC) counts and C-reactive protein (CRP) measurements. Enteral feeding was disrupted with on-going abdominal symptoms, severe diarrhea and increases in WBC counts and CRP, compatible with progressive ischemic-reperfusion damage. Patients clinically or biochemically suspected of re-stenosis or occlusion of the SMA received a contrast enhanced CT-scan. Treatment with dual platelet inhibitors, clopidogrel (for 6 months) and acetylsalicylic acid (as maintenance treatment) was started as soon as the bowel function restored.

After discharge, patients underwent mesenteric artery duplex ultrasound evaluation at three and six months and yearly thereafter.

Definitions

Technical success (based on intention to treat) was defined as successful completion of the procedure and <30% residual stenosis at the end of the procedure.(5, 6)

Primary patency was defined as uninterrupted patency with no extra procedures needed. (5, 6)

Primary assisted patency was defined as revision of the revascularization method to prevent impending occlusion or progression of stenosis.(5, 6)

Secondary patency was defined as restored patency after occlusion by thrombectomy, thrombolysis, or transluminal angioplasty, and/or any problems with the stent requiring revision or reconstruction.(5, 6)

Clinical success was defined as relief or improvement of presenting symptoms.(5, 6)

A serious adverse event (SAE) was defined as any clinical event, which resulted in death, or was life-threatening, produced permanent or significant disability/incapacity, resulted in patient hospitalization or prolongation of existing in-patient hospitalization, or required medical or surgical intervention to prevent permanent impairment of function or permanent damage to a body structure.(5, 6)

Outcome measures

Technical success, mortality, primary and secondary patency, clinical success, SAE rate at 30 days, 6 and 12 months of ROMS on an intention to treat base were assessed.

Results

Patient characteristics

A total of 644 patients with mesenteric ischemia were included in our vascular registry between January 2007 and September 2011. As shown in Figure 1, 68 patients presented with AMI needing urgent revascularization. In one patient no treatment was initiated because of the extremely poor health. He died within a couple of days. One patient underwent operative thrombectomy. Fifty-four were treated with PMAS of which 50 were successful and four failed. The reason for failing in all these four patients was technical impossibility of stent placement. One patient underwent percutaneous transluminal angioplasty (PTA) alone. Fifteen patients underwent ROMS. In eleven patients ROMS was the initial treatment, but in four patients unsuccessful PMAS was the initial treatment after which ROMS followed.

The characteristics of these 15 patients treated with ROMS are extensively described in Table 1 and 2. All patients suffered acute or acute on chronic mesenteric ischemia due to extended atherosclerosis of the mesenteric vessels. Median age was 66 (Inter Quartile Range (IQR) 54-73) years. Ten patients were female. Body Mass Index (BMI) was available in ten patients, the median was 19,85 (IQR 16,2 - 21) kg/m^2. In nine of the 15 patients all three mesenteric arteries were severely stenotic or occluded. Preoperative WBC counts were in normal range in six patients, elevated (>10.000) in eight patients and decreased (<4.000) in one patient. The median WBC-count was 10 *10^9 (IQR 8 - 26). In nine patients the CRP level was increased. The median CRP was 57 mg/L (IQR 10 – 129). The median Intensive Care (ICU) stay was two days (IQR 0 – 10 days) and the mean hospital stay was 19 days (IQR 15 – 25 days). The mean follow-up was 33 months (IQR –5 - 57 months).

Outcome

Table 3 extensively describes the peri-procedural details and results. Technical success was reached in 14 out of 15 patients. Six mm BE stents were used in all patients with a successful ROMS. In all patients only one vessel, the SMA, was treated. Five patients received more than one stent in the SMA.

In one patient ROMS was not possible due to the extent of calcification in all the mesenteric vessels and in the aortic wall. The SMA was occluded but the coeliac artery and the inferior mesenteric artery were not severely stenotic. The bowel showed no transmural ischemia. Consequently, we treated this patient conservatively with our strict refeeding protocol. After 12 months the patient was eating six times daily in small portions without weight loss.

During ROMS 13 patients had viable bowel. In one patient the viability of the small bowel restored after revascularisation. In one other patient, viability of the small bowel wasn't regained. A large part of the small bowel was resected, leaving only 90 cm of viable small bowel in situ.

In two patients a relaparotomy was needed because of suspicion of progression of bowel ischemia. In one patient an ischemic ileocoecum was resected and in the other patient 150 cm of ischemic small bowel was resected. Due to progressive multiple organ failure, the last patient deteriorated, which led to a cardiac arrest and death on the sixteenth postoperative day.

At 3 months follow up, one patient suffered some post-prandial abdominal pain. She had a normal diet and no weight loss was reported. Duplex of the stent showed no signs of stenosis. We decided on a wait-and-see approach, because ROMS had remarkably improved the symptoms. Thirty-nine months after ROMS the situation of the patient is stable and no signs of acute or chronic ischemia have been detected.

In one patient with adequate revascularization and abolishment of AMI after 6 months follow-up the duplex ultrasound and the CTA showed that the SMA recanalization was actually partial located unintentionally extraluminally with formation of a false aneurysm around the BE stent. We had thus created a 'false lumen' or unintended "stent bypass". A covered stent was placed via a left brachial approach within this BE stent to preserve SMA vascularization and to prevent further growth of the false aneurysm (Figure 5). The patient had an uneventful course thereafter.

Table 1: Pre-operative patient characteristics

Case	Age	Sex	Previous medical history	BMI	Number of vessels	WBC	CRP	Imaging
1	78	M	PAF, contracted kidney, COPD, RA, gout, CI, MVI	20,4	2	7,7	10	CT, MRA, Duplex, DSA
2	59	F	Haematuria, AP, sterilisation, resection of ileocoecum, PTCA		3	8,6	57	Echo, Duplex, DSA
3	59	M	COPD, Peripheral artery bypass, renal failure, PV, aortic bifurcation prosthesis, HT, inguinal hernia correction	19,7	2	7,8	10	CT, DSA, Duplex, Tonometry
4	77	F	COPD, HC, CI	16	1	8,4	10	CT, DSA, Duplex, gastroscopy, Tonometry
5	70	F	HT, HC, peptic ulcer		2	25,2	65	CT, DSA, Duplex
6	69	M	HT, HC, COPD, MI, aortic bifurcation prosthesis	21	3	6,8	10	CT, Duplex, Tonometry
7	76	F	HT, Appendectomy, diverticulosis, Peripheral artery stenting	21	3	11,3	68	CT, Duplex, DSA
8	76	M	CLI, TIA twice, CVA twice, HC, HT, melanoma, DM type 2		3	1,5	83	CT
9	57	F	No	21	3	31,3	49	Echo, CT, DSA
10	64	F	Multiple peptic ulcers	16,48	3	9,6		CT, DSA, tonometry, Duplex
11	54	F	Resection of ileocoecum, Bronchitis.	16,3	3	16,7	36	CT, DSA
12	55	F	Barret oesophagus, sliding hiatus hernia, Helicobacter pylori gastritis, peptic ulcer, IBS, Epilepsy, CVA, TIA, HC.	20	3	34,4	174	CT, DSA
13	69	M	TIA, HT, Peripheral PTA, appendectomy	16,1	3	31,4	305	CT, DSA
14	77	F	HT		2	25,3	312	CT, DSA
15	77	F	HT, DM, triple CABG, AVR, Peripheral artery bypass, Cholecystectomy		2	23.5		CT

AP = angina pectoris, AVR = aortic valve replacement, CABG = coronary artery bypass graft, CI = claudication intermittens, CLI = chronic limb ischemia, COPD = chronic obstructive pulmonary disease, CT = computer tomography, CVA = cerebrovascular accident, DM = diabetes mellitus, DSA = digital subtraction angiography, HC = hypercholesterolemia, HT = hypertension, IBS = irritable bowel syndrome, MRA = magnetic resonance imaging arthrography, MVI = mitral valve insufficiency, PAF = paroxysmal atrial fibrillation, PTCA = percutaneous transluminal coronary angioplasty, PV = polycythaemia vera, RA = rheumatoid arthritis, TIA = transient ischaemic attack.

Table 2 Summary of Patient Characteristics

Median age (IQR)*	66 (54-73)
Sex (M/F)	15 (5/10)
BMI (IQR)	19,85 (16,2-21)
1 vessel disease	1/15
2 vessel disease	5/15
3 vessel disease	9/15
Cardiac disease	4/15
Carotid disease	3/15
COPD	5/15
DM	2/15
Hyperlipidaemia	5/15
Hypertension	8/15
Renal failure	2/15
WBC	
Elevated	9/15
Median (IQR)	10 (8-26)
CRP	
Abnormal	9/14
Median (IQR)	57 (10-129)
IC admission** (IQR)	2 (0-10)
Ward admission** (IQR)	14 (9-18)
Hospitalization** (IQR)	19 (15-25)
Follow up*** (IQR)	33 (5-57)

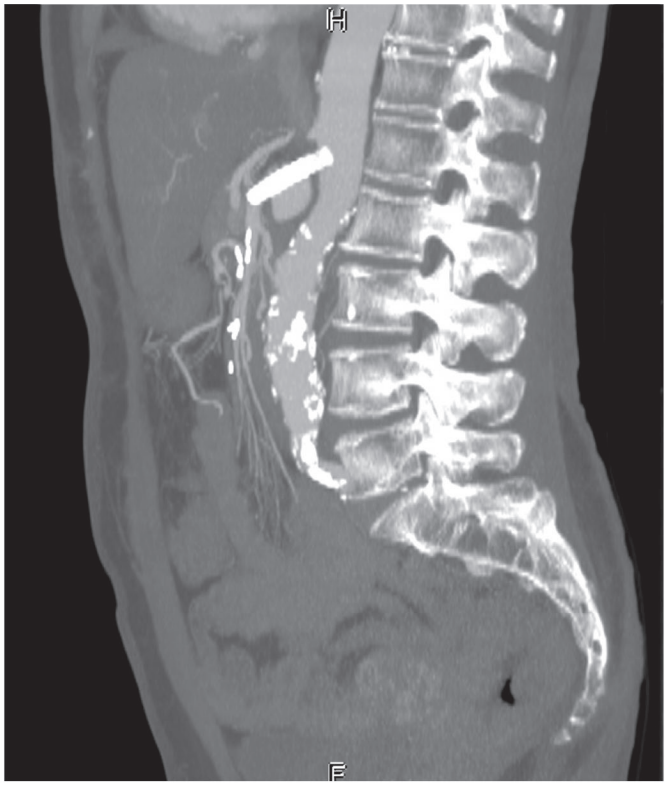
* IQR = Inter Quartile Range
** in days
*** in months
BMI = body mass index, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, DM = diabetes mellitus, ICU = intensive care unit, WBC = white blood cell counts.

Table 3: Perioperative patient outcome

Case	Technical success	Viable bowel at ROMS	Resection at ROMS	Clinical success	Relaparotomy planned (2nd look)	Relaparotomy unplanned	SAE	†	ICU stay (days)	Total in hospital stay (days)
1	Yes	Yes	No	Yes	No	Yes; Adhaesiolysis	Prolonged ileus	No	13	27
2	Yes	Yes	No	Yes	No	Yes; No abnormalities	Mesenteric haematoma, liver failure, wound infection	No	0	38
3	Yes	Yes	No	Yes	No	No	No	No	0	12
4	No	Yes	No	No	No	No	Rectus abdominus bleeding, coiling superior epigastric artery	No	0	14
5	Yes	Yes	No	Yes	No	Yes; 150 cm ischemic small bowel resected	Cardiac arrest, mesenteric haematoma	Yes	0	16
6	Yes	Yes	No	Yes	No	Yes; Haemostasis	Bleeding induced tear in the falciforme ligamentous	No	2	19
7	Yes	Yes	No	Yes	No	No	No	No	0	18
8	Yes	Yes	No	Yes	No	No	No	No	0	15
9	Yes	Yes	No	Yes	No	No	Reflux esophagitis, wound infection	No	0	24
10	Yes	Yes	No	Yes	No	Yes; No abnormalities	No	No	9	16
11	Yes	Yes	No	Yes	No	Yes Resection of ischemic ileocoecum	Sepsis (Central venous line infection)	No	2	21
12	Yes	Yes	No	Yes	No	Yes; No abnormalities	Pneumonia	No	10	24
13	Yes	Yes	No	Yes	No	Yes; No abnormalities	No	No	2	11
14	Yes	No; Small bowel	Yes; Small bowel	Yes	Yes; No resection	Controlled fistula*	Recurrent bowel perforation and abscesses	Yes	26	26
15	Yes	No; Small bowel	No**	No	Yes; No resection	Ileostomy	Multi organ failure	Yes	25	25

* Because of a poor condition (severe shock state) the patient was not able to undergo bowel resection. The intra-abdominal problems were treated in a conservative manner.
** After ROMS bowel perfusion improved clearly and consequently a resection was not performed.
† = deceased, ICU = intensive care unit, ROMS = retrograde open mesenteric stenting

Figure 5: The recanalization of the SMA was unintentional partially extraluminal with formation of a false aneurysm around the BE stent.



BE = balloon expandable, SMA = superior mesenteric artery.

Figure 6-8 show Kaplan Meier curves of the mortality, primary and primary assisted patency and clinical success. The mortality rate at 30 days and 6 and 12 months of follow-up was 3 out of 15 (20%). In these three patients the extend of the splanchnic ischemia and reperfusion damage was irreversible despite technical successful ROMS. Primary patency at 30 days was 11 out of 12 (92%). At 6 and 12 months it was respectively 10 out of 12 and 10 out of 12 (83% and 83% respectively). Primary assisted patency at 30 days, 6 months and 12 months, respectively, was 11 out of 12 (92%), 10 out of 11 (91%) and 10 out of 11 (91%). Secondary patency at 30 days, 6 and 12 months it was respectively 11 out of 12 (92%). Clinical success at 30 days was 11 out of 15 (73%). At 6 and 12 months it was 10 out of 15 (67%).

Figure 6: Overall mortality after ROMS

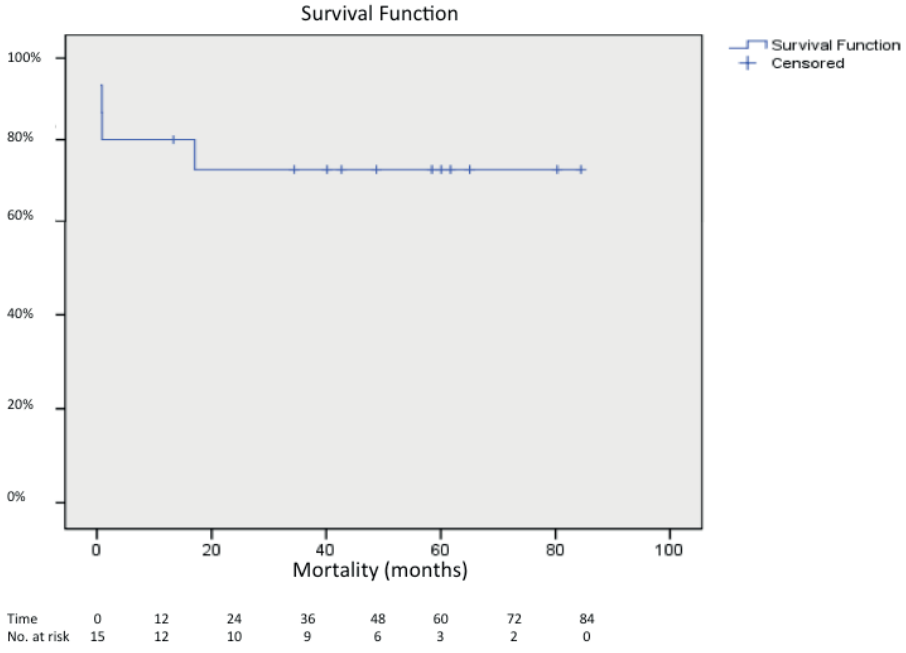


Figure 7 Primary and primary assisted patency of ROMS

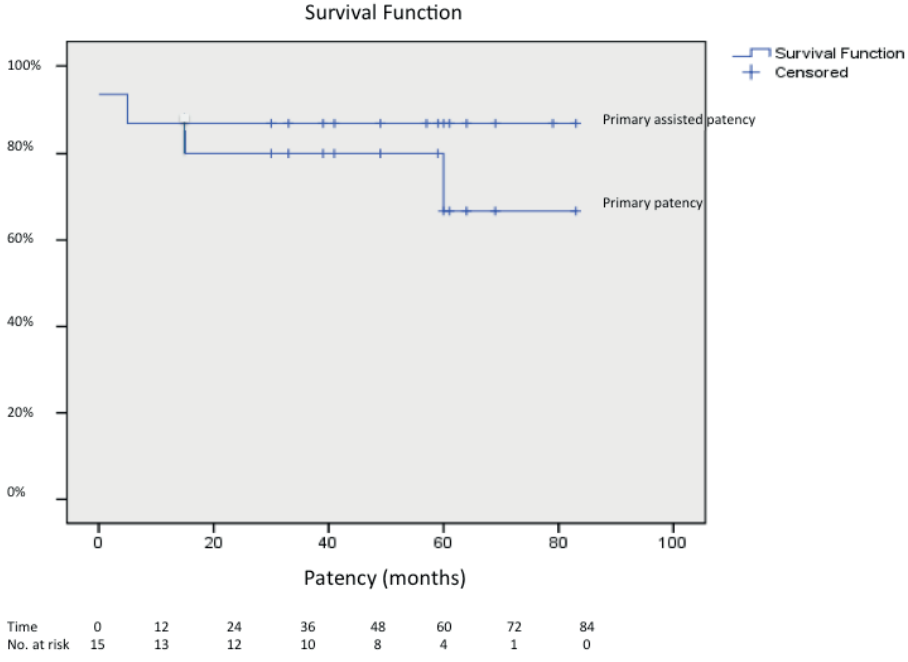
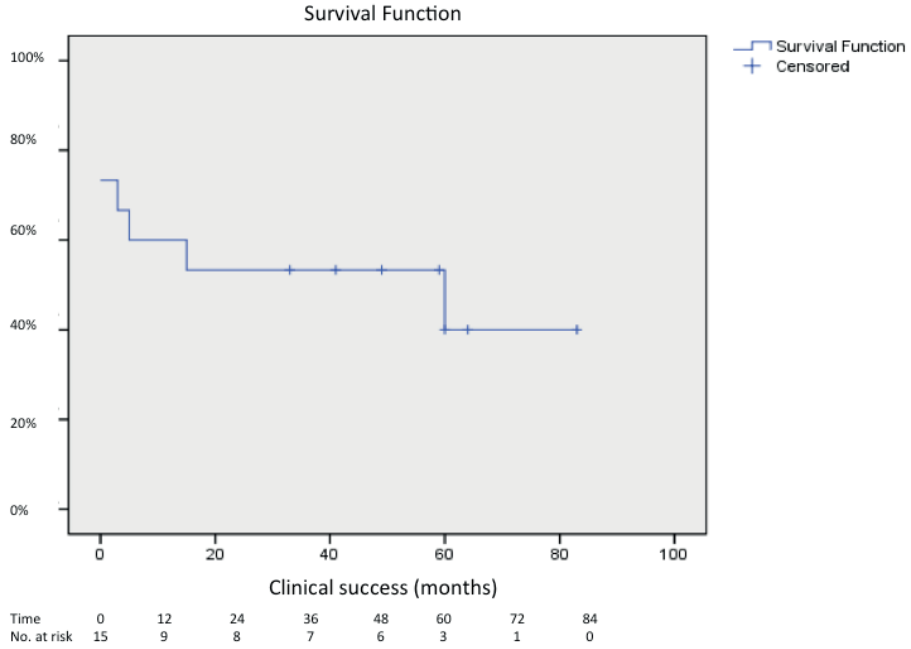


Figure 8: Clinical success after ROMS



Ten patients experienced a SAE in the first 30 days. Details are shown in Table 3. Ten patients underwent unplanned relaparotomy of which one patient needed resection of a large part of the small bowel. Due to the aggressive use of systemic anticoagulation in four of these patients, additional surgical haemostasis of the dissection area was needed.

Discussion

We demonstrated that ROMS is a hybrid technique that combines the advantages of open surgical and endovascular approaches in case of AMI. It creates the opportunity for an efficient minimally invasive revascularization and to assess bowel viability. The population described is severely ill, is very cachectic and has a high mortality risk. Even after revascularization, mortality and morbidity are high.(2, 7) PMAS is first choice therapy, but not feasible in 20% of cases. In our experience most AMI patients are not in an appropriate condition to undergo extended bypass surgery. Because of the superior long-term patency bypass surgery should be reserved for patients in good anabolic condition, with low comorbidity and young age. In all other patients the low treatment burden and low morbidity make PMAS the preferred choice. Our series of ROMS, second choice if PMAS is not feasible, shows a high technical success 93%. With primary, primary assisted and secondary patency exceeding 90% after 30 days and 83% after 6 and 12 months. Our clinical success is 67% after 12 months. The

number of SAE is substantial and was in large part attributed to bleeding complications of the dissection area due to our aggressive anticoagulation therapy. The hospital mortality rate of three out of 15 patients was acceptable in these severely ill patient population with failed attempt of PMAS in comparison with the current literature.(1, 2) We experienced that our strict refeeding protocol including daily clinical and haematological assessment diminished the detrimental effects of the ischemia/reperfusion cascade, previously seen in these patients.

Reports in literature about ROMS are rare, and include up to six patients (Table 4). Sonesson et al(8) were the first to report the use of ROMS in six patients after misalignment of a fenestrated aortic endoprothesis. Mortality, patency and complication rates are, unfortunately, not given. Wyers et al(9) described their ROMS technique in six patients with acute mesenteric occlusion. Almost all their patients had ROMS for a failed attempt of PMAS. After a mean follow-up of 13 months their mortality and patency rates were both 50%. The patients with restenosis in their series were also asymptomatic. Moyes et al(10) described ROMS in four patients with acute mesenteric occlusion. The in-hospital mortality rate was 25%. No information is given about patency and complication rates. The present series of 15 patients added substantial more inside in the outcome of ROMS.

Table 4: Review of the literature including present series

Literature	**Patients (N)**	**Mortality**	**Primairy patency**	**Follow-up*** **
Wyers et al.(9)	6	50%	50%	Mean 13±7
Sonesson et al.(8)	6	-	-	-
Moyes et al.(10)	4	25%	-	Range 6 days-36 months
Stout et al.(12)	3	0%	100%	8.4 (range: 1.2-16.6)
Milner et al.(13)	1	100%	100%	36
Do et al.(14)	1	0%	100%	12
Pisimisis et al.(15)	7	-	-	-
Present series	**15**	**20%**	**93%**	**33 (range 5-57)**

*** in months

In retrospect, the one patient in whom ROMS was unsuccessful suffered from one vessel disease. Although clinical presentation was severe and AMI was suspected for which ROMS was initiated, the bowel showed no signs of ischemia at ROMS. And afterwards the condition of the patient gradually stabilized when enteral feeding was addressed according to our strict refeeding protocol. In hindsight this patient didn't have AMI, but severe one vessel

CMI. In our experience bowel infarction in one vessel CMI is very rare. This patient died 17 months after ROMS of a COPD exacerbation.

In one patient ROMS was a bridge to an antegrade autologous aorta mesenteric bypass. At 16 months follow up the patient had no abdominal symptoms anymore and was gaining weight. But routine duplex followed by CTA showed an in-stent stenosis. Because of the improving clinical situation watchful waiting was the temporarily treatment of choice. As the condition of this relatively young patient had improved remarkably, the patient was fit enough to undergo the bypass operation three years after ROMS. The patient is doing well, eating without pain and gaining weight.

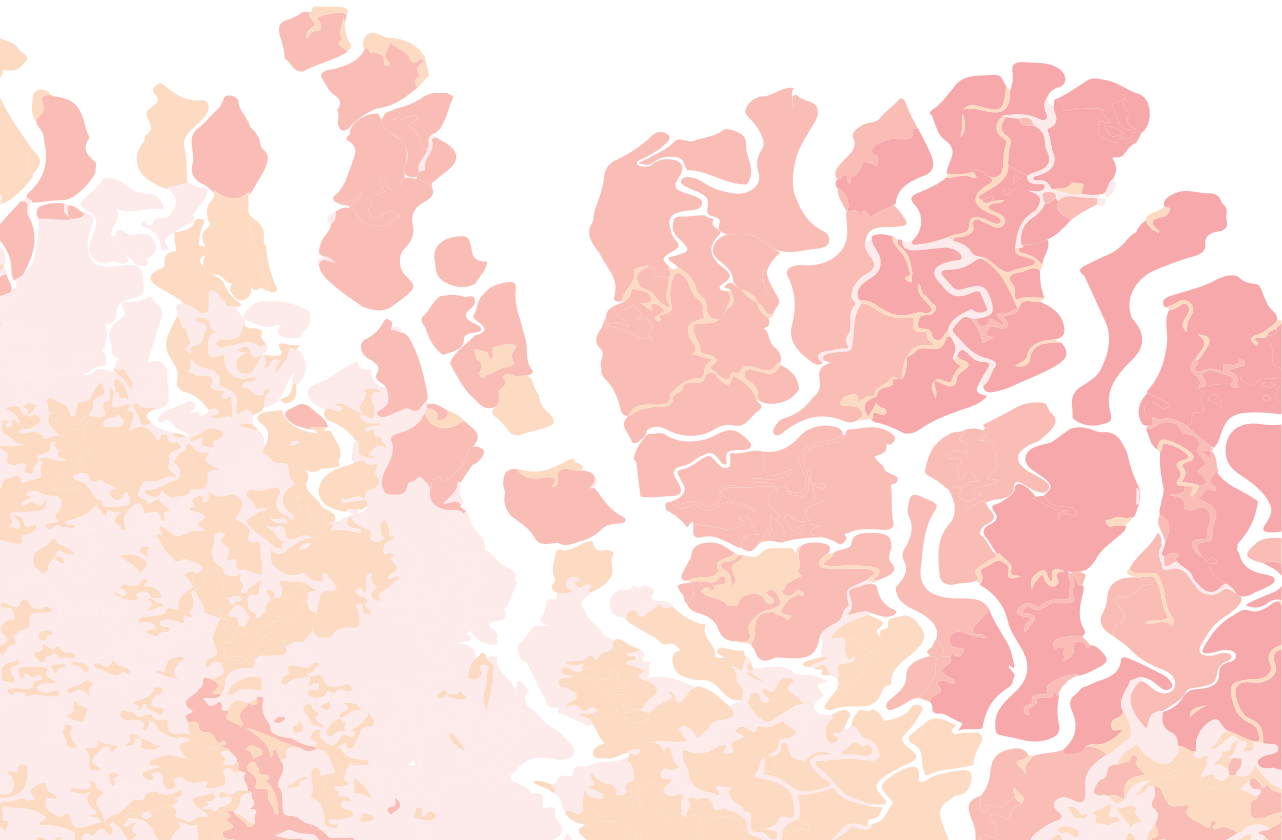
At 12 months our clinical success was 10/15 (67%) with a mortality of 3/15 (20%). This is better than described in the current literature on ROMS and is in line with the literature on PMAS. A review in 2002 for surgical treatment of AMI showed a mortality rate of 32% at 30 days and 57% at 12 months and a complication rate of 79%.(2) For PMAS the mortality rate is 38% at 30 days with a morbidity rate of 63%.(7) To improve the mortality, morbidity and clinical success in these mostly very fragile patients suffering of AMI we tried to optimize and individualize treatment including ROMS and our nine-step bowel rehabilitation scheme. By doing so, we believe we can identify ischemia and reperfusion injury in an earlier stage, and are able to act on it timely and appropriately.

Early detection of AMI is the key to survival. A high index of suspicion after a thorough history and physical examination serves still as the cornerstone.(3, 9) Because of its wide spread 24/7 availability nowadays a CTA is the modality of choice for confirming the diagnosis of AMI.(10, 11) In our series 14 out of 15 patients underwent an emergency CTA. One patient underwent only a Duplex, followed by a Digital Subtraction Angiography (DSA) instead. Because, at initial assessment, the patient did not need immediate revascularisation. So duplex was performed first, followed by angiography for antegrade revascularisation. Only PMAS failed, after which ROMS followed. Because of the good quality of the duplex and DSA, we didn't perform additional CTA.

We conclude that AMI is still a devastating event. ROMS is associated with favourable mortality and morbidity rate compared to extensive bypass surgery. ROMS should be the second choice when PMAS failed.

References

1. Arthurs ZM, Titus J, Bannazadeh M, Eagleton MJ, Srivastava S, Sarac TP, et al. A comparison of endovascular revascularization with traditional therapy for the treatment of acute mesenteric ischemia. J Vasc Surg. 2011;53(3):698-704; discussion -5.
2. Park WM, Gloviczki P, Cherry KJ, Jr., Hallett JW, Jr., Bower TC, Panneton JM, et al. Contemporary management of acute mesenteric ischemia: Factors associated with survival. J Vasc Surg. 2002;35(3):445-52.
3. Oldenburg WA, Lau LL, Rodenberg TJ, Edmonds HJ, Burger CD. Acute mesenteric ischemia: a clinical review. Arch Intern Med. 2004;164(10):1054-62.
4. van Petersen AS, Kolkman JJ, Beuk RJ, Huisman AB, Doelman CJ, Geelkerken RH, et al. Open or percutaneous revascularization for chronic splanchnic syndrome. J Vasc Surg. 2010;51(5):1309-16.
5. Diehm N, Baumgartner I, Jaff M, Do DD, Minar E, Schmidli J, et al. A call for uniform reporting standards in studies assessing endovascular treatment for chronic ischaemia of lower limb arteries. Eur Heart J. 2007;28(7):798-805.
6. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997;26(3):517-38.
7. Ryer EJ, Kalra M, Oderich GS, Duncan AA, Gloviczki P, Cha S, et al. Revascularization for acute mesenteric ischemia. J Vasc Surg. 2012;55(6):1682-9.
8. Sonesson B, Hinchliffe RJ, Dias NV, Resch TA, Malina M, Ivancev K. Hybrid recanalization of superior mesenteric artery occlusion in acute mesenteric ischemia. J Endovasc Ther. 2008;15(1):129-32.
9. Wyers MC, Powell RJ, Nolan BW, Cronenwett JL. Retrograde mesenteric stenting during laparotomy for acute occlusive mesenteric ischemia. J Vasc Surg. 2007;45(2):269-75.
10. Moyes LH, McCarter DHA, Vass DG, Orr DJ. Intraoperative retrograde mesenteric angioplasty for acute occlusive mesenteric ischaemia: a case series. Eur J Vasc Endovasc Surg. 2008;36(2):203-6.
11. Wyers MC. Acute mesenteric ischemia: diagnostic approach and surgical treatment. Semin Vasc Surg. 2010;23(1):9-20.
12. Stout CL, Messerschmidt CA, Leake AE, Veale WN, Stokes GK, Panneton JM. Retrograde open mesenteric stenting for acute mesenteric ischemia is a viable alternative for emergent revascularization. Vasc Endovascular Surg. 2010;44(5):368-71.
13. Milner R, Woo EY, Carpenter JP. Superior mesenteric artery angioplasty and stenting via a retrograde approach in a patient with bowel ischemia--a case report. Vasc Endovascular Surg. 2004;38(1):89-91.
14. Do N, Wisniewski P, Sarmiento J, Vo T, Aka PK, Hsu JH, et al. Retrograde superior mesenteric artery stenting for acute mesenteric arterial thrombosis. Vasc Endovascular Surg. 2010;44(6):468-71.
15. Pisimisis GT, Oderich GS. Technique of hybrid retrograde superior mesenteric artery stent placement for acute-on-chronic mesenteric ischemia. Ann Vasc Surg. 2011;25(1):132 e7-11.



Chapter 5

Mesenteric Vascular Treatment 2016: from open surgical repair to endovascular revascularization

Juliëtte Blauw, Tomas Bulut, Gustavo Oderich, Bob Geelkerken; Dutch Mesenteric Ischemia Study Group.

Best Practice & Research: Clinical Gastroenterology. 2017 Feb; 31(1): 75-84.

Abstract

The rise of endovascular techniques has improved the outcome of mesenteric ischemia. Key principle in reduction of morbidity and mortality is “revascularization first, resection later”. We believe that mesenteric ischemia is a clinical challenge demanding 24/7 multidisciplinary team availability. This article describes the current insights into treatment of mesenteric ischemia.

Introduction

Symptomatic mesenteric circulation disorders are relatively rare, but are characterized by significant morbidity, mortality and reduction in quality of life. Treatment of mesenteric ischemia has improved over the past two decades and has led to a reduction in morbidity and mortality. In this article we aim to describe current insights into diagnosis and treatment of mesenteric ischemia with focus on atherosclerotic etiology.

Terminology and Definitions

If the blood supply to the visceral organs diminishes more than 70% compared with normal (basal) blood flow, minimal metabolic needs are no longer met and bowel necrosis occurs. (1) After just 10 minutes of diminished blood flow, mucosal ischemia can occur. This is reversible. But if blood flow remains insufficient, (irreversible) transmural ischemia arises. (1) Untreated, this will ultimately result in transmural bowel infarction, which is associated with very high mortality rates.

Acute mesenteric ischemia (AMI) is defined as the occurrence of an abrupt cessation of the mesenteric blood flow with development of symptoms within minutes (in embolism) to hours (in atherothrombosis). The usual presenting symptom is severe abdominal pain that may progress to bowel necrosis and peritonitis in 8 hours up to days.(2, 3)

Chronic mesenteric ischemia (CMI) is defined as symptoms existing for more than 3 months due to mesenteric ischemia caused by gradually reduced oxygen delivery to the gastrointestinal tract. The typical presentation includes postprandial pain, weight loss due to fear of eating or unexplained diarrhoea.(2, 3)

Acute-on-chronic ischemia (AoCMI) is defined as AMI in patients who previously had typical complaints of CMI. Often, the complaints of CMI worsened over the preceding weeks with prolonged and more severe pain periods, pain even without eating, onset of diarrhoea or inability to eat at all.(2, 3)

Technical success (based on intention to treat) is defined as successful completion of the procedure and <30% residual stenosis at the end of the procedure.(2, 3)

Primary patency is defined as uninterrupted patency without need for any additional procedures.(2, 3)

Primary assisted patency is defined as revision of the revascularization method to prevent impending occlusion or progression of stenosis.(2, 3)

Secondary patency is defined as restored patency after occlusion by thrombectomy, thrombolysis, or transluminal angioplasty or any problems with the stent requiring revision or reconstruction.(2, 3)

Primary clinical success is defined as uninterrupted relief or improvement of presenting symptoms with a patent revascularized target vessel.(2, 3)

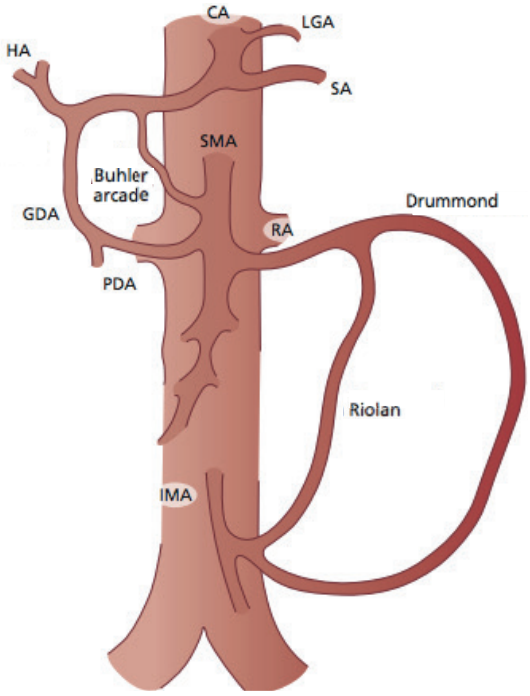
A *serious adverse event (SAE)* is defined as any clinical event that resulted in death or any life-threatening event, produced permanent or significant disability or incapacity, resulted in hospitalization of the patient or significant prolonged hospitalization, or required medical or surgical intervention to prevent permanent impairment of function or permanent damage to a body structure.(2, 3)

Significant stenosis is defined as a >70% hemodynamically relevant stenosis. The degree of stenosis is measured in line with the NASCET guidelines for Carotid lesions: stenosis = (1 - [narrowest lumen diameter within lesion/normal diameter]) x 100%.(4)

Anatomy

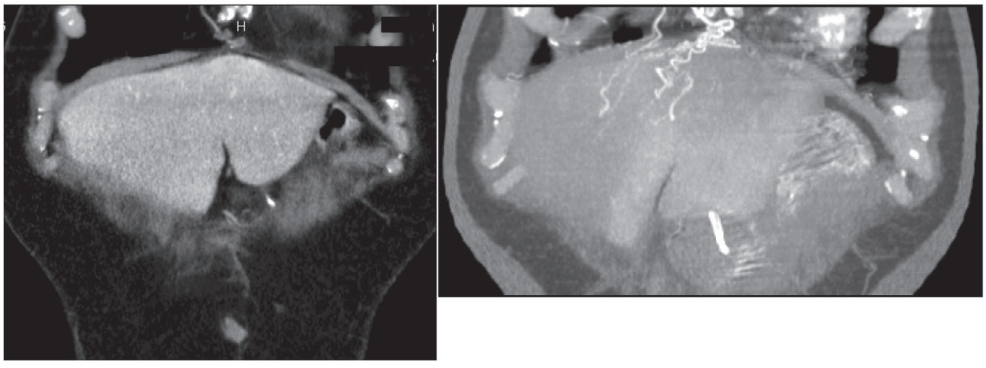
The three key vessels in mesenteric blood supply are the coeliac artery (CA), the superior mesenteric artery (SMA) and the inferior mesenteric artery (IMA). Although significant stenoses of the mesenteric arteries are common, only a small percentage of patients actually develop symptoms. This is due to an extensive collateral network, as illustrated by Figure 1.(5) The CA and the SMA are connected via the pancreatico-duodenal arteries and via Bühler's arcade.(6) The arcades of Riolan and Villemin anastomose the SMA and the IMA relatively central in the mesentery, while the marginal arcade of Drummond anastomoses more peripherally.(6) Between the internal iliac artery and the IMA is a comprehensive collateral network through the haemorrhoidal branches of the hypogastric artery with the superior hemorrhoidal branches of the IMA.(7) An extremely rare collateral circulation is between the mammary arteries and the superior epigastric artery via the coeliac trunk, which partially terminates in the inferior epigastric artery, partly emits a number of branches that anastomose with the arteria hepatica communis within the falciform ligament, Figure 2.(7)

Figure 1. Mesenteric anatomy.



CA = coeliac artery, GDA = gastroduodenal artery, HA = hepatic artery, IMA = inferior mesenteric artery, LGA = left gastric artery, PDA = pancreaticoduodenal artery, RA = renal artery, SA = splenic artery, SMA = superior mesenteric artery.

Figure 2. Antero-posterior CTA of a 68-year-old female with multivessel CMI.



Retrograde filling of the coeliac artery via a collateral network comprehending the right inferior mammary artery (RIMA). To the left of the 'H', the inferior part of the RIMA is shown, descending downward to the falciform ligament, eventually anastomosing the arteria hepatica.

Diagnosis

Asymptomatic stenosis of any of the mesenteric arteries can be found in 18% of people over 65 years of age. It has been estimated that 5% of these people will develop CMI or AMI.(5) Incidence is thought to be 1 in 1000 hospital admissions for AMI and 2 or 3 per 100.000 for CMI. In-hospital mortality rates range from 60 to 80% for AMI and 1 to 17% for CMI.(1, 8-10) In-hospital morbidity rates are substantial too: 39% for AMI(8) and 2 to 38% for CMI.(9, 10)

The single most important factor in patient survival for AMI patients is doctors' delay, meaning time from onset of pain to diagnosis.(1, 11, 12) Historically, when peritonitis was suspected, a laparotomy was performed to determine the cause and necrotic bowel was resected. Revascularization was considered afterwards if feasible. Mortality and morbidity were high.(1)

Nowadays, if AMI is suspected, an emergency computed tomography angiography (CTA, arterial phase 1 mm slices and venous phase 3 mm slices) is the preferred diagnostic imaging modality.(13) It is rapid, widely available and non-invasive. It gives appropriate information on the location and extent of arterial stenoses or occlusions as well as arterial or venous thrombosis or emboli and bowel perfusion. Other pathological findings, like the presence of pneumotosis intestinalis, can also be assessed.(1, 13, 14) It is thought to have a 96% sensitivity and 94% specificity.(15)

In CMI, the classic triad of chronic postprandial pain, upper abdominal bruit and weight loss, along with significant stenoses in two or three bowel arteries is found in only 22% of patients.(16, 17) The negative predictive value of this triad is 15% and the positive predictive value is 62%.(17) In diagnosing CMI, the anamnesis should co-inside with concomitant significant stenosis on duplex ultrasound or cross-sectional imaging (CTA or magnetic resonance imaging (MRI)). Although not yet practiced globally, we believe ischemia should be demonstrated via a functional test. Tonometry can distinguish symptomatic from asymptomatic stenoses and has a high diagnostic accuracy with 78% and 92% sensitivity and specificity.(17)

Many steps have been taken to minimize delay in diagnosis. More and more research is done to investigate the value of biomarkers. As far as we know, no definitive biomarker has yet been found, but promising developments are ongoing.

Practice point 1

- Computed tomography angiography (CTA) is the preferred diagnostic modality if acute mesenteric ischemia (AMI) is suspected.(13)

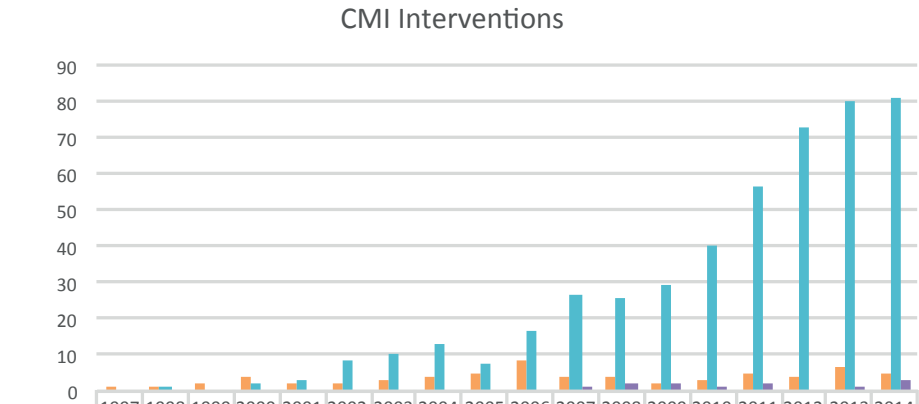
History of treatment of AMI and CMI

The history of CMI dates back almost 150 years. Chienne and Councilman described the clinical and anatomical manifestations of mesenteric artery occlusions in 1869 and 1894.(18, 19) In 1936, Dunphy described that 60% of patients who died of mesenteric infarction had a history of abdominal complaints, thus introducing the term “Intestinal angina”.(20) After that, Mikkelson(21) suggested surgical treatment of occlusive lesions of the SMA, followed by Shaw and Maynard in 1958, who performed the first successful revascularization using a surgical endarterectomy technique.(22) It wasn’t until 1980 that the percutaneous mesenteric artery angioplasty and stenting (PMAS) of CMI was first described.(23) Since then, endovascular treatment has grown from experimental, to a “bridging” option, to a first choice treatment in experienced hands.(24)

In 1951, Klass reported the first operative SMA embolectomy for AMI.(14) Boley and Clark experimented with angioplasty in the 1970’s,(14) but primary surgical exploration, revascularization and resection of infarcted bowel became the standard.(13)

Over the years, PMAS has improved significantly and is a less invasive alternative with equal or better outcomes than open surgical revascularization (OSR).(13, 25) In 2005 roughly 12% of AMI patients underwent PMAS against 30% in 2009.(11) And nowadays, 80% of CMI patients are treated endovascular in tertiary referral centers, Figure 3.

Figure 3. Relative percentage of patients treated for CMI in the Medical Spectrum Twente, Enschede, the Netherlands.



	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
OSMAR	1	1	2	4	2	2	3	4	5	9	4	4	2	3	5	4	7	5
PMAS	0	1	0	2	3	9	10	13	8	17	27	26	29	40	57	73	80	81
ROMS	0	0	0	0	0	0	0	0	0	0	1	2	2	1	2	0	1	3

Treatment of AMI

In line with the limb saving strategy in peripheral artery disease (PAD), more voices are heard that the old approach of "Cut first, revascularization later" should be changed in "Revascularization first, resection later". Not only for better survival, but also in order to ensure intestinal salvage and the prevention of short bowel syndrome(SBS).(14, 24, 26, 27)

We believe PMAS should be the first-choice treatment. First, because delay until revascularization is shorter with PMAS than with OSR.(28, 29) Second, because most AMI patients are frail with little physiological reserves, laparotomy can be avoided in most cases provided there is no evidence of peritonitis or frank bowel necrosis and that revascularization can be done expeditiously using endovascular techniques. Finally, a completion angiogram can be performed to ensure technical success.(26, 30)

There are no randomized controlled trials (RCT) comparing an endovascular treatment (EVT) first versus an OSR first approach and as a result, level I evidence is lacking. However, there are numerous observational studies with good validity. Zhao et al.(29) published a systemic review on articles published between 2000 and 2013. They concluded "although EVT has lower mortality and morbidity and may be considered a first-line therapy in selected patients who are not at risk for intestinal ischemia, OSR remains the treatment of choice for any patient who is suspected of intestinal ischemia or necrosis." In order to provide an up-to-date review of current literature, we performed a systemic literature search of the MEDLINE database to identify studies evaluating treatment of AMI between September 2013 and July 2016. Study designs included were RCT's, observational studies, and meta-analyses. Table 1 shows in- and exclusion criteria.

Table 1. In- and exclusion criteria systemic literature search of the MEDLINE database.

Inclusion criteria	Exclusion criteria
Publication sept 2013 – july 2016 English >10 patients	Aetiology: only thrombi or emboli, venous, dissection, non-occlusive mesenteric ischemia Re-interventions No abstract available

Ten articles were identified. Table 2a and 2b show the outcomes.(11, 26, 27, 31-37) We found that overall technical success was high, 82-100%,(27, 29, 31, 35, 37) and primary patency for EVT was 94-100%(29, 35) versus 52,5-91% for OSR.(27, 29, 34, 35). Secondary patency was 100% for EVT versus 79-95% for OSR.(34, 35) Furthermore, 30-day mortality was lower for EVT than OSR, respectively 0-45%(11, 26, 29, 31-33, 35, 36) versus 22-56% for OSR.(11,

26, 29, 32, 34-36) There was no significant difference in survival between EVT and OSR.(29, 31, 36) Lastly, morbidity was lower for EVT than OSR. Fewer patients underwent laparotomy after EVT with fewer bowel resections (7-38% versus 33-93%).(11, 27, 29, 32, 35) And a lesser amount of necrotic bowel was resected after EVT than OSR, reducing the risk of developing SBS.(28, 32) Indeed, 31% of patients after EVT didn't undergo additional laparotomy or second-look surgery when clinically observed.(28) From a socioeconomic point of view, one study showed that bowel resection not only increased mortality, respectively 15% without and 36% with resection, but that it also led to a significant increase in length of hospital stay, median 10 days versus 18 days, and concomitant costs, median $83.000 versus $147.588. (32) Median costs for EVT were significantly lower than for OSR, respectively $73.317 and $101.762 ($p<0.01$).(32)

We conclude from the current literature, and our own experience, that PMAS is the preferred treatment of choice for patients with AMI because it has better short-term outcome, lower mortality and morbidity and reduced costs.

Table 2a. Outcome measures of literature search for AMI.

			Patients	Technical Success	Technical failure	Mortality 30d	Survival	Morbidity
Zhao [30]	2000-2013	ER	234 (21%)		11%	27%	93%	
		OR	856 (77%)			40%	89%	
		overall	1090 (100%)					
Roussel [28]	2009-2014	ER	11 (34%)		18%			
		OR	18 (66%)					
		overall				7%		>34%
Forbig [38]	1999-2011	ER	19 (100%)	95%		42%		
		OR						
		overall						
Beaulieu [12]	2005-2009	ER	165 (24,3%)			25%		13%
		OR	679 (75,7%)			39%		24%
		overall						
Acosta [27]		ER	29%			23-33%		
		OR	24%			37-56%		
		overall						
Duran [35]	2001-2014	ER						
		OR	54 (100%)					

			Patients	Technical Success	Technical failure	Mortality 30d	Survival	Morbidity
		overall				31%		
Karkkainen [32]	2009-2013	ER Embolic	18 (36%)	94%				
		ER Thrombotic	32 (64%)	84%				
		OR						
		overall		88%		30%		
Puippe [34]	2003-2013	ER	13	38,50%				
		OR						
		overall						
Plumereau [37]	2002-2012	ER						
		OR + revasc	10 (23%)			0%		40%
		OR - revasc	13 (31%)			30%		23%
		Abstineren	20 (46%)					
		overall						
Arya [36]	2002-2012	ER	11 (32%)	100%		45%		64%
		OR	28 (78%)	100%		35%		70%
		overall				38%		68%
Eslami [33]	2003-2011	ER	990 (63%)			15%		
		OR	573 (37%)			22%		
		overall	1563 (100%)			18%		

ER = Endovascular revascularization, OR = Operative revascularization. Patients given in numbers. Data given in %.

Table 2b. Continued outcome measures of literature search for AMI.

		Primary Patency	Secundary Patency	Clinical success	Resection	Second Look	Complications	FU 1y survival	FU 2y survival	FU 5y survival
Zhao [30]	ER	94%			38%	43%	48%	90%	56%	16%
	OR	52,50%			61%	36%	62%	49%	45%	27%
	overall									
Roussel [28]	ER				7%					
	OR				93%					
	overall				52%				89%	
Forbig [38]	ER			53%			5%			
	OR									
	overall									

		Primary Patency	Secundary Patency	Clinical success	Resection	Second Look	Complications	FU 1y survival	FU 2y survival	FU 5y survival
Beaulieu [12]	ER				14%					
	OR				33%					
	overall									
Acosta [27]	ER									
	OR									
	overall									
Duran [35]	ER									
	OR	52% TEA								
		62% bypass								
		80% trans-position								
	overall									
Karkkainen [32]	ER Embolic				28%					
	ER Thrombotic				38%					
	OR									
	overall				34%	12%	10%	56%	53%	18%
Puippe [34]	ER			46,20%	38%	38,50%	38,50%			
	OR									
	overall									
Plumereau [37]	ER									
	OR + revasc				80%	50%		90%		
	OR - revasc					15%		68%		
	Abstineren									
	overall									
Arya [36]	ER	100%	100%		36%	64%				
	OR	91%	95%		44%	57%				
	overall				42%	59%			50%	
Eslami [33]	ER				9%					
	OR				15%					
	overall				11%					

ER = Endovascular revascularization, OR = Operative revascularization. Patients given in numbers. Data given in %.

Practice points 2 - 3

- "Revascularization first, resection later" is key in establishing better survival and intestinal salvage.(14, 24, 26, 27)
- Percutaneous mesenteric artery angioplasty and stenting (PMAS) is first choice treatment for acute mesenteric ischemia (AMI), because of better short-term outcome, lower mortality and morbidity and reduced costs.(11, 26, 27, 31-39)

Patient selection and preoperative evaluation

Treatment of AMI and end-stage CMI is a 24/7-time consuming multidisciplinary challenge.(13) An experienced team is crucial to the survival of AMI patients and they should be treated in centers with experience in both open and endovascular revascularization techniques, preferably in a hybrid operating room.(13) If a patient is referred to a secondary or tertiary center, we don't recommend performing bowel resection first before transporting the patient, because, vital time will be lost to salvage reversibly ischaemic bowel.

AoCMI should be treated like AMI and PMAS is the first-choice treatment. Retrograde open mesenteric stenting (ROMS) should be considered in all patients in whom PMAS was unsuccessful. Rates of restenosis are higher in heavily calcified or long (>30mm) lesions.(40)

Practice point 4

- Acute mesenteric ischemia (AMI) should be treated in centers with 24/7 service and experience in both open and endovascular revascularization.(13)

Treatment of CMI and patient selection

The main priorities in revascularization of CMI are improving quality of life (relief of abdominal symptoms) and prevention of bowel infarction. Secondary weight gain is a bonus. Like in AMI, the number of patients treated with PMAS has rapidly increased, making it a first-choice treatment.(10) However, when analyzing available literature there is some evidence for selection bias, which should be taken into account when drawing conclusions.

Literature shows that PMAS has lower mortality and morbidity, shorter length of stay and recovery time compared to OSR, but more frequent recurrence of symptoms, restenosis and re-interventions, Table 3a and 3b.(10, 25, 41-57) However, patients undergoing PMAS were older and had more comorbidities than patients undergoing OSR.(25, 49, 58, 59) So, more high-risk patients were treated with PMAS, making it assumable that reported outcomes

disadvantage PMAS. Tallarita et al. showed a 5-year survival of 69% for OSR and 44% for PMAS.(54) After using multivariate regression and comorbidity score matching, however, long-term survival didn't differ between OSR and PMAS, respectively 60% and 57% (p= 0.7). A retrospective analysis of data on PMAS in the Medical Spectrum Twente, Enschede, collected between November 2004 and November 2012 showed that primary patency was 77% at 1 year and 45% after 5 years.(60) Primary assisted patency was much better (90% and 69,8% respectively), and secondary patency was excellent (98,3% and 93,6% respectively). We also analyzed our OSR between 1997 and 2014.(61) The first group consisted of patients treated before 2006, the year we started treating patients with PMAS. The second group consisted of patients who were treated since 2006. Five-year survival of OSR improved, respectively 74% before 2006 and 89% since 2006, but at the same time the long-term primary patency decreased, respectively 88% before 2006 and 48% since 2006. The most likely explanation is that the indication for OSR has changed, patients in the group since 2006 have less comorbidity, but more extensive atherosclerotic disease, not suitable for PMAS. Although not significantly different, OSR patients had threefold more complications than PMAS patients, 33% versus 13% respectively.(49) Additionally, lengths of intensive care unit (ICU) and hospital stay were shorter for PMAS.(25) Therefore, we would like to conclude that PMAS should be the first-choice treatment for all CMI patients. Bypass surgery should only be used in low-risk patients who have unfavourable mesenteric lesions, failed PMAS or ROMS or multiple recurrences of in-stent stenosis/occlusion.(24, 48)

Practice points 5 - 6

- Percutaneous mesenteric artery angioplasty and stenting (PMAS) is the first-choice treatment for chronic mesenteric ischemia (CMI).(10, 25, 41-57)
- Bypass surgery should only be used in low-risk patients who have unfavourable mesenteric lesions, failed percutaneous mesenteric artery angioplasty and stenting (PMAS) or retrograde open mesenteric stenting (ROMS) or multiple recurrences of in-stent stenosis/occlusion.(24, 48)

Table 3a. Outcome measures of literature search for CMI.

	Atkins [49]		Biebl [47]		Davies [56]		Sivamurthy [52]		Kasirajan [44]		Zerbib [53]		Oderich [54]		Brown [57]		Summary	
	ER	OR	ER	OR	ER	OR	ER	OR	ER	OR	ER	OR	ER	OR	ER	OR	ER	OR
Patients	31	49	23	26	15	17	19	41	28	85	14	15	83	146	14	33	227	412
Technical success	97	100	93		93	100					95		93	100	95	100	95	100
Clinical improvement	61	83	75	89	73	100	20	59	66	87	71	93	92	96	93		74	88
30d Mortality	3,2	2	0	9	0	5,9	0	7,7	10,7	8,2	2,4	2,7	14,3	0	21	15	5	6
Primary Patency	58	90	75	100	54	83	83	68	51	86	58	70	41	88	27		51	86
Secundary patency	69	87			65	100			73	76			88	97			83	87
Morbidity	13	4	4	42	7	35	4	42	18	33	11	36	7	20	19	46	11	32
Recurrence of Symptoms	23	22	9	0	13	29	71	35	39	12	21	7	31	5			30	13
Recurrent stenosis	32	37	25	8			39	0	27	24	21	0	37	7	57		37	15
Reinterventions	16	22	13	0			5	12	4		0	0	31	5	53		20	9
Hospital stay (days)	4	12	2	10	4	14,2	1	12	5	13	3	12	20	22	1	23	5	15

ER = Endovascular revascularization, OR = Operative revascularization. Patients given in numbers. Data given in %.

Table 3b. Continued outcome measures of literature search for CMI.

	Arya [36]		Indes [46]		Tallarita [55]		Gupta [51]		Rawat [51]		Schermerhorn [11]		Zacharias [58]		Kougias [58]	
	ER	OR	ER	OR	ER	OR	ER	OR	ER	OR	ER	OR	ER	OR	ER	OR
Patients	26	55	347	280	156	187	684	714	36	40	3455	2128	116	45	48	96
Technical success							95,6									
Clinical improvement							87,8	94,4								
30d Mortality	0	0			4,1	5,8	4,1	4,5								
Primary Patency	64	92					78,5	91,4	32	69					82	91
Primary Patency 1 year							74,2	90,8					91	98		
Primary Patency 3 year													74	91		
Primary Patency 5 year							52	80,4								
Primary assisted Patency 1 year							85,7	96								
Primary assisted Patency 5 year							79	96								

	Arya [36]		Indes [46]		Tallarita [55]		Gupta [51]		Rawat [51]		Schermerhorn [11]		Zacharias [58]		Kougias [58]	
Secundary patency	82	98							50	89						
Morbidity	19	18														
Complications							14,1	34,7								
Perioperative death					2,6	2,7	4	5,6	11	7,5	3,7	15,4	5,2	11	0	1,2
Survival during Follow-up			89	80	44	69			72	90			95	78	79	82
Recurrence of Symptoms							38,7	24,3								
Reintervetions for restenosis					21	14										
Overall mortality					6,4	8										

ER = Endovascular revascularization, OR = Operative revascularization. Patients given in numbers. Data given in %.

Technical aspects of treatment

PMAS for AMI and CMI due to atherosclerotic disease.

After local anaesthesia, retrograde femoral artery access is established and a sheath is introduced. We prefer a femoral approach first,(13, 26) but if the angle of the mesenteric artery with the anterior aortic wall is below 30 degrees, brachial approach will ensure more wire and catheter pushability to pass the lesion. With brachial access, a long sheath is advanced into the descending aorta to just above the level of the diaphragm. For AMI due to SMA lesions, we favour to always leave a stent in the SMA instead of percutaneous transluminal angioplasty (PTA) only, because of better patency, freedom of symptoms, lack of reinterventions and survival.(26, 62) In CMI, multivessel disease is more common and flow has changed in the presence of stenosis and collaterals.(5) PMAS for 2 vessels in multivessel disease seems preferable.(25)

A flush catheter is advanced into the abdominal aorta, just above the level of the mesenteric arteries and a digital subtraction angiography (DSA) is performed in an antero-posterior (AP) position and focused laterally, perpendicular to the mesenteric artery, for lesion identification and assessment of vessel anatomy and any relevant collaterals.

Heparin (5,000 IU or 80 UI/kg) is given systemically to prevent arterial thrombosis, embolic events and thrombus formation on the introduced wires and catheters. The flush catheter is changed for a diagnostic catheter and a hydrophilic-coated wire is first choice to pass the lesion, subsequently advancing the diagnostic catheter. The hydrophilic-coated wire is

changed for a stiff 0.014- or 0.018-inch wire and the selected stent can be delivered to the target vessel. A short balloon-expandable stent is preferred for heavily calcified osteal lesions. Flexible self-expandable stents are preferred for longer, non-calcified lesions extending further into the main branch of the artery, because of better preservation of the artery's natural tortuosity and curvature. This might also lead to less vascular wall stress, wall inflammation, intima hyperplasia and restenosis. For the same reasons we don't oversize and a 6 mm stent is usually sufficient for the CA and SMA origin. Although literature is scarce, covered stents are associated with less restenosis, a lower clinical symptom recurrence rate, and fewer re-interventions when compared to bare metal stents (approximately 10% compared to 50%).(63) A nationwide Dutch RCT is currently performed and we hope to provide you with the results in the near future.

Completion angiography and pressure measurements across the lesions are standard of care. If residual pressure gradients exceed 12mmHg, additional angioplasty and/or stenting are advised.(64) Percutaneous access sites are preferably treated with closure devices, or manual compression if none are available.

Treatment of AMI due to embolic disease

In cases of acute thrombo-embolic events, treatment options are mostly dependent on institutional experiences, because scientific evidence is lacking. Next to laparotomy and open embolectomy, endovascular aspiration embolectomy is a fair treatment option. After retrograde sheath introduction into the common femoral artery, a guiding catheter is advanced up to the level of the occluded mesenteric artery. DSA is performed as described above by a diagnostic flush catheter to identify the embolic clot. An aspiration catheter is placed and thrombosuction can be performed, while advancing the catheter across the lesion and back. Often several aspirations are required to remove the thrombo-embolus. In case of a remaining stenosis or underlying chronic lesion, the procedure can be completed by PMAS.

Thrombolysis is a good alternative for incomplete aspiration embolectomy, but severe and fatal haemorrhages lurk, especially in end-stage bowel ischemia with very vulnerable mucosa. Different types of catheters can be advanced into the embolus (e.g. multiple side-hole or valved infusion catheter) and deliver thrombolytic agents over a 10 cm range. After regaining blood flow, thrombolysis is ended and treatment is continued with heparinization.

Retrograde open mesenteric stenting (ROMS)

Technical failure for EVT is seen in about 20-31% of AMI patients.(28, 38) If EVT fails, ROMS is a good alternative. It's a hybrid technique, combining the advantages of EVT and OSR.(1, 26) Besides an efficient and minimally invasive revascularization, it provides the opportunity for assessment of bowel viability.(26, 38) Blauw et al.(38) reported it had a high technical success of 93% with primary, primary assisted, and secondary patency exceeding 90% after 30 days and 83% after 12 months for AMI. In hospital mortality was 20%, climbing to 30% at 30 days after which it stabilised. Clinical success was 67% after 12 months.

Via a small transverse upper abdominal laparotomy, the SMA is exposed and incised distally from the occlusion after heparinization (5000 IU). A 6F flexible sheath is placed retrogradely. The lesion can be crossed transluminally or subluminally after which the aortic lumen is reached. We recommend a short 6-mm balloon-expandable stent. If needed, extension can be obtained with a flexible self-expandable stent. The proximal side of the stent should protrude 2-4 mm into the aortic lumen. A completion angiography is performed before sheath removal to assess technical success.(26, 38)

Open surgical treatment with mesenteric bypass

The level of evidence regarding preferential mesenteric bypass conduit material is low (IIb at most) and local preferences rule the opinion. On one hand, a couple of reports describe the use of an antegrade two-vessel polyester graft.(14, 42, 65, 66) On the other hand, and in our experience, an antegrade 2-vessel autologous vein bypass of the CA and SMA is the preferred technique, because of superior patency.(67, 68) Also, in the presence of soilage, prosthetic graft infection is a major risk which can be avoided by using venous grafts.(14) The greater saphenous vein and the superficial femoral vein are first and second preferred options. After a transperitoneal upper midline or bilateral subcostal incision, an abdominal retractor system is placed and exploration of the abdomen is performed, inspecting bowel viability. To access the diaphragmatic crura, the lesser omentum is opened, the left liver lobe and the stomach are retracted caudally and the oesophagus is retracted to the left lateral side. By opening the crurae, the supracoeliac aorta is exposed. The transverse mesocolon is retracted cranially and the mesenteric radix is incised longitudinally over the SMA just below the pancreas. The proximal SMA is isolated and controlled with vessel loops. 5000IU of heparin are administered before cross-clamping the supracoeliac aorta and a vertical aortotomy is made. The short main body of the graft is trimmed in an oblique fashion and anastomosed with 4-0 Prolene to the supracoeliac aorta in an end-to-side fashion. Aortic cross-clamping time should aim for 12 to 15 minutes to minimize risks of renal ischemia

or embolization. The left limb is anastomosed end-to-side to the SMA at the base of the mesentery distal to the pancreas with 4-0 Prolene after being tunnelled retropancreatically and anteriorly to the left renal vein. Keep in mind to retain enough length to avoid traction when tailoring the graft. An end-to-end anastomosis with the coeliac axis or an end-to side anastomosis with the common hepatic artery is performed. If a Dacron or polytetrafluoroethylene (PTFE) graft is used, formation of later graft-enteric fistula can be prevented by covering the intraperitoneal part of the graft with omentum.(14)

In an acute setting, or in patients with extensive cardiac and pulmonary comorbidities, a single retrograde SMA bypass may suffice, and aortic clamping can be avoided.(14, 42, 65, 66) We favour a “lazy-C” graft configuration from the left iliac artery to SMA, but the right iliac artery or a more proximal anastomosis to the antero-lateral wall of the infrarenal aorta is also possible. Avoidance of graft elongation, angulation, or kinking is critical. Two-vessel reconstructions can also be performed in a retrograde fashion. These grafts can either lay over or under the pancreas and curve in a “lazy-C” configuration toward the hepatic artery.

In open surgical embolectomy, the SMA is exposed in the radix mesenterica and a 3- or 4-French Fogarty catheter is used. Like in EVT, the result should be checked via completion angiography or with intra-abdominal Duplex ultrasonography.

Bowel viability; laparotomy and second-look

If the patient has signs of peritonitis, laparotomy should be performed to assess bowel viability and the extent and severity of transmural ischemia.(13) Literature shows that 28 to 59% of AMI patients need bowel resection after revascularization.(10, 24, 26, 28) It isn’t advised to perform laparoscopy, because manipulation and pneumoperitoneum are risk factors for perforation and the examination of the entire colon is difficult and sometimes not fully possible.(14, 26) Patchy cyanosis, dark red-purple or black discoloration, decreased or absent peristalsis and weak or no palpable pulsations in the mesentery are signs of ischemia.

Intestine with transmural ischemia should be resected. If the remaining bowel is vital, restoration of the continuity of the intestine can be performed. If on-going ischemia is suspected or it isn’t possible to determine whether or not additional resection is needed, we advise that restoration of bowel continuity should be postponed until second look laparotomy after 18-36 hours is performed. We don’t recommend ostomy creation, because this increases mortality and morbidity, risking high output ostomies and short bowel syndrome (SBS).(26)

Small intestine transplantation

Although SBS is uncommon in AMI, AMI accounts for 75% of patients with SBS. It is defined as a small intestinal remnant less than 50 cm with an intact ileocecal valve, or a 100 cm small intestine without a functioning ileocecal valve in adults and associated malabsorption. Timely diagnosis, urgent revascularization and damage control surgery with restraint of bowel resections are key in preventing SBS.(69) Many of these patients will need either temporarily or lifelong parenteral nutrition. Quality of life of home parenteral nutrition is moderate to good,(70) and the outcome of intestinal transplantation is improving.(71) Although intestinal transplantation may become a future possibility for (young) patients with SBS, treatment of mesenteric ischemia should be focused on intestinal salvage so SBS and intestinal transplantation can be prevented.

Practice point 7

- Postponed reconstruction of bowel continuity is advised with on-going ischemia or inability to determine if additional resection is needed. Schedule a second look laparotomy after 18-36 hours. Ostomy creation isn't advised.(26)

Postoperative treatment

Systemic heparin is administered postoperatively (with goal activated partial thromboplastin time (aPTT) between 40 and 60 seconds) in all patients. If preferred, low-molecular weight heparin (LMWH) in therapeutic doses is a good alternative. Hemodynamic or pulmonary instable patients will undergo supportive care in an ICU according to their needs. Non-occlusive mesenteric ischemia (NOMI) is a risk when administering vasoconstrictive drugs. Enteral feeding is preferred, but some patients may need parenteral nutrition.

In the Medical Spectrum Twente, Enschede, a strict refeeding protocol was introduced in 2000 for patients with AoCMI and AMI allowing a gradual start of enteral intake adjusted by clinical evaluation, daily white blood cell (WBC) counts, and C-reactive protein (CRP) measurements. On-going abdominal symptoms, severe diarrhea, and increases in WBC counts and CRP levels are compatible with progressive ischemia-reperfusion damage at which time enteral feeding will be discontinued, see Table 4. After introduction of this 9-step bowel rehabilitation program, the ischemia-reperfusion cascade is rarely clinically relevant. Patients with clinically or biochemically suspected restenosis or occlusion of the SMA require a contrast-enhanced CT to assess patency and secondary signs of infarction. If needed, relaparotomy is performed. If no abnormalities are found, the refeeding protocol is restarted.

Table 4. 9-step bowel rehabilitation scheme of the Medical Spectrum Twente, Enschede, the Netherlands.

Step		Oral intake
1	*Day 0*	No oral intake
2	*Day 1*	One sip of water or tea every half hour
3		Up to 75 ml (one glass) of clear drinks every two hours
4	*Day 2-3*	75 ml clear drinks every 2 hours + 1 slice of bread spread over six portions per day
5		1 to 2 sandwiches throughout the day + unlimited clear fluids
6	*Day 3-5*	1 to 2 sandwiches throughout the day + unlimited clear fluids + ¼ bright hot meal
7	*Day 4-6*	2 sandwiches throughout the day + unlimited clear fluids + possibly a hot meal divided in several portions of ¼ or ½
8	*Day 5-7*	Normal diet throughout the day in ¼ or ½ servings + unlimited fluids
9	*Day 6-8*	Normal nutrition. If necessary, expand 6 smaller portions spread over the day to normal amounts 3 times a day, depending on the patient's diet

Medical treatment

All patients need life-long antiplatelet therapy to prevent atherosclerosis.(1) When bowel function is restored dual platelet inhibitors are supplemented and the heparin is withdrawn. Clopidogrel is used for 6 months and acetylsalicylic acid is used as life-long maintenance treatment.

Practice points 8 - 9

- Life-long antiplatelet medication for all patients is advised.(1)
- Refeeding is best done in a gradual and strictly monitored way.

Follow-up

Continued patient surveillance for diagnosing and treating in-stent or graft restenosis is important, because AMI after mesenteric revascularization accounts for 6-8% of late deaths in CMI patients.(54) We recommend clinical evaluation and duplex imaging at 3-, 6-, 12-, 18- and 24 months, due to high in-stent restenosis rate in the first 2 years.(1, 72, 73) In our experience primary patency drops by 20% per year to approximately 60% after 2 years, with excellent results of re-treatment.(60) Because of the high risk of in-stent restenosis(74) and the need for re-intervention to prevent the serious consequences of stent occlusion,(73) CTA should be the next step, if symptoms recur or duplex imaging shows evidence for restenosis. (1, 74) After two years, imaging should be done in case of recurrent symptoms.(60)

Re-interventions appear to have a relatively low mortality (3%), high complication rates (27%) and good clinical success (92%).(74)

Practice point 10

- Regular follow-up should be performed during the first two post-procedural years and selectively thereafter.(1, 54, 72-74)

Conclusion

Mesenteric ischemia is a rare medical emergency for which treatment has improved over the last decade with the advent of endovascular techniques. Mortality and morbidity rates have been reduced for both AMI and CMI and QoL has improved due to better intestinal salvage and post-treatment care. The main motto is “revascularization first, resection later” and endovascular treatment is treatment of choice for AMI and CMI. Outcome of severe AMI may be improved by reducing the time interval to revascularization, minimizing length of the initial surgical procedure and extent of bowel resection with delayed abdominal closure and second look procedure 18-36 hours later. Investigations regarding plasma biomarkers of mesenteric ischemia are ongoing, and future development may aid in reducing time to diagnosis. Mesenteric ischemia poses a clinical challenge requiring 24/7 multidisciplinary team availability, and should therefore preferentially be treated in dedicated centers with high levels of experience.

References

1. Clair DG, Beach JM. Mesenteric Ischemia. N Engl J Med. 2016;374(10):959-68.
2. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997;26(3):517-38.
3. Diehm N, Baumgartner I, Jaff M, Do DD, Minar E, Schmidli J, et al. A call for uniform reporting standards in studies assessing endovascular treatment for chronic ischaemia of lower limb arteries. Eur Heart J. 2007;28(7):798-805.
4. Moneta GL, Edwards JM, Chitwood RW, Taylor LM, Jr., Lee RW, Cummings CA, et al. Correlation of North American Symptomatic Carotid Endarterectomy Trial (NASCET) angiographic definition of 70% to 99% internal carotid artery stenosis with duplex scanning. J Vasc Surg. 1993;17(1):152-7; discussion 7-9.
5. van Petersen AS, Kolkman JJ, Meerwaldt R, Huisman AB, van der Palen J, Zeebregts CJ, et al. Mesenteric stenosis, collaterals, and compensatory blood flow. J Vasc Surg. 2014;60(1):111-9, 9 e1-2.
6. Douard R, Chevallier JM, Delmas V, Cugnenc PH. Clinical interest of digestive arterial trunk anastomoses. Surg Radiol Anat. 2006;28(3):219-27.
7. Gray H. Anatomy of the Human Body1918.
8. Kougias P, Lau D, El Sayed HF, Zhou W, Huynh TT, Lin PH. Determinants of mortality and treatment outcome following surgical interventions for acute mesenteric ischemia. J Vasc Surg. 2007;46(3):467-74.
9. Lejay A, Georg Y, Tartaglia E, Creton O, Lucereau B, Thaveau F, et al. Chronic mesenteric ischemia: 20 year experience of open surgical treatment. Eur J Vasc Endovasc Surg. 2015;49(5):587-92.
10. Schermerhorn ML, Giles KA, Hamdan AD, Wyers MC, Pomposelli FB. Mesenteric revascularization: management and outcomes in the United States, 1988-2006. J Vasc Surg. 2009;50(2):341-8 e1.
11. Beaulieu RJ, Arnaoutakis KD, Abularrage CJ, Efron DT, Schneider E, Black JH, 3rd. Comparison of open and endovascular treatment of acute mesenteric ischemia. J Vasc Surg. 2014;59(1):159-64.
12. Naylor AR, Forbes TL. Trans-Atlantic Debate: Is an "Endovascular First" Strategy the Optimal Approach for Treating Acute Mesenteric Ischemia? Eur J Vasc Endovasc Surg. 2015;50(3):279-80.
13. Stone JR, Wilkins LR. Acute mesenteric ischemia. Tech Vasc Interv Radiol. 2015;18(1):24-30.
14. Wyers MC. Acute mesenteric ischemia: diagnostic approach and surgical treatment. Semin Vasc Surg. 2010;23(1):9-20.
15. Kirkpatrick ID, Kroeker MA, Greenberg HM. Biphasic CT with mesenteric CT angiography in the evaluation of acute mesenteric ischemia: initial experience. Radiology. 2003;229(1):91-8.
16. Mensink PB, Moons LM, Kuipers EJ. Chronic gastrointestinal ischaemia: shifting paradigms. Gut. 2011;60(5):722-37.
17. Kolkman JJ, Bargeman M, Huisman AB, Geelkerken RH. Diagnosis and management of splanchnic ischemia. World J Gastroenterol. 2008;14(48):7309-20.
18. Chienne. Complete obliteration of celiac and mesenteric arteries. Journal of Anatomical Physiology. 1869;3:63-72.
19. Councilman. Three cases of occlusion of the superior mesenteric artery. Boston Medical Surgery. 1894;1894;130:410-1.
20. Dunphy. Abdominal pain of vascular origin. Am J Med Sci. 1936;192:109-12.
21. Mikkelson. Intestinal angina. Its surgical significance. 94:262-9. 1957.

22. Shaw RS, Maynard EP, 3rd. Acute and chronic thrombosis of the mesenteric arteries associated with malabsorption; a report of two cases successfully treated by thromboendarterectomy. N Engl J Med. 1958;258(18):874-8.
23. Furrer J, Gruntzig A, Kugelmeier J, Goebel N. Treatment of abdominal angina with percutaneous dilatation of an arteria mesenterica superior stenosis. Preliminary communication. Cardiovasc Intervent Radiol. 1980;3(1):43-4.
24. Acosta S. Mesenteric ischemia. Curr Opin Crit Care. 2015;21(2):171-8.
25. van Petersen AS, Kolkman JJ, Beuk RJ, Huisman AB, Doelman CJ, Geelkerken RH, et al. Open or percutaneous revascularization for chronic splanchnic syndrome. J Vasc Surg. 2010;51(5):1309-16.
26. Acosta S, Bjorck M. Modern treatment of acute mesenteric ischaemia. Br J Surg. 2014;101(1):e100-8.
27. Roussel A, Castier Y, Nuzzo A, Pellenc Q, Sibert A, Panis Y, et al. Revascularization of acute mesenteric ischemia after creation of a dedicated multidisciplinary center. J Vasc Surg. 2015;62(5):1251-6.
28. Arthurs ZM, Titus J, Bannazadeh M, Eagleton MJ, Srivastava S, Sarac TP, et al. A comparison of endovascular revascularization with traditional therapy for the treatment of acute mesenteric ischemia. J Vasc Surg. 2011;53(3):698-704; discussion -5.
29. Zhao Y, Yin H, Yao C, Deng J, Wang M, Li Z, et al. Management of Acute Mesenteric Ischemia: A Critical Review and Treatment Algorithm. Vasc Endovascular Surg. 2016;50(3):183-92.
30. Block TA, Acosta S, Bjorck M. Endovascular and open surgery for acute occlusion of the superior mesenteric artery. J Vasc Surg. 2010;52(4):959-66.
31. Karkkainen JM, Lehtimaki TT, Saari P, Hartikainen J, Rantanen T, Paajanen H, et al. Endovascular Therapy as a Primary Revascularization Modality in Acute Mesenteric Ischemia. Cardiovasc Intervent Radiol. 2015;38(5):1119-29.
32. Eslami MH, Rybin D, Doros G, McPhee JT, Farber A. Mortality of acute mesenteric ischemia remains unchanged despite significant increase in utilization of endovascular techniques. Vascular. 2016;24(1):44-52.
33. Puippe GD, Suesstrunk J, Nocito A, Pfiffner R, Glenck M, Pfammatter T. Outcome of endovascular revascularisation in patients with acute obstructive mesenteric ischaemia - a single-centre experience. Vasa. 2015;44(5):363-70.
34. Duran M, Pohl E, Grabitz K, Schelzig H, Sagban TA, Simon F. The importance of open emergency surgery in the treatment of acute mesenteric ischemia. World J Emerg Surg. 2015;10:45.
35. Arya S, Kingman S, Knepper JP, Eliason JL, Henke PK, Rectenwald JE. Open Mesenteric Interventions Are Equally Safe as Endovascular Interventions and Offer Better Midterm Patency for Chronic Mesenteric Ischemia. Ann Vasc Surg. 2016;30:219-26.
36. Plumereau F, Mucci S, Le Naoures P, Finel JB, Hamy A. Acute mesenteric ischemia of arterial origin: importance of early revascularization. J Visc Surg. 2015;152(1):17-22.
37. Forbrig R, Renner P, Kasprzak P, Dahlke MH, Muller-Wille R, Stroszczynski C, et al. Outcome of primary percutaneous stent-revascularization in patients with atherosclerotic acute mesenteric ischemia. Acta Radiol. 2016.
38. Blauw JT, Meerwaldt R, Brusse-Keizer M, Kolkman JJ, Gerrits D, Geelkerken RH, et al. Retrograde open mesenteric stenting for acute mesenteric ischemia. J Vasc Surg. 2014;60(3):726-34.
39. Serracant Barrera A, Luna Aufroy A, Hidalgo Rosas JM, Canovas Moreno G, Fortuno Andres JR, Falco Fages J, et al. Acute mesenteric ischemia: Utility of endovascular techniques. Cir Esp. 2015;93(9):567-72.

40. Oderich GS MT, Malgor RD, Bower TC, Vritiska T, Duncan AA, et al. Natural History of Mesenteric Artery Stent Restenoses and Clinical and Anatomic Predictors for Re-intervention in Patients with Chronic Mesenteric Ischemia. J Vasc Surg. 2009;49(Suppl 1):A1-22,S1-S8, e1-2.
41. Moghadamyeghaneh Z, Carmichael JC, Mills SD, Dolich MO, Pigazzi A, Fujitani RM, et al. Early Outcome of Treatment of Chronic Mesenteric Ischemia. Am Surg. 2015;81(11):1149-56.
42. Oderich GS, Gloviczki P, Bower TC. Open surgical treatment for chronic mesenteric ischemia in the endovascular era: when it is necessary and what is the preferred technique? Semin Vasc Surg. 2010;23(1):36-46.
43. Kasirajan K, O'Hara PJ, Gray BH, Hertzer NR, Clair DG, Greenberg RK, et al. Chronic mesenteric ischemia: open surgery versus percutaneous angioplasty and stenting. J Vasc Surg. 2001;33(1):63-71.
44. Pecoraro F RZ, Lachat M, et al. Chronic mesenteric ischemia: critical review and guidelines for management. Ann Vasc Surg. 2013;27(1):113-122.
45. Indes JE, Giacovelli JK, Muhs BE, Sosa JA, Dardik A. Outcomes of endovascular and open treatment for chronic mesenteric ischemia. J Endovasc Ther. 2009;16(5):624-30.
46. Biebl M, Oldenburg WA, Paz-Fumagalli R, McKinney JM, Hakaim AG. Surgical and interventional visceral revascularization for the treatment of chronic mesenteric ischemia--when to prefer which? World J Surg. 2007;31(3):562-8.
47. Assar AN, Abilez OJ, Zarins CK. Outcome of open versus endovascular revascularization for chronic mesenteric ischemia: review of comparative studies. J Cardiovasc Surg (Torino). 2009;50(4):509-14.
48. Atkins MD, Kwolek CJ, LaMuraglia GM, Brewster DC, Chung TK, Cambria RP. Surgical revascularization versus endovascular therapy for chronic mesenteric ischemia: a comparative experience. J Vasc Surg. 2007;45(6):1162-71.
49. Gupta PK, Horan SM, Turaga KK, Miller WJ, Pipinos, II. Chronic mesenteric ischemia: endovascular versus open revascularization. J Endovasc Ther. 2010;17(4):540-9.
50. Rawat N, Gibbons CP, Joint Vascular Research G. Surgical or endovascular treatment for chronic mesenteric ischemia: a multicenter study. Ann Vasc Surg. 2010;24(7):935-45.
51. Sivamurthy N, Rhodes JM, Lee D, Waldman DL, Green RM, Davies MG. Endovascular versus open mesenteric revascularization: immediate benefits do not equate with short-term functional outcomes. J Am Coll Surg. 2006;202(6):859-67.
52. Zerbib P, Lebuffe G, Sergent-Baudson G, Chamatan A, Massouille D, Lions C, et al. Endovascular versus open revascularization for chronic mesenteric ischemia: a comparative study. Langenbecks Arch Surg. 2008;393(6):865-70.
53. Oderich GS, Malgor RD, Ricotta JJ, 2nd. Open and endovascular revascularization for chronic mesenteric ischemia: tabular review of the literature. Ann Vasc Surg. 2009;23(5):700-12.
54. Tallarita T, Oderich GS, Gloviczki P, Duncan AA, Kalra M, Cha S, et al. Patient survival after open and endovascular mesenteric revascularization for chronic mesenteric ischemia. J Vasc Surg. 2013;57(3):747-55; discussion 54-5.
55. Davies RS, Wall ML, Silverman SH, Simms MH, Vohra RK, Bradbury AW, et al. Surgical versus endovascular reconstruction for chronic mesenteric ischemia: a contemporary UK series. Vasc Endovascular Surg. 2009;43(2):157-64.
56. Brown DJ, Schermerhorn ML, Powell RJ, Fillinger MF, Rzucidlo EM, Walsh DB, et al. Mesenteric stenting for chronic mesenteric ischemia. J Vasc Surg. 2005;42(2):268-74.
57. Kougias P, Huynh TT, Lin PH. Clinical outcomes of mesenteric artery stenting versus surgical revascularization in chronic mesenteric ischemia. Int Angiol. 2009;28(2):132-7.

58. Zacharias N, Eghbalieh SD, Chang BB, Kreienberg PB, Roddy SP, Taggert JB, et al. Chronic mesenteric ischemia outcome analysis and predictors of endovascular failure. J Vasc Surg. 2016;63(6):1582-7.

59. Saedon M, Saratzis A, Karim A, Goodyear S. Endovascular Versus Surgical Revascularization for the Management of Chronic Mesenteric Ischemia. Vasc Endovascular Surg. 2015;49(1-2):37-44.

60. Bulut T O-BR, Geelkerken RH, Brusse-Keizer M, Stassen EJ, Kolkman JJ. Long- term results of endovascular treatment of atherosclerotic stenoses or occlusions of the celiac and superior mesenteric artery in patients with mesenteric ischemia. . European Journal of Vascular and Endovascular Surgery. Accepted for publication in 2017.

61. Blauw JTM BT, Eenhoorn P, Beuk RJ, Brusse-Keizer M, Kolkman JJ, Geelkerken RH. Chronic Mesenteric Ischemia: When and how to intervene on patients with celiac/SMA stenosis. Journal of Cardiovascular Surgery. accepted for publication in 2017.

62. Ahanchi SS, Stout CL, Dahl TJ, Carty RL, Messerschmidt CA, Panneton JM. Comparative analysis of celiac versus mesenteric artery outcomes after angioplasty and stenting. J Vasc Surg. 2013;57(4):1062-6.

63. Oderich GS, Erdoes LS, Lesar C, Mendes BC, Gloviczki P, Cha S, et al. Comparison of covered stents versus bare metal stents for treatment of chronic atherosclerotic mesenteric arterial disease. J Vasc Surg. 2013;58(5):1316-23.

64. Acosta S, Sonesson B, Resch T. Endovascular therapeutic approaches for acute superior mesenteric artery occlusion. Cardiovasc Intervent Radiol. 2009;32(5):896-905.

65. Oderich GS, Bower TC, Sullivan TM, Bjarnason H, Cha S, Gloviczki P. Open versus endovascular revascularization for chronic mesenteric ischemia: risk-stratified outcomes. J Vasc Surg. 2009;49(6):1472-9 e3.

66. Park WM, Cherry KJ, Jr., Chua HK, Clark RC, Jenkins G, Harmsen WS, et al. Current results of open revascularization for chronic mesenteric ischemia: a standard for comparison. J Vasc Surg. 2002;35(5):853-9.

67. Geelkerken RH, van Bockel JH, de Roos WK, Hermans J, Terpstra JL. Chronic mesenteric vascular syndrome. Results of reconstructive surgery. Arch Surg. 1991;126(9):1101-6.

68. Shah AS, Schwartz LB, Moawad J, Gewertz BL. Technique profile: mesenteric reconstructions for occlusive disease. Expert Rev Cardiovasc Ther. 2015;13(12):1445-58.

69. Thompson JS. Short Bowel Syndrome and Malabsorption - Causes and Prevention. Viszeralmedizin. 2014;30(3):174-8.

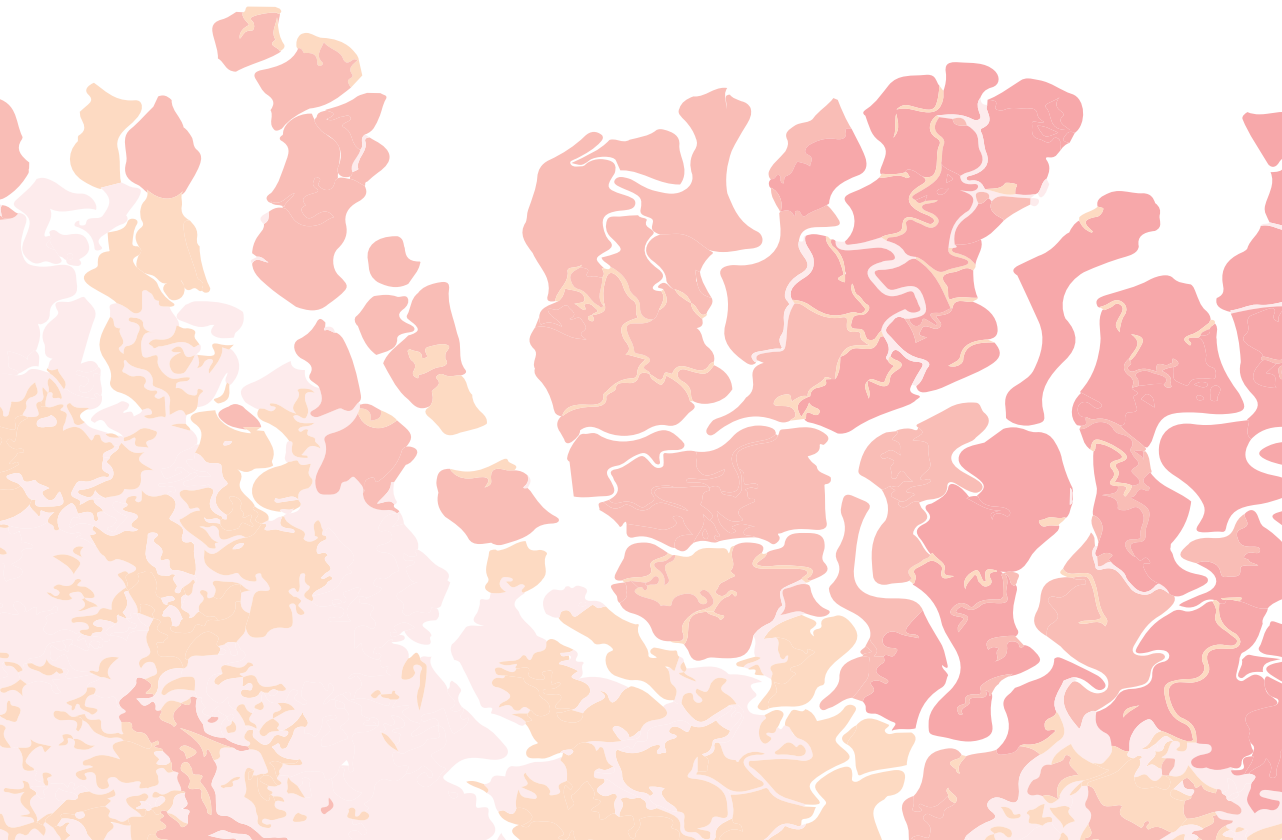
70. Huisman-de Waal G, Schoonhoven L, Jansen J, Wanten G, van Achterberg T. The impact of home parenteral nutrition on daily life-a review. Clin Nutr. 2007;26(3):275-88.

71. Sudan D. The current state of intestine transplantation: indications, techniques, outcomes and challenges. Am J Transplant. 2014;14(9):1976-84.

72. Sharafuddin MJ, Nicholson RM, Kresowik TF, Amin PB, Hoballah JJ, Sharp WJ. Endovascular recanalization of total occlusions of the mesenteric and celiac arteries. J Vasc Surg. 2012;55(6):1674-81.

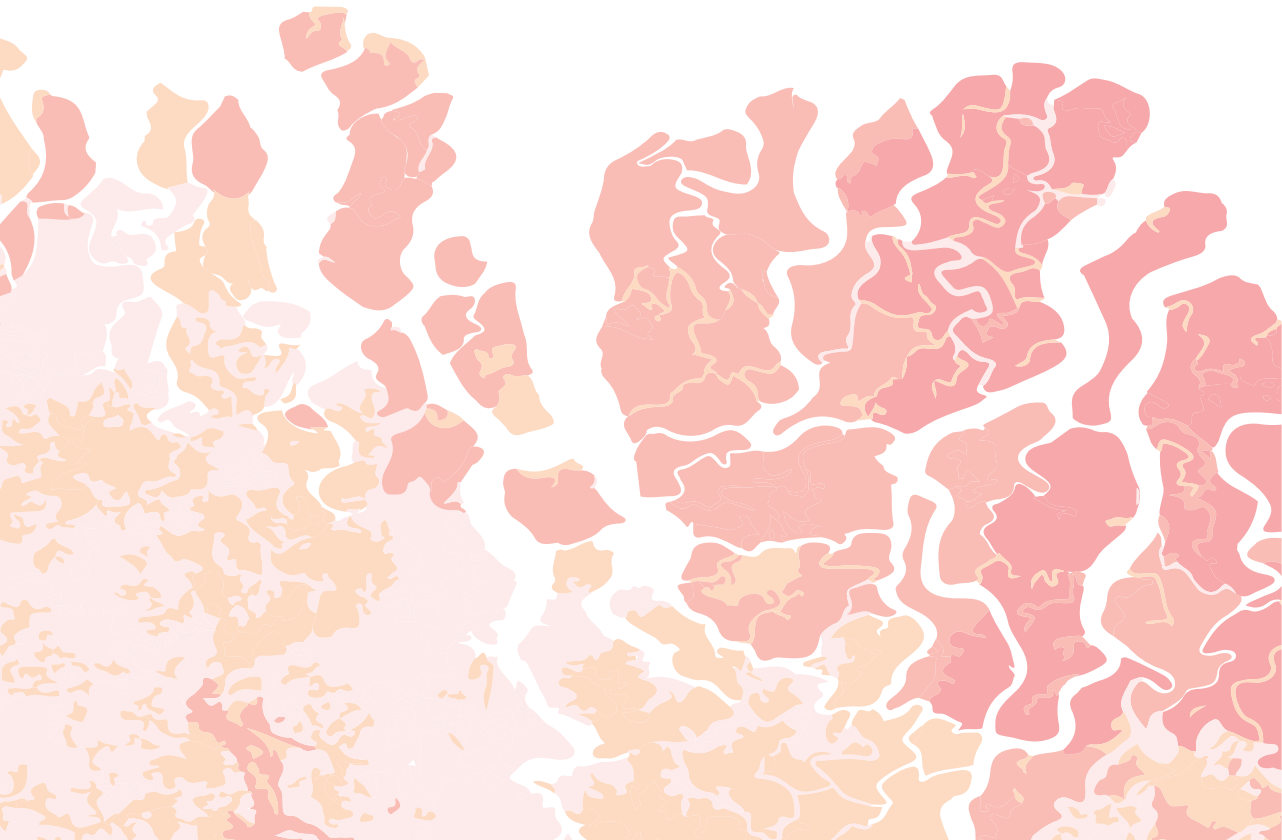
73. Bjornsson S, Resch T, Acosta S. Symptomatic mesenteric atherosclerotic disease-lessons learned from the diagnostic workup. J Gastrointest Surg. 2013;17(5):973-80.

74. Tallarita T, Oderich GS, Macedo TA, Gloviczki P, Misra S, Duncan AA, et al. Reinterventions for stent restenosis in patients treated for atherosclerotic mesenteric artery disease. J Vasc Surg. 2011;54(5):1422-9 e1.



PART II

Life after mesenteric ischemia



Chapter 6

A systematic review on the efficacy of treatment of the median arcuate ligament syndrome

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Submitted.

Abstract

Background Since the first description of the median arcuate ligament syndrome (MALS), the existence of the syndrome and the efficacy of treatment have been questioned. The last systematic review including 400 patients was performed ten years ago with the focus on coeliac artery (CA) release and suggested a 85% immediate symptom relief after surgical release of the CA with a late recurrence in respectively 7% and 6%. (1)

Methods We have performed a systematic review conform the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement with a broader view on treatment options for MALS including any kind of CA release, coeliac plexus resection and coeliac plexus blockage irrespective of age between 1963 and July 2021. Main outcome parameters were symptom relief and quality of life (QoL).

Results Thirty-eight studies were included describing 880 adult patients and 6 studies describing 196 patients below the age of 18 years. 468 (68%) of the adult patients became either free of symptoms (n=294) or reported clear reduction of symptoms (n=174) from 3 months up to 228 months after CA release. Two adult studies compared QoL before and after treatment for MALS and both showed an improved QoL after treatment. In the paediatric cohort, 146 (82%) of the patients became either free of symptoms (n=72) or reported a clear reduction of symptoms after laparoscopic CA release (n=74). Four studies reported an improved QoL after treatment. In the adult cohort thirty-five (92%) and in the pediatric cohort five (83%) studies scored a high or unclear risk of bias for the majority of the QUADAS-2 items. The meaning of coeliac plexus resection or blockage couldn't be substantiated.

Conclusion This systematic review confirmed sustainable symptom relief after surgical treatment for MALS in adult and pediatric patients, albeit with a high risk of bias as a result of predominantly highly diverse inclusion criteria and outcome parameters that are not uniformly presented. This outcome suggests a dire need of a good quality randomized controlled trial to give definitive conclusions.

Introduction

The median arcuate ligament syndrome (MALS), coeliac artery compression syndrome (CACS) or Dunbar syndrome, was defined as external compression of the celiac artery (CA) by the median arcuate ligament (MAL) causing symptoms of chronic mesenteric ischemia (CMI), including postprandial/epigastric abdominal pain, weight loss, nausea, diarrhoea and loss of energy.(1) Anatomic MAL compression, first described by Lipshutz in 1917,(2) is not rare with a prevalence of 3.4-7.3%.(3–7) Respiration movements of the diaphragm causing variations in the position of the MAL could result in the compression of the celiac artery and the coeliac plexus, mostly during expiration.(8)

The existence of MALS as a distinct entity(9) and the efficacy of the treatment of MALS has been questioned for a long time and the debate on the existence of MALS is still not settled and respected physicians draw opposing conclusions on the existing data(10–12) The combination of a varying patient presentation, non-specific abdominal symptoms and lack of validated non-invasive mesenteric perfusion tests makes the diagnosis MALS challenging to establish. The current international guidelines recommend that the diagnosis should be based on symptoms fitting CMI and imaging studies showing compression of the CA by the MAL evaluated by an experienced multidisciplinary team, consisting of dedicated gastroenterologists, vascular surgeons, and radiologists.(10,11)

In the expert panel of the European guidelines on CMI, 96% of the experts recommended that patients with MALS might be considered for surgical CA release, but consensus could not be reached on the first choice of treatment strategy and consequently clear recommendations are lacking.(11) Some publications reported that local coeliac plexus blockage could be an alternative effective treatment for MALS(13,14), but this has not been described as treatment option in the two comprehensive guidelines.(10,11)

In 2012, Jimenez et al. published a systematic review of 20 retrospective studies reporting a 85% immediate symptom improvement of 400 MALS patients from 6 months up to 23 years after laparoscopic and open CA release with a late recurrence in 19 patients in the open group (6.8%) and seven patients in the laparoscopic group (5.7%).(1) Limitations of the review by Jimenez et al. are that the evidence is based on a large number of small individual series, the age of the patients was not reported and the follow-up period in the laparoscopic treatment group is short. There are no aggregated data available on MALS treatment and outcome in the past decade. Furthermore, the most obvious outcome measure by today's standard, being the impact of MALS on quality of life (QoL) of patients before and after treatment, was not reported in the review.

The current systematic review therefore encompasses an update of the literature on treatment, including open, laparoscopic and robot assisted CA release techniques, coeliac plexus blockage, and outcomes including individual and societal gain of QoL for MALS in the last ten years in adult and paediatric patients. Furthermore, in case suitable data is available, meta-analyses will be performed.

Methods

Search strategy

The study protocol for this systematic review has been registered with the international prospective register of systematic reviews (PROSPERO), conform the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (PROSPERO CRD42021258592).(15) The literature search was performed according to standards of the PRISMA Statement.(15) First, systematic searches in Pubmed, Cochrane Library and Embase were performed to identify all relevant literature (the details of the search strategy are shown in Appendix 1). Secondly all references of the existing reviews on MALS were hand searched for additional citations.

Study selection

The search focused on studies describing the outcomes of treatment of MALS published between its first description in 1963 until July 16th 2021. Duplicates were removed. Patient cohorts could be included irrespective of age of presentation and treatment.

Table 1 In- and exclusion criteria of systemic review of treatment of Median Arcuate Ligament Syndrome

Inclusion:	**Exclusion:**
• Between 1963 up until July 16th 2021 • English • RCT, cohort, retro- and prospective studies • External compression of the celiac artery by the MAL on CTA, MRA, Duplex Ultrasound or Diagnostic Angiography • Abdominal symptoms for more than 3 months • Surgical treatment for MALS or Plexus Block • Outcomes of treatment reported	• Others than inclusion languages • Comments, letter to editor or other forms of own opinions without scientific substantiation • Less than 3 patients included • No abstract or full text available • No treatment performed • Surgery for MALS combined with other surgery

RCT = randomized controlled trial; MAL = median arcuate ligament; CTA = computerized tomographic angiography; MRA = magnetic resonance angiography; MALS = median arcuate ligament syndrome

The articles were independently selected by two authors (FM and JB), blinded from each other. A first selection was made by screening the titles and abstracts on the pre-defined inclusion and exclusion criteria (Table 1). Secondly, full articles were read to make a final selection, and consensus needed to be reached for inclusion. In case of disagreements a third screener (RHG) was involved in exchanging arguments and consensus decision-making. Full texts were accessed via PubMed and through national and international library requests. If full texts could not be retrieved, the article was excluded.

Outcome parameters

The main outcomes included symptom relief and QoL. Secondary outcomes included anatomical data (patency after treatment, duplex outcomes), clinical outcomes (loss of productivity, disability adjusted life years, BMI (Body Mass Index), use of analgesics, psychiatric diagnosis, mortality, complications).

Continuous variables were displayed as means (standard deviation) or median (interquartile range) for respectively parametric and non-parametric. Categorical variables were displayed as numbers (percentages). Patient cohorts below 18 years and adults from 18 years old were analysed separately. In the paediatric cohort (patients below 18 years old) the results were limited to the main outcomes symptom relief and QoL.

Assessment of methodological quality

The risk of bias and applicability of the articles was graded by using the QUADAS-2 tool.(16) The answers to the signalling questions and the applicability to our research were discussed after which final appraisal was defined (FM, JB, RG).

Data extraction

Data on study design, demographics of the patients and the outcome parameters were extracted from the included articles. Data on children (<18 years old) were separately reported.

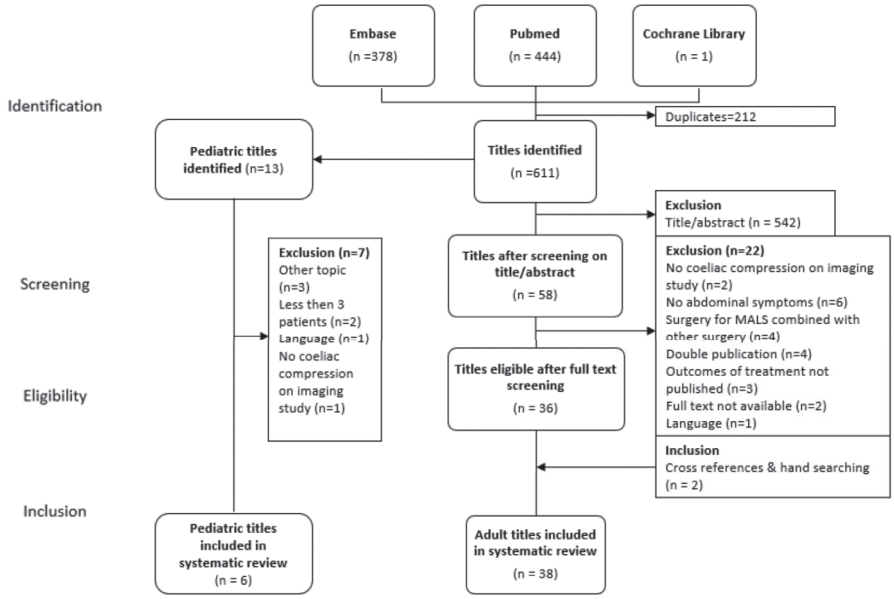
Results

Outcome of search and selection

A total of 611 papers were identified of which 58 papers including adults (>/=18 years old) and 13 papers including paediatric patients (<18 years old) were retrieved for full-text review.

Thirty-eight papers including adult patients and six papers including paediatric patients met our inclusion criteria and were ultimately selected for final critical appraisal (Figure 1).

Figure 1 Flowchart of search strategy for screening, eligibility and inclusion of included articles reporting treatment of Median Arcuate Ligament Syndrome



Study design and diagnostic criteria

Adult cohort

Thirty-eight studies describing adults were included in the systematic review describing the outcomes of 880 adult patients after treatment for MALS (Table 2).

Table 2 Study design and diagnostic criteria of systemic review of treatment of median arcuate ligament syndrome

Author	Year	Period of inclusion (years)	Study design	Follow-up (months)[1]	LTFU	Patients	Imaging Study	Abdominal symptoms >3 months	Multidisciplinary Diagnosis
Baccari (34)	**2009**	7	R	28		16	1 and 2 or 3	Y	N
Barbon (13)	**2021**	3	P			22	2	Y	N
Berard (28)	**2011**	6	R	35		11	2	Y, 3 months U	N
Berge (49)	**2020**	3	P	Median 18		12	2	Y, 3 months U	Y
Chaum (42)	**2021**	6	R			4	1 and 2 and 3	Y, 3 months U	N
Cienfuegos (19)	**2017**	12	R	Median 117		11	2 or 3 or 4	Y	Y

Coelho (56)	**2020**	5	P	3		6	1 or 3	Y	N
Columbo (30)	**2015**	13	R	Median 7		21	1 or 2 or 4	Y, 3 months U	N
De'Ath (48)	**2018**	11	P	Median 109		6	1 and 2 or 3 or 4	Y, 3 months U	N
Do (33)	**2013**	6	R			16	1 or 2 or 3 or 4	Y, 3 months U	N
Dunbar (9)	**1965**		R			13	4	Y, 3 months U	N
Evans (24)	**1974**		R			44	U	Y, 3 months U	N
Fernstrum (25)	**2020**	6	R	30	2	27	1 and 2	U	N
Geelkerken (18)	**1990**	12	R	228	3	10	4	Y	N
Grus (68)	**2018**	8	P	77		8	2	Y	N
Ho (17)	**2017**	15	R	Median 25	11	43	1 or 2 or 3 or 4	Y	N
Kafadar (35)	**2021**	5	R	6		10	2	Y	N
Khrucharoen (27)	**2020**	7	R	Median 16		41	1 or 2 or 3 or 4	Y, 3 months U	N
Kohn (36)	**2011**	10	R	49		6	U	Y, 3 months U	N
Marable (22)	**1968**	3	R		2	19	4	Y	N
Mihas (41)	**1977**		R			4	4	Y	N
Nguyen (37)	**2012**	4	R	Median 15		5	1 and 2	Y	N
Pather (29)	**2021**	19	R	96	54	100	1 or 2 or 3	Y	N
Reddy (26)	**2019**		R	15		3	1	Y	N
Reilly (38)	**1985**	17	R	108	7	51	4	Y, 3 months U	N
Rogers (21)	**1982**	26	R	58	1	7	4	Y, 3 months U	N
Roseborough (39)	**2009**	5	R	Median 44		15	2 or 4	Y	N
Sahm (46)	**2020**	2	P	5	9	18	1 and 2 or 3 or 4	Y	N
Skelly (47)	**2018**	6	P	18	44	95	1 and 2 or 3 or 4	Y, 3 months U	Y
Sultan (40)	**2013**	9	R	60		11	1 and 2	Y, 3 months U	N
Takach (45)	**1996**	15	R	44		7	4	Y, 3 months U	N
Terpstra (20)	**1966**		R	Median 12		5	4	Y	N
Thoolen (31)	**2015**	1	R	Median 6	1	9	1 and 2 or 3	Y, 3 months U	Y
Tulloch (32)	**2010**	10	R	14		14	1 or 2 or 3 or 4	Y	N
van Petersen (43)	**2017**	11	R	6		129	1 and 4	Y	Y
Vaziri (44)	**2008**		R	6		3	1 and 2 and 3	Y, 3 months U	N
Watson (23)	**1977**		R	Median 30	1	19	4	Y	N
Weber (14)	**2016**	7	R		14	39	1	Y, 3 months U	Y
Total			R: 31 P: 7	Range 30-228	149	880			

[1] displayed as mean, unless otherwise stated
Abbreviations: R=retrospective, P=prospective, U=Unknown ; N=No; Y=Yes
1=Duplex Ultrasound (DUS), 2=Computerized Tomographic Angiography (CTA) 3=Magnetic Resonance Angiography (CE-MRA), 4=Angiography
Y=Yes, N=No, U=Unspecified

In nine studies, not all of the reported adult patients (280 patients) met the inclusion criteria for the current review. Since the data were reported for every individual patient, the results of the 223 individual patients that did meet the criteria could be included in this systematic review.(13,17–24).

Eighty-two percent of the adult studies were retrospective cohort studies.(9,14,17–45) The mean and median follow-up ranged from 3 months up to 228 months. One hundred forty nine patients (16.9%) distributed over 12 studies were Lost to Follow Up (LTFU).(14,17,18,21–23,25,29,38,46,47)

In 18 adult studies, it was not clearly described whether patients had abdominal symptoms for at least three months (as determined in Table 1). The fact, however, that these patients received a comprehensive and time consuming evaluation and work-up makes it likely that symptoms were present for more than three months.(9,14,21,24,27,28,30,31,33,36,38,40,42,44,45,47–49) In one study, symptom relief after treatment suggested that patients were symptomatic although it was not clearly stated that patients indeed had abdominal symptoms at the time of inclusion.(25) Based on these considerations we included these studies in the present review. The main outcome parameters are also presented without the data of these 19 studies.

In one adult study, 1 out of 21 patients was a child of 16 years old(30) and in another study 2 out of 39 patients were children of 17 years old.(14) The data of these youngsters could not be separated from the other patients. Because of the low number (3 out of 60 patients, respectively 5%) and the fact that they were adolescents, both studies were included in the adults analysis of this systematic review.

In only 6 out of 38 adult studies (14,19,31,43,47,49), the diagnosis MALS was based on a consensus evaluation by a multidisciplinary team as recommended in the international guidelines.(10,11)

Paediatric cohort

Six studies describing 196 patients <18 years old were included in the systematic review (Table 3).(50–55) Thirty-three percent of these studies were retrospective cohort studies.(50,52) The follow-up in the paediatric cohort was between 6 and 62 months (Table 3). The diagnosis MALS was based on a consensus evaluation by a multidisciplinary team in 2 out of 6 studies(53,55), in one study(55) this team did not contain a radiologist as recommended in the international guidelines.(10,11)

Table 3 Characteristics and Outcomes of Pediatric Patients after Laparoscopic Median Arcuate Ligament Release

Author	Patients (n)	Follow-up (months)[1]	Age[1]	Asymptomatic[2] (n)	Improved symptoms[2] (n)	QoL preop[1]	QoL postop[1]
Aschenbach (50)	22		15	17 (77)	22 (100)		
Joyce (51)	6	13 (2-24)	16 (14-17)			CHQ-PF-50 Physical functioning 55 (20-90) Emotional 44 (6-83) Behavioral 59 (10-108) Physical 26 (3-59) Bodily Pain 10 (-6-26) Mental Health 42 (16-68) Self-Esteem 47 (29-66) General Health Perceptions 17 (2-33)	CHQ-PF-50 Physical Functioning 96 (68-104) Emotional 81 (49-113) Behavioral 83 (43-124) Physical 76 (37-115) Bodily Pain 57 (27-86) Mental Health 69 (48-89) Self-Esteem 76 (60-92) General Health Perceptions 48 (30-66)
Klimas (52)	58	Median 62	17	57 (98)			
Mak (53)	46	9	16 (16-17)		31 (67)	PedsQL 58	PedsQL 77
Moak (54)	31	22 (7-37)	17 (15-19)		19 (63)	Likert 4.5 (2.4-6.6)	Likert 5.3 (2.9-7.7)
Stiles-Shields (55)	32	6	15 (14-17)			PedsQL 64 (47-80)	PedsQL 74 (56-93)
Total	195	Range 6-62	Range 15-17	74 (93)	72 (73)		

[1] displayed as mean (95% Confidence Interval), or median with (Interquartile Range); [2] displayed as number with corresponding percentage (%)
Abbreviations: QoL=Quality of Life; Preop=Preoperative; Postop=Postoperative

QUADAS-2

Adult cohort

The QUADAS-2 appraisal of the articles including adult patients is shown in Table 4. Of note, 35/38 (92%) of the studies scored a high or unclear risk of bias for the majority of the items. There were zero studies with a low risk of bias for all items. The study by Thoolen et. al. scored a low risk of bias in all but one item, the index test, because they did not clearly define threshold values for the outcomes.(31) The study by van Petersen et. al.(43) scored

high on index test risk of bias and applicability because they solely reported symptom relief and no rates of asymptomatic patients. The study by Weber et. al. scored high on patient selection risk of bias because 14 out of 39 patients were LTFU.(14) They also scored high on index test risk of bias and applicability because they solely reported symptom relief and no rates of asymptomatic patients and they did not clearly define threshold values for the outcomes.

Table 4 QUADAS-2 Appraisal of articles included in systemic review of treatment of median arcuate ligament syndrome describing adult patients

		Risk of Bias				Applicability		
Author	**Year**	**Patient selection**	**Index test**	**Reference standard**	**Flow**	**Patient selection**	**Index test**	**Reference standard**
Baccari (34)	**2009**	Low	High	High	Low	High	Low	High
Barbon (13)	**2021**	High	High	High	Unclear	High	High	High
Berard (28)	**2012**	High	High	High	Unclear	High	High	High
Berge (49)	**2020**	High	High	Low	High	Low	High	Low
Chaum (42)	**2021**	Low	High	High	Unclear	High	High	High
Cienfuegos (19)	**2018**	High	High	High	Unclear	High	High	High
Coelho (56)	**2020**	Unclear	High	High	High	High	Low	High
Columbo (30)	**2015**	Low	High	High	Low	High	Low	High
De'Ath (48)	**2018**	Low	High	High	Low	High	Low	High
Do (33)	**2013**	Unclear	High	High	Unclear	High	Low	High
Dunbar (9)	**1965**	Low	High	High	Low	High	Low	High
Evans (24)	**1974**	Unclear	High	High	Unclear	High	Low	High
Fernstrum (25)	**2020**	Unclear	High	Unclear	High	High	High	High
Geelkerken (18)	**1990**	Low	High	High	Low	High	Low	High
Grus (68)	**2018**	Low	High	High	Low	High	Low	High
Ho (17)	**2017**	High	High	High	High	High	Low	High
Kafadar (35)	**2021**	Unclear	High	High	Unclear	High	Low	High
Khrucharoen (27)	**2020**	Unclear	High	High	High	High	Low	High
Kohn (36)	**2011**	Unclear	High	High	Unclear	High	Low	High
Marable (22)	**1968**	Low	High	High	Low	High	Low	High
Mihas (41)	**1977**	Unclear	High	High	Unclear	High	High	High
Nguyen (37)	**2012**	Unclear	High	High	Unclear	High	Low	High
Pather (29)	**2021**	High	High	High	High	High	Low	High
Reddy (26)	**2019**	Unclear	High	High	Unclear	Low	Low	High
Reilly (38)	**1985**	High	High	High	High	High	Low	High
Rogers (21)	**1982**	Low	High	High	Low	High	High	High
Roseborough (39)	**2009**	Unclear	High	High	Unclear	High	High	High
Sahm (46)	**2020**	Unclear	High	High	Unclear	High	Low	High
Skelly (47)	**2018**	High	High	Low	High	High	Low	Low
Sultan (40)	**2013**	Low	High	High	Low	High	Low	High
Takach (45)	**1996**	Unclear	High	High	Unclear	High	Low	High
Terpstra (20)	**1966**	Unclear	High	High	High	High	Low	High

		Risk of Bias				Applicability		
Author	**Year**	**Patient selection**	**Index test**	**Reference standard**	**Flow**	**Patient selection**	**Index test**	**Reference standard**
Thoolen (31)	**2015**	Low	High	Low	Low	Low	Low	Low
Tulloch (32)	**2010**	Low	High	High	Low	High	Low	High
van Petersen (43)	**2017**	Low	High	Low	Low	Low	High	Low
Vaziri (44)	**2008**	Low	High	High	Low	High	Low	High
Watson (23)	**1977**	Unclear	High	High	Unclear	High	Low	High
Weber (14)	**2016**	High	High	Low	Low	Low	High	Low

Paediatric cohort

In the paediatric cohort, five out of the six studies (83%) scored a high or unclear risk of bias for the majority of the items of the QUADAS-2 appraisal (Table 5). The sixth study scored a high on patient selection risk of bias because 28 patients were LTFU in the QoL assessment, they scored high on index test risk of bias and applicability because they solely reported symptom relief and no rates of asymptomatic patients and they did not clearly define threshold values for the outcomes.(53)

Table 5 QUADAS-2 Appraisal of articles included in systemic review of treatment of median arcuate ligament syndrome describing pediatric patients

		Risk of Bias				Applicability		
Author	**Year**	**Patient selection**	**Index test**	**Reference standard**	**Flow**	**Patient selection**	**Index test**	**Reference standard**
Aschenbach (50)	**2011**	High	High	High	High	High	High	High
Joyce (51)	**2014**	Low	High	High	Low	High	High	High
Klimas (52)	**2015**	Low	High	High	Low	High	High	High
Mak (53)	**2013**	High	High	Low	Low	Low	High	Low
Moak (54)	**2021**	Low	High	High	High	High	High	High
Stiles-Shields (55)	**2018**	High	High	Low	High	High	High	Low

Patient characteristics

Adult cohort

The mean and median age of the adult patients were in the range of 30-61 and 73% were female (Table 6). The duration of symptoms was published in twelve studies with a mean or median varying between 12 and 120 months. Thirteen adult studies reported BMI from which the mean or median ranged between 18 and 27. CA release was performed in 851 adult patients (97%) and the remaining 29 patients (3%) underwent a bypass, percutaneous mesenteric artery stenting procedure of the CA, plexus blockage or other operation on the coeliac artery.

Table 6 Patient demographics of adult patients before treatment for median arcuate ligament syndrome

Author	Female[1]	Age[2]	Duration symptoms[2] (months)	BMI[2]	Treatment	Additional procedure
Baccari (34)	11 (69%)	54	12	21	1	
Barbon (13)					4	
Berard (28)	9 (82%)	Median 52	Median 41	20	1: n=10 2: n=1	1
Berge (49)	8 (67%)	46		21	1	
Chaum (42)	4 (100%)	Median 30			1	2
Cienfuegos (19)	10 (91%)	Median 34		21	1	
Coelho (56)	4 (67%)	43			1	
Columbo (30)	16 (76%)	Median 42		20	1	
De'Ath (48)	5 (83)	Median 30		Median 18	1	0
Do (33)	10 (63%)		Median 16		1	
Dunbar (9)	12 (92%)	34.5	Median 12		1	
Evans (24)					1	
Fernstrum (25)	18 (67%)	49	57	27	1	
Geelkerken (18)		Median 47	24		1	
Grus (68)	5 (63%)	61		21	1	8
Ho (17)	33 (77%)	36			1	1
Kafadar (35)	6 (60%)	42			1	
Khrucharoen (27)	37 (77%)	Median 41		Median 21	1	
Kohn (36)	3 (50%)	38			1	
Marable (22)	18 (95%)	Median 37	Median 120		1	
Mihas (41)	4 (100%)	48			2: n=2, 5: n=2	
Nguyen (37)		Median 29	26		1	
Pather (29)	75 (75%)	38		23	1	25
Reddy (26)	2 (67%)	39			1	
Reilly (38)	39 (76%)	47	Median 12		1	18
Rogers (21)	6 (86%)	44			1	
Roseborough (39)	13 (87%)	Median 41			1	3
Sahm (46)	9 (50%)	39	34	22	1: n=16x, 2: n=3	
Skelly (47)	41 (80%)	31	69		1	
Sultan (40)	10 (91%)	50			1	3
Takach (45)	3 (43%)	65			1	5
Terpstra (20)	4 (80%)	Median 48			1	
Thoolen (31)	6 (67%)	46	Median 12	Median 22	1	
Tulloch (32)	12 (86%)	45			1	0
van Petersen (43)	106 (82%)	35			1	
Vaziri (44)	3 (100%)	44			1	
Watson (23)	11 (58%)	Median 41			1	
Weber (14)	33 (85%)	41		25	1	1
Total	568 (73%)	Range 30-61	Range 12-120	Range 18-27	1: n=851 2: n=3 3: n=2 4: n=22 5: n=2	67

[1] displayed as number with corresponding percentage (%); [2] displayed as mean (95% Confidence Interval), or median with (Interquartile Range)
Abbreviations:1= Median Arcuate Ligament Release, 2=Bypass, 3=Percutaneous Transluminal Angioplasty, 4=Plexus block 5=Other operation coeliac artery

Paediatric cohort

In the paediatric cohort the mean and median age were in the range of 15-17 (Table 3). All patients in the paediatric cohort underwent a laparoscopic MAL release (Table 3).

Main outcomes

Adult cohort

The main outcome parameters symptom relief and QoL after treatment of the articles including adult patients are reported in Table 7. Outcomes were not uniformly defined and reported. The number of patients with symptom relief was reported in 35 of the 38 adult studies. In these 35 studies 468 of 690 patients (68%) were either free of symptoms (n=294) or reported a clear reduction of symptoms after surgical CA release (n=174). Without the 19 studies with an unspecified duration of abdominal symptoms or with unspecified symptoms included, symptom relief was reported in 258 of 372 adult patients (69%).

Only one prospective adult study about plexus blockage met the inclusion criteria. This study showed symptom relief in 19 out of 22 patients (88%).(13)

Five adult studies reported on QoL after treatment measured by three different QoL instruments. The study by Skelly et al. was the only study comparing preoperative QoL to postoperative QoL showing a statistically significant improvement in QoL from 68 to of 80.3 ($P<0.01$) on a VAS (Visual Analogue Scale 0-100).(47) Berge et al.(49) reported on QoL only in patients who had symptom relief after surgery for MALS.(49) VAS scores of these 9 patients improved from 44 preoperatively to 62 postoperatively. In the EQ-5D-5L, four of the five dimensions improved (mobility, usual activities, pain/discomfort, and anxiety/depression). The study by Ho et. al. showed a numerical difference in the SF-12 (Short Form Health Survey) between surgically and conservatively treated MALS patients.(17) Comparing outcome of the physical and mental domain, the surgical group did better with -5 (95% CI -17-10) versus -9 (95% CI -22-4) and 1 (95% CI -6-8) versus -9 (95%CI -19-2), respectively. A fourth study by Pather et. al. showed a significantly higher mean Gastrointestinal Quality of Life Index (GIQLI) of 80 (95% CI 3-97) in patients in whom the symptoms had disappeared compared to 53 (95% CI 38-68) in patients with persisting symptoms up to eight years after surgery for MALS ($P<0.001$).(29) The fifth study by De'Ath et al. reported postoperative QoL scores only.(48)

Table 7 Main outcomes of adult patients after treatment for median arcuate ligament syndrome

Author	Asymptomatic[1] (n)	Improved symptoms[1] (n)	QoL preoperative or conservative[2]	QoL postoperative[2]
Baccari (34)	16 (100)			
Barbon (13)		19 (88)		
Berard (28)	8 (73)			
Berge (49)	7 (58)		VAS 44	VAS 62
Chaum (42)		3 (75)		
Cienfuegos (19)				
Coelho (56)	6 (100)			
Columbo (30)	18 (81)			
De'Ath (48)	6 (100)			GLIQLI 129
Do (33)	10 (63)			
Dunbar (9)		13 (100)		
Evans (24)	18 (41)			
Fernstrum (25)	17 (68)			
Geelkerken (18)	0			
Grus (68)	8 (100)			
Ho (17)	16 (37)		Conservative SF 12: Physical -9 (-22–4); Mental -9 (-19-2)	SF12: Physical -4.9 (-17-7) Mental 1 (-6-8)
Kafadar (35)	10 (100)			
Khrucharoen (27)	18 (44)			
Kohn (36)	6 (83)			
Marable (22)	13 (7)			
Mihas (41)	0			
Nguyen (37)	5 (100)			
Pather (29)	30 (65)			GLIQLI 71 (51-91)
Reddy (26)	3 (100)			
Reilly (38)	30 (68)			
Rogers (21)	2 (29)			
Roseborough (39)		14 (93)		
Sahm (46)				
Skelly (47)			68 (53-82)	80.3 (67-94)
Sultan (40)	8 (73)			
Takach (45)	7 (100)			
Terpstra (20)	3 (60)			
Thoolen (31)	4 (44)			
Tulloch (32)	9 (57)			
van Petersen (43)		92 (71)		
Vaziri (44)	2 (67)			
Watson (23)	14 (78)			
Weber (14)		33 (85)		
Total	294 (63)	174 (78)		

[1] displayed as number with corresponding percentage (%); [2] displayed as mean (95% Confidence Interval), or median with (Interquartile Range)

Paediatric cohort

In the paediatric cohort, symptom relief was reported in five out of six studies (n=178) (Table 3). 146 out of 178 patients (82%) were either free of symptoms (n=72) or reported a clear reduction of symptoms after surgical laparoscopic CA release (n=74). There were no pediatric studies reporting results of other treatment strategies.

Four pediatric studies reported an improved QoL after treatment. (Table 3). The study by Joyce et al. measured QoL on the Children Health Questionnaire – Parent Form 50 (CHQ-PF-50) reporting QoL in 7 domains reported by children and parents.(51) The children reported a significantly improved score in Physical Functioning from 55 (20-90) to 96 (68-104) (p=0.03), Mental Health from 42 (16-68) to 69 (48-89) (p=0.03) and Self Esteem from 47 (29-66) to 76 (60-92) (p=0.03). The study by Mak et al. reported a significantly improved paediatric quality of life inventory (PedsQL) from 58 to 77 ($P<0.01$).(53) The study by Moak et al. reported self-assessed QoL on a Likert scale from 1 to 10, the QoL improved from 4.5 (2.4-6.6) to 5.3 (2.9-7.7).(54) Stiles-Shields et al. reported a significantly improved PedsQL from 64 (47-80) to 74 (56-93) (p=0.004).(55)

Secondary Outcomes

Adult cohort

A variety of secondary clinical outcome parameters have been reported in adult patients (Table 8). One study did report return to work or school in 14 out of 19 (74%) patients(30) and one study reported a return to exercise in 3 out of 5 (60%) patients.(37) Five studies reported use of analgesics preoperatively in 42 out of 72 patients (58%) that was reduced to 16 out of 70 (23%) after surgery (2 patients were LTFU).(19,32,33,42) Nineteen studies (with a total of 707 patients) published on procedures performed during follow-up such as PTA or bypass performed in 93 out of 707 patients (13%).(14,17,19,23–25,27–34,38,39,43,45,47,48)

Loss of productivity and disability adjusted life years or burden of disease was not reported. Interestingly, Pather et. al. reported that preoperative symptoms severely restricted daily life activities for a median of 12 months (IQR 6-24) in 100 patients, indicating the burden of disease.(29)

Twenty-one adult studies (including 512 patients) reported complications in 60 patients (12%), the most common was intraoperative bleeding in 24 patients (41%).(14,17,19,23,25,27,29,31–35,39,40,44–48,56,57) The 'in hospital' and '30 days postoperative' mortality was zero, as reported in 21 studies totalling 368 patients.(13,14,20,21,23,26,27,29,30,32,33,35,39–

41,44,45,48,56–58) In the study by Rogers et. al. one patient died 2 months after MAL release, post-mortem examination failed to reveal the cause of death. Pre- or postoperative psychiatric diagnosis were reported by 9 studies, preoperative psychiatric diagnosis in 59 out of 299 patients (20%) and postoperative psychiatric diagnosis in 32 out of 164 patients (20%).(17,21,29,30,33,35,38,39,47)

The anatomical outcomes of surgical CA release of articles including adult patients are shown in Table 9. The adequacy of the CA release was determined with Doppler ultrasound in eight studies by reporting PSV values before and after surgery.(14,29,36,40,44,46,47,49) Two studies published preoperative and postoperative inspiratory and expiratory PSV,(29,46) one study only inspiratory values(47) one study only expiratory values(44), and in four studies this was not exemplified.(14,36,40,49) In nine studies including 274 patients, postintervention CA patency was determined with Duplex, CTA or MRA.(14,34,35,38,43,56–59) In 212 patients (77%) a patent CA was established.

Table 8 Secondary outcomes of adult patients after treatment for median arcuate ligament syndrome

Author	Narcotics preop[1] (n)	Narcotics postop[1] (n)	Mortality (n)	Complications (n)	Postop adjunct procedure[1] (n)	Psychiatric diagnosis preop[1] (n)	Psychiatric diagnosis postop[1] (n)
Baccari (34)				2 bleeding	2 (13)		
Barbon (13)			0				
Berard (28)			0		1 (9)		
Berge (49)							
Chaum (42)	4 (100)	3 (75)					
Cienfuegos (19)	1 (9)	0		1 chylus, 1 delayed gastric emptying	1 (9)		
Coelho (56)			0	1			
Columbo (30)			0		7 (33)		12 (57)
De'Ath (48)			0	0	0		
Do (33)	7 (44)	5 (31)	0	0	2 (13)		5 (42)
Dunbar (9)							
Evans (24)					1 (3)		
Fernstrum (25)	16 (59)	7 (28)		1	3 (11)		
Geelkerken (18)							
Grus (68)			0	1 subcutanous fistula			
Ho (17)				1 bleeding	1 (2)	2 (5)	
Kafadar (35)			0	1 lungembolism, 1 ileus		0	0
Khrucharoen (27)			0	0	7 (17)		

Author	Narcotics preop[1] (n)	Narcotics postop[1] (n)	Mortality (n)	Complications (n)	Postop adjunct procedure[1] (n)	Psychiatric diagnosis preop[1] (n)	Psychiatric diagnosis postop[1] (n)
Kohn (36)							
Marable (22)							
Mihas (41)			0				
Nguyen (37)							
Pather (29)			0	8 bleeding, 1 myocardial infection, 2 pancreatitis, 4 respiratory failure, 8 ileus, 7 wound infection	11 (11)	37 (37)	
Reddy (26)			0				
Reilly (38)					4 (8)	6 (12)	
Rogers (21)			1				2 (29)
Roseborough (39)			0	4 intraoperative bleeding, 1 Pancreatitis	6 (40)		0
Sahm (46)				2 bleeding, 1 retrogastric abcess			
Skelly (47)				1 bleeding	14 (15)	14 (28)	13 (26)
Sultan (40)			0	1 Renal failure and chest infection			
Takach (45)			0	0			
Terpstra (20)			0				
Thoolen (31)				1 diarrea, 2 constipation	0		
Tulloch (32)	14 (100)	1 (7)	0	2 bleeding	4 (29)		
van Petersen (43)					28 (22)		
Vaziri (44)			0	0			
Watson (23)			0	1 hematothorax	1 (5)		
Weber (14)			0	4 bleeding	0		
Total	42 (58)	16 (23)	0	60	93 (13)	59 (20)	32 (20)

[1] displayed as number with corresponding percentage (%); [2] displayed as mean (95% Confidence Interval), or median with (Interquartile Range)

Table 9 Anatomical outcomes of adult patients after treatment for median arcuate ligament syndrome

Author	PSV* preop[2] (inspiratory)	PSV* preop[2] (expiratory)	PSV* preop[2] (unspecified)	PSV* postop[2] (inspiratory)	PSV* postop[2] (expiratory)	PSV* postop[2] (unspecified)	Postop Imaging Patency[1]
Baccari (34)							14 (93)
Barbon (13)							
Berard (28)							9 (82)
Berge (49)			180 (95-270)			170 (150-185)	
Chaum (42)							3 (67)
Cienfuegos (19)							
Coelho (56)							6 (100)
Columbo (30)							
De'Ath (48)			Median 230 (210-288)				
Do (33)			Median 387 (264-449)				
Dunbar (9)							
Evans (24)							
Fernstrum (25)							
Geelkerken (18)							
Grus (68)							8 (100)
Ho (17)							
Kafadar (35)							10 (100)
Khrucharoen (27)	Median 242 (150-248)	Median 399 (189-437)					
Kohn (36)			Median 489 (416-522)			Median 166 (158-174)	
Marable (22)							
Mihas (41)							
Nguyen (37)							
Pather (29)	214 (129-299)	292 (177-407)		183 (121-245)	203 (141-265)		
Reddy (26)							
Reilly (38)							19 (68)
Rogers (21)							
Roseborough (39)							
Sahm (46)	199 (88-310)	286 (162-410)		151 (109-192)	178 (126-232)		
Skelly (47)	381			227			
Sultan (40)			390 (309-471)			275 (151-399)	
Takach (45)							
Terpstra (20)							
Thoolen (31)			Median 324				
Tulloch (32)							
van Petersen (43)							120 (93)
Vaziri (44)		370			164		
Watson (23)							
Weber (14)			370			216	23 (77)
Total							212 (77)

[1] displayed as number with corresponding percentage (%); [2] displayed as mean (95% Confidence Interval), or median with (Interquartile Range)
***PSV = Peak Systolic Value in (cm/sec)**

Paediatric cohort

The secondary outcomes were not collected for the paediatric cohort.

Discussion

In conclusion, this systematic review including thirty-eight studies describing the outcomes of 880 adult patients and six studies describing the outcomes of 196 paediatric patients suggests a sustainable symptom relief of 68% in adult patients from 3 months up to 228 months after treatment for MALS and 82% in paediatric patients from 6 months up to 62 months after treatment for MALS. CA release can be performed safely with a very low complication rate and nearly zero chance of mortality. Only one study, including 22 adult patients, reported a symptom relief of 88% after coeliac plexus blockage.(13) Two adult studies compared QoL before and after surgical treatment for MALS and both showed an improved QoL after treatment. Four paediatric studies compared QoL before and after laparoscopic MAL release showed an improved QoL after treatment.

These results must be interpreted with caution, because none of the articles included in the present review was of sufficient quality to meet the criteria for 'low risk' score according to the QUADAS-2 tool. Most importantly, in the majority of studies outcome parameters were ill defined and not uniformly defined and/or presented, with risk for confounding and selection bias. The consequence is that a formal meta-analysis on the efficacy of the treatment for MALS is not feasible and therefore only a descriptive systematic review on the main outcome parameters is appropriate.

The sustainable relief of symptoms after CA release of 68% in adult MALS patients is substantial higher than an expected placebo effect of 30%.(60–64) This percentage in the present review is about 10% lower than the symptom relief that was reported by Jimenez et al. in 2012.(1) The most obvious explanation for this lower symptom relief is our longer follow-up period of 3 months up to 228 months compared to the short-term symptom relief that was measured by Jimenez et. al. A second argument for the lower symptom relief in the present review could be a more stringent selection. Our systematic review included only studies if patients had external compression of the celiac artery by the MAL on imaging studies and abdominal symptoms (for more than three months) whereas Jimenez included all studies that presented outcomes after surgical treatment for MALS. A third explanation for the difference in main outcome parameter could be the inclusion of additional patients: our systematic review included forty-four studies including adult and pediatric patients (in total 1096 patients), seventeen studies (266 patients) that were also included in the study by Jimenez and twenty-seven new studies (830 patients).

This systematic review included a separate analysis of pediatric studies showing a sustainable symptom relief of 82% after laparoscopic MAL release. Jimenez et al. did include pediatric studies but those results were not separately reported. The present review underlined that MALS below the age of 12 years is very rare, supporting the hypothesis that compression of the coeliac artery arises during puberty as the thorax/abdominal ratio increases.

Two prospective cohort studies provide convincing arguments that the abdominal symptoms of MALS have an ischemic and not a neurogenic origin with improvement of validated mesenteric mucosal perfusion tests after successful CA release.(49,65) Moreover, in a study amongst 129 patients, 91 patients (71%) experienced a relief of symptoms irrespective of the fact that the coeliac plexus had been left untouched during surgery.(43) The present systematic review undermines the half century old statement of Szilagy(12) that 'no patient had ever been proven, on scientific grounds, to have an abnormality of intestinal structure or function which was caused by extraluminal compression of the coeliac artery, or supposed relief from the operation could be anything other than a placebo effect'. The present review supports both guideline committees, acknowledging that MALS exists as disease entity, but that studies of sufficient scientific quality are lacking to recommend specific treatments.(10,11) To facilitate the development of evidence-based guidelines for the management of MALS, both guideline committees recommend to perform a blinded, randomised controlled trial comparing a CA release with a sham operation. A systemic review reconsidering the ethics of sham interventions concluded that sham interventions are acceptable, provided the pre-conditions of scientific necessity, reasonable risks, and valid informed consent are fulfilled.(66) The suggestion of a randomized placebo-controlled patient and observer blinded clinical superiority trial in suspected MALS patients will give the irrefutable answer needed by patients and clinicians. Included patients should fulfil the chronic mesenteric ischemia criteria(67) and be treated with either surgical CA release or a sham operation. Besides analysing anatomical and clinical success, the outcome parameters should represent QoL, psychiatric disorders and societal burden of disease. If these criteria are met, the Szilagyi debate may finally be settled and it will either underline the usefulness of surgical CA release as a (cost)effective treatment for MALS or it will prevent patients with disabling abdominal complaints from undergoing an ineffective intervention.

Appendix 1:

Pubmed search: 444

(Median Arcuate Ligament Syndrome [mesh] OR "Median Arcuate Ligament" [tiab] OR MALS [tiab] OR ((celiac [tiab] OR coeliac [tiab]) AND compression [tiab]) OR (dunbar [tiab] AND syndrome [tiab])) AND (Decompression, surgical [mesh] OR Celiac artery / surgery [mesh] OR Ligaments / surgery [mesh] OR Surgical Procedures, Operative [mesh] OR Decompression [tiab] OR Release [tiab] OR plexus block [tiab] OR Celiac Sympathectomy [tiab] OR Endoscopic CA release [tiab] OR eCAR [tiab])

Cochraine search: 1

ID	Search
#1	("Median Arcuate Ligament" OR MALS OR ((celiac OR coeliac) AND compression) OR (dunbar AND syndrome)):ti,ab,kw
#2	MeSH descriptor: [Median Arcuate Ligament Syndrome] explode all trees
#3	#1 OR #2
#4	(Decompression OR Release OR plexus block OR Celiac sympathectomy OR eCAR):ti,ab,kw
#5	MeSH descriptor: [Decompression, Surgical] explode all trees
#6	MeSH descriptor: [Celiac Artery] explode all trees
#7	MeSH descriptor: [Ligaments] explode all trees
#8	MeSH descriptor: [Surgical Procedures, Operative] explode all trees
#9	#5 OR #6 OR #7 OR #8
#10	#5 OR #8
#11	#3 AND #9
#12	#3 AND #10

Embase search: 378

(median:ti,ab,kw AND arcuate:ti,ab,kw AND ('ligament'/exp OR ligament:ti,ab,kw) OR mals:ti,ab,kw OR (c?eliac:ti,ab,kw AND (compression:ti,ab,kw OR 'compression'/exp)) OR (dunbar:ti,ab,kw AND (syndrome:ti,ab,kw OR 'syndrome'/exp))) AND ('decompression surgery'/exp OR 'celiac artery'/exp/dm_su OR 'ligament'/exp/dm_su OR 'surgery'/exp OR 'surgery':ti,ab,kw OR 'nerve block'/exp OR (nerve:ti,ab,kw AND block:ti,ab,kw) OR 'celiac plexus'/exp OR (celiac:ti,ab,kw AND plexus:ti,ab,kw) OR decompression:ab,ti,kw OR release:ab,ti,kw OR (celiac:ab,ti,kw AND sympathectomy:ab,ti,kw) OR ecar OR (plexus:ab,ti,kw AND block:ab,ti,kw)) AND [embase]/lim NOT [conference abstract*]/lim*

References

1. Jimenez JC, Harlander-Locke M, Dutson EP. Open and laparoscopic treatment of median arcuate ligament syndrome. J Vasc Surg [Internet]. 2012 Sep;56(3):869–73. Available from: http://dx.doi.org/10.1016/j.jvs.2012.04.057
2. Lipshutz B. A composite study of the hypogastric artery and its branches. Ann Surg [Internet]. 1918 May;67(5):584–608. Available from: http://journals.lww.com/00000658-191805000-00012
3. Park CM, Chung JW, Kim HB, Shin SJ, Park JH. Celiac Axis Stenosis: Incidence and Etiologies in Asymptomatic Individuals. Korean J Radiol [Internet]. 2001;2(1):8. Available from: https://www.kjronline.org/DOIx.php?id=10.3348/kjr.2001.2.1.8
4. Kazan V, Qu W, Al-Natour M, Abbas J, Nazzal M. Celiac artery compression syndrome: a radiological finding without clinical symptoms? Vascular [Internet]. 2013 Oct 13;21(5):293–9. Available from: http://journals.sagepub.com/doi/10.1177/1708538113478750
5. Soman S, Sudhakar SV, Keshava SN. Celiac axis compression by median arcuate ligament on computed tomography among asymptomatic persons. Indian J Gastroenterol [Internet]. 2010 May 25;29(3):121–3. Available from: http://link.springer.com/10.1007/s12664-010-0028-x
6. Petnys A, Puech-Leão P, Zerati AE, Ritti-Dias RM, Nahas WC, Neto ED, et al. Prevalence of signs of celiac axis compression by the median arcuate ligament on computed tomography angiography in asymptomatic patients. J Vasc Surg [Internet]. 2018 Dec;68(6):1782–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0741521418310255
7. Terlouw LG, Verbeten M, van Noord D, Brusse-Keizer M, Beumer RR, Geelkerken RH, et al. The Incidence of Chronic Mesenteric Ischemia in the Well-Defined Region of a Dutch Mesenteric Ischemia Expert Center. Clin Transl Gastroenterol [Internet]. 2020 Aug;11(8):e00200. Available from: https://journals.lww.com/10.14309/ctg.0000000000000200
8. Reuter SR, Bernstein EF. The anatomic basis for respiratory variation in median arcuate ligament compression of the celiac artery. Surgery [Internet]. 1973 Mar;73(3):381–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4687796
9. Dunbar J. DAVID, Molnar W, Beman FF, Marable SA. Compression of the celiac trunk and abdominal angina. Am J Roentgenol [Internet]. 1965 Nov;95(3):731–44. Available from: http://www.ajronline.org/doi/10.2214/ajr.95.3.731
10. Björck M, Koelemay M, Acosta S, Bastos Goncalves F, Kölbel T, Kolkman JJ, et al. Editor□s Choice □ Management of the Diseases of Mesenteric Arteries and Veins. Eur J Vasc Endovasc Surg [Internet]. 2017 Apr 1;53(4):460–510. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1078588417300588
11. Terlouw LG, Moelker A, Abrahamsen J, Acosta S, Bakker OJ, Baumgartner I, et al. European guidelines on chronic mesenteric ischaemia – joint United European Gastroenterology, European Association for Gastroenterology, Endoscopy and Nutrition, European Society of Gastrointestinal and Abdominal Radiology, Netherlands Association of Hepa. United Eur Gastroenterol J [Internet]. 2020 May;8(4):371–95. Available from: https://onlinelibrary.wiley.com/doi/10.1177/2050640620916681
12. Szilagyi DE, Rian RL, Elliott JP, Smith RF. The celiac artery compression syndrome: Does it exist? Surgery. 1972;72(6):849–63.
13. Barbon DA, Hsu R, Noga J, Lazzara B, Miller T, Stainken BF. Clinical Response to Celiac Plexus Block Confirms the Neurogenic Etiology of Median Arcuate Ligament Syndrome. J Vasc Interv Radiol [Internet]. 2021 Jul;32(7):1081–7. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2012120595&from=export

14. Weber JM, Boules M, Fong K, Abraham B, Bena J, El-Hayek K, et al. Median Arcuate Ligament Syndrome Is Not a Vascular Disease. Ann Vasc Surg [Internet]. 2016 Jan;30:22–7. Available from: http://dx.doi.org/10.1016/j.avsg.2015.07.013

15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ [Internet]. 2021 Mar 29;372:n71. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.n71

16. Whiting PF. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Ann Intern Med [Internet]. 2011 Oct 18;155(8):529. Available from: http://annals.org/article.aspx?doi=10.7326/0003-4819-155-8-201110180-00009

17. Ho KKF, Walker P, Smithers BM, Foster W, Nathanson L, O'Rourke N, et al. Outcome predictors in median arcuate ligament syndrome. J Vasc Surg [Internet]. 2017 Jun;65(6):1745–52. Available from: https://pubmed.ncbi.nlm.nih.gov/28189355/

18. Geelkerken RH, van Bockel JH, De Roos WK, Hermans J. Coeliac artery compression syndrome: The effect of decompression. Br J Surg [Internet]. 2005 Dec 8;77(7):807–9. Available from: https://pubmed.ncbi.nlm.nih.gov/2383757/

19. Cienfuegos JA, Estevez MG, Ruiz-Canela M, Pardo F, Diez-Caballero A, Vivas I, et al. Laparoscopic Treatment of Median Arcuate Ligament Syndrome: Analysis of Long-Term Outcomes and Predictive Factors. J Gastrointest Surg [Internet]. 2018 Apr 28;22(4):713–21. Available from: http://link.springer.com/10.1007/s11605-017-3635-3

20. Terpstra JL. Intestinal angina secondary to compression of the coeliac axis. Arch Chir Neerl [Internet]. 1966;18(4):245–53. Available from: https://pubmed.ncbi.nlm.nih.gov/5971511/

21. Rogers DM, Thompson JE, Garrett WILSON V., Talkington, Patman RD. Mesenteric Vascular Problems. Ann Surg [Internet]. 1982 May;195(5):554–65. Available from: https://pubmed.ncbi.nlm.nih.gov/7073353/

22. Marable SA, Kaplan MF, Beman FM, Molnar W. Celiac compression syndrome. Am J Surg [Internet]. 1968 Jan;115(1):97–102. Available from: https://pubmed.ncbi.nlm.nih.gov/5634682/

23. Watson WC. Celiac Axis Compression. Ann Intern Med [Internet]. 1977 Mar 1;86(3):278. Available from: https://pubmed.ncbi.nlm.nih.gov/842985/

24. Evans WE. Long-term evaluation of the celiac band syndrome. Surgery. 1974;76(6).

25. Fernstrum C, Pryor M, GP W, AM W. Robotic Surgery for Median Arcuate Ligament Syndrome. JSLS J Soc Laparoendosc Surg [Internet]. 2020;24(2). Available from: https://pubmed.ncbi.nlm.nih.gov/32518479/

26. Reddy EV, Shroff G, Reddy VB, Somayajulu AVP. Laparoscopic Management of Median Arcuate Ligament Syndrome: Single Center Experience. World J Laparosc Surg with DVD [Internet]. 2019 Apr 1;12(1):39–42. Available from: https://www.wjols.com/doi/10.5005/jp-journals-10033-1358

27. Khrucharoen U, YY J, Sanaiha Y, JP F, JC J, EP D. Factors Associated with Symptomology of Celiac Artery Compression and Outcomes following Median Arcuate Ligament Release. Ann Vasc Surg [Internet]. 2020;62:248–57. Available from: https://pubmed.ncbi.nlm.nih.gov/31449931/

28. Berard X, Cau J, Déglise S, Trombert D, Saint-Lebes B, Midy D, et al. Laparoscopic Surgery for Coeliac Artery Compression Syndrome: Current Management and Technical Aspects. Eur J Vasc Endovasc Surg [Internet]. 2012 Jan;43(1):38–42. Available from: https://pubmed.ncbi.nlm.nih.gov/22001148/

29. Pather K, Kärkkäinen JM, Tenorio ER, Bower TC, Kalra M, DeMartino R, et al. Long-term symptom improvement and health-related quality of life after operative management of median arcuate ligament syndrome. J Vasc Surg [Internet]. 2021;73(6):2050-2058.e4. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2011342109&from=export

30. Columbo JA, Trus T, Nolan B, Goodney P, Rzucidlo E, Powell R, et al. Contemporary management of median arcuate ligament syndrome provides early symptom improvement. J Vasc Surg [Internet]. 2015 Jul;62(1):151–6. Available from: http://dx.doi.org/10.1016/j.jvs.2015.01.050

31. Thoolen SJJ, van der Vliet WJ, Kent TS, Callery MP, Dib MJ, Hamdan A, et al. Technique and outcomes of robot-assisted median arcuate ligament release for celiac artery compression syndrome. J Vasc Surg [Internet]. 2015 May;61(5):1278–84. Available from: http://dx.doi.org/10.1016/j.jvs.2014.10.084

32. Tulloch AW, Jimenez JC, Lawrence PF, Dutson EP, Moore WS, Rigberg DA, et al. Laparoscopic versus open celiac ganglionectomy in patients with median arcuate ligament syndrome. J Vasc Surg [Internet]. 2010 Nov;52(5):1283–9. Available from: https://pubmed.ncbi.nlm.nih.gov/20630683/

33. Do M V., Smith TA, Bazan HA, Sternbergh WC, Abbas AE, Richardson WS. Laparoscopic versus robot-assisted surgery for median arcuate ligament syndrome. Surg Endosc [Internet]. 2013 Nov 12;27(11):4060–6. Available from: https://pubmed.ncbi.nlm.nih.gov/23846363/

34. Baccari P, Civilini E, Dordoni L, Melissano G, Nicoletti R, Chiesa R. Celiac artery compression syndrome managed by laparoscopy. J Vasc Surg [Internet]. 2009;50(1):134–9. Available from: https://pubmed.ncbi.nlm.nih.gov/19563961/

35. Kafadar M, Oguz A, Aday U, Bilge H, Basol Ö. Median arcuate ligament (Dunbar) syndrome: Laparoscopic management and clinical outcomes of a single centre. J Minim Access Surg [Internet]. 2021;17(3):363–8. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L635425161&from=export

36. Kohn GP, Bitar RS, Farber MA, Marston WA, Overby DW, Farrell TM. Treatment Options and Outcomes for Celiac Artery Compression Syndrome. Surg Innov [Internet]. 2011 Dec 16;18(4):338–43. Available from: https://pubmed.ncbi.nlm.nih.gov/21330306/

37. Nguyen T, Neale M, Lane R, Schiavone V, JS S, TJ H. Laparoscopic management of the median arcuate ligament syndrome. ANZ J Surg [Internet]. 2012;82(4):265–8. Available from: https://pubmed.ncbi.nlm.nih.gov/22510185/

38. Reilly, LM, Ammar A, Stoney R, Ehrenfeld W. Late results following operative repair for celiac artery compression syndrome. J Vasc Surg [Internet]. 1985;2(1):79–91. Available from: https://pubmed.ncbi.nlm.nih.gov/3965762/

39. Roseborough GS. Laparoscopic management of celiac artery compression syndrome. J Vasc Surg [Internet]. 2009 Jul;50(1):124–33. Available from: https://pubmed.ncbi.nlm.nih.gov/19563960/

40. Sultan S, Hynes N, Elsafty N, Tawfick W. Eight years experience in the management of median arcuate ligament syndrome by decompression, celiac ganglion sympathectomy, and selective revascularization. Vasc Endovascular Surg [Internet]. 2013;47(8):614–9. Available from: https://pubmed.ncbi.nlm.nih.gov/23942948/

41. Mihas AA, Laws HL, Jander HP. Surgical treatment of the celiac axis compression syndrome. Am J Surg [Internet]. 1977 Jun;133(6):688–91. Available from: https://pubmed.ncbi.nlm.nih.gov/869119/

42. Chaum M, Shouhed D, Kim S, Walts AE, Marchevsky AM. Clinico-pathologic findings in patients with median arcuate ligament syndrome (celiac artery compression syndrome). Ann Diagn Pathol [Internet]. 2021 Jun 1;52:151732. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1092913421000320

43. van Petersen AS, Kolkman JJ, Gerrits DG, van der Palen J, Zeebregts CJ, Geelkerken RH, et al. Clinical significance of mesenteric arterial collateral circulation in patients with celiac artery compression syndrome. J Vasc Surg [Internet]. 2017 May;65(5):1366–74. Available from: https://pubmed.ncbi.nlm.nih.gov/28259570/

44. Vaziri K, Hungness ES, Pearson EG, Soper NJ. Laparoscopic Treatment of Celiac Artery Compression Syndrome: Case Series and Review of Current Treatment Modalities. J Gastrointest Surg [Internet]. 2009 Feb 26;13(2):293–8. Available from: https://pubmed.ncbi.nlm.nih.gov/18818978/

45. Takach TJ, Livesay JJ, Reul GJ, Cooley DA. Celiac compression syndrome: tailored therapy based on intraoperative findings. J Am Coll Surg [Internet]. 1996 Dec;183(6):606–10. Available from: https://pubmed.ncbi.nlm.nih.gov/8957463/

46. Sahm M, Otto R, Pross M, Scholbach T, Mantke R. Laparoscopic therapy of the coeliac artery compression syndrome: a critical analysis of the current standard procedure. Ann R Coll Surg Engl [Internet]. 2020 Feb;102(2):104–9. Available from: https://publishing.rcseng.ac.uk/doi/10.1308/rcsann.2019.0121

47. Skelly CL, Stiles-Shields C, Mak GZ, Speaker CR, Lorenz J, Anitescu M, et al. The impact of psychiatric comorbidities on patient-reported surgical outcomes in adults treated for the median arcuate ligament syndrome. J Vasc Surg [Internet]. 2018 Nov;68(5):1414–21. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0741521418302787

48. De'Ath HD, Wong S, Szentpali K, Somers S, Peck T, Wakefield CH. The Laparoscopic Management of Median Arcuate Ligament Syndrome and Its Long-Term Outcomes. J Laparoendosc Adv Surg Tech [Internet]. 2018 Nov;28(11):1359–63. Available from: https://pubmed.ncbi.nlm.nih.gov/29781769/

49. Berge ST, Safi N, Medhus AW, Sundhagen JO, Hisdal J, Kazmi SS. Perioperative Microcirculatory Changes Detected with Gastroscopy Assisted Laser Doppler Flowmetry and Visible Light Spectroscopy in Patients with Median Arcuate Ligament Syndrome. Vasc Health Risk Manag [Internet]. 2020 Aug;Volume 16:331–41. Available from: https://pubmed.ncbi.nlm.nih.gov/32982262/

50. Aschenbach R, Basche S, Vogl TJ. Compression of the Celiac Trunk Caused by Median Arcuate Ligament in Children and Adolescent Subjects: Evaluation with Contrast-enhanced MR Angiography and Comparison with Doppler US Evaluation. J Vasc Interv Radiol [Internet]. 2011 Apr;22(4):556–61. Available from: https://pubmed.ncbi.nlm.nih.gov/21316263/

51. Joyce DD, Antiel RM, Oderich G, Gloviczki P, Tung J, Grothe R, et al. Pediatric Median Arcuate Ligament Syndrome: Surgical Outcomes and Quality of Life. J Laparoendosc Adv Surg Tech [Internet]. 2014 Feb;24(2):104–10. Available from: https://pubmed.ncbi.nlm.nih.gov/24328507/

52. Klimas A, Lemmer A, Bergert H, Brodhun M, Scholbach T, Großer K. Laparoscopic treatment of celiac artery compression syndrome in children and adolescents. Vasa [Internet]. 2015;44(4):305–12. Available from: https://pubmed.ncbi.nlm.nih.gov/26314363/

53. Mak GZ, Speaker C, Anderson K, Stiles-Shields C, Lorenz J, Drossos T, et al. Median arcuate ligament syndrome in the pediatric population. J Pediatr Surg [Internet]. 2013 Nov;48(11):2261–70. Available from: http://dx.doi.org/10.1016/j.jpedsurg.2013.03.003

54. Moak JP, Ramwell C, Fabian R, Hanumanthaiah S, Darbari A, Kane TD. Median Arcuate Ligament Syndrome with Orthostatic Intolerance: Intermediate-Term Outcomes following Surgical Intervention. J Pediatr [Internet]. 2021 Apr;231:141–7. Available from: https://doi.org/10.1016/j.jpeds.2020.12.024

55. Stiles-Shields C, CL S, GZ M, Speaker C, Boyd H, O'Brien S, et al. Psychological Factors and Outcomes in the Surgical Treatment of Pediatric Patients With Median Arcuate Ligament Syndrome. [Internet]. Vol. 66, Journal of pediatric gastroenterology and nutrition. United States; 2018. p. 866–71. Available from: https://pubmed.ncbi.nlm.nih.gov/29373439/

56. Coelho JCU, Hosni AV El, Claus CM, Aguilera YSH, Abot GP, Freitas ATC de, et al. Treatment of median arcuate ligament syndrome: outcome of laparoscopic approach. ABCD Arq Bras Cir Dig (São Paulo) [Internet]. 2020;33(1):295–6. Available from: https://pubmed.ncbi.nlm.nih.gov/26734806/

57. Grus T, Lambert L, Vidim T, Grusova G, Klika T. Intraoperative measurement of pressure gradient in median arcuate ligament syndrome as a rationale for radical surgical approach. Acta Chir Belg [Internet]. 2018;118(1):36–41. Available from: https://pubmed.ncbi.nlm.nih.gov/28859519/

58. Berard X, Cau J, Déglise S, Trombert D, Saint-lebes B, Midy D, et al. European Journal of Vascular and Endovascular Surgery Laparoscopic Surgery for Coeliac Artery Compression Syndrome : Current Management and Technical Aspects. Eur J Vasc Endovasc Surg [Internet]. 2012;43(1):38–42. Available from: http://dx.doi.org/10.1016/j.ejvs.2011.09.023

59. Chaum M, Shouhed D, Kim S, Walts AE, Marchevsky AM. Annals of Diagnostic Pathology Clinico-pathologic findings in patients with median arcuate ligament syndrome (celiac artery compression syndrome). Ann Diagn Pathol [Internet]. 2021;52(March):151732. Available from: https://doi.org/10.1016/j.anndiagpath.2021.151732

60. Swank D, Swank-Bordewijk S, Hop W, van Erp W, Janssen I, Bonjer H, et al. Laparoscopic adhesiolysis in patients with chronic abdominal pain: a blinded randomised controlled multi-centre trial. Lancet [Internet]. 2003 Apr;361(9365):1247–51. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673603129790

61. Boelens OB, van Assen T, Houterman S, Scheltinga MR, Roumen RM. A Double-Blind, Randomized, Controlled Trial on Surgery for Chronic Abdominal Pain Due to Anterior Cutaneous Nerve Entrapment Syndrome. Ann Surg [Internet]. 2013 May;257(5):845–9. Available from: https://journals.lww.com/00000658-201305000-00010

62. Roumen RMH, Groenendijk RPR, Sloots CEJ, Duthoi KES, Scheltinga MRM, Bruijninckx CMA. Randomized clinical trial evaluating elective laparoscopic appendicectomy for chronic right lower-quadrant pain. Br J Surg [Internet]. 2008 Jan 14;95(2):169–74. Available from: https://academic.oup.com/bjs/article/95/2/169/6142761

63. Guyuron B, Reed D, Kriegler JS, Davis J, Pashmini N, Amini S. A Placebo-Controlled Surgical Trial of the Treatment of Migraine Headaches. Plast Reconstr Surg [Internet]. 2009 Aug;124(2):461–8. Available from: http://journals.lww.com/00006534-200908000-00015

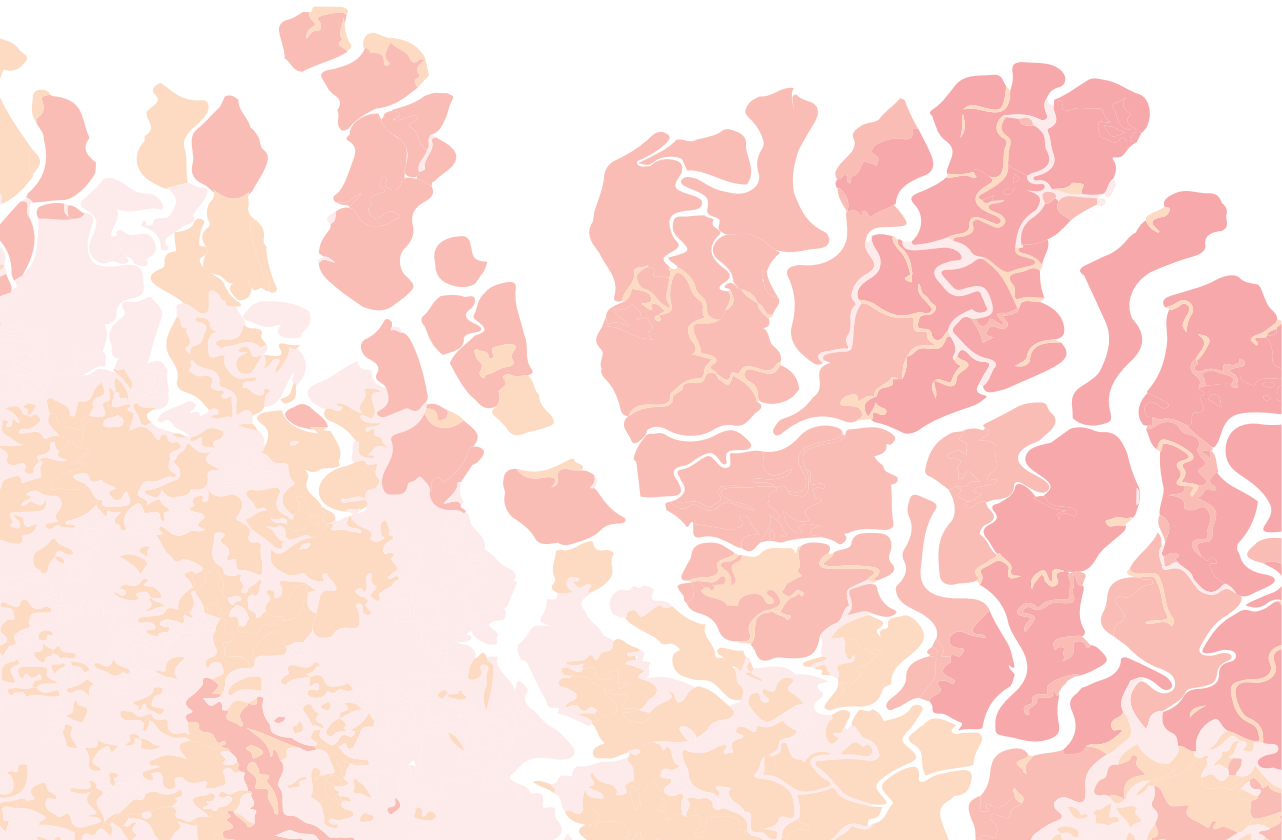
64. Abbot J, Hawe J, Hunter D, Holmes M, Finn P, Garry R. Laparoscopic excision of endometriosis: A randomized, placebo-controlled trial. Fertil Steril [Internet]. 2004 Oct;82(4):878–84. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0015028204012750

65. Mensink PBF, van Petersen AS, Kolkman JJ, Otte JA, Huisman AB, Geelkerken RH. Gastric exercise tonometry: The key investigation in patients with suspected celiac artery compression syndrome. J Vasc Surg [Internet]. 2006 Aug;44(2):277–81. Available from: https://linkinghub.elsevier.com/retrieve/pii/S074152140600557X

66. Niemansburg SL, van Delden JJM, Dhert WJA, Bredenoord AL. Reconsidering the ethics of sham interventions in an era of emerging technologies. Surgery [Internet]. 2015 Apr;157(4):801–10. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0039606014007867

67. Dijk LJ, Noord D, Vries AC, Kolkman JJ, Geelkerken RH, Verhagen HJM, et al. Clinical management of chronic mesenteric ischemia. United Eur Gastroenterol J [Internet]. 2019 Mar;7(2):179–88. Available from: https://onlinelibrary.wiley.com/doi/10.1177/2050640618817698

68. Grus T, Klika T, Grusová G, Lindner J, Lambert L. Dunbar syndrome - single-center experience with surgical treatment. Rozhl Chir [Internet]. 2018;97(11):514–7. Available from: https://pubmed.ncbi.nlm.nih.gov/30646742/



Chapter 7

A nationwide randomized placebo-controlled patient and observer blinded clinical trial assessing the efficacy and cost-effectiveness of endoscopic coeliac artery release in patients suspected of the median arcuate ligament syndrome; The CARoSO study

Juliëtte Blauw, Flores Metz, Marjolein Brusse-Keizer, Pepijn Rijnja, Jeroen Kolkman, Olaf Bakker, Erik Koffijberg, Monique Poessé-Vennevertloo, Hence Verhagen, Marco Bruno, Robert Geelkerken, Dutch Mesenteric Ischemia Studygroup.

Submitted.

Introduction

To end the ongoing debate and to enable the development of evidence-based guidelines for the management of median arcuate ligament syndrome (MALS), guideline committees, professions and patient representatives recommend to perform a blinded, randomised controlled trial comparing a coeliac artery (CA) release with a sham operation in patients suspected of MALS.

Research question / Hypothesis:

We assume that endoscopic coeliac artery release ((e)CAR) results in a significant reduction of abdominal symptoms (as measured with a disease specific composite endpoint) at 6 months in 70% of patients suspected of MALS, when compared with a reduction in symptoms in 30% of patients after a sham operation.

Study population

Individuals in the Netherlands suspected of MALS determined in consensus in a dedicated mesenteric ischemia multidisciplinary team.(1) Consensus diagnosis MALS is based on the criteria of van Dijk.(2)

In- and Exclusion criteria

To be eligible to participate in this study, a subject must meet all of the following criteria:

- Patients with a consensus diagnosis of MALS based on a multidisciplinary discussion (vascular surgeon, gastroenterologist, radiologist). Consisting of an expert panel with members from different hospitals.
- Typical complaints: post-prandial pain and at least two of the following: dietary modification, unexplained weight loss, unexplained diarrhea.
- Eccentric stenosis of ≥70% of the CA at the medial arcuatum ligament (MAL), demonstrated by two imaging techniques (duplex, digital subtraction angiography (DSA), magnetic resonance angiography (MRA) or computed tomography angiography (CTA)), including at least an inspiration and expiration CTA with 1mm sections. (Definition percent stenosis according to ECST 1998 formula: % stenosis = (1 - [diameter at the site of stenosis/estimated original diameter at the site of the stenosis]) x 100).
- Ultrasound Abdomen without other more common abnormalities.
- Gastroduodenoscopy without abnormalities, unless appropriate for mucosal ischemia.
- Age >18 years.

To be eligible to participate in this study, a subject must not fulfil one or more of the following criteria:

- Patient not suitable for endoscopic CA release (e.g., previous surgery in the operating area).
- Pregnancy.
- Previous (endovascular) intervention of the visceral arteries.
- A significant stenosis in the superior or in the inferior mesenteric artery

Intervention

Endoscopic coeliac artery release (eCAR); The MAL will be cleaved via an endoscopic retroperitoneal approach using a 4-trocar technique described in detail by van Petersen.(3) To rule out learning curves and procedural variation all the procedures will be performed by two experienced (e)CAR surgeons in the MST-Dutch Expert Centre of Gastrointestinal Ischemia. All procedures will be videotaped. Both (e)CAR surgeons will not be involved in the follow up procedures.

Comparison

The sham operation consists of making 4 incisions up to the fascia similar to (e)CAR. After 60 to 75 minutes of general anaesthesia, in accordance with the average operating time of (e)CAR, the sham operation is ended. This study design allows for patient and observer blinding and for the sham group the (e)CAR approach is still feasible if the CARoSO outcome supports this.

Outcome measures

The primary endpoint is the number of patients with significant reduction in abdominal symptoms at 6 months after randomization measured by a composite disease specific primary end point (CPE). A significant reduction in abdominal symptoms is defined as:

- A reduction in abdominal pain visual analogue scale (VAS) of $\geq$50% compared to baseline

and/or

- “Much improved” or “very much improved” symptoms on the patient global impression of improvement (PGI-I).

Patient representatives and professions were unanimous in their opinion that the chosen CPE is the most appropriate to prove or reject the hypothesis. Secondary endpoints include cost-effectiveness, health related quality of life and productivity loss.

Secondary endpoints

Evaluating the effect of an CA release compared to a sham operation on:

- Abdominal pain measured with mean abdominal pain VAS after 3 months and 24 (6 months already for primary endpoint).
- Change in complaints measured with the PGI-I after 3 and 24 months (6 months already for primary endpoint).
- Abdominal pain measured with worst abdominal pain VAS after 3, 6 and 24 months.
- Health-related quality of life (HR-QoL) measured with the EQ-5D-5L (euro quality of life – 5 dimensions and 5 levels), SF-36 after (short form health survey) 3, 6 and 24 months. (4-6)
- Productivity loss measured with the iPCQ (institute for medical technology assessment productivity cost questionnaire) after 3, 6 and 24 months.(7)
- Healthcare consumption measured with the iMCQ (institute for medical technology assessment medical cost questionnaire) after 3, 6 and 24 months.(8)
- Cost effectiveness of CA release compared to a sham operation (see cost-effectiveness paragraph).
- The number of anatomically successful procedures, defined as $\leq$30% stenosis measured with a CTA/MRA after 6 months (diameter permeated lumen/diameter artery*100).
- The number of days until return to a normal diet.
- Weight after 3, 6 and 24 months.
- Success of blinding, measured after 6 months.
- 30-day complications classified in the Clavien-Dindo classification.(9)
- Percentage of patients undergoing additional percutaneous transluminal angioplasty (PTA) within 24 months following an CA release.

Follow-up time

All patients are followed up in a blinded way for at least six months. In case the (e)CAR treatment is as effective as expected (as described in the hypothesis) after completion and analyses on the 6 months composite disease specific primary end point (CPE) for all included subjects, the study will be unblinded for ethical reasons. In addition, all patients will be

followed for the remaining months until they completed the total follow up of 24 months per patient either in a blinded or unblinded way.

Study Design

A nationwide randomized placebo-controlled patient and observer blinded clinical superiority trial. Patients are randomized in a 1:1 fashion for either (e)CAR or a sham operation. Thereby, patients will be stratified for baseline VAS score and gender.

Sample size and data-analysis

Assuming that 70% in the (e)CAR and 30% in the sham group will achieve the CPE (α of 0.05, power 0.9, drop-out rate 10%), in total 70 patients should be included (35 in (e)CAR and 35 in sham group). The expected success rate of 0.7 for (e)CAR is based on two observational studies. The expected success rate of 0.3 for the sham operation is based on five RCTs with sham operations.

The hypothesis will be tested, based on intention to treat analysis, with the Chi-square test and the univariate logistic regression analysis or generalized estimating equation (GEE) in case of missing values. If necessary, potential confounders will be corrected for by means of a multivariate logistic regression or GEE analysis.

Cost effectiveness analysis (CEA)

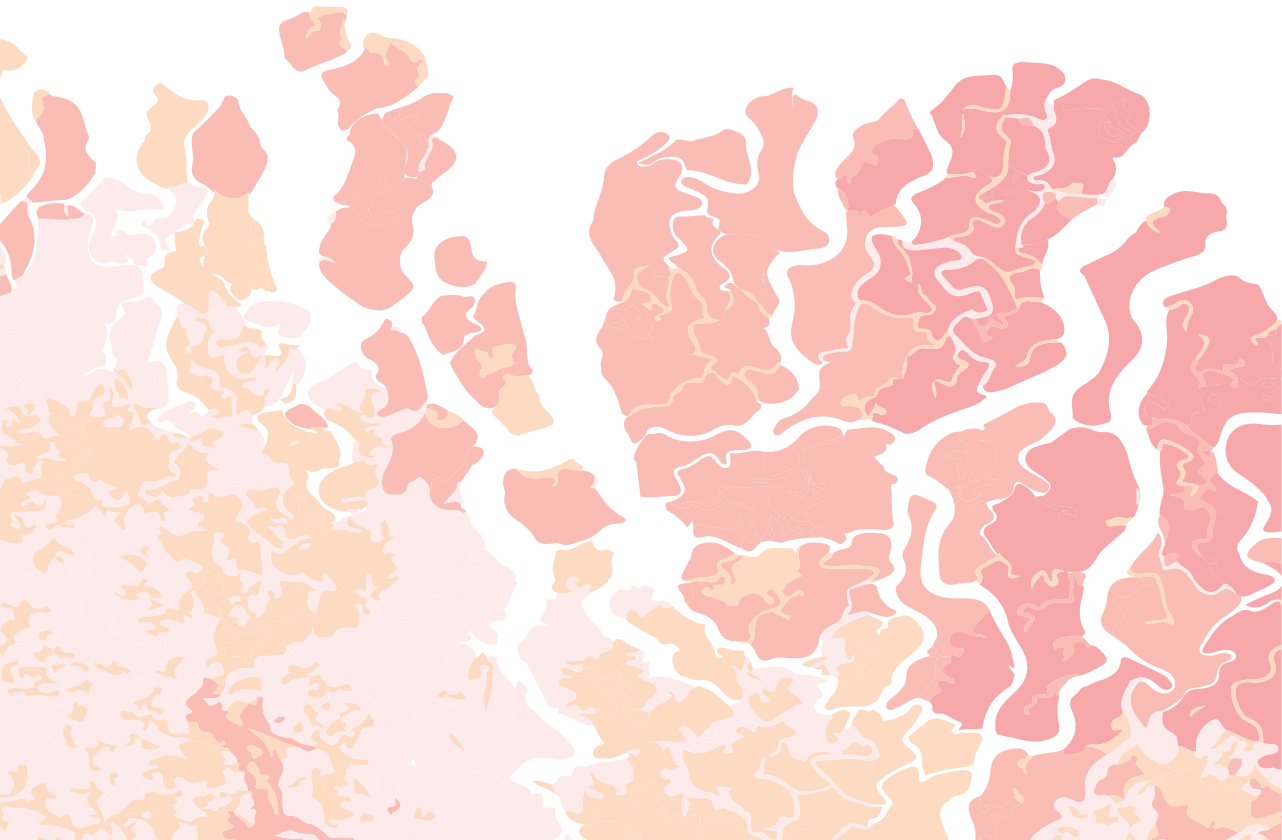
The cost-effectiveness analysis will be carried out in accordance with the Dutch guideline for economic evaluations in health care and will use a societal perspective. Quality of life will be measured with the EQ-5D-5L, using the Dutch tariff for the analyses. Volumes of healthcare resource use will be obtained from hospital administration data and from the iMTA Medical Consumption Questionnaire. Prices will be based on the cost manual, internal hospital calculations or Dutch average tariffs. Productivity losses will be measured with the iMTA Productivity Cost Questionnaire. Differences in health outcomes, expressed in quality-adjusted life years and costs between the two groups, will be evaluated over the period from baseline to 6-month follow-up. Then the incremental cost-utility ratio of (e) CAR compared to the sham operation will be calculated for this 6-month time horizon. Results will be presented in incremental cost-effectiveness planes and cost-effectiveness acceptability curves.

Budget impact analysis (BIA)

The BIA will be designed as a linear extrapolation of evidence collected in this project, and will be performed separately for a societal, a government, and health insurance company's perspective. The BIA will be performed following the Dutch guidelines and international guidelines. In the analyses, results will be expressed in M€ (millions of Euros), results will not be discounted and a 5-year time horizon will be applied. BIA results will be reported separately for each year within the time horizon and indexation will be applied. In the BIA, different scenarios will be considered with respect to the speed with which (e)CAR uptake increases following this study, and a comprehensive sensitivity analysis will be included, with results presented in Tornado diagrams.

References

1. Rutjes AW, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PM. Evaluation of diagnostic tests when there is no gold standard. A review of methods. Health Technol Assess. 2007;11(50):iii, ix-51.
2. van Dijk LJ, van Noord D, de Vries AC, Kolkman JJ, Geelkerken RH, Verhagen HJ, et al. Clinical management of chronic mesenteric ischemia. United European Gastroenterol J. 2019;7(2):179-88.
3. van Petersen AS, Vriens BH, Huisman AB, Kolkman JJ, Geelkerken RH. Retroperitoneal endoscopic release in the management of celiac artery compression syndrome. J Vasc Surg. 2009;50(1):140-7.
4. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.
5. ten Klooster PM, Vonkeman HE, Taal E, Siemons L, Hendriks L, de Jong AJ, et al. Performance of the Dutch SF-36 version 2 as a measure of health-related quality of life in patients with rheumatoid arthritis. Health Qual Life Outcomes. 2013;11:77.
6. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.
7. Bouwmans C, Krol M, Severens H, Koopmanschap M, Brouwer W, Hakkaart-van Roijen L. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. Value Health. 2015;18(6):753-8.
8. Bouwmans C ea. Handleiding iMTA Medical Cost Questionnaire (iMCQ). Rotterdam: iMTA, Erasmus Universiteit Rotterdam. 2013.
9. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery. 2004;240(2):205-13.



Chapter 8

The impact of revascularisation on quality of life in chronic mesenteric ischemia

Juliëtte Blauw, Hilde Pastoors, Marjolein Brusse-Keizer, Roland Beuk, Jeroen Kolkman, Robert Geelkerken; Dutch Mesenteric Ischemia Study group.

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Abstract

Background Chronic mesenteric ischemia (CMI) is characterized by longstanding abdominal symptoms due to insufficient mesenteric circulation. Data on the effect of revascularization on quality of life (QoL) for CMI is scarce. This study is the first to evaluate the impact of revascularization on quality of life.

Methods Seventy-nine patients with CMI or acute-on-chronic mesenteric ischemia (AoCMI) underwent an intervention of one or more mesenteric arteries between January 2010 and July 2012. QoL before and after intervention was measured with the EuroQol-5D. Pre-intervention questionnaires were standard care. Post-intervention data was obtained by resending a questionnaire to the patients between February and May 2013. To investigate the clinical relevance of our findings the minimal clinically important difference (MCID) was used. Since there isn't a MCID established for CMI we used a literature reference MCID of inflammatory bowel syndrome (IBS) of 0.074.

Results Fifty-five (69.6%) of 79 patients returned their questionnaire and 23 (29.1%) were completely filled out. There was a significant increase of the median EQ-index score from 0.70 to 0.81 (p=0.02) and a significant reduction of symptoms in the domains usual activities (34.4%) and pain/discomfort (32.3%). There was a significant improvement of 17% in overall current health condition (VAS) (p=0.001). The MCID between baseline and postoperative EQ-5D index score was 0.162 indicating a clinically relevant improvement of quality of life after revascularisation

Conclusion Quality of life of CMI patients is improved after mesenteric artery revascularization.

Introduction

Chronic mesenteric ischemia (CMI) is characterized by chronic abdominal pain from ischemia, caused in most cases by significant stenosis in at least two mesenteric arteries, although an isolated stenosis can be symptomatic as well.(1) Complaints include postprandial pain, weight loss, nausea with or without vomiting and diarrhea.(1-4) Typically patients eat small meals, 6-8 times a day, low in calories and develop a fear of eating which leads to unintentional weight loss and malnutrition.(5)

The etiology of the mesenteric artery stenosis is diverse, including atherosclerosis (1,6) and external compression by the median arcuate ligament syndrome (MALS). (1,7)

Revascularization is indicated in patients with multi-vessel stenoses and otherwise unexplained abdominal complaints,(1) or in single-vessel stenosis with typical complaints and proven ischemia. Nowadays the treatment of choice is endovascular antegrade(1, 6-10) or retrograde(11) stenting in case of atherosclerotic intraluminal stenosis and celiac artery release in case of MALS. (1,7)

In chronic pain patients it has been shown that abdominal symptoms often lead to psychological effects (12), including a high prevalence of depression. Both pain and depression reduce the quality of life, and therefore reduce health-related quality of life (HRQoL) compared to unaffected individuals.(12, 13)

HRQoL instruments are increasingly used to measure patients' health status and to evaluate the effectiveness of health-care interventions.(14) However, the effect of treatment on physical and psychological well-being in CMI patients is still an unexplored frontier.(1) The aim of this study was to measure the impact of revascularization on HRQoL in patients with CMI.

Methods

A retrospective analysis was performed to investigate the impact of revascularization of the mesenteric arteries in patients with CMI on HRQoL. Consecutive patients with CMI and acute-on-chronic mesenteric ischemia (AoCMI) admitted to our tertiary referral centre for treatment of mesenteric ischemia between January 2010 and July 2012 were eligible for inclusion. The clinical symptoms were evaluated by a multidisciplinary group, including a gastroenterologist, interventional radiologist and a vascular surgeon, as previously reported. (15) The inclusion and exclusion criteria are listed in Table 1.

Relevant clinical characteristics, including HRQoL data of patients with CMI measured by the EuroQol-5D (EQ-5D) questionnaire,(16) were prospectively registered in our vascular database. All patients were asked to complete this EQ-5D questionnaire during their first hospital admission. Between February and May 2013 all CMI and AoCMI patients who underwent revascularisation between January 2010 and July 2012 were asked to fill in a second EQ-5D questionnaire to collect post-interventional data. The Medical Ethics Committee Twente judged that no further judgement of the study protocol by the committee was required nor was an informed consent procedure necessary, according to the Dutch law on scientific medical research in humans.

Table 1 In- and exclusion criteria

Inclusion criteria
• Patients aged 18+ years
• Mastering the Dutch language, living in the Netherlands
• Chronic mesenteric ischemia (CMI) or acute-on-chronic mesenteric ischemia (AoCMI)
• Underwent one or more interventions for CMI in one hospital admission between 01-01-2010 and 01-07-2012
Exclusion criteria
• Deceased between hospitalization and second EQ-5D measurement
• Acute mesenteric ischemia (AMI)
• Lost-to-follow up
• Underwent multiple interventions of one of more mesenteric arteries related to CMI in different hospital admissions
• Only diagnostic procedure, no revascularisation performed

Outcome measures

The EQ-5D is a five-dimensional health state classification, consisting the domains mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain is assessed by a single question on a three-point ordinal scale (no, some or extreme problems). The EQ-5D also contains a self-rating on a 20 centimetre visual analogue scale (VAS), anchored with 100 (‘best imaginable health state’) at the top and 0 (‘worst imaginable health state’) at the bottom (EQ VAS).(16)

The EQ-5D index score can be regarded as a continuous outcome scored on a -0.59 to 1.00 scale, with 1.00 indicating ‘full health’ and 0 representing dead. The negative scores represent certain health states valued worse than dead.(16) The EQ-5D index score could only be calculated in completed questionnaires.

Since interpretation in HRQoL scores raises many issues, a minimal clinically important difference (MCID) for the EQ-5D has been developed, in order to allow clinicians to make

meaningful interpretations of the effect of their treatment. It was defined as 'smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management'.(17) These are derived from comparison of scores from complex, calculated scores to 'simple' clinical outcomes (improved or disappeared pain for example) and result in a minimal difference in score outcome that corresponds with clinical important benefit, and thus changes via a clinical intervention that are meaningful for the patient. (18) In essence, it links an increase of the EQ-5D with patient relevant outcomes, usually improved, or greatly improved on a Likert-scale, the so-called anchor of the MCID. There has not been an established MCID for CMI until this day. So, for this study we used literature for diseases with corresponding abdominal complaints, like irritable bowel syndrome (IBS). The MCID for the EQ-5D in one study ranged from 0.011 to 0.140 with a mean of 0.074, we have chosen this as a reference point for the comparisons in our study.(19)

Definitions

CMI is defined as symptoms of mesenteric ischemia for more than 3 months.(1) The typical presentation includes postprandial pain, weight loss due to fear of eating or unexplained diarrhoea.(20, 21) *AoCMI* is defined as acute mesenteric ischemia in patients who previously had typical complaints of CMI.(1) Often, the complaints of CMI worsened over the preceding weeks with prolonged and more severe pain periods, pain even without eating, onset of diarrhoea or inability to eat at all.(20, 21) *MALS* is defined as epigastric or postprandial pain and weight loss due to external compression of the coeliac artery by the median arcuate ligament.(1) *Technical success* (based on intention to treat) is defined as successful completion of the procedure and <30% residual stenosis at the end of the procedure(20, 21). *Primary patency* is defined as uninterrupted patency without need for any additional procedures(20, 21). *Clinical success* is defined as uninterrupted relief or improvement of presenting symptoms with a patent revascularized target vessel.(20, 21)

Statistical analyses

Baseline characteristics are displayed as mean with standard deviation or median with differences in pre- and postoperative EQ-5D index score, scores per domain and EQ-VAS were analysed using the paired *t*-test or Wilcoxon signed rank test, as appropriate. For categorical variables (domains), these differences were tested with a McNemar test. Differences in baseline characteristics between responders and non-responders were tested with either an independent T-test or Wilcoxon rank sum test for continuous variables and with a Chi-square or Fisher's exact test for categorical variables. Data were analysed using SPSS 21.0.

Results

Between January 2010 and July 2012, 196 consecutive patients were treated for CMI (192 patients) or AoCMI (4 patients). Seventy-Nine patients with CMI or AoCMI met the inclusion criteria for participation (Figure 1). Fifty-five patients (69.6%) answered the post-intervention questionnaire and were included in the data-analysis. Table 2 shows the patient characteristics of these 55 patients. Their mean age was 58 years and 36 (65.5%) were female. Thirty-three patients (60%) underwent endovascular treatment. Fifty-two patients (94.5%) were suffering from CMI. Three patients (5.5%) were diagnosed with AoCMI. Twenty-five patients (45.5%) were diagnosed with single vessel CMI. Nineteen of these 25 patients (76%) were diagnosed with MALS. Seventeen of them underwent a retroperitoneal endoscopic coeliac artery release and two responders an open transabdominal release. The remaining six of the 25 patients underwent endovascular stenting because of single vessel intraluminal atherosclerotic stenoses. Thirty patients (54.5%) were diagnosed with multi-vessel (two or three affected mesenteric arteries) intraluminal stenosis. Twenty-seven of them underwent antegrade and one retrograde endovascular stenting. The remaining two patients underwent antegrade autologous reversed greater saphenous vein two vessel bypass revascularization. The mean time between hospital admission and postoperative measurements (n=55) was 20 months (SD±8.2). Technical success was 87%, one-year primary patency was 79% and one-year clinical success was achieved in 80% of the patients (Table 2).

The 23 patients who completed the questionnaire were significantly younger than the 32 who did not complete the questionnaires (51±19 vs. 63±15 years) (p=0.008). Fifteen (65.2%) of those 23 patients had single-vessel CMI compared to 31.2% of those who did not complete the questionnaire (p=0.04). The time between the intervention and receiving the questionnaire was significant longer in the completed questionnaire group, respectively 22±9 months, versus 18±7 months in the incomplete questionnaire group (p=0.05). No difference in sex (p=0.54) or intervention type (p=0.28) between both groups was found. The power to show a difference in EQ-index for the entire group (n = 23) was 0.96 and therefore above the usual 0.8 that you use for a power analysis.

Figure 1 Flowchart of patient inclusion.

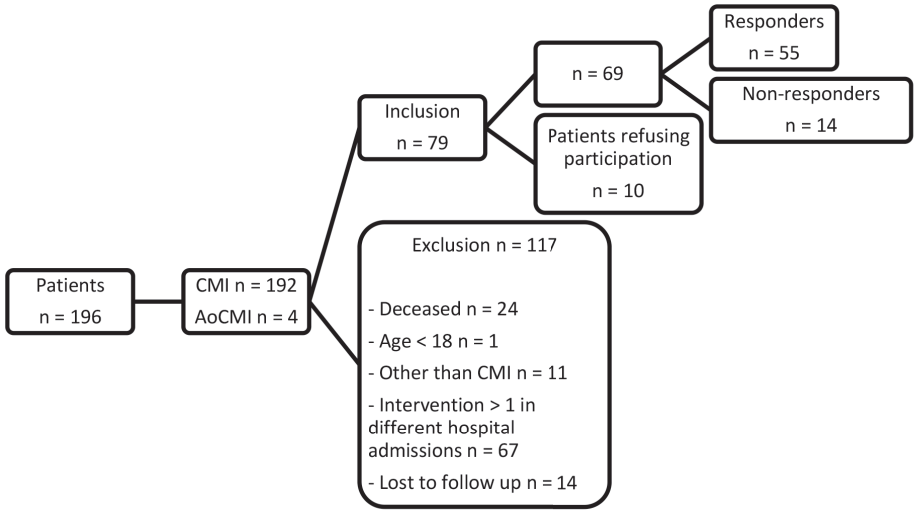


Table 2 Patient characteristics of responding patients

	Patients *n* = 55
Age at hospital admission (years), mean ± *SD*	58 ± 17.5
Time between hospital admission and post-operative measurement (months), mean ± *SD*	19.6 ± 8.2
Gender, *n* (%)	
Man	19 (34.5%)
Woman	36 (65.5%)
Complication/recurrent complaints, *n* (%)	
During hospital admission	9 (16.4%)
After hospital admission	15 (27.3%)
Intervention type, *n* (%)	
Endovascular	33 (60.0%)
Open repair	5 (9.1%)
CA-release	17 (30.9%)
x-Vessel disease	
1	25 (45.5%)
2	14 (25.5%)
3	16 (29.0%)
CMI vs. Acute-on-chronic, *n* (%)	
Chronic	52 (94.5%)
Acute-on-chronic	3 (5.5%)
Technical success	48 (87.3%)
Primary patency	30 out of 38 (79%)
Clinical success	44 out of 55 (80%)

CA = coeliac artery, CMI = chronic mesenteric ischemia

Table 3 EQ-5D index score before and after revascularisation

	Before	After	*P*
Total (*n* = 23)	0.70 (0.43-0.77)[1]	0.81 (0.67-0.93)	*P* = 0.02
AS[2] (*n* = 20)	0.65 (0.38-0.77)	0.82 (0.77-0.93)	*P* = 0.03
AU[3] (*n* = 3)	0.70 (0.60-0.70)	0.67 (0.67-0.81)	*P* = 0.29

[1] Given Median (IQR)
[2] Anatomical success, confirmed by diagnostic imaging
[3] Anatomical unsuccessful and/or not confirmed by diagnostic imaging

The EQ-5D index score

The EQ-5D index score is shown in Table 3. Twenty-three (41.8%) of 55 patients completed all the 5 domains of the questionnaire after revascularisation. Therefore, there were 32 incomplete questionnaires that were not useful to calculate this index score. Again, preoperative characteristics, treatment and clinical success of the cohorts' complete and partial responders were matching. The median EQ-5D index score (n=23) increased from 0.70 at baseline to 0.81 (p=0.02) after treatment. In three (13%) patients there was no technical success and their median EQ-5D index score was 0.70 before and 0.67 after intervention (p=0.29). The median index score of the twenty patients (87%) in whom technical success was achieved increased from 0.65 to 0.82 (p=0.03).

The difference between baseline and postoperative EQ-5D index score was 0.162 (SD±0.312, 95%CI 0.027-0.297), which exceeds the range of accepted MCID□s in previous studies of 0.074,(16) indicating a clinically relevant improvement of quality of life after revascularisation.

There was no correlation between neither the EQ-5D index score (r=0.021, p=0.88) nor the EQ-VAS score (r=-0.091, p=0.53) with the time between the intervention and receiving the questionnaire.

Domains EQ-5D

In order to analyse each domain (i.e. pain/discomfort, mobility), only pre- and postoperative measurements of the same patient per domain were useful. Because of missing data, each domain shows a different number of patients.

Table 4 shows the outcomes per domain. Data-analysis showed a significant reduction in limitation of daily activities and pain/discomfort ($p<0.05$), and a numerical reduction of complaints in the domains mobility and anxiety/depression.

Table 4 EQ-5D scores per domain and EQ-VAS score

Domain	All n = 55 Pre	Post
Number (%)		
Mobility, *n* [1]		
No problems	16 (50.0%)	19 (59.5%)
Some problems	15 (46.8%)	13 (40.5%)
Extreme problems	1 (3.2%)	-
Self-care, *n* [1]		
No problems	29 (90.6%)	28 (87.5%)
Some problems	3 (9.4%)	4 (12.5%)
Extreme problems	-	-
Usual activities, *n* [1]		*
No problems	5 (15.6%)	16 (50.0%)
Some problems	19 (59.4%)	15 (46.9%)
Extreme problems	8 (25.0%)	1 (3.1%)
Pain/discomfort, *n* [2]		*
No problems	1 (3.2%)	11 (35.5%)
Some problems	22 (71.0%)	17 (54.8%)
Extreme problems	8 (25.8%)	3 (9.7%)
Anxiety/depression, *n* [3]		
No problems	7 (29.2%)	17 (70.8%)
Some problems	15 (62.5%)	6 (25.0%)
Extreme problems	2 (8.3%)	1 (4.2%)
EQ-VAS 'current health condition', *mean (SD)* [2]	51.6 (19.7)	* 68.2 (17.2)

[1] Missing data in 23 of 55 responders (All: n = 32, AS: n = 29, NAS: n = 3)
[2] Missing data in 24 of 55 responders (All: n = 31, AS: n = 28, NAS: n = 3)
[3] Missing data in 31 of 55 responders (All: n = 24, AS: n = 21, NAS: n = 3)
* $p < 0.05$

EQ-VAS

Table 4 also shows the outcome of the EQ-VAS. Because of missing data, the VAS-scores of 31 patients (56.4%) were analysed. The mean VAS-score increased by 17% from 52 at baseline to 68 after intervention (p=0.001). The mean VAS score of the 28 patients who underwent an anatomically successful intervention showed a significant increase from 52 to 69 (p=0.001), but also the mean VAS score of the three remaining patients who did not have an anatomically successful intervention showed a comparable increase from 49 to 57 (p=0.08).

Discussion

The present study evaluates the effect of CMI treatment on physical and psychological well-being and demonstrates improved quality of life. The latter was shown in three different measures. First, treatment of CMI patients had a clinically relevant beneficial outcome to their health-related quality of life. The increase in median EQ-index of 0.162 exceeds MCID's found in other studies (19) Second, our results show a significant improvement of almost 17% in overall current health condition (VAS). Third, we found a significant reduction of symptoms in the domains usual activities and pain/discomfort after treatment.

Our literature search showed 2 studies on quality of life after CMI revascularisation. The first, by Skelly et al. (24), describes psychiatric comorbidities in MALS patients undergoing surgery, trying to determine whether these comorbidities are predictive of patient-reported quality of life outcomes. They concluded that patient-reported quality of life significantly improved after surgical therapy for MALS patients, but that a pre-existing psychiatric disorder has a poorer outcome in some domains. In contrast to our study, they focussed on MALS patients only. Our data give a broader perspective on the CMI population. The second study is a retrospective analysis by Wagenhäuser et al. (25). They evaluated the use of the 36-item health survey (SF-36) questionnaire as a tool to investigate HRQoL after revascularisation in CMI patients. They analysed questionnaires of 32 out of their 100 patients, dealing with the same issues we encountered. They showed that CMI patients consider their physical and mental health inferior to the normal German population. However, they didn't describe how patients experienced their quality of life before revascularization. Therefore, it's not possible to assess whether revascularization has led to improvement of HRQoL and thus if revascularisation has a positive effect on HRQoL.

We couldn't identify any studies on the quality of life in CMI patients using the MCID. Consequently, we cannot compare our data with CMI studies, and turned to studies in diseases with abdominal complaints, like IBS. Gralnek et al.(22) showed HRQoL (using Short-Form-36 questionnaire) in IBS-patients is lower than the U.S. general population, patients with gastroesophageal reflux disease or diabetes, for example. Furthermore, it has been shown that HRQoL in IBS-patients, using an IBS specific QoL questionnaire, significantly improved after medicinal treatment.(23, 24) Wang et al.(25) showed that IBS was significantly associated with four of the five EQ-5D dimensions (except self-care; p=0.77), which is in line with our findings.

The EQ-5D was developed as alternative for the very large, and time-consuming, SF-36. The EQ-5D as measure of HRQoL has been reported for ulcerative colitis (UC) and Crohn's

disease (CD). Gibson et al.(26) showed that the mean EQ-5D for 175 UC patients' scores was greater for patients in remission (0.81) than for patients with active disease (0.72). In a large German study by Stark et al.(27) the EQ-5D was said to be "valid, reliable, and responsive in the Inflammatory Bowel Disease (IBD) population studied". They showed that EQ-VAS and EQ-index scores improved after treatment and that there was a significant difference between the index for active disease and remission. Probert et al.(28) used the EQ-5D in patients with CU before and after medicinal treatment (and with or without placebo). They showed a significant improvement in the domains mobility, usual activity and anxiety/depression.(28) Another study in patients with CU shows that 90% of the responders report their general health situation to be better after surgery than before.(29) And patients with CU scored better in the domains pain/discomfort and anxiety/depression after surgical treatment than the group of patients receiving medicinal treatment.(30) The mean VAS in these surgically intervened patients was 80.9, which is higher than our results (mean VAS post-operative 68.2, n = 31).

The increase in EQ-5D index score of 0.162 is in line with similar published data on EQ-5D changes after treatment. In a report on 11 studies on the MCID of EQ-5D in various diseases, ranging from IBS to leg ulcers, a mean MCID of 0.074 was reported.(19) It may be difficult to translate outcome of leg ulcers to abdominal pain in CMI. Still, in one of these 11 studies, 161 IBS patients were studied, with an established MCID of 0.065.(19) Luo(31) et al. showed that the MCID for the EQ-5D (United Kingdom) ranged from 0.036 to 0.204, with the mean being 0.082. Our MCID range of 0.050-0.084 for EQ-5D was within the range of MCID estimates of other disease states. In general, patients who have severe disability had higher MCIDs than patients who had mild-moderate disability. Additional analysis to verify these EQ-5D health status index MCID estimates in an independent data set should be performed.

The small number of patients (n=3) with an anatomical unsuccessful revascularisation or success not confirmed by diagnostic imaging scored a numerical reduction of complaints in the domains "usual activities" and "anxiety/depression" and a significant increase in VAS of 7.4%, beyond expectation. Also, our results show an increase in median EQ-5D index score, even in patients who had post-intervention complications or recurrence of complaints, although we found no statistical significance. However, an explanation of this increase could be that post-intervention complications are no longer present and the complaints are less than before intervention.

There are a couple of limitations to our study. First, a potential bias could be the time between treatment and completion of the questionnaire, with more pronounced effects

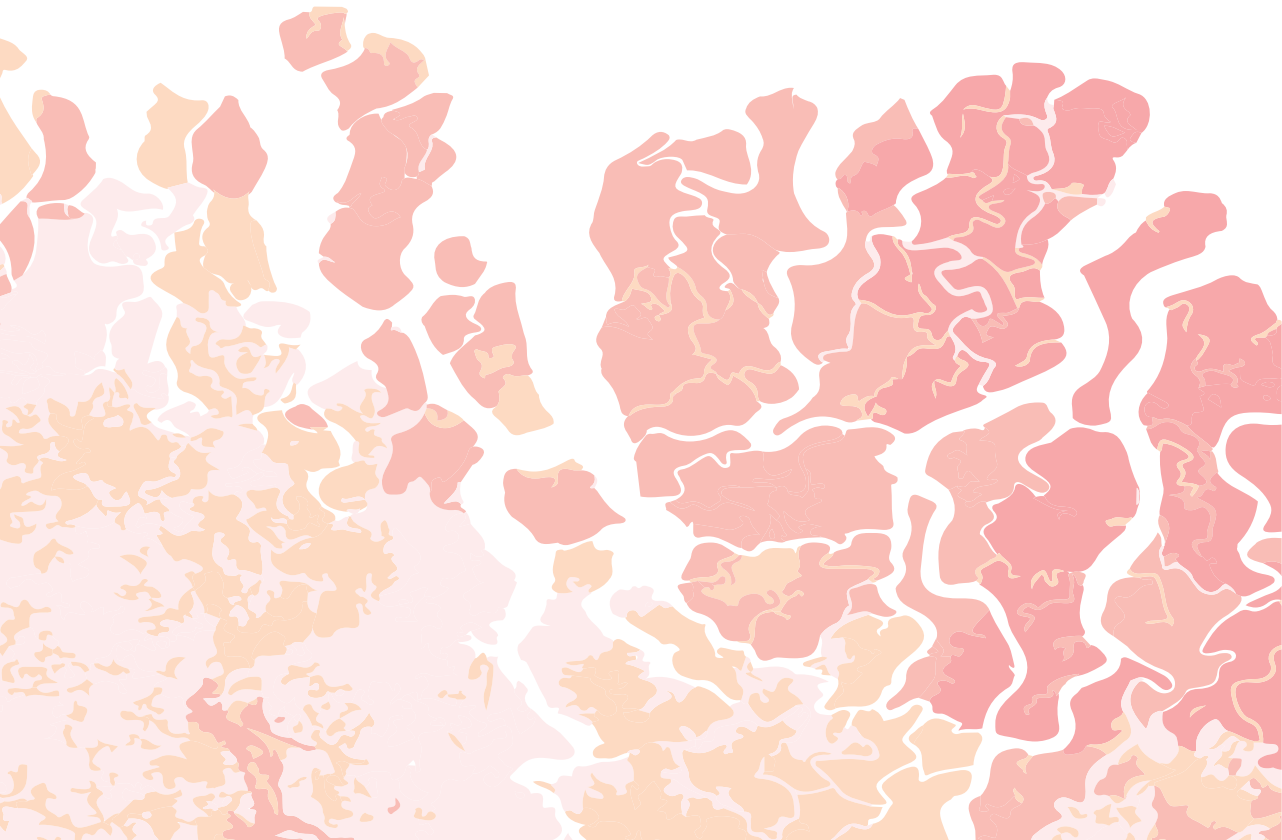
shortly after treatment. The mean time between revascularization and completing the postoperative questionnaire (n=55) was 20 months (SD±8.2). We found no correlation between neither the EQ-5D index score (r=0.021, p=0.88) nor the EQ-VAS score (r=-0.091, p=0.53) with the interval time. Second, only 79 of 196 patients (40.3%) were eligible for inclusion. Third, of 55 patients responded, in 32 questionnaires one or more questions were missing. It is unclear why questions weren't answered. It did not concern a specific domain. When we analysed the missing questions, they were evenly distributed over the domains, and between potential outcomes (responders, partial responders and non-responders). We therefore think these missing data do not represent an important bias on the outcomes. Fourth, we can't rule out a placebo effect. Ideally, a RCT including a sham intervention cohort should be performed to see QoL related improvement after therapy. However, given the severity of symptoms and available literature data, it is unlikely that such an RCT study will ever be performed in patients with severe chronic mesenteric ischemia.

In conclusion, this study is the first to demonstrated improvement on quality of life in CMI patients after mesenteric artery revascularization measured with the EQ-5D. The measured differences are in line with other studies in treatment of abdominal complaints. Prospective research should follow this retrospective study to limit the chance of missing data. It can help us to better identify these patient groups by including larger subgroups of patients in order to study differences between subgroups. Establishing the MCID as a disease-related quality of life measurement instrument for mesenteric ischemia in order to provide more detailed information about this category of patients both for better understanding the patient's expectations as well as future studies on treatment effects can also be investigated.

Reference list

1. Bjorck M, Koelemay M, Acosta S, Bastos Goncalves F, Kolbel T, Kolkman JJ, et al. Editor's Choice - Management of the Diseases of Mesenteric Arteries and Veins: Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2017;53(4):460-510.
2. ter Steege RW, Sloterdijk HS, Geelkerken RH, Huisman AB, van der Palen J, Kolkman JJ. Splanchnic artery stenosis and abdominal complaints: clinical history is of limited value in detection of gastrointestinal ischemia. World J Surg. 2012;36(4):793-9.
3. Hogendoorn W, Hunink MG, Schlosser FJ, Moll FL, Muhs BE, Sumpio BE. A comparison of open and endovascular revascularization for chronic mesenteric ischemia in a clinical decision model. J Vasc Surg. 2014;60(3):715-25 e2.
4. Chandra A, Quinones-Baldrich WJ. Chronic mesenteric ischemia: how to select patients for invasive treatment. Semin Vasc Surg. 2010;23(1):21-8.
5. Johnston KW, Lindsay TF, Walker PM, Kalman PG. Mesenteric arterial bypass grafts: early and late results and suggested surgical approach for chronic and acute mesenteric ischemia. Surgery. 1995;118(1):1-7.
6. Atkins MD, Kwolek CJ, LaMuraglia GM, Brewster DC, Chung TK, Cambria RP. Surgical revascularization versus endovascular therapy for chronic mesenteric ischemia: a comparative experience. J Vasc Surg. 2007;45(6):1162-71.
7. Schermerhorn ML, Giles KA, Hamdan AD, Wyers MC, Pomposelli FB. Mesenteric revascularization: management and outcomes in the United States, 1988-2006. J Vasc Surg. 2009;50(2):341-8 e1.
8. Pecoraro F RZ, Lachat M, et al. Chronic mesenteric ischemia: critical review and guidelines for management. Ann Vasc Surg. 2013;27(1):113-122.
9. van Petersen AS, Kolkman JJ, Beuk RJ, Huisman AB, Doelman CJ, Geelkerken RH, et al. Open or percutaneous revascularization for chronic splanchnic syndrome. J Vasc Surg. 2010;51(5):1309-16.
10. Bulut T O-BR, Geelkerken RH, Brusse-Keizer M, Stassen EJ, Kolkman JJ. Long- term results of endovascular treatment of atherosclerotic stenoses or occlusions of the celiac and superior mesenteric artery in patients with mesenteric ischemia. . European Journal of Vascular and Endovascular Surgery. Accepted for publication in 2017.
11. Blauw JT, Meerwaldt R, Brusse-Keizer M, Kolkman JJ, Gerrits D, Geelkerken RH, et al. Retrograde open mesenteric stenting for acute mesenteric ischemia. J Vasc Surg. 2014;60(3):726-34.
12. Banz VM, Paul K, de Moya M, Zimmermann H, Candinas D, Exadaktylos AK. Ignoring non-specific abdominal pain in emergency department patients may be related to decreased quality of life. A follow up of an underestimated problem. Swiss Med Wkly. 2011;141:w13167.
13. Bovenschen HJ, Laheij RJ, Tan AC, Witteman EM, Rossum LG, Jansen JB. Health-related quality of life of patients with gastrointestinal symptoms. Aliment Pharmacol Ther. 2004;20(3):311-9.
14. Detmar SB, Muller MJ, Schornagel JH, Wever LD, Aaronson NK. Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. JAMA. 2002;288(23):3027-34.
15. Kolkman JJ, Mensink PB, van Petersen AS, Huisman AB, Geelkerken RH. Clinical approach to chronic gastrointestinal ischaemia: from 'intestinal angina' to the spectrum of chronic splanchnic disease. Scand J Gastroenterol Suppl. 2004(241):9-16.
16. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001;33(5):337-43.

17. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials. 1989;10(4):407-15.
18. Gerlinger C, Schumacher U, Faustmann T, Colligs A, Schmitz H, Seitz C. Defining a minimal clinically important difference for endometriosis-associated pelvic pain measured on a visual analog scale: analyses of two placebo-controlled, randomized trials. Health Qual Life Outcomes. 2010;8:138.
19. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res. 2005;14(6):1523-32.
20. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997;26(3):517-38.
21. Diehm N, Baumgartner I, Jaff M, Do DD, Minar E, Schmidli J, et al. A call for uniform reporting standards in studies assessing endovascular treatment for chronic ischaemia of lower limb arteries. Eur Heart J. 2007;28(7):798-805.
22. Gralnek IM, Hays RD, Kilbourne A, Naliboff B, Mayer EA. The impact of irritable bowel syndrome on health-related quality of life. Gastroenterology. 2000;119(3):654-60.
23. Hou X, Chen S, Zhang Y, Sha W, Yu X, Elsawah H, et al. Quality of life in patients with Irritable Bowel Syndrome (IBS), assessed using the IBS-Quality of Life (IBS-QOL) measure after 4 and 8 weeks of treatment with mebeverine hydrochloride or pinaverium bromide: results of an international prospective observational cohort study in Poland, Egypt, Mexico and China. Clin Drug Investig. 2014;34(11):783-93.
24. Cremonini F, Nicandro JP, Atkinson V, Shringarpure R, Chuang E, Lembo A. Randomised clinical trial: alosetron improves quality of life and reduces restriction of daily activities in women with severe diarrhoea-predominant IBS. Aliment Pharmacol Ther. 2012;36(5):437-48.
25. Wang YT, Lim HY, Tai D, Krishnamoorthy TL, Tan T, Barbier S, et al. The impact of irritable bowel syndrome on health-related quality of life: a Singapore perspective. BMC Gastroenterol. 2012;12:104.
26. Gibson PR, Vaizey C, Black CM, Nicholls R, Weston AR, Bampton P, et al. Relationship between disease severity and quality of life and assessment of health care utilization and cost for ulcerative colitis in Australia: a cross-sectional, observational study. J Crohns Colitis. 2014;8(7):598-606.
27. Stark RG, Reitmeir P, Leidl R, Konig HH. Validity, reliability, and responsiveness of the EQ-5D in inflammatory bowel disease in Germany. Inflamm Bowel Dis. 2010;16(1):42-51.
28. Probert CS, Dignass AU, Lindgren S, Oudkerk Pool M, Marteau P. Combined oral and rectal mesalazine for the treatment of mild-to-moderately active ulcerative colitis: rapid symptom resolution and improvements in quality of life. J Crohns Colitis. 2014;8(3):200-7.
29. de Buck van Overstraeten A, Wolthuis AM, Vermeire S, Van Assche G, Laenen A, Ferrante M, et al. Long-term functional outcome after ileal pouch anal anastomosis in 191 patients with ulcerative colitis. J Crohns Colitis. 2014;8(10):1261-6.
30. Malik BA, Gibbons K, Spady D, Lees G, Otley A, Huynh HQ. Health-related quality of life in pediatric ulcerative colitis patients on conventional medical treatment compared to those after restorative proctocolectomy. Int J Colorectal Dis. 2013;28(3):325-33.
31. Luo N, Johnson J, Coons SJ. Using instrument-defined health state transitions to estimate minimally important differences for four preference-based health-related quality of life instruments. Med Care. 2010;48(4):365-71.



Chapter 9

Quality of life temporarily improved in patients in whom the diagnosis chronic mesenteric ischemia wasn't confirmed after multidisciplinary evaluation in a tertiary referral centre

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Abstract

Background Chronic mesenteric ischemia (CMI) is a disease in which abdominal symptoms are caused by insufficient mesenteric blood supply. Treatment results in improved quality of life (QoL). To put these results into perspective, the QoL of patients with symptoms potentially complying with CMI but without confirmation of the diagnosis was studied from six months up to four years.

Methods Between May and July 2020 follow-up questionnaires were sent to 144 patients that were suspected of CMI but in whom the diagnosis was not confirmed after a thorough multidisciplinary evaluation in a CMI expert centre. The baseline QoL was measured at first presentation. Three cohorts were included: 50 patients with a follow-up of six months, 45 patients with a follow-up of two years, and 49 patients with a follow-up of four years were invited to participate. The QoL was measured on a 100 points Visual Analogue Scale (VAS). A minimal clinically important difference of 7.5 was used as non-inferiority threshold.

Results The response rates were 34/50 (68%), 33/45 (73%), and 34/49 (69%). QoL improved in the six months group, with a mean change of 19 in VAS score (95% CI 11-27), in which baseline QoL was inferior to the QoL at follow-up (lower bound 95%CI above >7.5 threshold). The change in QoL was inconclusive in the other two groups, respectively 15(95% CI 6-24) and 3(95% CI -6-13). Furthermore, there was no significant change in QoL between patients without mesenteric stenosis and with one or two vessel stenosis (p=0.36) and between patients with occlusive stenosis and anatomic Median Arcuate Ligament Syndrome (MALS) (p=0.53).

Discussion The QoL of patients suspected for CMI was clinically significantly improved after six months without additional treatment. However, this improvement faded completely after four years.

Introduction

Chronic mesenteric ischemia (CMI) has been defined as insufficient mesenteric blood supply causing abdominal symptoms for at least three months.(1) Diagnosing CMI is challenged by the highly variable abdominal symptoms(2) and the high incidence of asymptomatic mesenteric artery stenosis (6 to 29% of general population).(3–11) Also, CMI is not rare with a reported incidence up to 9.3 per 100,000 people.(12) Symptoms and anatomy of patients suspected of CMI should be evaluated in a multidisciplinary team, consisting of gastroenterologists, vascular surgeons, and radiologists who are experienced with this pathology.(1, 13) The multidisciplinary team either confirms the suspicion of CMI and patients are treated accordingly, or rejects the suspicion of CMI and patients are referred back to their primary physician.

Although sustainable relief of abdominal symptoms after successful mesenteric artery revascularisation and thus restoring quality of life (QoL) is the primary goal of treatment, only three studies have focused on the QoL (after mesenteric revascularisation).(14,15,16) Two of these studies demonstrated a significantly improved QoL after revascularisation treatment suggesting that the treatments were successful.(14,15) The third study showed a significantly higher QoL in patients where the symptoms had disappeared compared to patients with persisting symptoms after surgical treatment for median arcuate ligament syndrome (MALS) (16), suggesting that the symptoms decreased the experienced QoL. To put the results of these studies into perspective, this comparison study was performed in patients with symptoms potentially complying with CMI that were not treated.

The present study aims to assess the QoL evolution over short-, mid-, and long-term follow-up for patients in whom a CMI diagnosis was rejected. We hypothesized that the QoL of these patients would not improve because the patients did not receive CMI treatment.

Methods

Study population

All patients suspected of CMI referred to the Medisch Spectrum Twente (MST), a tertiary referral centre for mesenteric ischemia, were included in a standardized digital mesenteric research database since 2014. The following parameters were registered: medical history, present symptoms, QoL measurement and visualization of mesenteric anatomy. The inclusion and exclusion criteria for the current study are listed in Table 1. The referral letter and accompanying computed tomography angiography (CTA) or magnetic resonance

angiography (MRA) of each referred patient were assessed "on paper" by the mesenteric ischemia group (MIG), a multidisciplinary team consisting of gastroenterologists, vascular surgeons and radiologists, to decide whether CMI was suspected based on symptoms CMI and/or significant mesenteric artery stenosis. In case of a suspicion of CMI, the patients were independently evaluated by a gastroenterologist and a vascular surgeon in the outpatient clinic. The findings were discussed in the MIG which then decided whether the diagnosis CMI should be confirmed (patients received a proposal for treatment) or rejected (patients were referred back to their primary physician).

For the current study three patient groups of the MST digital mesenteric research database were identified based on the duration of follow-up: group I) a cohort with a six months follow-up (multidisciplinary evaluation between June 2019 and January 2020), group II) a cohort with a two years follow-up (multidisciplinary evaluation between January and July 2018), and group III) a cohort with a four years follow-up (multidisciplinary evaluation between January and July 2016). Eligible patients were contacted by phone and email and asked to complete a second survey to collect their present QoL. Non-responders were approached to a maximum of five times.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
- Suspicion of mesenteric ischemia based on paper assessment by the multidisciplinary team - CMI or AMI rejected by the multidisciplinary team - No primary treatment for CMI or AMI - QoL survey was completed at intake	- Not fulfilling the inclusion criteria

AMI = acute mesenteric ischemia, CMI = chronic mesenteric ischemia, QoL = quality of life

Outcome measures

QoL was measured using a single-item self-rating 20cm VAS (Visual Analogue Scale), marked from 0 (worst imaginable quality of life) to 100 (best imaginable quality of life). This is a valid and reliable instrument for global QoL, and used for example in patients with inflammatory bowel disease (IBD). (17) A validated survey for CMI is not available. The baseline and follow-up QoL were measured with the same instrument, the patients were not reminded of their previous score.

To decide whether the follow-up QoL was significantly different compared to their baseline QoL, the minimal clinically important difference (MCID) was used. Because an MCID for CMI

on the VAS QoL scale has not been determined, we used an MCID of 7.5 based on scores calculated for chronic obstructive pulmonary disease (COPD), stroke and obesity patients. (18–20)

Statistical analysis

A sample size of 34 patients per group was calculated with a one-sided power analysis with alpha 2.5%, an assumed difference of 0, a standard deviation (SD) of 15 between the QoL at follow-up and the QoL at intake and a non-inferiority threshold of 7.5 to achieve a power of 80%.

Continuous variables were displayed as means (SD) or median (interquartile range, IQR) for respectively parametric and non-parametric. Categorical variables were displayed as numbers (percentages). Normally distributed continuous variables were compared between the different groups with an ANOVA test with post hoc Tukey's Honestly Significant Difference test. Not normally distributed continuous variables were compared with a Kruskal-Wallis test with post hoc Bonferroni Holm corrected Mann-Whitney U test. Categorical variables were compared with a Chi Square test or in case of small sample sizes with a Fisher Exact test. Paired continuous variables were compared with a paired samples T-test. The α-level was set on 0.05. To prove non-inferiority, the 95% confidence interval (95% CI) of the difference in QoL between baseline and follow-up should not exceed the defined non-inferiority threshold of 7.5.

The change in QoL (follow-up QoL minus baseline QoL) was analysed for three groups based on follow-up period: group I, group II and group III. The mean change in QoL was also analysed for two groups based on the number of mesenteric artery stenosis: group A) the patients with zero vessel stenosis, and group B) the patients with one or two vessel stenosis. Group B was then subdivided based on type of significant stenosis: group B1) the patients with a significant one or two vessel atherosclerotic stenosis, and group B2) the patients with anatomic MALS. A multivariate analysis was performed to investigate whether these results of comparison A/B were biased by a difference in follow-up period between the groups. Furthermore, to detect a possible selection bias the baseline characteristics between the responding patients, non-responding patients and the patients whose QoL VAS scale at intake was not registered because of an administrative error were compared.

The power calculation was performed with PASS 11.0 (NCSS, LLC. Kaysville, Utah, USA) and the statistical analyses were performed using SPSS Statistics version 27.0 (IBM Corporation, Armonk, NY, USA).

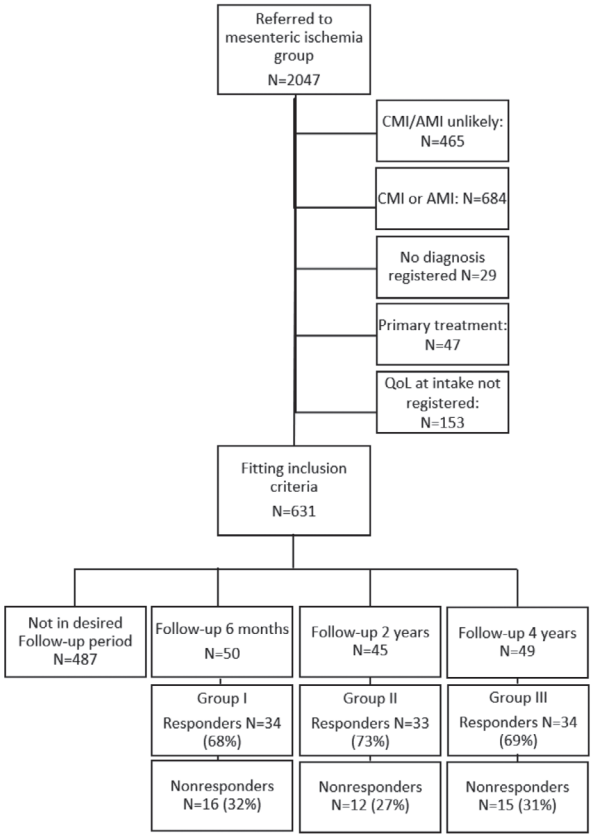
This study was exempted from approval from the Institutional Review Board.

Results

Patient population

Within the inclusion period, 631 patients registered in the database met the inclusion criteria. From these 631 patients, 144 were eligible to participate in the study: group I n=50, group II n=45, and group III n=49. Of these patients, 43 patients were excluded, because they did not respond after five approaches (n=30), refused participation (n=10) or passed away (n=3). This resulted in a final inclusion of 34 patients in group I, 33 patients in group II and 34 in group III, see Figure 1.

Figure 1 Flowchart inclusion process



AMI = acute mesenteric ischemia, CMI = chronic mesenteric ischemia, QoL = quality of life

Table 2 shows the baseline characteristics between the different follow-up groups. There were significantly more zero vessel stenosis in group III compared to groups I and II ($p<0.01$).

Table 2. Patient characteristics in groups based on follow-up period

	Group I 6 months follow-up (n=34)	Group II 2 years follow-up (n=33)	Group III 4 years follow-up (n=34)	p-value
Gender, women, n (%)	23 (68)	28 (85)	23 (68)	0.19[#]
Age at intake (IQR)	56 (32-69)	65 (54-71)	57 (48-65)	0.14[##]
Number of mesenteric stenosis (%)				**<0.01**[###]
0	11 (32)	12 (36)	23 (68)	
1	23 (68)	18 (55)	11 (32)	
2		3 (9)		
3				
Secondary treatment, n(%)				
Surgical	1 (3)			
Medication			(3)	

[#] Chi Square test
[##] Kruskal-Wallis test
[###] Fisher Exact test

Supplemental Table 1 reported the basic characteristics of the responding, the non-responding and the patients whose QoL VAS scale at intake was not registered. There was no significant difference in gender, age at intake, number of mesenteric stenosis and QoL at intake between these groups.

Change in QoL

Group I showed a significantly improved QoL with an increase of 19 points on the VAS scale (95% CI 11-27), in which baseline QoL was inferior to the QoL at follow-up (lower bound 95%CI above >7.5 threshold). The change in QoL was inconclusive in the other two groups, Table 3. The difference in change in QoL between the three follow-up groups was significant (p=0.04) and originated from the significant difference in change in QoL between group I and group III of 16 points (p=0.04).

Table 3. Quality of Life (QoL) before and after follow-up in groups based on follow-up period

Patients	Group I 6 months (n=34)	Group II 2 years (n=33)	Group III 4 years (n=34)	P
Mean change QoL * (95% CI)	**19 (11-27)**	15 (6-24)	3 (-6-13)	**0.04**[#]
Median QoL intake (IQR)	35 (27-60)	45 (20-68)	50 (30-66)	0.51[##]
Median QoL follow-up (IQR)	68 (47-79)	66 (45-80)	56 (44-68)	0.08[##]

[*] Follow-up QoL minus baseline QoL
[#] ANOVA test
[##] Kruskal-Wallis test

Furthermore, there was no significant change in QoL between patients without mesenteric stenosis (Group A) and with one or two vessel stenosis (Group B) in a follow-up period between six months and four years (p=0.36) (Table 4). Within group B, there was no significant difference in change in QoL between patients with atherosclerotic mesenteric artery stenosis (B1) and anatomic MALS (Group B2) (p=0.53) (Supplemental Table 2). Due to a difference in follow-up time between patients with and without mesenteric stenosis, a multivariate linear regression analysis was performed to correct for this potential confounder. After correction for follow-up, the change in QoL between group A and B (p=0.07) and between group B1 and B2 was still not significant (p=0.67).

Table 4. Quality of Life (QoL) before and after follow-up in groups based on number of mesenteric stenosis.

Patients		Group A 0 vessel stenosis (n=46)	Group A 1 or 2 vessel stenosis (n=55)	P
Gender, women, n (%)		34 (74)	40 (73)	0.89[#]
Age at intake (IQR)		62 (44-67)	56 (41-70)	0.67[##]
Follow-up Group (%)	**I (6 months)**	11 (24)	23 (42)	**<0.01**[#]
	II (2 years)	12 (26)	21 (38)	
	III (4 years)	23 (50)	11 (20)	
Mean change QoL * (95% CI)		14 (6-23)	10 (3-17)	0.36[###]
QoL intake (IQR)		45 (30-61)	47 (20-68)	1.00[##]
QoL follow-up (IQR)		64 (46-80)	60 (40-73)	0.39[##]

* Follow-up QoL minus baseline QoL

[#] Chi Square test

[##] Mann-Whitney test [####]ANOVA test

Discussion

This study is the first to evaluate the evolution of QoL in patients in which the diagnosis of CMI was rejected after multidisciplinary evaluation. The hypothesis that the follow-up QoL would be non-inferior compared to the baseline QoL, was rejected for the six months follow-up group. The QoL of these patients improved clinically significantly with a mean increase of 19 on a 100 points VAS scale After two years, the QoL was numerically lower and baseline QoL was no longer inferior to Qol at follow-up, the effect completely faded after four years. The short-term increase in QoL may have been an effect of the attention and thorough evaluation at the expert centre for mesenteric ischemia. In the present study there was no significant difference in QoL improvement between patients with zero vessel stenosis and one or two vessel stenosis and between patients with coeliac artery compression and with one or two vessel atherosclerotic stenosis.

This study was performed to put the results of three studies on QoL after revascularization in CMI patients into perspective. Blauw et al. (15) investigated QoL after revascularisation in CMI patients using VAS scores of 31 patients that were measured between six months and three years after revascularisation treatment which improved with a mean change of 16 compared to intake measurement. Skelly et al. (14) investigated the health-related quality of life (HRQoL) in 51 MALS patients before and six months after surgery which improved with a mean change of 12. Pather et al. (16) investigated the gastrointestinal quality of life index (GIQLI) of 46 MALS patients after coeliac artery release with a mean follow up of 8 years after surgery, with a significantly higher mean QoL of 80 GIQLI in 30 patients where the symptoms had disappeared compared to 53 in 16 patients with persisting symptoms. Since our patients with symptoms potentially complying with CMI showed a comparable short-term increase in QoL without treatment, the improvement in QoL in studies with follow-up of six months (14,15), could be (partially) caused by another effect then treatment. The short-term increase in QoL seemed temporarily and disappeared completely after four years, the appropriate follow-up period to detect real changes in QoL may even be four years.

Attention and recognition for the disabling symptoms influences the patient's perceived QoL; 151 hospitalised older adults demonstrated that 70% of the participants changed their VAS score more than 5 points after a detailed explanation of their extremely good or poor health status (21). Also, patients with irritable bowel syndrome (IBS), showed improved QoL caused by psychological therapy. (22–25) Consequently, the improvement in QoL in the first months after a thorough analyses of the symptoms as observed in the present study may

occur without an objective change in underlying health state and should be interpreted with caution. In other words, this indicates that for assessment of the QoL improvement of an intervention, a six months period may be too short, or should be corrected for the effect in patients that did not receive treatment.

This study is thus far the largest study investigating the development of the QoL in a representative population of patients with symptoms potentially complying with CMI but after multidisciplinary evaluation ultimately rejected diagnosis of CMI with a follow-up period varying from six months to four years. The evaluation took place in the National Expert Centre for Gastrointestinal Ischemia. During the study period the procedure of the evaluation did not change. The transversal study design offers the opportunity to compare the follow-up score to the intake measurement of the same patient.

A limitation of the transversal study design is a potential difference in characteristics and baseline QoL between the three follow-up groups. However, the only significant difference that was found was that the four years follow-up group (group III) comprised of more patients with zero vessel stenosis whereas the other two groups comprised of more patients with one vessel stenosis. Nevertheless, no significant difference in QoL change was shown between the patients with zero vessel stenosis and one or two vessel stenosis in current research. Another limitation of the study is a potential selection bias caused by the group of patients in which the intake VAS score was not registered, and the non-responders. However, the basic characteristics of these patients were not significantly different from the characteristics of the responders (data in supplemental table 1), making it unlikely that the selection bias was actually present.

Conclusion

QoL improves clinically and statistically significant in patients with chronic abdominal pain, but not diagnosed with CMI, within the first six months after an intensive diagnostic trajectory without any therapeutic intervention. However, this QoL improvement completely faded after four years follow-up. Hence, attention and extensive evaluation for the unexplained complaints at an expert centre may lead to short-term improvement of experienced QoL. This indicates that for assessment of the QoL improvement of an intervention, the appropriate follow-up period to detect real changes in QoL may be four years.

Appendix: Supplemental Tables

Supplemental Table 1. Patient characteristics of the excluded patients

	Responders (n=101)	Non-responders (n=43)	QoL at intake not registered (n=153)	P
Gender, women, n (%)	74 (73)	31 (72)	102 (67)	0.50[#]
Age at intake (IQR)	60 (43-70)	56 (45-69)	60 (40-73)	0.54[##]
Number of mesenteric stenosis (%)				
0	46 (46)	13 (30)	75 (49)	0.13[###]
1	52 (52)	27 (63)	66 (43)	
2	3 (3)	3 (7)	11 (7)	
3	-	-	1 (1)	
Median QoL at intake (IQR)	45 (25-65)	28 (10-67)	-	0.09[##]

[#] Chi Square test

[##] Kruskal-Wallis test

[###] Fisher Exact test

Supplemental Table 2. Quality of Life (QoL) before and after follow-up in groups based on type of significant stenosis

Patients	Group B1 Occlusive vessel stenosis (n=20)	Group B2 Anatomic MALS (n=35)	P
Mean change QoL * (95% CI)	8 (-5-20)	12 (4-20)	0.53[#]
Median QoL intake (IQR)	38 (18-69)	50 (20-77)	0.66[##]
Median QoL follow-up (IQR)	53 (36-67)	66 (45-75)	0.26[##]

* Follow-up QoL minus baseline QoL

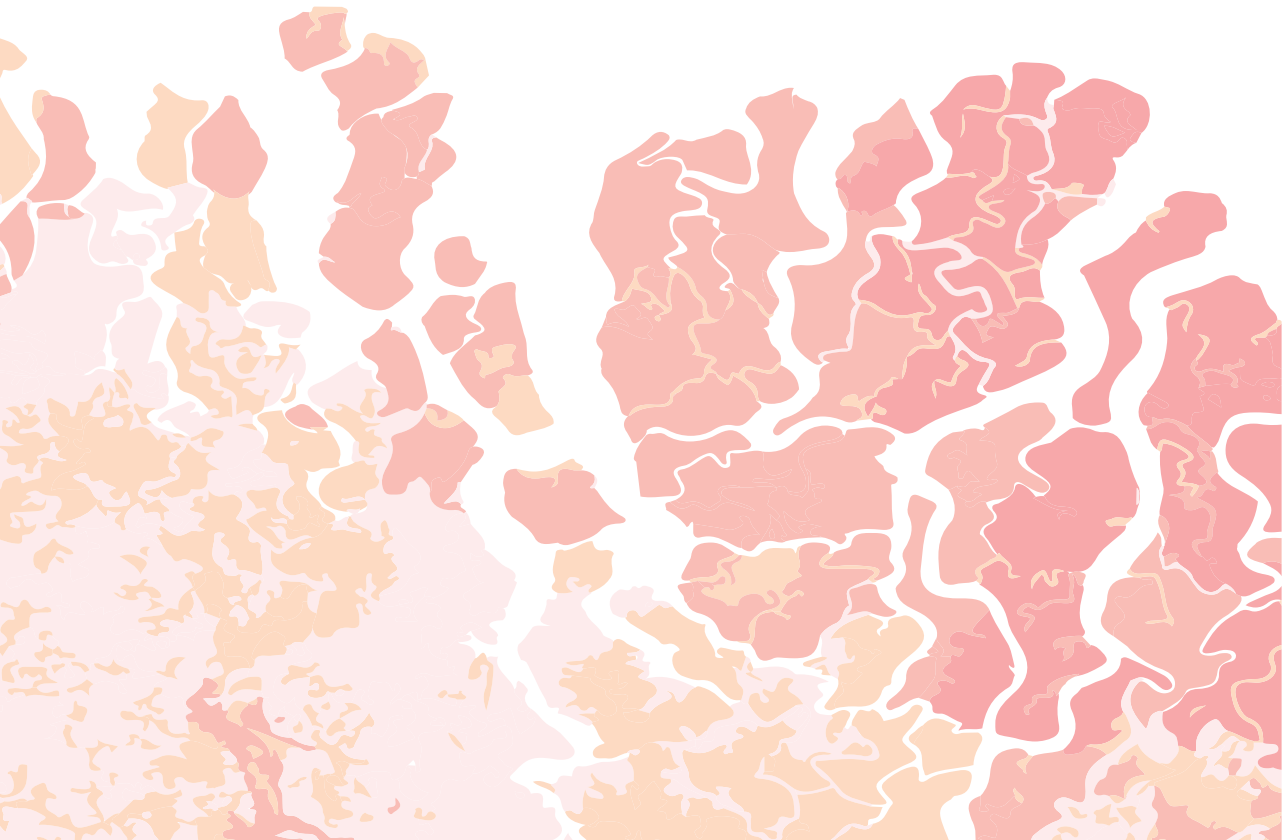
[#] ANOVA test

[##] Mann-Whitney test

References

1. Björck M, Koelemay M, Acosta S, Bastos Goncalves F, Kölbel T, Kolkman JJ, et al. Editor's Choice – Management of the Diseases of Mesenteric Arteries and Veins: Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2017 Apr 1;53(4):460–510. DOI: 10.1016/j.ejvs.2017.01.010.
2. van Dijk LJD, Noord D van, de Vries AC, Kolkman JJ, Geelkerken RH, Verhagen HJM, et al. Clinical management of chronic mesenteric ischemia. United Eur Gastroenterol J. 2019;7(2):179–88. DOI: 10.1177/2050640618817698.
3. Derrick JR, Pollard HS, Moore RM. The pattern of arteriosclerotic narrowing of the celiac and superior mesenteric arteries. Ann Surg. 1959;149(5):684–9. DOI: 10.1097/00000658-195905000-00009.
4. Croft RJ, Menon GP, Marston A. Does 'intestinal angina' exist? A critical study of obstructed visceral arteries. Br J Surg. 1981 May;68(5):316–8. DOI: 10.1002/bjs.1800680509.
5. Järvinen O, Laurikka J, Sisto T, Salenius JP, Tarkka MR. Atherosclerosis of the visceral arteries. Vasa. 1995;24(1):9–14. http://www.ncbi.nlm.nih.gov/pubmed/7725785.
6. Bron KM, Redman HC. Splanchnic Artery Stenosis and Occlusion. Radiology. 1969 Feb;92(2):323–8. DOI: 10.1148/92.2.323.
7. Mensink PBF, Moons LMG, Kuipers EJ. Chronic gastrointestinal ischaemia: shifting paradigms. Gut. 2011 May 1;60(5):722–37. DOI: 10.1136/gut.2009.199695.
8. Glockner JF. Incidental findings on renal MR angiography. Am J Roentgenol. 2007 Sep;189(3):693–700. DOI:10.2214/AJR.07.2151.
9. Hansen KJ, Wilson DB, Craven TE, Pearce JD, English WP, Edwards MS, et al. Mesenteric artery disease in the elderly. J Vasc Surg. 2004 Jul;40(1):45–52. DOI: 10.1016/j.jvs.2004.03.022.
10. Park CM, Chung JW, Kim HB, Shin SJ, Park JH. Celiac Axis Stenosis: Incidence and Etiologies in Asymptomatic Individuals. Korean J Radiol. 2001;2(1):8. DOI: 10.3348/kjr.2001.2.1.8.
11. Roobottom CA, Dubbins PA. Significant disease of the celiac and superior mesenteric arteries in asymptomatic patients: predictive value of Doppler sonography. Am J Roentgenol. 1993 Nov;161(5):985–8. DOI: 10.2214/ajr.161.5.8273642.
12. Terlouw LG, Verbeten M, van Noord D, Brusse-Keizer M, Beumer RR, Geelkerken RH, et al. The Incidence of Chronic Mesenteric Ischemia in the Well-Defined Region of a Dutch Mesenteric Ischemia Expert Center. Clin Transl Gastroenterol. 2020 Aug;11(8):e00200. DOI: 10.14309/ctg.0000000000000200.
13. Terlouw LG, Moelker A, Abrahamsen J, Acosta S, Bakker OJ, Baumgartner I, et al. European guidelines on chronic mesenteric ischaemia – joint United European Gastroenterology, European Association for Gastroenterology, Endoscopy and Nutrition, European Society of Gastrointestinal and Abdominal Radiology, Netherlands Association of Hepa. United Eur Gastroenterol J. 2020 May 16;8(4):371–95. DOI: 10.1177/2050640620916681.
14. Skelly CL, Stiles-Shields C, Mak GZ, Speaker CR, Lorenz J, Anitescu M, et al. The impact of psychiatric comorbidities on patient-reported surgical outcomes in adults treated for the median arcuate ligament syndrome. J Vasc Surg. 2018. Nov;68(5):1414–21. DOI: 10.1016/j.jvs.2017.12.078.
15. Blauw JTM, Pastoors HAM, Brusse-Keizer M, Beuk RJ, Kolkman JJ, Geelkerken RH, et al. The Impact of Revascularisation on Quality of Life in Chronic Mesenteric Ischemia. Can J Gastroenterol Hepatol. 2019 Nov 12;2019:1–7. DOI: 10.1155/2019/7346013.

16. Pather K, Kärkkäinen JM, Tenorio ER, Bower TC, Kalra M, DeMartino R, et al. Long-term symptom improvement and health-related quality of life after operative management of median arcuate ligament syndrome. J Vasc Surg [Internet]. 2020 Nov;S0741-5214(20):32480–0. DOI: 10.1016/j.jvs.2020.10.074
17. Stark RG, Reitmeir P, Leidl R, König H-H. Validity, reliability, and responsiveness of the EQ-5D in inflammatory bowel disease in Germany. Inflamm Bowel Dis. 2010 Jan;16(1):42–51. DOI: 10.1002/ibd.20989.
18. Zanini A, Aiello M, Adamo D, Casale S, Cherubino F, Della Patrona S, et al. Estimation of Minimal Clinically Important Difference in EQ-5D Visual Analog Scale Score After Pulmonary Rehabilitation in Subjects With COPD. Respir Care. 2015 Jan 1;60(1):88–95. DOI:10.4187/respcare.03272.
19. Chen P, Lin K-C, Liing R-J, Wu C-Y, Chen C-L, Chang K-C. Validity, responsiveness, and minimal clinically important difference of EQ-5D-5L in stroke patients undergoing rehabilitation. Qual Life Res. 2016 Jun 30;25(6):1585–96. DOI: 10.1007/s11136-015-1196-z.
20. Warkentin LM, Majumdar SR, Johnson JA, Agborsangaya CB, Rueda-Clausen CF, Sharma AM, et al. Weight loss required by the severely obese to achieve clinically important differences in health-related quality of life: two-year prospective cohort study. BMC Med. 2014 Dec 15;12(1):175. DOI: 10.1186/s12916-014-0175-5.
21. McPhail S, Beller E, Haines T. Reference bias: presentation of extreme health states prior to EQ-VAS improves health-related quality of life scores. A randomised crossover trial. Health Qual Life Outcomes. 2010 Dec 2;8(1):146. DOI: 10.1186/1477-7525-8-146.
22. Altayar O, Sharma V, Prokop LJ, Sood A, Murad MH. Psychological Therapies in Patients with Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Gastroenterol Res Pract. 2015;2015:1–19. DOI: 10.1155/2015/549308.
23. Basnayake C, Kamm MA, Salzberg MR, Wilson-O'Brien A, Stanley A, Thompson AJ. Delivery of care for functional gastrointestinal disorders: A systematic review. J Gastroenterol Hepatol [Internet]. 2020 Feb 3;35(2):204–10. DOI: 10.1111/jgh.14830.
24. Kruimel J, Leue C, Winkens B, Marcus D, Schoon S, Dellink R, et al. Integrated medical–psychiatric outpatient care in functional gastrointestinal disorders improves outcome. Eur J Gastroenterol Hepatol. 2015 Jun;27(6):721–7. DOI 10.1097/MEG.0000000000000335.
25. Kinsinger SW, Ballou S, Keefer L. Snapshot of an integrated psychosocial gastroenterology service. World J Gastroenterol. 2015;21(6):1893. DOI: 10.3748/wjg.v21.i6.1893.



Chapter 10

Summary

The aim of this thesis was to make a significant contribution to the improvement of quality of life (QoL) and organ-sparing treatment for patients with mesenteric ischemia by providing more insight into contemporary diagnostic and therapeutic developments. Creating more awareness is the first step in abandoning old routines and beliefs.

Part I Developments in Diagnostics and the evolution of Treatment

First of all, it is important to improve the diagnostic process, because diagnostic delay is the number one contributing factor in the overall morbidity, mortality and societal burden of mesenteric ischemia, mainly for acute mesenteric ischemia (AMI) patients. Therefore, to start Part I, we focussed on the present status of diagnostic developments in occlusive AMI patients. Patients and their physicians are in desperate need of a more accurate, less invasive, rapidly and 24/7 available cost-effective diagnostic test. The gold standard now is a high index of suspicion combined with a 1-mm abdominal multislice multiphase computer tomography angiography (CTA) scan.(1) Although CTA has a 73% to 100% and 90% to 100% sensitivity and specificity for diagnosing acute superior mesenteric artery (SMA) occlusion, the possible presence of mesenteric ischemia must be recognized and acknowledged before the radiological images can and will be correctly assessed.(1) There has been an increasing interest in the possible use of biomarkers to shorten diagnostic delay. In **Chapter 2** we have conducted a systemic review to define whether biomarkers have any potential diagnostic value for AMI. We included 49 suitable articles describing a total of 60 different biomarkers. However, we observed an enormous heterogeneity in the used inclusion and exclusion criteria, study populations and control groups, normal values and cut-off values, making it virtually impossible to compare the outcomes. Furthermore, the overall methodological quality of the articles was low. Primarily due to the high number of retrospective studies and the use of laparotomy as the reference test. Since diagnosis during a laparotomy often means that it is already too late. Based on this review we conclude that up to know no final decision can be made based on any biomarker or combination of biomarkers in the diagnostic process of AMI patients. This also accounts for leukocytes, lactate and D-dimer. The actual diagnosis of AMI can currently only be made on the basis of a high index of suspicion followed by a multislice CTA.

In order to be able to act in a truly organ-saving manner and to improve QoL, the outcome of treatment must of course improve. Therefore, we continued Part I with a focus on the evolution of treatment strategies and techniques that are now available. But also, on the additional and supportive measures we can offer our patients. Minimally invasive endovascular treatment options had been emerging since the 80s', with the advantages of

less in-hospital mortality and morbidity, shorter hospital stay and more availability in high-risk patients, but with lower primary patency and higher symptom recurrence rates then open surgical treatment.(2, 3) In 2006, percutaneous mesenteric artery stenting (PMAS) became the primary treatment option for mesenteric ischemia patients in Medisch Spectrum Twente (MST). To see whether there still was a place for open surgical mesenteric artery repair (OSMAR), we evaluated the outcome of OSMAR in chronic mesenteric ischemia (CMI) patients with coeliac artery (CA) or SMA stenosis treated between 1997 and 2014 in MST in **Chapter 3**. Patients were divided in a before 2006 group or a from 2006 group. Technical success was achieved in all patients, with more clinical failures in the historical group, 30.4% versus 34.1%. The only significant difference found was the superior primary patency of SMA reconstructions in the historical group (1-, 3- and 5 years follow-up). There were trends of less multivessel repairs, less antegrade situated bypasses, decreased clinical success but improved 30 days- and long-term survival after OSMAR. The most obvious explanations for this could be the more extensive mesenteric atherosclerosis and the severity of the patients' condition undergoing OSMAR in the “PMAS first” period from 2006. This study showed that elective OSMAR should only be used in patients with substantial physiologic reserve, with unfavourable mesenteric lesions, failed repeated PMAS or multiple recurrences of in-stent stenosis/occlusion. It strengthened our believe that PMAS is no longer a “bridge to surgery” for CMI patients, but a strong first choice treatment, with a side note of a “bridge to repeated PMAS”.

In **Chapter 4** we went a step further, to show that OSMAR should not even be second choice in AMI patients, because we presented a better alternative which combines the advantages of open surgical and endovascular approaches, retrograde open mesenteric stenting (ROMS). It is a hybrid technique in which, via a small transverse upper abdominal laparotomy, retrograde stenting of the SMA can be performed with the direct possibility of assessing bowel vitality. Between January 2007 and September 2011, we included 15 consecutive patients undergoing ROMS for AMI. Technical success was achieved in 14 patients. Two patients had severely ischemic small bowel of which one needed a partial bowel resection due to irreversible transmural ischemia. Thirty days mortality rate was 20% and primary patency was 92%. Ten patients underwent unplanned relaparotomy of which one needed resection of a large part of the small bowel. Twelve months mortality rate was still 20%, with primary patency of 83%. Primary assisted patency was 91% and secondary patency was 100%. Clinical success at 30 days and 12 months was 73% and 67%, respectively. We were not the first to show the great outcome of ROMS, but we showed the biggest patient population until that time. And our results were part of the substantiation of

Recommendation 26 in the ESVS 2017 Guideline that ROMS is the second-choice treatment option for AMI patients.(1)

And to finally make our statement on the advantages of PMAS for AMI patients we described the current insights in treatment options for mesenteric ischemia in **Chapter 5.** We also performed a small systematic review on articles between September 2013 and July 2016 comparing PMAS and OSMAR for mesenteric ischemia, leading to multiple practice points for clinicians to integrate in their daily practices. The most essential message in improving survival, QoL and intestinal salvage for AMI is to “Revascularize first, resect later” and that these patients need centers with 24/7 service and experience in both open and endovascular revascularization.(4-8) This statement paved the way for Recommendation 10 in the ESVS 2017 Guideline.(1) We also showed that PMAS is first choice treatment for AMI and CMI, with better short-term outcome, lower mortality and morbidity and reduced costs.(2, 3, 5, 6, 9-35) And that OSMAR should only be used in low-risk patients with unfavourable mesenteric lesions, failed repeated PMAS or ROMS or multiple recurrences of in-stent stenosis or occlusion.(4, 27) In case of on-going ischemia or inability to determine if additional resection is needed, a second look laparotomy after 18-36 hours is advised. Delayed reconstruction of bowel continuity is preferred as opposed to ostomies, due to the impact on morbidity and QoL.(5) Gradually and strictly monitored refeeding is crucial and all patients should be on lifelong anticoagulant therapy.(36)

Part II Life after mesenteric ischemia

Since 2017, 3 guidelines have been published that have come to the same conclusions as this thesis has described so far. The biggest gap in the current literature, however, is research into the impact of mesenteric ischemia and its treatment on our patients and their QoL. In other words, do we actually heal our patients and improve their QoL? This was discussed in Part II, for CMI and non-CMI patients.

The existence of the median arquate ligament syndrome (MALS), also known as Dunbar’s Syndrome or the coeliac artery compression syndrome (CACS), has been the subject of debate since its first description in the late 1950's early 1960's, leading to 'believers' and 'non-believers'. Many discussions have already taken place about the existence or non-existence of this disease and thus whether patients should be treated and whether that treatment is useful in improving QoL and reducing the burden of disease and lowering social and financial burdens on society. In **Chapter 6** we performed a systematic review on the impact of surgical decompression of the median arcuate ligament (MAL) on symptoms and

QoL in MALS patients. Overall quality of the articles was very low with great heterogeneity and most articles presented less than 10 patients. The treatment of MALS did improve QoL in 68% of patients supporting our believe of the existence of MALS and the possible positive effect of treatment with endoscopic coeliac artery release, (e)CAR. However, we showed a dire need for a good, prospective randomised controlled trial (RCT) to really show whether MALS exists and if (e)CAR is the answer for those who suffer from it. This review further showed that there is no reasonable support for a neurogenic origin of MALS and thus that there is no place for a plexus block in the treatment of these patients.

On behalf of the Dutch Mesenteric Ischemia Study Group (DMIS) we presented our application for the 'Promising care' project of the National Healthcare Institute for this double-blind prospective sham controlled RCT, the CARoSO study in **Chapter 7**. We hope that funding will be allocated in February of 2022, for us to publish the study protocol and start the study. Seventy patients will be randomised into a treatment group ((e)CAR) and a sham group to establish if retroperitoneal endovascular MAL release does relieve symptoms and improve QoL (measured with the EQ-5D-5L) in a two-year follow-up. The study will either demonstrate that (e)CAR is a (cost)effective minimally invasive treatment for MALS. Or it will prevent patients from being exposed to a futile intervention. If the effectiveness of (e)CAR is proven, it is estimated that up to 490 patients with chronically debilitating abdominal complaints in the Netherlands alone can be treated annually. Due to the relatively young age of between 20-40 years of this patient population, an average health gain of 6.05 Quality Adjusted Life Years (QALYs)/patient is expected. In addition, up to €4.3 million societal costs per year could be saved, due to a reduction of the substantial loss of productivity and healthcare consumption caused by MALS. As the necessity of conducting this study has been underlined by 2 recent international guidelines,(1, 37) the outcome of the CARoSO study will be translated into strong recommendations in the upcoming updates of all relevant (inter)national guidelines and, if effective, (e)CAR will become the standard treatment for MALS.

So, there is little known about the impact treatment has on the QoL of MALS patients, but do we know anything about the impact treatment has on the QoL of CMI patients in general? That is what we investigated in **Chapter 8** and it turned out that we were the first to evaluate the impact of revascularization on quality of life in CMI patients. We compared pre- and post-intervention QoL data measured with the EuroQol-5D by analysing the minimum clinically important difference (MCID) to see if there was any clinical relevance. For this we used the MCID of irritable bowel syndrome (IBS) of 0.074, because there has not been a MCID established for CMI. We showed that the median EQ-index score increased

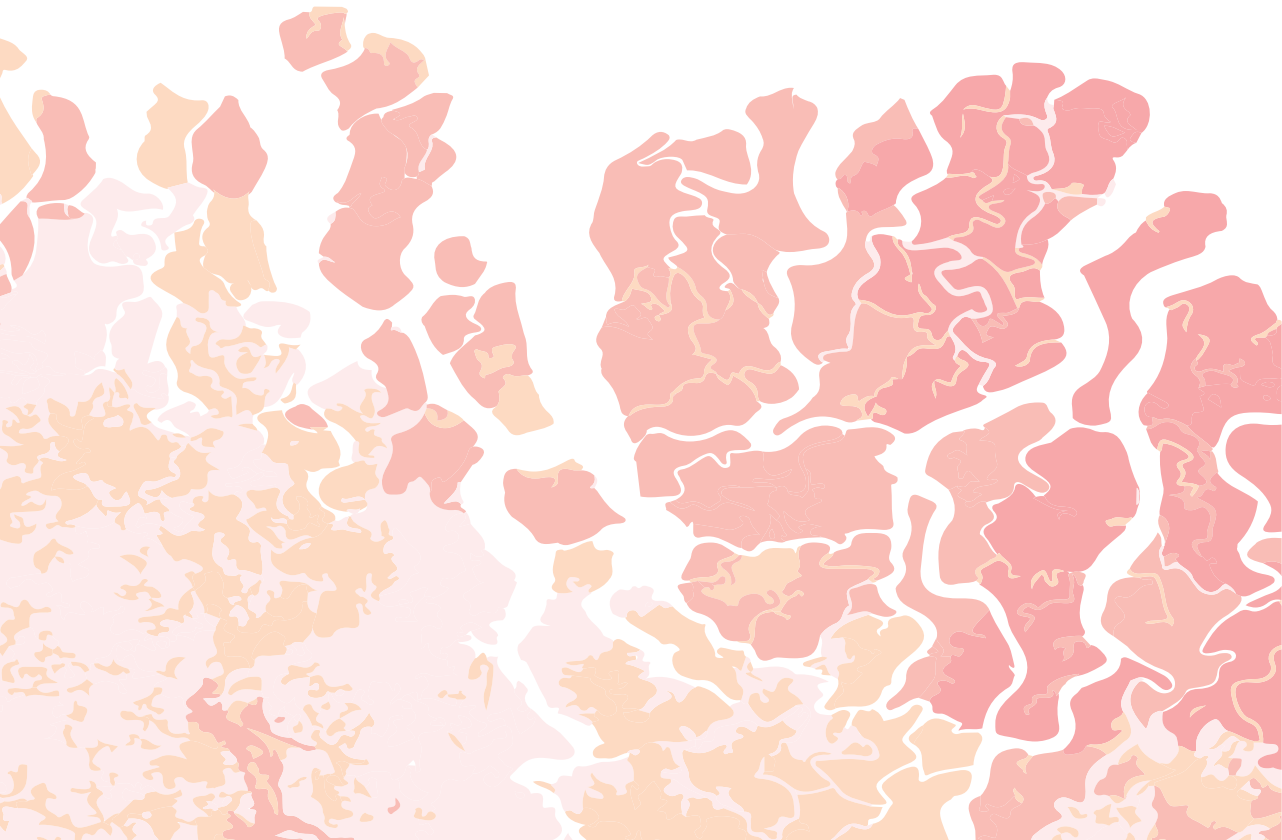
significantly from 0.70 to 0.81 (p=0.02) with a mean difference of 0.162 which exceeds the MCID. Furthermore, patients had a significant reduction of symptoms in the domains usual activities (34.4%) and pain/discomfort (32.3%). Also, the overall current health condition expressed in the visual analogue scale (VAS) improvement significantly with 17% from 52 to 69 (p=0.001). These findings indicate that there is a clinically relevant improvement of QoL after revascularisation for CMI patients.

As the MST is a tertiary referral center for patients with chronic abdominal symptoms suspected of mesenteric ischemia, treating around 400 patients with mesenteric ischemia each year, the number of referred patients is higher, because naturally not all patients do have mesenteric ischemia. In **Chapter 9** we performed a follow-up on patients diagnosed as not having CMI by the multidisciplinary expert panel to investigate whether the extensive diagnostic work up, including shared decision making, influenced their QoL. Six months after the assessment the QoL was clinically significantly improved without the patients actually undergoing treatment. However, this effect faded after two years to completely be gone after four years. The short-term increase in QoL may have been an effect of the attention and thorough evaluation at the expert centre for mesenteric ischemia. Consequently, the improvement in QoL in the first months after a thorough analyses of the symptoms as observed in the present study may occur without an objective change in underlying health state and should be interpreted with caution. In other words, this indicates that for assessment of the QoL improvement of an intervention, a six months period may be too short.

References

1. Björck M, Koelemay M, Acosta S, Bastos Goncalves F, Kölbel T, Kolkman JJ, et al. Editor's Choice - Management of the Diseases of Mesenteric Arteries and Veins: Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2017;53(4):460-510.
2. Oderich GS, Malgor RD, Ricotta JJ, 2nd. Open and endovascular revascularization for chronic mesenteric ischemia: tabular review of the literature. Ann Vasc Surg. 2009;23(5):700-12.
3. van Petersen AS, Kolkman JJ, Beuk RJ, Huisman AB, Doelman CJ, Geelkerken RH, et al. Open or percutaneous revascularization for chronic splanchnic syndrome. J Vasc Surg. 2010;51(5):1309-16.
4. Acosta S. Mesenteric ischemia. Curr Opin Crit Care. 2015;21(2):171-8.
5. Acosta S, Bjorck M. Modern treatment of acute mesenteric ischaemia. Br J Surg. 2014;101(1):e100-8.
6. Roussel A, Castier Y, Nuzzo A, Pellenc Q, Sibert A, Panis Y, et al. Revascularization of acute mesenteric ischemia after creation of a dedicated multidisciplinary center. J Vasc Surg. 2015;62(5):1251-6.
7. Wyers MC. Acute mesenteric ischemia: diagnostic approach and surgical treatment. Semin Vasc Surg. 2010;23(1):9-20.
8. Stone JR, Wilkins LR. Acute mesenteric ischemia. Tech Vasc Interv Radiol. 2015;18(1):24-30.
9. Beaulieu RJ, Arnaoutakis KD, Abularrage CJ, Efron DT, Schneider E, Black JH, 3rd. Comparison of open and endovascular treatment of acute mesenteric ischemia. J Vasc Surg. 2014;59(1):159-64.
10. Blauw JT, Meerwaldt R, Brusse-Keizer M, Kolkman JJ, Gerrits D, Geelkerken RH, et al. Retrograde open mesenteric stenting for acute mesenteric ischemia. J Vasc Surg. 2014;60(3):726-34.
11. Karkkainen JM, Lehtimaki TT, Saari P, Hartikainen J, Rantanen T, Paajanen H, et al. Endovascular Therapy as a Primary Revascularization Modality in Acute Mesenteric Ischemia. Cardiovasc Intervent Radiol. 2015;38(5):1119-29.
12. Eslami MH, Rybin D, Doros G, McPhee JT, Farber A. Mortality of acute mesenteric ischemia remains unchanged despite significant increase in utilization of endovascular techniques. Vascular. 2016;24(1):44-52.
13. Serracant Barrera A, Luna Aufroy A, Hidalgo Rosas JM, Canovas Moreno G, Fortuno Andres JR, Falco Fages J, et al. Acute mesenteric ischemia: Utility of endovascular techniques. Cir Esp. 2015;93(9):567-72.
14. Puippe GD, Suesstrunk J, Nocito A, Pfiffner R, Glenck M, Pfammatter T. Outcome of endovascular revascularisation in patients with acute obstructive mesenteric ischaemia - a single-centre experience. Vasa. 2015;44(5):363-70.
15. Duran M, Pohl E, Grabitz K, Schelzig H, Sagban TA, Simon F. The importance of open emergency surgery in the treatment of acute mesenteric ischemia. World J Emerg Surg. 2015;10:45.
16. Arya S, Kingman S, Knepper JP, Eliason JL, Henke PK, Rectenwald JE. Open Mesenteric Interventions Are Equally Safe as Endovascular Interventions and Offer Better Midterm Patency for Chronic Mesenteric Ischemia. Ann Vasc Surg. 2016;30:219-26.
17. Plumereau F, Mucci S, Le Naoures P, Finel JB, Hamy A. Acute mesenteric ischemia of arterial origin: importance of early revascularization. J Visc Surg. 2015;152(1):17-22.
18. Forbrig R, Renner P, Kasprzak P, Dahlke MH, Muller-Wille R, Stroszczynski C, et al. Outcome of primary percutaneous stent-revascularization in patients with atherosclerotic acute mesenteric ischemia. Acta Radiol. 2016.
19. Schermerhorn ML, Giles KA, Hamdan AD, Wyers MC, Pomposelli FB. Mesenteric revascularization: management and outcomes in the United States, 1988-2006. J Vasc Surg. 2009;50(2):341-8 e1.

20. Moghadamyeghaneh Z, Carmichael JC, Mills SD, Dolich MO, Pigazzi A, Fujitani RM, et al. Early Outcome of Treatment of Chronic Mesenteric Ischemia. Am Surg. 2015;81(11):1149-56.
21. Oderich GS, Gloviczki P, Bower TC. Open surgical treatment for chronic mesenteric ischemia in the endovascular era: when it is necessary and what is the preferred technique? Semin Vasc Surg. 2010;23(1):36-46.
22. Kasirajan K, O'Hara PJ, Gray BH, Hertzer NR, Clair DG, Greenberg RK, et al. Chronic mesenteric ischemia: open surgery versus percutaneous angioplasty and stenting. J Vasc Surg. 2001;33(1):63-71.
23. Pecoraro F RZ, Lachat M, et al. Chronic mesenteric ischemia: critical review and guidelines for management. Ann Vasc Surg. 2013;27(1):113-122.
24. Indes JE, Giacovelli JK, Muhs BE, Sosa JA, Dardik A. Outcomes of endovascular and open treatment for chronic mesenteric ischemia. J Endovasc Ther. 2009;16(5):624-30.
25. Biebl M, Oldenburg WA, Paz-Fumagalli R, McKinney JM, Hakaim AG. Surgical and interventional visceral revascularization for the treatment of chronic mesenteric ischemia--when to prefer which? World J Surg. 2007;31(3):562-8.
26. Assar AN, Abilez OJ, Zarins CK. Outcome of open versus endovascular revascularization for chronic mesenteric ischemia: review of comparative studies. J Cardiovasc Surg (Torino). 2009;50(4):509-14.
27. Atkins MD, Kwolek CJ, LaMuraglia GM, Brewster DC, Chung TK, Cambria RP. Surgical revascularization versus endovascular therapy for chronic mesenteric ischemia: a comparative experience. J Vasc Surg. 2007;45(6):1162-71.
28. Gupta PK, Horan SM, Turaga KK, Miller WJ, Pipinos, II. Chronic mesenteric ischemia: endovascular versus open revascularization. J Endovasc Ther. 2010;17(4):540-9.
29. Rawat N, Gibbons CP, Joint Vascular Research G. Surgical or endovascular treatment for chronic mesenteric ischemia: a multicenter study. Ann Vasc Surg. 2010;24(7):935-45.
30. Sivamurthy N, Rhodes JM, Lee D, Waldman DL, Green RM, Davies MG. Endovascular versus open mesenteric revascularization: immediate benefits do not equate with short-term functional outcomes. J Am Coll Surg. 2006;202(6):859-67.
31. Zerbib P, Lebuffe G, Sergent-Baudson G, Chamatan A, Massouille D, Lions C, et al. Endovascular versus open revascularization for chronic mesenteric ischemia: a comparative study. Langenbecks Arch Surg. 2008;393(6):865-70.
32. Tallarita T, Oderich GS, Gloviczki P, Duncan AA, Kalra M, Cha S, et al. Patient survival after open and endovascular mesenteric revascularization for chronic mesenteric ischemia. J Vasc Surg. 2013;57(3):747-55; discussion 54-5.
33. Davies RS, Wall ML, Silverman SH, Simms MH, Vohra RK, Bradbury AW, et al. Surgical versus endovascular reconstruction for chronic mesenteric ischemia: a contemporary UK series. Vasc Endovascular Surg. 2009;43(2):157-64.
34. Brown DJ, Schermerhorn ML, Powell RJ, Fillinger MF, Rzucidlo EM, Walsh DB, et al. Mesenteric stenting for chronic mesenteric ischemia. J Vasc Surg. 2005;42(2):268-74.
35. Kougias P, Huynh TT, Lin PH. Clinical outcomes of mesenteric artery stenting versus surgical revascularization in chronic mesenteric ischemia. Int Angiol. 2009;28(2):132-7.
36. Clair DG, Beach JM. Mesenteric Ischemia. N Engl J Med. 2016;374(10):959-68.
37. Terlouw LG, Moelker A, Abrahamsen J, Acosta S, Bakker OJ, Baumgartner I, et al. European guidelines on chronic mesenteric ischaemia - joint United European Gastroenterology, European Association for Gastroenterology, Endoscopy and Nutrition, European Society of Gastrointestinal and Abdominal Radiology, Netherlands Association of Hepatogastroenterologists, Hellenic Society of Gastroenterology, Cardiovascular and Interventional Radiological Society of Europe, and Dutch Mesenteric Ischemia Study group clinical guidelines on the diagnosis and treatment of patients with chronic mesenteric ischaemia. United European Gastroenterol J. 2020;8(4):371-95.



Chapter 11

General discussion and future perspectives

Improving patient outcome by developing diagnostic and therapeutic modalities

With this thesis we have shown that outcome for mesenteric ischemia patients has improved over time with the introduction of minimally invasive treatment options and increased awareness of the disease, organ-sparing treatments and quality of life. This has reduced mortality and morbidity. **Chapter 3, 4 and 5** showed that mortality for acute mesenteric ischemia (AMI) has been reduced from 90%(1) to 0-45%(2-9) for endovascular treatment (EVT), 20% for retrograde open mesenteric stenting (ROMS) and 22-56% for open surgical repair (OSR).(2-4, 7-10) Morbidity has been reduced from 39%-78%,(11, 12) to 13-64% for EVT and 24-70% for OSR. In specialized centers such as Medisch Spectrum Twente (MST) this even decreased to 25.1%. (Vascular registry, available at www.mst.nl) For chronic mesenteric ischemia (CMI) in-hospital mortality has been reduced from 1-17%,(13-16) to median 5% for EVT and 6% for OSR,(2-4, 7-10) and even 1.2% in specialized centers such as MST (Vascular registry, available at www.mst.nl) with comparable long-term survival of 44-95% for EVT and 69-90% for OSR, as was shown in **Chapter 5**. Morbidity decreased from 38% to 4-19% for EVT and 5-10% for OSR, as was shown in **Chapter 3**.(13-16) CMI revascularization has improved QoL with 17% as was shown in **Chapter 8**. In addition, the socio-economic burden can decrease in costs for society as well as in the substantial loss of productivity and the large healthcare consumption. In **Chapter 7** we calculated that if endoscopic coeliac artery release ((e)CAR) is an effective treatment for median arquate ligament syndrome (MALS), expected gained quality adjusted life years (QALYs)/patient could be 6.05 and an estimated €4.3 million a year could be saved as a result of reduction of the substantial productivity loss and healthcare consumption caused by MALS. Furthermore, with the introduction of EVT, outcomes for AMI and CMI have improved compared to OSR, with lesser complications (EVT 5-48% versus OSR 62%)(2, 6, 17) and fewer laparotomies leading to fewer and smaller bowel resections (7-38% versus 33-93%),(2, 3, 7, 8, 18) reducing the risk of short bowel syndrome (SBS), mortality (36% versus 15%) and costs ($147.588 versus $83.000).(8, 19) As a result, median costs for EVT are significantly lower than for OSR, respectively $73.317 and $101.762 ($P<0.01$).(8) Another positive effect of EVT is that more severely ill patients can be treated because of the less invasive character of the treatment.

In **Chapter 5** we showed that primary and secondary patency for EVT in AMI were better than for OSR, respectively 94-100%(2, 7) and 100%(7, 10) versus 52,5-91%(2, 7, 10, 18) and 79-95%.(7, 10) There is, however, more recurrence of symptoms for EVT, 9-71% versus 0-35% for OSR. This means more maintenance treatment.(16, 20-37) An explanation for this could be that older, more severely ill and more high-risk patients with more comorbidities are

being treated with EVT in contrast to OSR.(20, 29, 38, 39) In addition, EVT has an excellent secondary patency, Therefore, EVT is now chosen as the primary treatment option and OSR, on the other hand, is more suited for more advanced macrovascular abnormalities.(20, 29, 38, 39)

Interestingly enough, Bulut et al.(40) presented their outcome of PMAS in AMI and CMI in MST in 2017. Primary patency at 1- and 5-years for AMI and CMI combined was 77% and 45%, with an overall secondary patency of 98.3% and 93.6%. They also showed that there were no significant differences in primary, primary assisted and secondary patencies between the coeliac artery (CA) and the superior mesenteric artery (SMA). They concluded that their outcomes were in line with literature at that time.(40) For instance, Oderich et al.(41) reported a 5-year primary patency in CMI of 88% for OSR and 41% for EVT, with secondary patency at 97% for OSR and 88% for EVT, respectively. In **Chapter 5**, we showed primary patency of OSR for CMI ranged between 68-100% with a median of 86%. Primary patency of EVT for CMI ranged between 27-83% with a median of 51%. The outcomes of Oderich et al.(41) were included in our study. These outcomes only substantiate our claim that EVT is the primary treatment option for AMI and CMI and that is can be beneficial for more high-risk patients.

However, although the 5-year survival of OSR (69%) is better than that of EVT (44%), multivariate regression and comorbidity score matching show no significant difference, 60% and 57%, respectively (p=0.7).(34) This was also visible in an analysis of OSR in MST between 1997 and 2014.(61) Where the five-year survival of OSR was better since 2006 (89%) than before 2006 (74%), but at the same time the primary patency in the long-term was less, respectively 88% before 2006 and 48% since 2006. This led to the recommendation that OSR is indicated for low-risk patients with unfavourable mesenteric lesions, failed EVT (percutaneous mesenteric artery stenting (PMAS) or ROMS) or multiple recurrences of in-stent stenosis or occlusion.(28, 42)

In addition, not only the shift from OSR to EVT as the primary treatment option for AMI and CMI is thought to be of importance on outcome. There is still an ongoing debate on whether to use bare-metal or covered stents. Therefore, the CoBaGi study prospectively assessed the patency of bare-metal versus covered stents in CMI patients.(43) Inclusion is closed and the first results are expected in 2022.

Although we have already achieved a lot, there is always room for improvement. Delayed diagnosis is the main cause of the high morbidity and mortality in AMI, with doctor's delay, meaning time from onset of symptoms to diagnosis, being the primary reason for this.(1,

11, 12) A 'high index of suspicion' is still the cornerstone of the diagnostic process, but delay is caused by a combination of unfamiliarity with the disease and the vague symptoms that patients may have.(12, 44-48) Although computed tomographic angiography (CTA) has a high sensitivity and specificity of 73% to 100% and 90% to 100%, respectively for diagnosing acute SMA occlusion,(44) it can only be used optimally if the suspicion of AMI is actually mentioned in the referral for the radiologist, which only occurs in 31% of referrals in daily practice.(49, 50) Otherwise, there is still a high risk of underdiagnosis.(49-53) With decreasing survival rates by 20% for every 24h delay, outcome can only be improved by reducing time to diagnosis and time to start appropriate treatment.(54) In **Chapter 2**, we explained that there is an enormous need for a better diagnostic tool to improve timely diagnosis and that biomarkers are thought to be the solution, because serum is almost always collected in daily practice.(45, 46, 48, 54) They are thought to form a highly accurate, minimally invasive, rapid, 24/7 available and cost-effective tool that can be used between onset of symptoms and the CTA to stir healthcare professionals in the direction of AMI, eliminating the uncertainty of 'having a suspicion' and speed up the deployment of a CTA with a good referral. Furthermore, it would be even better if a biomarker or combination of biomarkers could provide an indication of the stage and severity of the disease.

In the quest of finding a suitable biomarker, using the QUADAS-2 tool to assess the quality of the available studies on risk of bias and applicability, we found that the overall quality of studies was low. Predominantly because of the high number of retrospective studies and the use of laparotomy as the reference test. So, there is an urgent need for high quality research. To prevent the same (methodological) mistakes from being made again in the future, there is an urgent need for uniformity of normal and cut-off values and units to use. Examining biomarkers in a population of acute abdomen patients is also very important, because it allows establishment of prevalence. Furthermore, a reference test for AMI should comprehend the combination of clinical, laboratory and imaging parameters fitting AMI, in other words a combination of the clinical suspicion and the results of the CTA. This creates the opportunity for different researchers to conduct research with reproducible results that are actually suitable for meta-analysis and validation. Ideally, these studies are conducted in (inter)national collaborations in order to obtain larger and more coherent patient groups. Centralization of care could play an important part in this. Due to the presence of more specialized knowledge and care, patients can be treated better prospectively and in an earlier phase, with the additional benefit of lager patient cohorts to study.

Improving awareness

To improve the diagnostic process, it is important to create more awareness of the disease and all its appearances. This will accelerate recognition, which leads to earlier and more effective use of additional diagnostic modalities such as the CTA. Education is key, and guidelines aid in this process. Since 2017, three important guidelines on CMI, one of them also including AMI, have emerged to help healthcare professionals to say goodbye to certain old adages and use the already available, but still improving new insights and techniques. (44, 55, 56) In addition, more and more national and international organizations and conferences offer a platform for experts in the field to speak on this subject.

Simultaneously with the international bloom of mesenteric ischemia, there was also a need for experts to come together in the Netherlands. This is an important reason why the Dutch Mesenteric Ischemia Study Group (DMIS) was founded in 2015. It is a multicentre and multidisciplinary group of specialists in the field from all over the Netherlands with the aim of improving all aspects of mesenteric ischemia through collaboration, centralisation and research. Together, we have contributed to two international guidelines on mesenteric ischemia(44, 56) and several articles have been published already on its behalf. By participating in DMIS, I was able to contribute to creating more awareness about this disease, by organizing reference meetings and giving oral presentations, designing and conducting various studies, publishing various articles of this thesis, publishing two chapters in textbooks for medical students and recruiting and obtaining funding for various studies. (57, 58)

Another example of my work within the DMIS was the use of the grant I received in 2017 from the Pioneers in Health Care Fund. Between 2003 and 2011 a biobank was formed in MST by collecting serum of 223 non-consecutive patients, 141 patients with mesenteric ischemia and 82 controls. The aim was to find a biomarker or combination of biomarkers that could aid in the diagnostic process of AMI. The samples were analysed in Erasmus MC. Based on literature research the following biomarkers were analysed: Intestinal fatty-acid binding protein (I-FABP), Ischemia Modified Albumin (IMA), Vascular endothelial growth factor (VEGF), Angiopoietin, Somatostatine, Transgelin smooth muscle 22 (SM22) and Cytokeratin-18 (CK-18). Unfortunately, due to multiple problems with the processing and storing of the samples, the quality of our samples was not good enough to come to sufficient conclusions. The most important lesson we have learned is that a good biobank protocol must be available everywhere, for everyone and at all times. This must contain clear rules and agreements made in advance about how, by whom and when material may

be collected, processed and used. Because of the ongoing quest for a usable biomarker, these lessons were discussed in several DMIS meetings and therefore formed a good basis for other studies. Like the TACTIC trial, in which a panel of plasma and volatile biomarkers is investigated that potentially allow early and accurate identification of AMI patients. For this study a new biobank is formed and the material can be used for additional research on biomarkers in the future performed in a DMIS collaboration.

Another good example of a national, multidisciplinary DMIS collaboration is the proposed CARoSO study, described in **Chapter 7**. To settle the discussion about the existence of MALS and the effectiveness of the (e)CAR once and for all, we are competing in the final battle of the Dutch National Health Institute's 'Promising Care' project. With the approval in February 2022, all patients suspected of MALS throughout the Netherlands will be treated exclusively in MST during the inclusion period to minimize the risk of bias. Extensive meetings have been held within the DMIS to optimize the protocol and all hospitals have unanimously agreed to participate. As described in **Chapters 6 and 7**, the aim is to finally have a definite answer to improve quality of life of these patients and decrease the societal burden, as the outcomes are expected to result in major savings on healthcare costs that can go up to millions of Euros each year. In addition, from a patient perspective there is finally light at the end of the tunnel if the existence and the treatment of MALS is recognized.

The 2017 ESVS Guideline also addresses the need for function tests. Currently, tonometry is the only validated function test available for CMI.(44) However, it is only available in MST and the manufacturing of the device has been stopped, which means that no new tonometers will be available and this test will become extinct. Due to the relatively low specificity of 60%, the visual light spectroscopy (VLS) is considered less suitable to completely replace tonometry.(44, 56, 59) The importance of a good function test is enormous and there are many possible implications. Predominantly for diagnosing CMI. And in the specific case of **Chapter 7**, MALS. This will allow better understanding, interpretation and comparison of outcomes of CMI interventions. And the development of better outcome parameters for patency and re-interventions for recurrent symptoms can be defined.

In an attempt of filling the gap, tonometry will leave, experimental studies with portal vein lactate measurement using magnetic spectroscopy are being performed. This is another great example of a DMIS collaboration formed between MST, University Twente (UT) and University Medical Center Utrecht (UMCU). Technical medicine and biomedical engineering students are performing tests with the 7Tesla magnetic resonance imaging (7TMRI) under the guidance of prof. dr. Dennis Klomp (Professor of high precision structural and metabolic

imaging at UMCU) to research the possible use of magnetic resonance angiography (MRA) and spectrometry (MRS) for measuring prehepatic portal Lactate in AMI patients. By using MRS with double quantum coherence filtering in the ultra-high field 7TMRI lipids can be suppressed in the portal vein as a result of which only Lactate was measured. The results demonstrated the potential clinically relevance of double quantum coherence as a function test for mesenteric ischemia and formed the basis for further research.

Mesenteric ischemia patients are always intriguing, but sometimes you come across strange and unexplained cases. In recent years, for example, a couple of pregnant women have been referred to the Dutch Expert Centre of Gastro-Intestinal Ischemia because of symptoms resembling MALS. There was one 28 weeks pregnant patient in which the symptoms of postprandial abdominal discomfort were that serious and severe that the pregnancy was at risk with possible loss of the baby. After extensive analysis and multidisciplinary consultation with the involvement of the treating gynaecologists, it was decided to perform an (e)CAR. The alternatives, ten weeks of total parenteral nutrition (TPN) or maximal stretching of the pregnancy and an early caesarean section, was both rated as riskier. Post-operatively, the patient recovered to such an extent that she was able to give birth to a full-term and healthy baby. This motivated the Bob Geelkerken and myself in such a way that, in collaboration with MST gynaecologists (dr. J.H. Baalman), a study is currently being conducted by Flores Metz, investigating mesenteric blood flow in the 3 different stages of pregnancy, as this disease and any flow changes through and during pregnancy have never been described before (MST trial number K19-47). An already validated questionnaire for CMI is also administered to these women to see whether the women also experience any CMI-related symptoms. The results will be compared with the currently available mesenteric flow data and form the basis for a more extensive longitudinal study of the mesenteric flow in pregnant women in the future.

In conclusion, we can state that there is a lot important and ground-breaking research being performed, supported by DMIS. In doing so, we must not lose sight of our patients, their wishes and the most important outcomes. This is mainly how life can be lived with the highest possible QoL.

Focussing on Quality of Life (QoL)

This is the endgame. This is why we work so hard and keep researching and improving. Enhancing quality of life and life-expectancies. Curing patients of a disabling disease, giving them back their lives, for them to lead it as they wish and restart participating in society.

Consequently, reducing the burden of disease and the economic impact this disease has. Interestingly enough, research on QoL in AMI patients is very scarce, as we have shown in **Chapters 6, 8 and 9**. We were the first to show the impact of revascularisation on QoL in CMI patients in **Chapter 8**. This is a real hiatus. Future research should include the development and evaluation of a minimum clinically important difference (MCID) and patient reported outcome measures (PROMs) before and after an intervention for both AMI and CMI, because they are crucial in improving outcomes of interventions and to support shared decision-making. Long-term follow-up is essential, as we have shown in **Chapter 9**, because the impact treatment has on QoL can evolve over time. That is one of the reasons for choosing a 2-year follow-up in the CARoSO study.

Saving bowel is saving life

If at any time, peritonitis or necrotic bowel is suspected, a laparotomy should be performed after revascularisation to assess bowel vitality. The assessment of bowel vitality is a subjective estimate of the degree of transmural ischemia and the possibility of recovery due to restoration of blood flow. However, various studies have shown that this estimate is often negative for the preservation of intestinal segments, resulting in massive resection of apparently necrotic intestines in severe cases, possibly resulting in a short bowel. On behalf of the DMIS, the use of a standard classification scheme is tested in MST. Herein, the results of visual observations by the surgeon as well as palpation of arteries and veins and results of Doppler signals are combined to give a result on a three-point Likert scale. The proposal is to carry out a validation study after the pilot phase in which different assessments are compared and validated in order to eventually be able to introduce this method nationally in daily practice.

Another opportunity is presented by the use of indocyanine green (ICG). Where ICG has already made its appearance in colorectal surgery for the assessment of anastomoses and the vitality of the omentum, it is also expected to the be used as an intraoperative aid in tissue perfusion assessment for mesenteric ischemia. Vaassen et al.(60) performed the Flight study in MST in which they investigated the use of ICG in fluorescence angiography (FA) to assess tissue perfusion with the use of near-infrared (NIR) light and attempted to develop a reliable and easily implementable FA quantification method and investigated the correlation of influx parameters with in vivo intestinal perfusion status. Data from healthy subjects was correlated to patients with mesenteric blood flow problems. The patients with mesenteric blood flow problems showed a significantly different median time to peak (TTP) compared to the patients without blood flow problems. After revascularization, the

median TTP returned to normal. This presented FA quantification is directly applicable intraoperatively. Further research will be performed to identify different FA parameters for different clinical outcomes.(60)

Life after mesenteric ischemia

In **Chapters 3 and 5** we clearly showed that endovascular treatment is always preferable to open surgical treatment and that revascularisation should always proceed resection of non-vital bowel.(61, 62) However, many patients today are still diagnosed at laparotomy with subsequent resection of non-vital bowel before revascularization is performed.(**Chapter 2**,(44, 61, 62)) As a result, the ischemic time is even longer, resulting in even more irreversible transmural damage, leading to even larger bowel resections. For these patients short bowel syndrome (SBS) looms, due to massive resections of necrotic bowel, which is most likely caused by late diagnosis or treatment.(63) This can lead to Intestinal Failure (IF), when the intestines are unable to absorb enough water, macronutrients (carbohydrate, protein, and fat), micronutrients, and electrolytes, leading to malnutrition and/or dehydration. Looking at the data of the two major IF facilities of the Netherlands, mesenteric ischemia plays a prominent role in the referrals. Thirty-nine of the 138 (28%) IF patients treated in the Amsterdam University Medical Centers (AUMC) in 2019 had AMI as main diagnosis. In the University Medical Center Groningen (UMCG) more than half of the total IF population has had AMI. These patients rely on TPN at home (HPN) with estimated costs at €63.000,- per year per person.(64-68) And although HPN has a good survival of 88-93%, 74%, 64-71%, 59%, and 28% at respectively 1-, 3-, 5-, 10- and 20-year and reports on SBS survival are 80% and 70% at 2-yr and 5-yr, respectively, it is always better to prevent these situation than to cure it, because this may be the worst outcome for our patients after death.(67-69)

These numbers show that the economic burden of these patients is excessive. But what kind of life is to be expected by the patients that develop IF? Data on QoL of IF patients is very scarce,(68) but one study(70) showed that patients perceive their HPN as a “lifeline” and “nutritional safety net” accepting all drawbacks, because without the HPN they would not have been alive anymore. And that their QoL was “good” to “wonderful” when defined as “enjoying life,” “being happy, satisfied or content with life,” and “being able to do what you want to do when you want to do it”. The main factors influencing this were health, stamina, the absence of an ostomy and flexibility in infusion schedules. In addition, a positive attitude with confidence of a good outcome, a good social network and financial security play an important role. The perception of good QoL could exist because the patients had adjusted their life goals and expectations after accepting their situation. This and the HPN had given

them a degree of autonomy, which allowed them to engage in activities such as working, contributing to the household and participating in social activities with family and friends, such as exercising, traveling, and going to parties and restaurants.(70)

So, it is very important to realize that the worst outcome, other than death, does not necessarily mean the end of life for our patients. Even more important to realize is that there is a good path to freedom from HPN. This process is called intestinal rehabilitation which encompasses the restoration of enteral autonomy and requires a multi-modality approach of dietary, medical and surgical strategies.(67) For this, bowel adaptation, the bowels' attempt to increase fluid and nutrient absorption, is the most important process in intestinal rehabilitation. It can occur in the first two to three years by actual increasing the size and absorptive surface through intestinal mucosa hyperplasia (structural changes) and decreased gastrointestinal transit for increased absorption time (functional changes).(67) In recent years, advances in enteral and parenteral nutritional support, hormone therapy and autologous gastrointestinal reconstruction (AGR) techniques have significantly improved the overall outcomes and survival of IF patients.(71) A recent study by the AUMC showed that 73% of Type 2 acute intestinal failure patients, whom need TPN for several weeks or months, achieved enteral autonomy and discontinued TPN.(72) This shows that there can be life after mesenteric ischemia! And we hope that surgeons take this to heart and give patients the benefit of the doubt in cases where much bowel is lost.

Conclusion

Optimizing outcome and quality of life for mesenteric ischemia patients by improving diagnostic and treatment strategies. That was, still is and always will be the goal. Mesenteric ischemia is not a rare disease! Therefore, every healthcare professional should always have a high index of suspicion on the presence of mesenteric ischemia. And revascularisation should always proceed resection.(44, 61, 62) Because the end of the villus, is the end of the bowel, is the end of the patient. Only if we, as healthcare professionals, work following these standards, we will be able to improve life for our patients.

With this thesis I hope to have contributed to QoL improvement for my mesenteric ischemia patients. Since 2011, I have also been infected with the mesenteric ischemia virus by Bob Geelkerken. And although writing this conclusion marks the end of a decade full of lessons learned, challenges, highs, setbacks and growth, the battle is far from over. I hope to have intrigued and inspired the reader. And hopefully also saved a life. Because where there is love, there is life.

References

1. Naazar AA, Omair A, Chu SH, Keane KG, Weber DG. A Shifting Trend Towards Endovascular Intervention in the Treatment of Acute Mesenteric Ischemia. Cureus. 2021;13(10):e18544.
2. Zhao Y, Yin H, Yao C, Deng J, Wang M, Li Z, et al. Management of Acute Mesenteric Ischemia: A Critical Review and Treatment Algorithm. Vasc Endovascular Surg. 2016;50(3):183-92.
3. Beaulieu RJ, Arnaoutakis KD, Abularrage CJ, Efron DT, Schneider E, Black JH, 3rd. Comparison of open and endovascular treatment of acute mesenteric ischemia. J Vasc Surg. 2014;59(1):159-64.
4. Acosta S, Bjorck M. Modern treatment of acute mesenteric ischaemia. Br J Surg. 2014;101(1):e100-8.
5. Karkkainen JM, Lehtimaki TT, Saari P, Hartikainen J, Rantanen T, Paajanen H, et al. Endovascular Therapy as a Primary Revascularization Modality in Acute Mesenteric Ischemia. Cardiovasc Intervent Radiol. 2015;38(5):1119-29.
6. Puippe GD, Suesstrunk J, Nocito A, Pfiffner R, Glenck M, Pfammatter T. Outcome of endovascular revascularisation in patients with acute obstructive mesenteric ischaemia - a single-centre experience. Vasa. 2015;44(5):363-70.
7. Arya S, Kingman S, Knepper JP, Eliason JL, Henke PK, Rectenwald JE. Open Mesenteric Interventions Are Equally Safe as Endovascular Interventions and Offer Better Midterm Patency for Chronic Mesenteric Ischemia. Ann Vasc Surg. 2016;30:219-26.
8. Eslami MH, Rybin D, Doros G, McPhee JT, Farber A. Mortality of acute mesenteric ischemia remains unchanged despite significant increase in utilization of endovascular techniques. Vascular. 2016;24(1):44-52.
9. Plumereau F, Mucci S, Le Naoures P, Finel JB, Hamy A. Acute mesenteric ischemia of arterial origin: importance of early revascularization. J Visc Surg. 2015;152(1):17-22.
10. Duran M, Pohl E, Grabitz K, Schelzig H, Sagban TA, Simon F. The importance of open emergency surgery in the treatment of acute mesenteric ischemia. World J Emerg Surg. 2015;10:45.
11. Newton WB, 3rd, Sagransky MJ, Andrews JS, Hansen KJ, Corriere MA, Goodney PP, et al. Outcomes of revascularized acute mesenteric ischemia in the American College of Surgeons National Surgical Quality Improvement Program database. Am Surg. 2011;77(7):832-8.
12. Cudnik MT, Darbha S, Jones J, Macedo J, Stockton SW, Hiestand BC. The diagnosis of acute mesenteric ischemia: A systematic review and meta-analysis. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 2013;20(11):1087-100.
13. Clair DG, Beach JM. Mesenteric Ischemia. N Engl J Med. 2016;374(10):959-68.
14. Kougias P, Lau D, El Sayed HF, Zhou W, Huynh TT, Lin PH. Determinants of mortality and treatment outcome following surgical interventions for acute mesenteric ischemia. J Vasc Surg. 2007;46(3):467-74.
15. Lejay A, Georg Y, Tartaglia E, Creton O, Lucereau B, Thaveau F, et al. Chronic mesenteric ischemia: 20 year experience of open surgical treatment. Eur J Vasc Endovasc Surg. 2015;49(5):587-92.
16. Schermerhorn ML, Giles KA, Hamdan AD, Wyers MC, Pomposelli FB. Mesenteric revascularization: management and outcomes in the United States, 1988-2006. J Vasc Surg. 2009;50(2):341-8 e1.
17. Forbrig R, Renner P, Kasprzak P, Dahlke MH, Müller-Wille R, Stroszczynski C, et al. Outcome of primary percutaneous stent-revascularization in patients with atherosclerotic acute mesenteric ischemia. Acta Radiol. 2017;58(3):311-5.
18. Roussel A, Castier Y, Nuzzo A, Pellenc Q, Sibert A, Panis Y, et al. Revascularization of acute mesenteric ischemia after creation of a dedicated multidisciplinary center. J Vasc Surg. 2015;62(5):1251-6.

19. Arthurs ZM, Titus J, Bannazadeh M, Eagleton MJ, Srivastava S, Sarac TP, et al. A comparison of endovascular revascularization with traditional therapy for the treatment of acute mesenteric ischemia. J Vasc Surg. 2011;53(3):698-704; discussion -5.
20. van Petersen AS, Kolkman JJ, Beuk RJ, Huisman AB, Doelman CJ, Geelkerken RH, et al. Open or percutaneous revascularization for chronic splanchnic syndrome. J Vasc Surg. 2010;51(5):1309-16.
21. Moghadamyeghaneh Z, Carmichael JC, Mills SD, Dolich MO, Pigazzi A, Fujitani RM, et al. Early Outcome of Treatment of Chronic Mesenteric Ischemia. Am Surg. 2015;81(11):1149-56.
22. Oderich GS, Gloviczki P, Bower TC. Open surgical treatment for chronic mesenteric ischemia in the endovascular era: when it is necessary and what is the preferred technique? Semin Vasc Surg. 2010;23(1):36-46.
23. Kasirajan K, O'Hara PJ, Gray BH, Hertzer NR, Clair DG, Greenberg RK, et al. Chronic mesenteric ischemia: open surgery versus percutaneous angioplasty and stenting. J Vasc Surg. 2001;33(1):63-71.
24. Pecoraro F RZ, Lachat M, et al. Chronic mesenteric ischemia: critical review and guidelines for management. Ann Vasc Surg. 2013;27(1):113-122.
25. Indes JE, Giacovelli JK, Muhs BE, Sosa JA, Dardik A. Outcomes of endovascular and open treatment for chronic mesenteric ischemia. J Endovasc Ther. 2009;16(5):624-30.
26. Biebl M, Oldenburg WA, Paz-Fumagalli R, McKinney JM, Hakaim AG. Surgical and interventional visceral revascularization for the treatment of chronic mesenteric ischemia--when to prefer which? World J Surg. 2007;31(3):562-8.
27. Assar AN, Abilez OJ, Zarins CK. Outcome of open versus endovascular revascularization for chronic mesenteric ischemia: review of comparative studies. J Cardiovasc Surg (Torino). 2009;50(4):509-14.
28. Atkins MD, Kwolek CJ, LaMuraglia GM, Brewster DC, Chung TK, Cambria RP. Surgical revascularization versus endovascular therapy for chronic mesenteric ischemia: a comparative experience. J Vasc Surg. 2007;45(6):1162-71.
29. Gupta PK, Horan SM, Turaga KK, Miller WJ, Pipinos, II. Chronic mesenteric ischemia: endovascular versus open revascularization. J Endovasc Ther. 2010;17(4):540-9.
30. Rawat N, Gibbons CP, Joint Vascular Research G. Surgical or endovascular treatment for chronic mesenteric ischemia: a multicenter study. Ann Vasc Surg. 2010;24(7):935-45.
31. Sivamurthy N, Rhodes JM, Lee D, Waldman DL, Green RM, Davies MG. Endovascular versus open mesenteric revascularization: immediate benefits do not equate with short-term functional outcomes. J Am Coll Surg. 2006;202(6):859-67.
32. Zerbib P, Lebuffe G, Sergent-Baudson G, Chamatan A, Massouille D, Lions C, et al. Endovascular versus open revascularization for chronic mesenteric ischemia: a comparative study. Langenbecks Arch Surg. 2008;393(6):865-70.
33. Oderich GS, Malgor RD, Ricotta JJ, 2nd. Open and endovascular revascularization for chronic mesenteric ischemia: tabular review of the literature. Ann Vasc Surg. 2009;23(5):700-12.
34. Tallarita T, Oderich GS, Gloviczki P, Duncan AA, Kalra M, Cha S, et al. Patient survival after open and endovascular mesenteric revascularization for chronic mesenteric ischemia. J Vasc Surg. 2013;57(3):747-55; discussion 54-5.
35. Davies RS, Wall ML, Silverman SH, Simms MH, Vohra RK, Bradbury AW, et al. Surgical versus endovascular reconstruction for chronic mesenteric ischemia: a contemporary UK series. Vasc Endovascular Surg. 2009;43(2):157-64.

36. Brown DJ, Schermerhorn ML, Powell RJ, Fillinger MF, Rzucidlo EM, Walsh DB, et al. Mesenteric stenting for chronic mesenteric ischemia. J Vasc Surg. 2005;42(2):268-74.

37. Kougias P, Huynh TT, Lin PH. Clinical outcomes of mesenteric artery stenting versus surgical revascularization in chronic mesenteric ischemia. Int Angiol. 2009;28(2):132-7.

38. Zacharias N, Eghbalieh SD, Chang BB, Kreienberg PB, Roddy SP, Taggert JB, et al. Chronic mesenteric ischemia outcome analysis and predictors of endovascular failure. J Vasc Surg. 2016;63(6):1582-7.

39. Saedon M, Saratzis A, Karim A, Goodyear S. Endovascular Versus Surgical Revascularization for the Management of Chronic Mesenteric Ischemia. Vasc Endovascular Surg. 2015;49(1-2):37-44.

40. Bulut T, Oosterhof-Berktas R, Geelkerken RH, Brusse-Keizer M, Stassen EJ, Kolkman JJ. Long-Term Results of Endovascular Treatment of Atherosclerotic Stenoses or Occlusions of the Coeliac and Superior Mesenteric Artery in Patients With Mesenteric Ischaemia. Eur J Vasc Endovasc Surg. 2017;53(4):583-90.

41. Oderich GS, Bower TC, Sullivan TM, Bjarnason H, Cha S, Gloviczki P. Open versus endovascular revascularization for chronic mesenteric ischemia: risk-stratified outcomes. J Vasc Surg. 2009;49(6):1472-9 e3.

42. Acosta S. Mesenteric ischemia. Curr Opin Crit Care. 2015;21(2):171-8.

43. van Dijk LJD, Harki J, van Noord D, Verhagen HJM, Kolkman JJ, Geelkerken RH, et al. Covered stents versus Bare-metal stents in chronic atherosclerotic Gastrointestinal Ischemia (CoBaGI): study protocol for a randomized controlled trial. Trials. 2019;20(1):519.

44. Björck M, Koelemay M, Acosta S, Bastos Goncalves F, Kölbel T, Kolkman JJ, et al. Editor's Choice - Management of the Diseases of Mesenteric Arteries and Veins: Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2017;53(4):460-510.

45. Derikx JP, Schellekens DH, Acosta S. Serological markers for human intestinal ischemia: A systematic review. Best practice & research Clinical gastroenterology. 2017;31(1):69-74.

46. Oldenburg WA, Lau LL, Rodenberg TJ, Edmonds HJ, Burger CD. Acute mesenteric ischemia: a clinical review. Arch Intern Med. 2004;164(10):1054-62.

47. Tilsed JV, Casamassima A, Kurihara H, Mariani D, Martinez I, Pereira J, et al. ESTES guidelines: acute mesenteric ischaemia. European journal of trauma and emergency surgery : official publication of the European Trauma Society. 2016;42(2):253-70.

48. Acosta S, Nilsson T. Current status on plasma biomarkers for acute mesenteric ischemia. Journal of thrombosis and thrombolysis. 2012;33(4):355-61.

49. Lehtimaki TT, Karkkainen JM, Saari P, Manninen H, Paajanen H, Vanninen R. Detecting acute mesenteric ischemia in CT of the acute abdomen is dependent on clinical suspicion: Review of 95 consecutive patients. European journal of radiology. 2015;84(12):2444-53.

50. Karkkainen JM. Acute Mesenteric Ischemia: A Challenge for the Acute Care Surgeon. Scandinavian journal of surgery : SJS : official organ for the Finnish Surgical Society and the Scandinavian Surgical Society. 2021;110(2):150-8.

51. Karkkainen JM, Acosta S. Acute mesenteric ischemia (part I) - Incidence, etiologies, and how to improve early diagnosis. Best practice & research Clinical gastroenterology. 2017;31(1):15-25.

52. Lemma AN, Tolonen M, Vikatmaa P, Mentula P, Vikatmaa L, Kantonen I, et al. Choice of First Emergency Room Affects the Fate of Patients With Acute Mesenteric Ischaemia: The Importance of Referral Patterns and Triage. Eur J Vasc Endovasc Surg. 2019;57(6):842-9.

53. Wiesner W, Khurana B, Ji H, Ros PR. CT of acute bowel ischemia. Radiology. 2003;226(3):635-50.

54. van den Heijkant TC, Aerts BA, Teijink JA, Buurman WA, Luyer MD. Challenges in diagnosing mesenteric ischemia. World J Gastroenterol. 2013;19(9):1338-41.

55. Huber TS, Bjorck M, Chandra A, Clouse WD, Dalsing MC, Oderich GS, et al. Chronic mesenteric ischemia: Clinical practice guidelines from the Society for Vascular Surgery. J Vasc Surg. 2021;73(1S):87S-115S.

56. Terlouw LG, Moelker A, Abrahamsen J, Acosta S, Bakker OJ, Baumgartner I, et al. European guidelines on chronic mesenteric ischaemia - joint United European Gastroenterology, European Association for Gastroenterology, Endoscopy and Nutrition, European Society of Gastrointestinal and Abdominal Radiology, Netherlands Association of Hepatogastroenterologists, Hellenic Society of Gastroenterology, Cardiovascular and Interventional Radiological Society of Europe, and Dutch Mesenteric Ischemia Study group clinical guidelines on the diagnosis and treatment of patients with chronic mesenteric ischaemia. United European Gastroenterol J. 2020;8(4):371-95.

57. JTM Blauw DvN, RH Geelkerken. Leerboek Chirurgie, H26 Mesenteriale vaten2021.

58. JTM Blauw WvW, RH Geelkerken. Probleemgeorienteerd denken in de Chirurgie, H392022.

59. Van Noord D, Sana A, Benaron DA, Pattynama PM, Verhagen HJ, Hansen BE, et al. Endoscopic visible light spectroscopy: a new, minimally invasive technique to diagnose chronic GI ischemia. Gastrointestinal endoscopy. 2011;73(2):291-8.

60. Vaassen HGM, Wermelink B, Geelkerken RH, Lips DJ. Fluorescence-Based Quantification of Gastrointestinal Perfusion: A Step Towards an Automated Approach. Journal of laparoendoscopic & advanced surgical techniques Part A. 2021.

61. Blauw JT, Bulut T, Oderich GS, Geelkerken BR, Dutch Mesenteric Ischemia Study G. Mesenteric vascular treatment 2016: from open surgical repair to endovascular revascularization. Best practice & research Clinical gastroenterology. 2017;31(1):75-84.

62. Blauw JTM BT, Eenhoorn P, Beuk RJ, Brusse-Keizer M, Kolkman JJ, Geelkerken RH. Chronic Mesenteric Ischemia: When and how to intervene on patients with celiac/SMA stenosis. Journal of Cardiovascular Surgery. accepted for publication in 2017.

63. Weale AR, Edwards AG, Bailey M, Lear PA. Intestinal adaptation after massive intestinal resection. Postgraduate medical journal. 2005;81(953):178-84.

64. Harrison E, Allan P, Ramu A, Vaidya A, Travis S, Lal S. Management of intestinal failure in inflammatory bowel disease: small intestinal transplantation or home parenteral nutrition? World J Gastroenterol. 2014;20(12):3153-63.

65. Roskott AM, Huisman-de Waal G, Wanten GJ, Jonkers-Schuitema C, Serlie MJ, Baxter JP, et al. Screening for psychosocial distress in patients with long-term home parenteral nutrition. Clin Nutr. 2013;32(3):396-403.

66. Allan P, Lal S. Intestinal failure: a review. F1000Res. 2018;7:85.

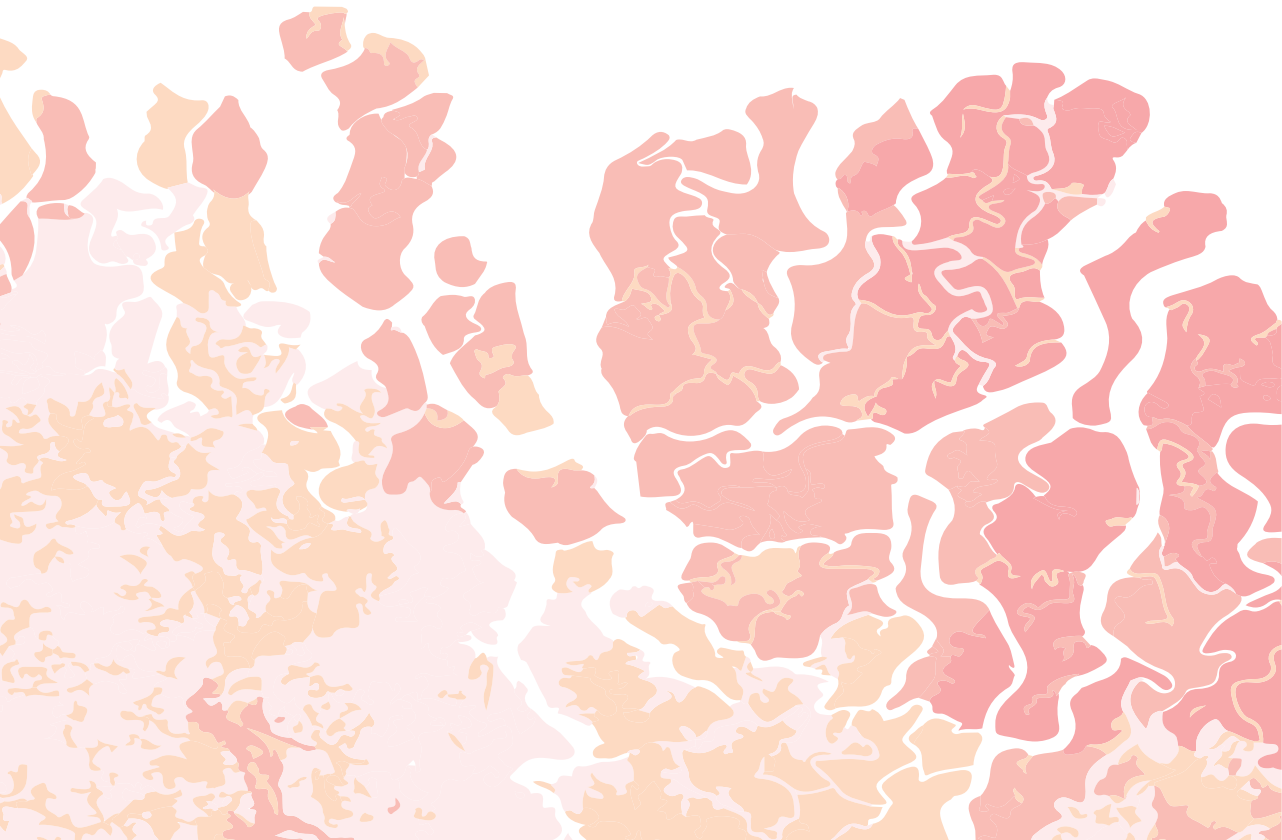
67. DiBaise JK, Young RJ, Vanderhoof JA. Intestinal rehabilitation and the short bowel syndrome: part 1. The American journal of gastroenterology. 2004;99(7):1386-95.

68. Pironi L, Corcos O, Forbes A, Holst M, Joly F, Jonkers C, et al. Intestinal failure in adults: Recommendations from the ESPEN expert groups. Clin Nutr. 2018;37(6 Pt A):1798-809.

69. Dibb M, Soop M, Teubner A, Shaffer J, Abraham A, Carlson G, et al. Survival and nutritional dependence on home parenteral nutrition: Three decades of experience from a single referral centre. Clin Nutr. 2017;36(2):570-6.

70. Winkler MF, Hagan E, Wetle T, Smith C, Maillet JO, Touger-Decker R. An exploration of quality of life and the experience of living with home parenteral nutrition. JPEN Journal of parenteral and enteral nutrition. 2010;34(4):395-407.

71. Cruz RJ, Jr., McGurgan J, Butera L, Poloyac K, Roberts M, Stein W, et al. Gastrointestinal Tract Reconstruction in Adults with Ultra-Short Bowel Syndrome: Surgical and Nutritional Outcomes. Surgery. 2020;168(2):297-304.
72. Atema JJ, Mirck B, Van Arum I, Ten Dam SM, Serlie MJ, Boermeester MA. Outcome of acute intestinal failure. Br J Surg. 2016;103(6):701-8.



Appendices

Nederlandse Samenvatting

Abbreviations

Definitions

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Dankwoord

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Nederlandse samenvatting

Het doel van dit proefschrift was om een significante bijdrage te leveren aan de verbetering van de kwaliteit van leven (KvL) en de orgaan-sparende behandeling van patiënten met mesenteriale ischemie door meer inzicht te geven in de hedendaagse diagnostische en therapeutische ontwikkelingen. Meer bewustzijn creëren is de eerste stap in het loslaten van oude routines en overtuigingen.

Deel I Ontwikkelingen in de diagnostiek en de evolutie van de behandeling

Allereerst is het belangrijk om het diagnostisch proces te verbeteren, omdat diagnostische vertraging de belangrijkste factor is in de algehele morbiditeit, mortaliteit en maatschappelijke last van mesenteriale ischemie, voornamelijk voor patiënten met acute mesenteriale ischemie (AMI). In Deel I hebben we ons daarom gericht op de huidige status van diagnostische ontwikkelingen bij occlusieve AMI-patiënten. Patiënten en hun artsen hebben dringend behoefte aan een nauwkeurigere, minder invasieve, snelle en 24/7 beschikbare, kosteneffectieve diagnostische test. De gouden standaard is nu een 'hoge verdenking' gecombineerd met een 1-mm abdominale multislice meerfasen computer tomografische angiography (CTA)-scan.(1) Hoewel een CTA een sensitiviteit en specificiteit van 73-100% en 90-100% heeft voor het diagnosticeren van een acute occlusie van de arteria mesenterica superior (SMA), moet de mogelijke aanwezigheid van mesenteriale ischemie wel op voorhand herkend en erkend worden zodat de radiologische beelden correct kunnen en zullen worden beoordeeld.(1) Daarom, is er een toenemende belangstelling voor het mogelijke gebruik van biomarkers om diagnostische vertraging te verkorten. In **Hoofdstuk 2** hebben we een systematische review uitgevoerd om te bepalen of biomarkers enige diagnostische waarde hebben in het diagnostisch proces van AMI. We hebben 49 geschikte artikelen opgenomen die in totaal 60 verschillende biomarkers beschreven. We zagen echter een enorme heterogeniteit in de gebruikte in- en exclusiecriteria, patiënten populaties en controlegroepen, normaalwaarden en afkapwaarden, waardoor het vrijwel onmogelijk is om de uitkomsten met elkaar te vergelijken. Bovendien was de algehele methodologische kwaliteit van de artikelen laag. Voornamelijk vanwege het hoge aantal retrospectieve onderzoeken en het gebruik van een laparotomie als referentietest. Aangezien diagnostisering tijdens een laparotomie vaak betekent dat het al te laat is. Op basis van deze review concluderen we dat er tot nu toe geen definitieve beslissing kan worden genomen in het diagnostische proces van AMI-patiënten op basis van een biomarker of combinatie van biomarkers. Dit geldt ook voor leukocyten, lactaat en D-dimeer. De daadwerkelijke diagnose

van AMI kan op dit moment alleen worden gesteld op basis van een hoge verdenking gevolgd door een multislice CTA.

Om echt orgaan-sparend te kunnen handelen en de KvL te verbeteren, moet natuurlijk het resultaat van de behandeling verbeteren. Daarom hebben we ons in Deel I vervolgens gefocust op de evolutie van behandelstrategieën en technieken die tegenwoordig beschikbaar zijn. Maar ook over de aanvullende en ondersteunende maatregelen die we onze patiënten kunnen bieden. Minimaal invasieve endovasculaire behandelingsopties zijn sinds de jaren 80 in opkomst en hebben als voordelen minder ziekenhuis gerelateerde mortaliteit en morbiditeit, kortere ziekenhuisopname en meer mogelijkheden voor hoog risicopatiënten, maar met een lagere primaire doorgankelijkheid en hogere percentages recidief klachten dan bij open chirurgische behandeling.(2, 3) In 2006 werd percutane mesenteriale arterie stenting (PMAS) de primaire behandelingsoptie voor patiënten met mesenteriale ischemie in het Medisch Spectrum Twente (MST). Om te zien of er nog plaats was voor open chirurgische mesenteriale arterie revascularisatie (OSMAR), evalueerden we de uitkomst van OSMAR bij patiënten met chronische mesenteriale ischemie (CMI) met stenosen van de arteria coeliaca (CA) of SMA die tussen 1997 en 2014 in het MST werden behandeld in **Hoofdstuk 3**. Patiënten werden ingedeeld in een groep van vóór 2006 of een groep na 2006. Technisch succes werd bij alle patiënten behaald, met meer klinisch falen in de historische groep, 30,4%, dan in de hedendaagse groep, 34,1%. De superieure primaire doorgankelijkheid van SMA-reconstructies in de historische groep (1-, 3- en 5 jaar follow-up) was het enige significante verschil. Er waren trends van minder meertaks reconstructies, minder antegrade gelegen bypasses, verminderd klinisch succes maar verbeterde 30-dagen en lange termijn overleving na OSMAR. De meest voor de hand liggende verklaring hiervoor zou de uitgebreidere mesenteriale atherosclerose kunnen zijn en de ernst van de klinische situatie van de patiënt die OSMAR ondergaat in de "PMAS-first"-periode vanaf 2006. Deze studie toonde aan dat electieve OSMAR alleen mag worden gebruikt bij patiënten met een aanzienlijke fysiologische reserve, met ongunstige mesenteriale laesies, mislukte herhaalde PMAS of meerdere recidief stenoses of in-stent occlusies. Het versterkte ook onze overtuiging dat PMAS niet langer een "brug naar chirurgie" is voor CMI-patiënten, maar een sterke eerste keuzebehandeling, met een kanttekening van een "brug naar herhaalde PMAS".

In **Hoofdstuk 4** gingen we een stap verder om aan te tonen dat OSMAR niet eens tweede keus zou moeten zijn bij AMI-patiënten, omdat we een beter alternatief presenteerden waarbij de voordelen van open chirurgische en endovasculaire benaderingen gecombineerd worden, genaamd retrograde open mesenteriale stenting (ROMS). Het is een hybride

techniek waarbij, via een kleine transversale bovenbuiklaparotomie, retrograad een stent in de SMA kan worden geplaatst met tevens de mogelijkheid om direct de darmvitaliteit te beoordelen. Tussen januari 2007 en september 2011 hebben we 15 opeenvolgende patiënten geïncludeerd die ROMS ondergingen voor AMI. Technisch succes werd behaald bij 14 patiënten. Twee patiënten hadden een ernstig ischemische dunne darm, waarvan één een gedeeltelijke darmresectie nodig had vanwege onomkeerbare transmurale ischemie. De 30-dagen mortaliteit was 20% en de primaire doorgankelijkheid was 92%. Tien patiënten ondergingen een ongeplande re-laparotomie, waarvan er één een resectie van een groot deel van de dunne darm nodig had. De 1-jaarsmortaliteit bleef 20%, met een primaire doorgankelijkheid van 83%. Primair ondersteunde doorgankelijkheid was 91% en de secundaire doorgankelijkheid was 100%. Klinisch succes na 30 dagen en 12 maanden was respectievelijk 73% en 67%. We waren niet de eersten die het geweldige resultaat van ROMS lieten zien, maar we toonden wel de grootste patiëntenpopulatie tot dan toe. En onze resultaten vormden onderdeel van de onderbouwing van Aanbeveling 26 in de ESVS 2017-richtlijn dat ROMS de tweede keus behandelingsoptie is voor AMI-patiënten.(1)

En om definitief ons statement te maken over de voordelen van PMAS voor AMI-patiënten, hebben we de huidige inzichten in behandelingsopties voor mesenteriale ischemie beschreven in **Hoofdstuk 5**. We hebben ook een kleine systematische review uitgevoerd van artikelen tussen september 2013 en juli 2016 waarin PMAS met OSMAR werd vergeleken. De uitkomsten vormen meerdere adviezen voor clinici om te integreren in hun dagelijkse praktijk. De meest essentiële boodschap bij het verbeteren van overleving, KvL en intestinale preservatie bij AMI is om "eerst te revasculariseren, alvorens te reserceren" en dat deze patiënten centra nodig hebben waar 24/7 specialistische zorg wordt geleverd, met ervaring in zowel open als endovasculaire revascularisatie.(4-8) Deze boodschap maakte de weg vrij voor Aanbeveling 10 in de ESVS 2017-richtlijn.(1) We toonden ook aan dat PMAS de eerste keus behandeling is voor AMI en CMI, met betere korte termijn resultaten, lagere mortaliteit en morbiditeit en lagere kosten.(2, 3, 5, 6, 9-35) En dat OSMAR alleen mag worden gebruikt bij laag risico patiënten met ongunstige mesenteriale laesies, mislukte herhaalde PMAS of ROMS of meerdere recidieven van in-stent stenose of occlusie.(4, 27) Bij aanhoudende ischemie of het onvermogen om te bepalen of aanvullende resectie nodig is, wordt een ‘second look’ laparotomie geadviseerd na 18-36 uur. Uitgestelde reconstructie van de darmcontinuïteit heeft de voorkeur boven het aanleggen van stoma's, vanwege de impact op morbiditeit en kwaliteit van leven.(5) Geleidelijke en strikt gecontroleerde herintroductie van voeding is cruciaal en alle patiënten moeten levenslang anticoagulantia krijgen.(36)

Deel II Leven na mesenteriale ischemie

Sinds 2017 zijn er 3 richtlijnen gepubliceerd die tot dezelfde conclusies zijn gekomen als dit proefschrift tot nu toe heeft beschreven. De grootste lacune in de huidige literatuur is onderzoek naar de impact van mesenteriale ischemie en de behandeling ervan op onze patiënten en hun kwaliteit van leven. Met andere woorden, genezen we onze patiënten daadwerkelijk en verbeteren we hun kwaliteit van leven? Dit werd voor zowel CMI- als niet-CMI-patiënten besproken in Deel II.

Het bestaan van mediane arquate ligament syndroom (MALS), ook wel bekend als het syndroom van Dunbar of het coeliacus arterie compressie syndroom (CACS), is al onderwerp van discussie sinds de eerste beschrijving ervan eind jaren vijftig, begin jaren zestig, wat leidde tot 'gelovigen' en 'niet-gelovigen'. Er zijn al veel discussies geweest over het al dan niet bestaan van deze ziekte en dus of patiënten behandeld moeten worden en of die behandeling zinvol is om de kwaliteit van leven te verbeteren, de ziektelast te verminderen en de sociale en financiële lasten voor de samenleving te verlagen. In **Hoofdstuk 6** hebben we een systematische review uitgevoerd naar de impact van chirurgische decompressie van het mediane arcuate ligament (MAL) op symptomen en kwaliteit van leven bij MALS-patiënten. De kwaliteit van de artikelen was erg laag met een grote heterogeniteit en de meeste artikelen presenteerden minder dan 10 patiënten. De behandeling van MALS verbeterde de kwaliteit van leven bij 68% van de patiënten. Dit ondersteund onze overtuiging van het bestaan van MALS en het mogelijke positieve effect van behandeling met endoscopische coeliacus arterie release, (e)CAR. Er is een grote behoefte aan een goede, prospectieve gerandomiseerde gecontroleerde studie (RCT) om echt te laten zien of MALS bestaat en of (e)CAR het antwoord is voor degenen die er last van hebben. Deze review toonde verder aan dat er geen redelijke ondersteuning is voor een neurogene oorsprong van MALS en dat er dus geen plaats is voor een plexusblokkade bij de behandeling van deze patiënten.

Namens de Dutch Mesenteric Ischemia Study Group (DMIS) hebben we in **Hoofdstuk 7** onze aanvraag voor het project 'Veelbelovende zorg' van het Zorginstituut voor deze dubbelblinde prospectieve ‘sham’ gecontroleerde RCT, de CARoSO-studie, gepresenteerd. Eventuele toekenning wordt verwacht in februari 2022, waarna we het onderzoeksprotocol kunnen publiceren en de studie kunnen starten. Zeventig patiënten zullen worden gerandomiseerd in een behandelingsgroep ((e)CAR) en een sham-groep om vast te stellen of het retroperitoneaal endovasculair klieven van de MAL de symptomen verlicht en de kwaliteit van leven verbetert (gemeten met de EQ-5D-5L) in een follow-up van twee jaar. De studie zal ofwel aantonen dat (e)CAR een (kosten)effectieve minimaal

invasieve behandeling voor MALS is. Of het voorkomt dat in de toekomst patiënten een nutteloze interventie ondergaan. Als de effectiviteit van (e)CAR is bewezen, kunnen naar schatting alleen al in Nederland jaarlijks tot 490 patiënten met chronisch invaliderende buikklachten worden behandeld. Vanwege de relatief jonge leeftijd van 20-40 jaar van deze patiëntenpopulatie wordt een gemiddelde gezondheidswinst van 6,05 quality adjusted life years (QALY's)/patiënt verwacht. Daarnaast zou er tot € 4,3 miljoen maatschappelijke kosten per jaar kunnen worden bespaard, door een vermindering van het substantiële verlies aan productiviteit en zorgconsumptie veroorzaakt door MALS. Aangezien de noodzaak van het uitvoeren van deze studie is onderstreept door 2 recente internationale richtlijnen,(1, 37) zal de uitkomst van de CARoSO-studie worden vertaald in krachtige aanbevelingen in de komende updates van alle relevante (inter)nationale richtlijnen en, indien effectief, zal (e) CAR de standaardbehandeling voor MALS worden.

Er is dus weinig bekend over de impact die behandeling heeft op de kwaliteit van leven van MALS-patiënten, maar weten we iets over de impact die behandeling heeft op de kwaliteit van leven van CMI-patiënten in het algemeen? Dat hebben we onderzocht in **Hoofdstuk 8** en het bleek dat we de eersten waren die de impact van revascularisatie op de kwaliteit van leven van CMI-patiënten evalueerden. We vergeleken pre- en post-interventie KvL-gegevens gemeten met de EuroQol-5D door het minimale klinisch relevante verschil (MCID) te analyseren om te zien of er enige klinische relevantie was. Hiervoor hebben we de MCID van het prikkelbare darm syndroom (PDS) van 0,074 gebruikt, omdat er geen MCID is vastgesteld voor CMI. We toonden aan dat de mediane EQ-indexscore significant toenam van 0,70 naar 0,81 (P=0,02) met een gemiddeld verschil van 0,162, wat de MCID overschrijdt. Bovendien hadden patiënten een significante vermindering van symptomen in de domeinen ‘dagelijkse activiteiten’ (34,4%) en ‘pijn/ongemak’ (32,3%). Verder verbeterde de algehele huidige gezondheidstoestand uitgedrukt in de visueel analoge schaal (VAS) significant met 17% van 52 naar 69 (p=0,001). Deze bevindingen geven aan dat er een klinisch relevante verbetering van de kwaliteit van leven is na revascularisatie voor CMI-patiënten.

Het MST is een tertiair verwijzingscentrum voor patiënten met chronische abdominale klachten die verdacht worden van mesenteriale ischemie. Jaarlijks worden ongeveer 400 patiënten met mesenteriale ischemie behandeld, maar het aantal verwezen patiënten ligt hoger, omdat natuurlijk niet alle verwezen patiënten mesenteriale ischemie hebben. In **Hoofdstuk 9** voerden we een follow-up uit van patiënten die door het multidisciplinaire expertpanel geclassificeerd waren als ‘klachten niet passend bij CMI’, om te onderzoeken of het uitgebreide diagnostische werk, inclusief gedeelde besluitvorming, hun KvL beïnvloedde. Zes maanden na de beoordeling was de KvL klinisch significant verbeterd

zonder dat de patiënten daadwerkelijk een behandeling hadden ondergaan. Dit effect verminderde echter na twee jaar en was na vier jaar volledig verdwenen. De korte termijn stijging van de kwaliteit van leven is mogelijk een gevolg van de aandacht en grondige evaluatie in het expertisecentrum voor mesenteriale ischemie. Hierdoor kan de verbetering van de kwaliteit van leven in de eerste maanden na een grondige analyse van de symptomen, zoals waargenomen in de huidige studie, optreden zonder een objectieve verandering in de onderliggende gezondheidstoestand en moet deze met voorzichtigheid worden geïnterpreteerd. Met andere woorden, dit geeft aan dat voor beoordeling van de KvL-verbetering van een interventie, een follow-up periode van zes maanden mogelijk te kort is.

Referenties

1. Björck M, Koelemay M, Acosta S, Bastos Goncalves F, Kölbel T, Kolkman JJ, et al. Editor's Choice - Management of the Diseases of Mesenteric Arteries and Veins: Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2017;53(4):460-510.
2. Oderich GS, Malgor RD, Ricotta JJ, 2nd. Open and endovascular revascularization for chronic mesenteric ischemia: tabular review of the literature. Ann Vasc Surg. 2009;23(5):700-12.
3. van Petersen AS, Kolkman JJ, Beuk RJ, Huisman AB, Doelman CJ, Geelkerken RH, et al. Open or percutaneous revascularization for chronic splanchnic syndrome. J Vasc Surg. 2010;51(5):1309-16.
4. Acosta S. Mesenteric ischemia. Curr Opin Crit Care. 2015;21(2):171-8.
5. Acosta S, Bjorck M. Modern treatment of acute mesenteric ischaemia. Br J Surg. 2014;101(1):e100-8.
6. Roussel A, Castier Y, Nuzzo A, Pellenc Q, Sibert A, Panis Y, et al. Revascularization of acute mesenteric ischemia after creation of a dedicated multidisciplinary center. J Vasc Surg. 2015;62(5):1251-6.
7. Wyers MC. Acute mesenteric ischemia: diagnostic approach and surgical treatment. Semin Vasc Surg. 2010;23(1):9-20.
8. Stone JR, Wilkins LR. Acute mesenteric ischemia. Tech Vasc Interv Radiol. 2015;18(1):24-30.
9. Beaulieu RJ, Arnaoutakis KD, Abularrage CJ, Efron DT, Schneider E, Black JH, 3rd. Comparison of open and endovascular treatment of acute mesenteric ischemia. J Vasc Surg. 2014;59(1):159-64.
10. Blauw JT, Meerwaldt R, Brusse-Keizer M, Kolkman JJ, Gerrits D, Geelkerken RH, et al. Retrograde open mesenteric stenting for acute mesenteric ischemia. J Vasc Surg. 2014;60(3):726-34.
11. Karkkainen JM, Lehtimaki TT, Saari P, Hartikainen J, Rantanen T, Paajanen H, et al. Endovascular Therapy as a Primary Revascularization Modality in Acute Mesenteric Ischemia. Cardiovasc Intervent Radiol. 2015;38(5):1119-29.
12. Eslami MH, Rybin D, Doros G, McPhee JT, Farber A. Mortality of acute mesenteric ischemia remains unchanged despite significant increase in utilization of endovascular techniques. Vascular. 2016;24(1):44-52.
13. Serracant Barrera A, Luna Aufroy A, Hidalgo Rosas JM, Canovas Moreno G, Fortuno Andres JR, Falco Fages J, et al. Acute mesenteric ischemia: Utility of endovascular techniques. Cir Esp. 2015;93(9):567-72.
14. Puippe GD, Suesstrunk J, Nocito A, Pfiffner R, Glenck M, Pfammatter T. Outcome of endovascular revascularisation in patients with acute obstructive mesenteric ischaemia - a single-centre experience. Vasa. 2015;44(5):363-70.
15. Duran M, Pohl E, Grabitz K, Schelzig H, Sagban TA, Simon F. The importance of open emergency surgery in the treatment of acute mesenteric ischemia. World J Emerg Surg. 2015;10:45.
16. Arya S, Kingman S, Knepper JP, Eliason JL, Henke PK, Rectenwald JE. Open Mesenteric Interventions Are Equally Safe as Endovascular Interventions and Offer Better Midterm Patency for Chronic Mesenteric Ischemia. Ann Vasc Surg. 2016;30:219-26.
17. Plumereau F, Mucci S, Le Naoures P, Finel JB, Hamy A. Acute mesenteric ischemia of arterial origin: importance of early revascularization. J Visc Surg. 2015;152(1):17-22.
18. Forbrig R, Renner P, Kasprzak P, Dahlke MH, Muller-Wille R, Stroszczynski C, et al. Outcome of primary percutaneous stent-revascularization in patients with atherosclerotic acute mesenteric ischemia. Acta Radiol. 2016.
19. Schermerhorn ML, Giles KA, Hamdan AD, Wyers MC, Pomposelli FB. Mesenteric revascularization: management and outcomes in the United States, 1988-2006. J Vasc Surg. 2009;50(2):341-8 e1.

20. Moghadamyeghaneh Z, Carmichael JC, Mills SD, Dolich MO, Pigazzi A, Fujitani RM, et al. Early Outcome of Treatment of Chronic Mesenteric Ischemia. Am Surg. 2015;81(11):1149-56.
21. Oderich GS, Gloviczki P, Bower TC. Open surgical treatment for chronic mesenteric ischemia in the endovascular era: when it is necessary and what is the preferred technique? Semin Vasc Surg. 2010;23(1):36-46.
22. Kasirajan K, O'Hara PJ, Gray BH, Hertzer NR, Clair DG, Greenberg RK, et al. Chronic mesenteric ischemia: open surgery versus percutaneous angioplasty and stenting. J Vasc Surg. 2001;33(1):63-71.
23. Pecoraro F RZ, Lachat M, et al. Chronic mesenteric ischemia: critical review and guidelines for management. Ann Vasc Surg. 2013;27(1):113-122.
24. Indes JE, Giacovelli JK, Muhs BE, Sosa JA, Dardik A. Outcomes of endovascular and open treatment for chronic mesenteric ischemia. J Endovasc Ther. 2009;16(5):624-30.
25. Biebl M, Oldenburg WA, Paz-Fumagalli R, McKinney JM, Hakaim AG. Surgical and interventional visceral revascularization for the treatment of chronic mesenteric ischemia--when to prefer which? World J Surg. 2007;31(3):562-8.
26. Assar AN, Abilez OJ, Zarins CK. Outcome of open versus endovascular revascularization for chronic mesenteric ischemia: review of comparative studies. J Cardiovasc Surg (Torino). 2009;50(4):509-14.
27. Atkins MD, Kwolek CJ, LaMuraglia GM, Brewster DC, Chung TK, Cambria RP. Surgical revascularization versus endovascular therapy for chronic mesenteric ischemia: a comparative experience. J Vasc Surg. 2007;45(6):1162-71.
28. Gupta PK, Horan SM, Turaga KK, Miller WJ, Pipinos, II. Chronic mesenteric ischemia: endovascular versus open revascularization. J Endovasc Ther. 2010;17(4):540-9.
29. Rawat N, Gibbons CP, Joint Vascular Research G. Surgical or endovascular treatment for chronic mesenteric ischemia: a multicenter study. Ann Vasc Surg. 2010;24(7):935-45.
30. Sivamurthy N, Rhodes JM, Lee D, Waldman DL, Green RM, Davies MG. Endovascular versus open mesenteric revascularization: immediate benefits do not equate with short-term functional outcomes. J Am Coll Surg. 2006;202(6):859-67.
31. Zerbib P, Lebuffe G, Sergent-Baudson G, Chamatan A, Massouille D, Lions C, et al. Endovascular versus open revascularization for chronic mesenteric ischemia: a comparative study. Langenbecks Arch Surg. 2008;393(6):865-70.
32. Tallarita T, Oderich GS, Gloviczki P, Duncan AA, Kalra M, Cha S, et al. Patient survival after open and endovascular mesenteric revascularization for chronic mesenteric ischemia. J Vasc Surg. 2013;57(3):747-55; discussion 54-5.
33. Davies RS, Wall ML, Silverman SH, Simms MH, Vohra RK, Bradbury AW, et al. Surgical versus endovascular reconstruction for chronic mesenteric ischemia: a contemporary UK series. Vasc Endovascular Surg. 2009;43(2):157-64.
34. Brown DJ, Schermerhorn ML, Powell RJ, Fillinger MF, Rzucidlo EM, Walsh DB, et al. Mesenteric stenting for chronic mesenteric ischemia. J Vasc Surg. 2005;42(2):268-74.
35. Kougias P, Huynh TT, Lin PH. Clinical outcomes of mesenteric artery stenting versus surgical revascularization in chronic mesenteric ischemia. Int Angiol. 2009;28(2):132-7.
36. Clair DG, Beach JM. Mesenteric Ischemia. N Engl J Med. 2016;374(10):959-68.
37. Terlouw LG, Moelker A, Abrahamsen J, Acosta S, Bakker OJ, Baumgartner I, et al. European guidelines on chronic mesenteric ischaemia - joint United European Gastroenterology, European Association for Gastroenterology, Endoscopy and Nutrition, European Society of Gastrointestinal and Abdominal Radiology, Netherlands Association of Hepatogastroenterologists, Hellenic Society of Gastroenterology, Cardiovascular and Interventional Radiological Society of Europe, and Dutch Mesenteric Ischemia Study group clinical guidelines on the diagnosis and treatment of patients with chronic mesenteric ischaemia. United European Gastroenterol J. 2020;8(4):371-95.

Abbreviations

General

A	Artery
AA	Acute Abdomen
AAA	Acute Abdominal Aorta
ABSU	Absorbance Units
ACS	Abdominal Compartment Syndrome
AGR	Autologous Gastrointestinal Reconstruction
AMI	Acute Mesenteric Ischaemia
AMEA	Acute Mesenteric Arterial Embolism
AMAT	Acute Mesenteric Arterial Thrombosis
AoCMI	Acute on Chronic Mesenteric Ischemia
AP	Abdominal Pain
AUC	Area Under the Receiver Operating Curve
AVR	Aortic Valve Replacement
BE	Balloon Expandable
BMI	Body Mass Index
CA	Coeliac Artery
CABG	Coronary Artery Bypass Graft
CACS	Coeliac Artery Compression Syndrome (syn: MALS)
CHA	Common Hepatic Artery
CI	Confidence Interval
CIF	Chronic Intestinal Failure
CLI	Chronic Limb Ischemia
CMI	Chronic Mesenteric Ischaemia
CO	Cardiac Output
COPD	Chronic Obstructive Pulmonary Disease
CPE	Composite Disease Specific Primary End Point
CT	Computed Tomography
CTA	Computed Tomography Angiography
CU	Colitis Ulcerosa
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
DSA	Digital Subtraction Angiography
DUS	Duplex Ultrasound
DVT	Deep Vein thrombosis
ECG	Electrocardiography
(e)CAR	Endoscopic Coeliac Artery Release
EDV	End-Diastolic Velocity

EJVES	European Journal of Vascular and Endovascular Surgery
ELISA	Enzyme-linked immuno-sorbent assay
ePTFE	expanded PolyTetraFluoroEthylene
EQ-5D-5L	Euro Quality of Life – 5 dimensions and 5 levels
ER	Endovascular Revascularization
ESVS	European Society for Vascular Surgery
EVAR	EndoVascular Aneurysm Repair
EVT	Endovascular Treatment
GDA	Gastroduodenal Artery
GEE	Generalized Estimating Equation
GI	Gastro-Intestinal
HA	Hepatic Artery
HC	Hypercholesterolemia
HPN	Home Parenteral Nutrition
HR-QoL	Health-Related Quality of Life
HT	Hypertension
ICU	Intensive Care Unit
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
IF	Intestinal Failure
IMA	Inferior Mesenteric Artery
iMCQ	Institute for Medical Technology Assessment Medical Cost Questionnaire
iPCQ	Institute for Medical Technology Assessment Productivity Cost Questionnaire
IV	Intravenous
IQR	Inter Quartile Range
LGA	Left Gastric Artery
LIMA	Left inferior mammary artery
LMWH	Low-Molecular Weight Heparin
LR	Likelihood Ratio
LR+	Positive Likelihood Ratio
LR-	Negative Likelihood Ratio
MAL	Median Arcuate Ligament
MALS	Median Arcuate Ligament Syndrome (syn: CACS, Coeliac Artery Compression Syndrome)
MDCT	Multidetector Computed Tomography
MODS	Multi-Organ Dysfunction Syndrome
MRA	Magnetic Resonance Arthrography
MVI	Mitral Valve Insufficiency
NOMI	Non-Occlusive Mesenteric Ischemia
NPV	Negative Predictive Value
NVBN	Non-Vascular Bowel Necrosis

NVI	Non-Vascular Ischemia
OR	Operative Revascularization
OSMAR	Open Surgical Mesenteric Artery Revascularization
OSR	Open surgical revascularization
PAD	Peripheral Artery Disease
PAF	Paroxysmal Atrial Fibrillation
PDA	Pancreaticoduodenal Artery
PGI-I	Patient Global Impression of Improvement
PMAS	Percutaneous Mesenteric Artery Stenting
PPV	Positive Predictive Value
PTA	Percutaneous Transluminal Angioplasty
PTCA	Percutaneous Transluminal Coronary Angioplasty
Pts	Patients
PTSD	Post-Traumatic Stress Disorder
PV	Polycythaemia Vera
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RA	Renal Artery
RAAA	Ruptured Acute Abdominal Aorta
RCT	Randomized Controlled Trial
RIMA	right inferior mammary artery
ROMS	Retrograde Open Mesenteric Stenting
SA	splenic artery
SAE	Serious Adverse Event
SBI	Small Bowel Ischemia
SBS	Short Bowel Syndrome
SF-36	Short Form Health Survey 36
SMA	Superior Mesenteric Artery
SMAE	Superior Mesenteric Artery Embolus
SMV(T)	Superior Mesenteric Venous Thrombosis
TE	Thrombo-Embolic
TIA	Transient Ischaemic Attack
TPN	Total Parenteral Nutrition
VAS	Visual Analogue Scale

Biomarkers

ADH	Alcohol Dehydrogenase
aGST	a-Glutathione S-Transferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ALT	Alanine Transaminase
ALP	Alkaline Phosphatase
BE	Base Excess
BUN	Blood Urea Nitrogen
C3a	Complement Factor 3 split product
Ca	Calcium
CABA	Cobalt–Albumin-Binding Assay
CBC	Complete Blood Count
CK	Creatine Kinase
CK-BB	Creatine Kinase isoenzyme BB
CK-MB	Creatine Kinase isoenzyme MB
Cl	Chloride
CPK	Creatine Phosphokinase
CRP	C-reactive Protein
DNA	Deoxyribonucleic Acid
EarPI	Elastase-a1 Proteinase Inhibitor-complex
FibA	Fibrinopeptide A
GGT	γ - Glutamyl Transpeptidase
Hb	Haemoglobin
Ht	Haematocrit
I-FABP	Intestinal Fatty-acid Binding Protein
I-BABP	Ileal Bile Acid-binding Protein
IL-6	Interleukine-6
IL-8	Interleukine-8
IMA	Ischemia Modified Albumin
INR	International Normalized Ratio
K	Kalium
LDH	Lactate Dehydrogenase
L-FABP	Liver-type Fatty Acid-binding Protein
MCH	Mean Corpuscular Haemoglobin
MCV	Mean Corpuscular Volume
MPV	Mean Platelet Volume
Na	Natrium
NLR	Neutrophil to Lymphocyte Ratio
PC	Platelet Count

PGE2	Prostaglandin E2
pH	Potential of Hydrogen
PLR	Platelet-to-Lymphocyte Ratio
PT	Prothrombin Time
QT	Quick Time
RDW	Red Cell Distribution Width
SGOT	Serum Glutamate-Oxaloacetate Transaminase
TNFa	Tumor Necrosis Factor alpha
WBC	White Blood Cell Count

Definitions

Acute mesenteric ischemia (AMI) is defined as the occurrence of an abrupt cessation of the mesenteric blood flow with development of symptoms within minutes (in embolism) to hours (in atherothrombosis). The usual presenting symptom is severe abdominal pain that may progress to bowel necrosis and peritonitis in 8 hours up to days.(1, 2)

Chronic mesenteric ischemia (CMI) is defined as symptoms existing for more than 3 months due to mesenteric ischemia caused by gradually reduced oxygen delivery to the gastrointestinal tract. The typical presentation includes postprandial pain, weight loss due to fear of eating or unexplained diarrhoea.(1, 2)

Acute-on-chronic ischemia (AoCMI) is defined as AMI in patients who previously had typical complaints of CMI. Often, the complaints of CMI worsened over the preceding weeks with prolonged and more severe pain periods, pain even without eating, onset of diarrhoea or inability to eat at all.(1, 2)

Technical success (based on intention to treat) is defined as successful completion of the procedure and <30% residual stenosis at the end of the procedure.(1, 2)

Primary patency is defined as uninterrupted patency without need for any additional procedures.(1, 2)

Primary assisted patency is defined as revision of the revascularization method to prevent impending occlusion or progression of stenosis.(1, 2)

Secondary patency is defined as restored patency after occlusion by thrombectomy, thrombolysis, or transluminal angioplasty or any problems with the stent requiring revision or reconstruction.(1, 2)

(Primary) Clinical success is defined as uninterrupted relief or improvement of presenting symptoms with a patent revascularized target vessel.(1, 2)

A *serious adverse event (SAE)* is defined as any clinical event that resulted in death or any life-threatening event, produced permanent or significant disability or incapacity, resulted in hospitalization of the patient or significant prolonged hospitalization, or required medical or surgical intervention to prevent permanent impairment of function or permanent damage to a body structure.(1, 2)

Significant stenosis is defined as a >70% hemodynamically relevant stenosis. The degree of stenosis is measured in line with the NASCET guidelines for Carotid lesions: stenosis = (1 - [narrowest lumen diameter within lesion/normal diameter]) x 100%.(3)

Intestinal failure: the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation (IVS) is required to maintain health and/or growth.(4)

Table 1 Defining intestinal failure subtypes.(5)

Subtype	Type 1	Type 2	Type 3
Presentation timing	Acquired	Congenital/acquired	Congenital/acquired
Speed of onset	Acute	Acute	Chronic
Locality of disease	GI and systemic	GI and systemic	GI and systemic
Pathology	Benign and malignant (postoperative paralytic ileus)	Benign and malignant, complicated postoperative period (i.e., ostomies, fistula, sepsis)	Benign and malignant (short bowel syndrome or chronic intestinal motility disorders)
Duration	<28 days	Weeks to months	Months to years
Character	Most common, reversible and Self-limiting	More complex course	(Ir)reversible
Treatment	Conservatively, enteral or parenteral nutritional support for a limited period	Parenteral nutritional support, adequate treatment of sepsis is essential, 'bridging-to-surgery', restoration surgery	Long term parenteral nutritional support

References

1. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997;26(3):517-38.
2. Diehm N, Baumgartner I, Jaff M, Do DD, Minar E, Schmidli J, et al. A call for uniform reporting standards in studies assessing endovascular treatment for chronic ischaemia of lower limb arteries. Eur Heart J. 2007;28(7):798-805.
3. Moneta GL, Edwards JM, Chitwood RW, Taylor LM, Jr., Lee RW, Cummings CA, et al. Correlation of North American Symptomatic Carotid Endarterectomy Trial (NASCET) angiographic definition of 70% to 99% internal carotid artery stenosis with duplex scanning. J Vasc Surg. 1993;17(1):152-7; discussion 7-9.
4. Pironi L, Arends J, Baxter J, Bozzetti F, Pelaez RB, Cuerda C, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015;34(2):171-80.
5. Atema JJ, Mirck B, Van Arum I, Ten Dam SM, Serlie MJ, Boermeester MA. Outcome of acute intestinal failure. Br J Surg. 2016;103(6):701-8.

List of publications

Blauw JTM, Metz FM, Nuzzo A, van Etten – Jamaludin FS, Brusse-Keizer M, Boermeester MA, Peppelenbosch M, Geelkerken RH; Dutch Mesenteric Ischemia Study Group. The diagnostic value of biomarkers in mesenteric ischemia is insufficiently substantiated, a systematic review. Submitted to Gut.

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Metz FM, **Blauw JTM**, Brusse-Keizer M, Kolkman JJ, Bruno MJ, Geelkerken RH, Dutch Mesenteric Ischemia Study Group. A systematic review on the efficacy of treatment of the Median Arcuate Ligament Syndrome. Accepted for publication in The European Journal of Vascular and Endovascular Surgery.

Metz FM, **Blauw JTM**, Brusse-Keizer M, Kolkman JJ, Geelkerken RH. Quality of life temporarily improved in patients in whom the diagnosis chronic mesenteric ischemia wasn't confirmed after multidisciplinary evaluation in a tertiary referral centre. Japanese J Gastroenterol Res. 2022; 2(1): 1052.

Blauw JTM, Pastoors HAM, Brusse-Keizer M, Beuk RJ, Kolkman JJ, Geelkerken RH, Dutch Mesenteric Ischemia Study Group. The Impact of Revascularisation on Quality of Life in Chronic Mesenteric Ischemia. Can J Gastroenterol Hepatol. 2019 Nov 12;2019:7346013.

Blauw JT, Bulut T, Oderich GS, Geelkerken BR; Dutch Mesenteric Ischemia Study Group. Mesenteric vascular treatment 2016: from open surgical repair to endovascular revascularization. Best Pract Res Clin Gastroenterol. 2017 Feb;31(1):75-84.

Blauw J, Bulut T, Eenhoorn P, Beuk RJ, Brusse-Keizer M, Kolkman JJ, Geelkerken RH. Chronic mesenteric ischemia: when and how to intervene on patients with celiac/SMA stenosis. J Cardiovasc Surg (Torino). 2017 Apr;58(2):321-328.

Blauw JT, Meerwaldt R, Brusse-Keizer M, Kolkman JJ, Gerrits D, Geelkerken RH, Multidisciplinary Study Group of Mesenteric Ischemia. Retrograde open mesenteric stenting for acute mesenteric ischemia. J Vasc Surg. 2014 Sep;60(3):726-34.

Book chapters

Robert H. Geelkerken, **Juliëtte Blauw**, Desiree van Noord. Hoofdstuk 26: Mesenteriale vaten. Leerboek Chirurgie. Derde herziene druk, 2021.

Juliëtte Blauw, W. van de Water, R.H. Geelkerken. Hoofdstuk 39: Buikpijn die van kwaad tot erger gaat. Probleemgeoriënteerd denken in de Chirurgie. Eerste druk, 2022.

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En van alles wat nog mag komen. Ik kijk er naar uit.

Curriculum Vitae

Juliëtte Theresia Maria Blauw werd op 1 augustus 1985 geboren als oudste dochter van Ton en Trees en groeide samen met zus Noor op in Bunnik en Utrecht. Een aantal jaar na het overlijden van Trees ontmoetten Ton en Theta elkaar, waarna ze in 1998 trouwden. In 2003 behaalde Juliëtte haar Gymnasium eindexamen aan het Christelijk Gymnasium Utrecht.

In de zomer van 2003 verhuisde zij naar Groningen voor haar studie Geneeskunde en behaalde in 2004 haar propedeuse. Haar 1ste jaar coschappen deed zij in het UMCG, waarna zij naar Enschede verhuisde voor de laatste 2 jaar van haar coschappen. De wetenschapsstage die ze verrichte onder leiding van plastisch chirurg dr. plastisch chirurg dr. Oliver Zöphel werd bekroond met een 10 en haar semi-artsstage Chirurgie bij prof. dr. Bob Geelkerken met een 9.

Na het behalen van haar artsexamen begon Juliëtte als ANIOS Chirurgie in het MST Enschede in 2010. In 2011 raakte zij geïnteresseerd in mesenteriaal ischemie en begon zij met haar promotieonderzoek bij prof. dr. Bob Geelkerken. Dit heeft zij gedurende haar gehele opleiding naast haar klinische werkzaamheden gedaan. In 2017 werd haar een grant toegekend van €50.000,- van het Pioneers in HealthCare Fund om een deel van haar onderzoek mee te doen. Toen Juliëtte in 2012 werd aangenomen voor de opleiding Heelkunde verhuisde zij naar Zwolle om in de Isala Klinieken van september 2012 tot oktober 2016 als AIOS te werken. Na hersteld te zijn van haar ziekte, verruilde Juliëtte de Groningse opleidingsregio in 2016 voor Regio Leiden en begon 1 oktober 2016 als AIOS in het LUMC. Gedurende heel 2019 werkte zij als GE-differentiant in het Alrijne. Voor verdere verdieping in Abdominal Wall Reconstruction en Intestinal failure, organiseerde Juliëtte een stage binnen haar differentiatie bij prof. dr. Marja Boermeester in het AMC in 2020. Op 22 oktober 2020 ronde zij haar opleiding af en mocht Juliëtte zich GE-chirurg noemen.

Van november 2021 tot maart 2021 was zij fellow Abdominal Wall Reconstruction en Intestinal failure bij prof. dr. Marja Boermeester in het AMC. Vanaf april 2021 heeft Juliëtte zich fulltime toegelegd op het afronden van haar promotie. Vanaf januari 2022 tot heden werkt zij in het Alrijne ziekenhuis op de Intensive Care en bij de Heelkunde als waarnemend mammachirurg.

Juliëtte is getrouwd met Dennis en trotse moeder van Viviënne.