The Incidence of Chronic Mesenteric Ischemia in the Well-Defined Region of a Dutch Mesenteric Ischemia Expert Center

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INTRODUCTION: **This study aimed to determine the incidence of chronic mesenteric ischemia (CMI) and to examine the influence of the etiological cause, location, and severity of a mesenteric artery stenosis on the probability of having CMI.**

METHODS: **A prospective database, containing the details of all patients with suspected CMI referred to a renowned CMI expert center, was used. Patients residing within the expert centers' well-defined region, between January 2014 and October 2019, were included. CMI was diagnosed when patients experienced sustained symptom improvement after treatment.**

RESULTS: **This study included 358 patients, 75 had a ≥50% atherosclerotic stenosis of 1 vessel (CMI 16%), 96 of 2 or 3 vessels (CMI 81%), 81 celiac artery compression (CMI 25%), and 84 no stenosis (CMI 12%). In total, 138 patients were diagnosed with CMI, rendering a mean incidence of 9.2 (95% confidence interval [CI] 6.2–13.7) per 100,000 inhabitants. Atherosclerotic CMI was most common, with a mean incidence of 7.2 (95% CI 4.6–11.3), followed by median arcuate ligament syndrome 1.3 (95% CI 0.5–3.6) and chronic nonocclusive mesenteric ischemia 0.6 (95% CI 0.2–2.6). The incidence of CMI was highest in female patients (female patients 12.0 [95% CI 7.3–19.6] vs male patients 6.5 [95% CI 3.4–12.5]) and increased with age. CMI was more prevalent in the presence of a ≥70% atherosclerotic single-vessel stenosis of the superior mesenteric artery (40.6%) than the celiac artery (5.6%).**

DISCUSSION: **The incidence of CMI is higher than previously believed and increases with age. Probability of CMI seems highest in suspected CMI patients with multivessel disease or a ≥70% atherosclerotic single-vessel superior mesenteric artery stenosis.**

INTRODUCTION

Chronic mesenteric ischemia (CMI) is characterized by complaints of postprandial pain and weight loss from the fear of eating. CMI is the result of a compromised oxygen supply to the gut and can be caused by occlusive mesenteric ischemia or nonocclusive mesenteric ischemia (NOMI) (1). Occlusive CMI is caused by stenosis or occlusion of ≥1 mesenteric artery, which can be caused by atherosclerosis, vasculitis, or celiac artery (CA) compression. The latter can result in median arcuate ligament syndrome (MALS). Chronic NOMI is defined as CMI in the absence of a mesenteric artery stenosis and is associated with cardiac forward failure, pulmonary hypertension, severe chronic obstructive pulmonary disease, hemodialysis, or vasospasms of the mesenteric arteries (1–3).

The incidence of CMI is presumed to be very low, which may result in insufficient awareness among clinicians and underestimation of the magnitude of this disease. Atherosclerotic mesenteric artery stenoses are the most common cause of CMI

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and are frequently found in the general population. The prevalence of atherosclerotic mesenteric artery stenosis is 6%–29% and increases with age (1,4,5). Despite the high prevalence of mesenteric artery stenosis, only a minority will result in ischemia and become symptomatic because the gut is protected against ischemia by an extensive collateral circulation. Previous retrospective studies report higher clinical success rates of revascularization in patients with ≥2 stenotic mesenteric arteries than in patients with a single-vessel mesenteric artery stenosis because the collateral circulation is more likely to be compromised in patients with multivessel disease (6–9). Experts believe that the risk of developing CMI also depends on the etiological cause of the stenosis (e.g., atherosclerosis and CA compression) and the location of the stenosis (i.e., CA, superior mesenteric artery [SMA] and inferior mesenteric artery); however, conclusive evidence supporting this belief is unavailable (10).

The purpose of this study was to determine the incidence of CMI and to examine the influence of the etiological cause, location, and severity of a mesenteric artery stenosis on the occurrence of CMI in symptomatic patients with suspected CMI.

METHODS
Study design
This cohort study is based on a prospective database of patients analyzed for suspected mesenteric ischemia in Medisch Spectrum Twente, a mesenteric ischemia expert center. Data regarding medical history, presenting symptoms, diagnostic tests, severity of mesenteric artery stenosis, diagnosis, treatment, and follow-up were collected and pseudoanonymized with a unique code. Inclusion in the database started in January 2014; follow-up data until October 2019 was used in the current study. Informed consent was obtained from all participating patients. The local medical research ethics committee decided that the Medical Research Involving Human Subjects Act does not apply to this study (K19-52). The investigators complied with the Helsinki declaration on research ethics. The STROBE checklist for cohort studies was used to write this study (11).

Study cohort
All patients analyzed for suspected CMI living within the region of the study center were included in the study. Patients not residing within the region and patients diagnosed with acute mesenteric ischemia, without preceding symptoms of CMI, were excluded. The study center is located in a rural area and has a well-defined region with approximately 263,500 inhabitants—approximately 133,400 male and 130,100 female patients. The study center is a national mesenteric ischemia expert center, analyzing and treating patients with mesenteric ischemia from all over the country and is the region's only expert center. For several decades, the study center has made a great effort to raise awareness for CMI within their region. The "Dutch Hospital Data" database, containing data of the Dutch health reimbursement system, was searched to verify whether patients treated for mesenteric ischemia residing within the region presented in the study center (used diagnosis code DBC 405, ischemia of the intestine). During the study period, adherence of the region's mesenteric ischemia patients to the study center was 98.8%.

Diagnostic workup and diagnosis of CMI
A standardized diagnostic workup was performed in all patients with suspected CMI and consisted of assessment of symptoms, imaging of the mesenteric arteries (duplex ultrasound or computed tomography angiography), and, when indicated, assessment of mucosal ischemia by gastrointestinal tonometry (12). The results of the workup were discussed by an experienced multidisciplinary expert team consisting of gastroenterologists, interventional radiologists, and vascular surgeons. Treatment decisions were based on a consensus diagnosis of CMI, which was established when CMI was deemed to be a likely explanation for the presenting symptoms, in the absence of a possible alternative diagnosis (12). A definitive diagnosis of CMI was established when symptoms improved or resolved at 3 months after revascularization or in case of chronic NOMI during treatment with a vasodilator. Patients with a consensus diagnosis of no CMI or those initially labeled as CMI, but without improvement of symptoms after treatment, were classified as non-CMI.

Primary outcome
The primary outcome is the annual incidence rate of all-cause CMI. All-cause CMI is defined as the sum of the incidences of the definitive diagnoses of atherosclerotic CMI, MALS, and chronic NOMI. Incidence rates are shown per 100,000 inhabitants. The number of inhabitants residing within the region on the first of January of each year was retrieved from Statistics Netherlands (CBS) and used to calculate the annual incidence. Because data of 2019 had been collected until October, an expected number of atherosclerotic CMI, MALS, and chronic NOMI patients was calculated based on the number of patients presenting in the month of January until October.

Secondary outcomes
Four secondary outcomes were formulated. First, the incidence rate specified per etiological cause, i.e., atherosclerotic CMI, MALS, and chronic NOMI, including stratification by age and sex. Second, the differences in cause, location, and number of stenotic mesenteric arteries between patients with a definitive diagnosis of CMI and non-CMI. The grade of stenosis was calculated according to the North American Symptomatic Carotid Endarterectomy Trial method, which is one minus the ratio of the smallest diameter at the level of the occlusive lesion and the diameter of a normal part of artery distal to the stenosis converted to percent (13). A stenosis of <50% was labeled as no stenosis, ≥50% and <70% as an intermediate stenosis, and ≥70% as a severe stenosis. Third, the clinical success rates of revascularization in patients with atherosclerotic CMI and patients with MALS. Clinical success was defined as sustained improvement or disappearance of symptoms after successful revascularization. Fourth, the survival, starting at diagnosis, of patients with a definitive diagnosis of atherosclerotic CMI, a definitive diagnosis of MALS, and non-CMI.

Statistical analysis
Statistical analyses were performed with R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) using packages epiR, survival, and GGAlly. Numerical baseline characteristics were not equally distributed and are, therefore, shown as median and interquartile ranges (IQR). Baseline characteristics of patients with CMI and patients without CMI were compared using χ^2 tests for categorical variables and Wilcoxon signed-rank tests for numerical variables. Overall and age-specific and sex-specific incidence rates were based on the number of cases with CMI and each etiological cause and were expressed as number of cases per 100,000 inhabitants. The reported overall incidence

rates comprise the mean incidence over the 6-year study period. Incidence rates and confidence intervals (CIs) were calculated using R package epiR, the used method was "prop.single." The relationship between the location and number of mesenteric artery stenoses and a definitive diagnosis of CMI was assessed by the χ^2 or fisher exact tests. Survival of patients without CMI, patients with atherosclerotic CMI, and patients with MALS was assessed by the Kaplan-Meier method and compared using the logrank test. The hazard ratio (HR), with 95% CI of mortality in atherosclerotic CMI patients and non-CMI patients with an atherosclerotic mesenteric artery stenosis, was calculated using an univariate cox proportional hazard regression model.

RESULTS

Patient characteristics

During the study period, 2,188 patients with suspected CMI were analyzed at the study center, of whom 358 (16.4%) resided within the region of the study center. A definitive diagnosis of CMI was established in 138 (38.5%) of the regional patients, the remaining 220 patients were classified as non-CMI. Comparison of baseline characteristics of both groups revealed that patients with CMI were significantly older (median [IQR] CMI 72 [55–79] vs non-

CMI 58 [34–73]; $P < 0.001$) and had a significantly shorter durations of follow-up (median [IQR] CMI 19 [6–36] months vs non-CMI 30 [12–48] months; $P < 0.001$). The cardiovascular risk factors dyslipidemia, hypertension, and history of cardiovascular disease were more frequently present in patients with CMI, $P < 0.001$ (Table 1). Of the reported presenting symptoms, weight loss and an adapted eating pattern were significantly more frequent in patients with CMI, whereas weight and body mass index were significantly lower in patients with CMI than in patients without CMI. The subgroup of patients with MALS had a median age of 28 years (IQR 23–43), and 80% were female patients.

Incidence rates

Table 2 shows that the incidence of all-cause CMI increased from 7.2 (95% CI 4.6–11.3) per 100,000 inhabitants in 2014 to up to 11.1 (95% CI 7.8–15.9) in 2019. Resulting in a mean incidence of all-cause CMI of 9.2 (95% CI 6.2–13.7). The mean incidence of atherosclerotic CMI was 7.3 (95% CI 4.6–11.3) and showed an increasing trend with an incidence of 4.9 (95% CI 2.9–8.4) in 2014 increasing up to 10.1 (95% CI 6.9–14.7) in 2019 (Figure 1). The incidence of MALS (mean incidence [95% CI] 1.3 [0.5–3.6]) and chronic NOMI (mean incidence [95% CI] 0.6 [0.2–2.6])

Table 1. Baseline characteristics

Baseline characteristic	All patients (N = 358)	CMI (N = 138)	Non-CMI (N = 220)	P value
Female sex	60.3%	63.8%	58.2%	0.347
Age	64 (43–76)	72 (55–79)	58 (34–73)	<0.001
Follow-up (mo)	26 (10–43)	19 (6–36)	30 (12–48)	<0.001
Risk factors				
Cardiovascular disease	35.5%	48.6%	27.3%	<0.001
Peripheral artery disease	20.1%	31.2%	13.2%	<0.001
Coronary artery disease	23.2%	31.9%	17.7%	0.003
Cerebrovascular disease	10.1%	12.3%	8.6%	0.344
Dyslipidemia	22.6%	34.1%	15.5%	<0.001
Hypertension	34.4%	47.8%	25.9%	<0.001
Diabetes	15.4%	18.1%	13.6%	0.320
Family history of CVD	7.0%	6.5%	7.3%	0.953
Smoking	70.6%	78.2%	65.6%	0.067
Pack years	29 (10–40)	30 (11–46)	22 (10–40)	0.807
Presenting symptoms				
Weight loss	63.5%	75.8%	54.9%	0.002
Weight (kg)	66 (56–78)	62 (55–74)	68 (57–82)	0.005
Body mass index	23 (20–26)	22 (19–26)	23 (20–27)	0.049
Abdominal pain	84.6%	85.1%	84.2%	0.980
Duration abdominal pain (mo)	6 (2–12)	6 (2–12)	6 (2–12)	0.497
Postprandial abdominal pain	62.1%	65.7%	59.7%	0.419
Exercise induced abdominal pain	50.0%	48.7%	50.8%	0.886
Adapted eating pattern	68.0%	76.9%	62.1%	0.044
Nausea	62.0%	62.6%	61.6%	0.984

CMI, chronic mesenteric ischemia; CVD, cardiovascular disease.

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Table 2. Annual incidence rates of CMI and the annual number of new CMI cases

No. of patients	2014	2015	2016	2017	2018	2019[a]	Mean
Referred for suspected CMI	53	63	61	68	65	64	62.3
All-cause CMI	19	25	21	27	24	29	24.2
Atherosclerotic CMI	13	17	15	23	20	26	19.0
MALS	2	6	4	2	4	3	3.5
Chronic NOMI	4	2	2	2	0	0	1.7

Incidence rates per 100,000 (95% CI)	2014	2015	2016	2017	2018	2019[a]	Mean
All-cause CMI	7.2 (4.6–11.3)	9.5 (6.4–14.0)	8.0 (5.2–12.2)	10.3 (7.1–14.9)	9.1 (6.1–13.6)	11.1 (7.8–15.9)	9.2 (6.2–13.7)
Atherosclerotic CMI	4.9 (2.9–8.4)	6.5 (4.0–10.3)	5.7 (3.5–9.4)	8.7 (5.8–13.1)	7.6 (4.9–11.7)	10.1 (6.9–14.7)	7.3 (4.6–11.3)
MALS	0.8 (0.2–2.8)	2.3 (1.0–5.0)	1.5 (0.6–3.9)	0.8 (0.2–2.8)	1.5 (0.6–3.9)	1.0 (0.3–3.2)	1.3 (0.5–3.6)
Chronic NOMI	1.5 (0.6–3.9)	0.8 (0.2–2.8)	0.8 (0.2–2.8)	0.8 (0.2–2.8)	0.0	0.0	0.6 (0.2–2.6)

CI, confidence interval; CMI, chronic mesenteric ischemia; MALS, median arcuate ligament syndrome; NOMI, non-occlusive mesenteric ischemia.
[a]Predicted number of patients based on first 9 months.

remained relatively stable. Stratification for sex showed a higher mean incidence of all-cause CMI, atherosclerotic CMI, and MALS in female patients (Figure 2a). Stratification for age showed that the mean incidence of all-cause CMI and atherosclerotic CMI increased with age, whereas the mean incidence of MALS decreased with age (Figure 2b).

Cause and severity of mesenteric artery stenosis in patients with suspected CMI
One hundred ninety of the 358 patients (53%) with suspected CMI had ≥1 atherosclerotic mesenteric artery stenosis on imaging. CA compression was present in 81 patients (23%), a combination of CA compression and atherosclerosis was present in 3 patients (1%), and the remaining 84 (23%) patients had no stenosis on imaging. Table 3 shows that most patients with an atherosclerotic stenosis had a definitive diagnosis of CMI (55.3%). CMI was present in 12 of 75 patients (16.0%) with a single-vessel atherosclerotic stenosis, 67 of 85 patients (78.8%) with 2 atherosclerotic mesenteric artery stenoses, and 26 of 30 patients (86.7%) with 3 atherosclerotic mesenteric artery stenoses. Twenty of 81 patients (24.7%) with CA compression was diagnosed with MALS. Chronic NOMI was diagnosed in 10 of 84 patients (11.9%) without a mesenteric artery stenosis.

Grading of stenosis severity was available in a subgroup of 166 patients with an atherosclerotic mesenteric artery stenosis, of whom 75 had a definitive diagnosis of CMI. Table 4 shows that CMI was most frequent in patients with a severe stenosis of both CA and SMA (87.3%). The proportion of atherosclerotic CMI patients with a severe CA stenosis and no SMA stenosis is low (5.6%). By contrast, CMI was more frequent in patients with a severe SMA stenosis and no CA stenosis (40.6%).

Clinical success
One hundred nineteen patients underwent a revascularization procedure. Hundred patients underwent revascularization of an atherosclerotic stenosis, the remaining 19 patients underwent an endoscopic retroperitoneal CA release for MALS. The clinical success rate of revascularization was 91.9% in patients with an atherosclerotic

stenosis (Table 5). Patients with multivessel atherosclerotic stenoses had a higher clinical success rate (95.4%) than patients with a single-vessel atherosclerotic stenosis (69.2%). The clinical success rate of CA release was 89.5%. Revascularization was not performed in 19 patients with a consensus diagnosis of atherosclerotic CMI or MALS. Reasons not to revascularize were severe comorbidities in 9 patients, refusal of treatment in 8 patients, and death before revascularization in 2 patients, of whom 1 died of acute on CMI.

Survival
Sixty-four patients (17.9%) referred for suspected CMI died during follow-up (38 CMI vs 26 non-CMI). Mesenteric ischemia
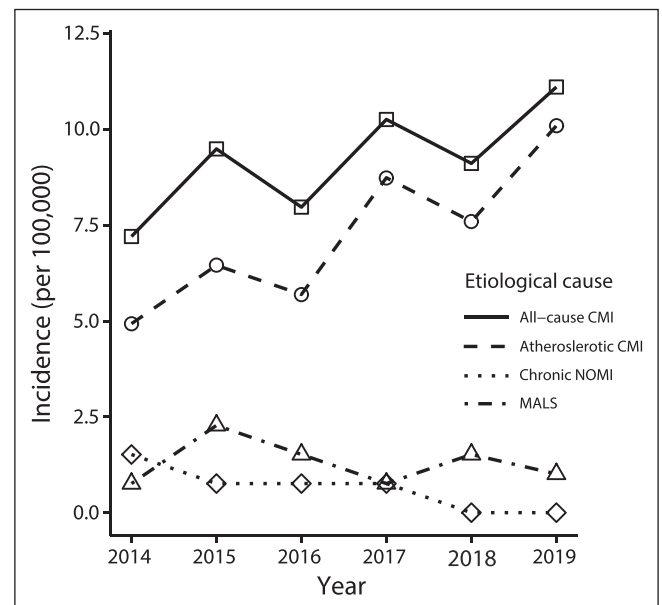

Figure 1. Incidence rates of all-cause CMI, atherosclerotic CMI, MALS, and chronic NOMI. CMI, chronic mesenteric ischemia; MALS, median arcuate ligament syndrome; NOMI, nonocclusive mesenteric ischemia.
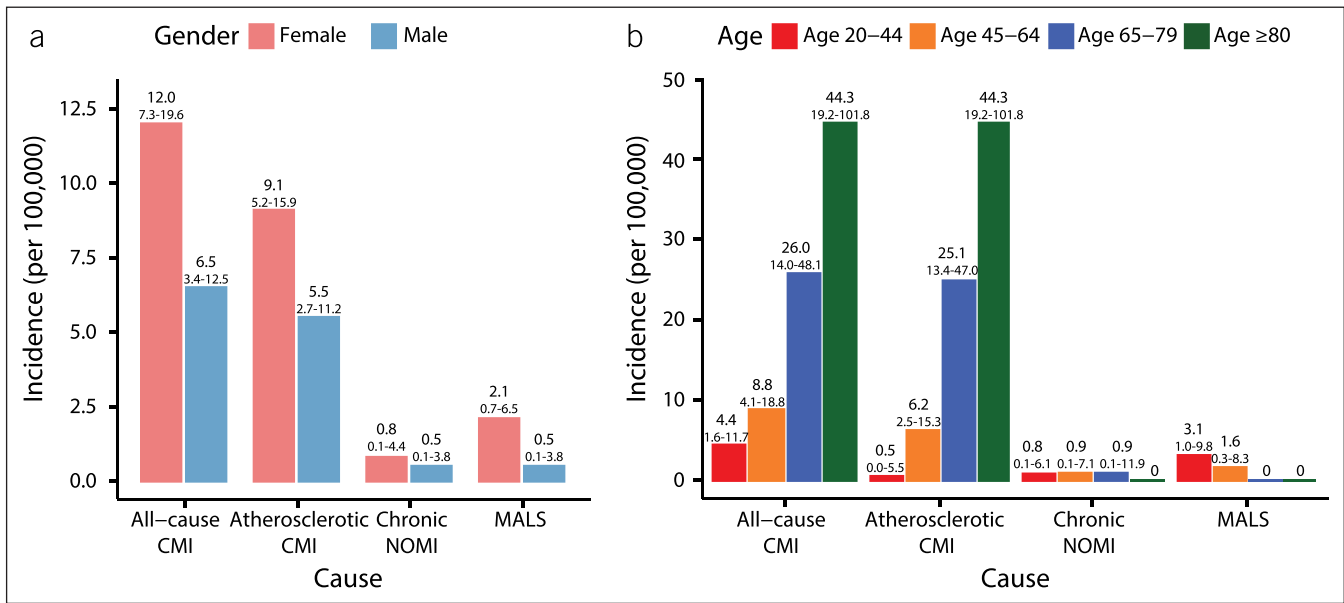
Figure 2. (**a**) Mean incidence rates with 95% CI of all-cause CMI, atherosclerotic CMI, MALS, and chronic-NOMI stratified by sex. (**b**) Mean incidence rates with 95% CI of all-cause CMI, atherosclerotic CMI, MALS, and chronic-NOMI stratified by age. CI, confidence interval; CMI, chronic mesenteric ischemia; MALS, median arcuate ligament syndrome; NOMI, non-occlusive mesenteric ischemia.

was the cause of death in 9 CMI patients, of whom 8 patients had multivessel stenoses and 1 patient had no stenosis. No non-CMI patients died of mesenteric ischemia. Survival analysis of all patients showed that the mortality at 24 months of follow-up was 36.6% (95% CI 24.7%–46.6%) in patients with CMI, 0% (95% CI 0%–0%) in patients with MALS, and 10.8% (95% CI 6.3%–15.1%) in patients without CMI (Figure 3). Survival of patients with atherosclerotic CMI was significantly worse than survival of patients without CMI and patients with MALS. Subgroup analysis of patients with an atherosclerotic mesenteric artery stenosis showed a significantly higher risk of mortality in patients with atherosclerotic CMI (HR [95% CI] 2.57 [1.38–4.73]; $P = 0.002$).

DISCUSSION

This study is the first to report the incidence of all-cause CMI, encompassing atherosclerotic CMI, MALS, and chronic NOMI. The observed incidence of all-cause CMI of at least 9.2 per 100,000 inhabitants overrules the notion that CMI is a rare disease. Furthermore, this study suggests that the probability of developing CMI is influenced by the nature of a mesenteric artery stenosis (atherosclerotic or compression) and single-vessel or multivessel involvement.

For decades, CMI has been assumed to be a rare disease. The current study sheds a different light on this widespread misconception (1). In this well-defined cohort, all-cause CMI was found to have an incidence of 9.2 per 100,000 inhabitants, which approximates the incidence of Crohn's disease (10.9 per 100,000)—established over a 20-year period in a Dutch cohort (14). Examining the incidence of other vascular diseases, the incidence of all-cause CMI is higher than the incidence of ruptured abdominal aortic aneurysms (7.0 per 100.000) (15) and almost twice as high as the incidence of occlusive acute mesenteric ischemia (4.5–5.4 per 100,000) (16). This study reports a higher incidence of atherosclerotic CMI and MALS in female patients

and confirms the female predisposition reported by other studies (1,17,18). The observation that the incidence of atherosclerotic CMI increases with age is plausible because the prevalence of mesenteric artery stenosis has been reported to increase with age as well (4,5). These new data emphasize the urgent need to improve awareness about the existence of CMI and its clinical burden including severe symptoms, loss of quality of life, and increased mortality among patients with atherosclerotic CMI. Importantly, clinicians should be educated about the fact that in over 90% of patients with CMI, symptom improvement can be reached.

Interestingly, the rise in the incidence of all-cause CMI during the study period was exclusively explained by an increasing number of patients diagnosed with atherosclerotic CMI. The incidence of MALS and chronic NOMI remained relatively stable. This increase may signify a true increase in the incidence of atherosclerotic CMI related to an increasing prevalence of

Table 3. Cause of mesenteric artery stenosis in patients with suspected CMI stratified by a definitive diagnosis of CMI

Cause mesenteric artery stenosis	CMI N = 138	Non-CMI N = 220	% Ischemia
No stenosis	10	74	11.9
Atherosclerosis	105	85	55.3
1 vessel atherosclerosis	12	63	16.0
2 vessel atherosclerosis	67	18	78.8
3 vessel atherosclerosis	26	4	86.7
Atherosclerosis and CA compression	3	0	100
CA compression	20	61	24.7
CA, celiac artery; CMI, chronic mesenteric ischemia.			

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Table 4. Severity of atherosclerotic CA and SMA stenosis and presence of CMI

| | SMA stenosis | | | | | |
| | ≤50% | | 51%–70% | | >70% | |
	N	% CMI	N	% CMI	N	% CMI
CA stenosis						
≤50%	25	12.0	10	10.0	32	40.6
51%–70%	12	0.0	2	0.0	8	100.0
>70%	18	5.6	4	25.0	55	87.3

CA, celiac artery; CMI, chronic mesenteric ischemia; N, number of CMI and non-CMI patients with a stenosis; SMA, superior mesenteric artery.

cardiovascular risk factors in an aging western population because the prevalence of atherosclerotic mesenteric artery stenosis also increases with age (4,5). However, increased awareness for atherosclerotic CMI could be another likely explanation for this increase in CMI incidence.

Experts in the field of CMI have always claimed that the severity, location, and cause of a mesenteric artery stenosis are important denominators that influence the probability of having CMI; but, evidence to support this claim was limited to circumstantial evidence (10). The importance of the cause of a mesenteric artery stenosis is suggested by the relatively high proportion of CMI in symptomatic patients with an atherosclerotic stenosis (55.3%). The proportion of MALS in patients with symptoms suggestive of CMI in combination with a mesenteric artery stenosis caused by CA compression was 24.7%. This indicates that alternative diagnoses should be considered and excluded because MALS is not the cause of the symptoms in 75.3% of the patients with CA compression. CMI was most frequently present in symptomatic patients with multivessel atherosclerotic mesenteric artery stenoses (81%), compared with only 16% in symptomatic patients with an atherosclerotic stenosis of a single mesenteric artery. In symptomatic patients with a single-vessel atherosclerotic mesenteric artery stenosis, the location of the stenosis seemed of importance because CMI was present in 40.6% of the patients with a severe SMA stenosis, but in only 5.6% of the patients with a severe CA stenosis. The probability of CMI seems, therefore, highest in symptomatic patients with either multivessel mesenteric artery stenoses or a single-vessel atherosclerotic SMA stenosis.

Reported clinical success rates of revascularizations in multivessel disease are excellent (90%–100%) (6,7,9). The

Table 5. Clinical success of mesenteric artery revascularization

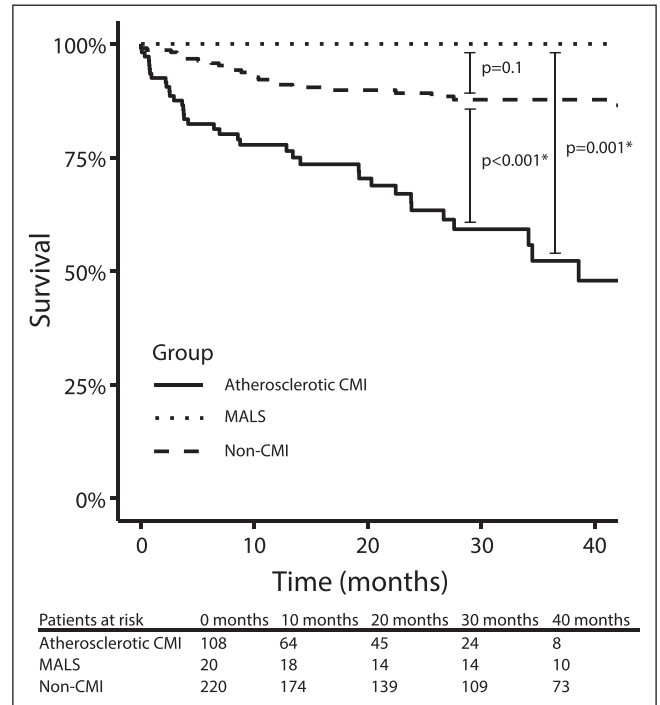| Cause mesenteric artery stenosis	Clinical success % (N)
Atherosclerotic stenosis	91.9 (91)
Single-vessel atherosclerotic stenosis	69.2 (9)
Multivessel atherosclerotic stenosis	95.4 (83)
CA artery compression	89.5 (17)

CA, celiac artery.

Figure 3. Kaplan-Meyer survival analysis of patients without CMI, patients with atherosclerotic CMI, and patients with MALS. *Statistically significant difference in survival between groups. CMI, chronic mesenteric ischemia; MALS, median arcuate ligament syndrome.

current study supports these findings with a clinical success rate of 95.4% in patients with multivessel disease. A lower clinical success rate of 73% is reported in patients with single-vessel atherosclerotic CMI (8). Based on a relatively low number of patients, the current study shows a comparable clinical success rate of 69.2%. A systematic review reporting on 400 patients treated by a CA release showed sustained clinical success in 80% of patients (19). The slightly higher reported clinical success rate of CA release of 89.5% in the current study might be explained by some statistical variation because of the relatively low number of included cases or a more appropriate patient selection because of the use of gastrointestinal tonometry (20).

In the literature, definitions for a mesenteric artery stenosis range from 50% to 70% but are still a topic of discussion (7,8,21–23). This study suggests that a ≥70% cutoff would be appropriate in patients with single-vessel disease because the probabilities of CMI in isolated intermediate stenosis were 0% and 10% for the CA and SMA, respectively. A ≥70% cutoff could reduce the risk of overtreatment, which is currently 27–31% (8). A cutoff of ≥50% seems appropriate in patients with a stenosis of both CA and SMA because the probability of CMI was 83% in this group of patients. Overtreatment is less of an issue in multi-vessel disease of CA and SMA, since clinical success ranges from 90% to 100% (6,7,9).

Figure 3 shows the survival rates of patients with MALS, patients with atherosclerotic CMI, and patients without CMI. The observed differences in mortality might be explained by differences in disease mechanism and baseline characteristics. The 0% mortality rate of MALS is a logical consequence of the younger age of these patients (median age 28 years) and the fact

that the cause of this disease is mechanical, i.e., local CA compression, and not a systemic disease. Mortality at the 24-month follow-up was 36.6% in the atherosclerotic CMI population and 10.8% among patients without CMI. A previous study comparing mortality in patients with atherosclerotic CMI with the expected mortality in the general population, using age- and sex-specific mortality rates, reported an increased standardized mortality risk of 3.55 in patients with CMI, supporting the findings of the current study (24). The higher mortality in atherosclerotic CMI could be due to the systemic nature of atherosclerosis because atherosclerosis also affects other vascular beds. However, the currently reported subgroup analysis in patients with an atherosclerotic mesenteric artery stenosis showed a significantly increased mortality risk in patients with atherosclerotic CMI compared to patients without CMI (HR 2.57). The increased mortality could be due to CMI or more extensive and severe atherosclerosis in patients with CMI, but a detailed cause of death was not available for all deceased patients. Additional studies are, therefore, needed to confirm these results and examine whether the cause of death is related to cardiovascular events.

This study has several limitations inherent to database studies. First, incidence rates are based on a relatively limited number of patients with CMI presenting in a single expert center. The number of missed CMI cases seems low because adherence of the regional patients with CMI to the study center approximated 100%. Underestimation of the true incidence of all-cause CMI is, however, still probable because limited knowledge and awareness among general practitioners and clinicians is likely to result in underdiagnosing of CMI patients. Second, the outcomes regarding clinical success rates, location, and cause of mesenteric artery stenosis are based on limited numbers of patients, which is caused by the epidemiological nature of the study, restricting patient inclusion to residents of the catchment area of the expert center. Despite the limitations, this study provides a valuable approximation of the incidence rates of CMI.

In conclusion, the estimated incidence of CMI of 9.2 per 100,000 is higher than previously estimated and comparable with some other well-known gastrointestinal diseases such as Crohn's disease. Its incidence shows an increasing trend that seems mainly attributable to atherosclerotic CMI. Probability of CMI seems highest in suspected patients with CMI with multivessel disease. The minimally relevant percentage stenosis to develop CMI seems 70% for single-vessel stenosis, whereas in multivessel disease a 50% stenosis already suffices.

CONFLICTS OF INTEREST
Guarantor of the article: Jeroen J. Kolkman, MD, PhD.
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Study Highlights

WHAT IS KNOWN
✔ CMI is a debilitating disease with an unknown incidence.
✔ Asymptomatic mesenteric artery stenoses are frequently observed in the general population.

WHAT IS NEW HERE
✔ The incidence of CMI is 9.2 per 100,000 inhabitants (12.0 in women and 6.5 in men).
✔ CMI is most common in symptomatic patients with atherosclerotic multivessel disease.
✔ A SMA stenosis seems of greater clinical relevance than a CA stenosis.

REFERENCES
1. Mensink PB, Moons LM, Kuipers EJ. Chronic gastrointestinal ischaemia: Shifting paradigms. Gut 2011;60(5):722–37.
2. Harki J, Vergouwe Y, Spoor JA, et al. Diagnostic accuracy of the combination of clinical symptoms and CT or MR angiography in patients with chronic gastrointestinal ischemia. J Clin Gastroenterol 2017;51(6): e39–47.
3. Kolkman JJ, Mensink PB. Non-occlusive mesenteric ischaemia: A common disorder in gastroenterology and intensive care. Best Pract Res Clin Gastroenterol 2003;17(3):457–73.
4. Jarvinen O, Laurikka J, Sisto T, et al. Atherosclerosis of the visceral arteries. Vasa 1995;24(1):9–14.

5. Roobottom CA, Dubbins PA. Significant disease of the celiac and superior mesenteric arteries in asymptomatic patients: Predictive value of Doppler sonography. AJR Am J Roentgenol 1993;161(5):985–8.

6. Char D, Hines G. Chronic mesenteric ischemia: Diagnosis and treatment. Heart Dis 2001;3(4):231–5.

7. Mensink PB, van Petersen AS, Geelkerken RH, et al. Clinical significance of splanchnic artery stenosis. Br J Surg 2006;93(11):1377–82.

8. van Dijk LJD, Moons LMG, van Noord D, et al. Persistent symptom relief after revascularization in patients with single-artery chronic mesenteric ischemia. J Vasc Surg 2018;68(3):779–85.

9. Silva JA, White CJ, Collins TJ, et al. Endovascular therapy for chronic mesenteric ischemia. J Am Coll Cardiol 2006;47(5):944–50.

10. Terlouw LG, Moelker A, Abrahamsen J, et al. European guideline on chronic mesenteric ischemia—Joint UEG, EAGEN, ESGAR, NVMDL, HSG, CIRSE, and DMIS clinical guideline on the diagnosis and treatment of patients with chronic mesenteric ischemia. UEG J 2020; 8(4):371–95.

11. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. Lancet 2007;370(9596):1453–7.

12. van Dijk LJ, van Noord D, de Vries AC, et al. Clinical management of chronic mesenteric ischemia. United European Gastroenterol J 2019;7(2): 179–88.

13. North American Symptomatic Carotid Endarterectomy Trial Collaborators, Barnett HJM, Taylor DW, Haynes RB, et al. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991;325(7):445–53.

14. van den Heuvel TRA, Jeuring SFG, Zeegers MP, et al. A 20-year temporal change analysis in incidence, presenting phenotype and mortality, in the Dutch IBDSL cohort-can diagnostic factors explain the increase in IBD incidence? J Crohns Colitis 2017;11(10):1169–79.

15. Howard DP, Banerjee A, Fairhead JF, et al. Age-specific incidence, risk factors and outcome of acute abdominal aortic aneurysms in a defined population. Br J Surg 2015;102(8):907–15.

16. Karkkainen JM, Acosta S. Acute mesenteric ischemia (part I)—Incidence, etiologies, and how to improve early diagnosis. Best Pract Res Clin Gastroenterol 2017;31(1):15–25.

17. Alahdab F, Arwani R, Pasha AK, et al. A systematic review and meta-analysis of endovascular versus open surgical revascularization for chronic mesenteric ischemia. J Vasc Surg 2018;67(5):1598–605.

18. Kim EN, Lamb K, Relles D, et al. Median arcuate ligament syndrome-review of this rare disease. JAMA Surg 2016;151(5):471–7.

19. Jimenez JC, Harlander-Locke M, Dutson EP. Open and laparoscopic treatment of median arcuate ligament syndrome. J Vasc Surg 2012;56(3): 869–73.

20. Otte JA, Geelkerken RH, Huisman AB, et al. What is the best diagnostic approach for chronic gastrointestinal ischemia? Am J Gastroenterol 2007;102(9):2005–10.

21. Lejay A, Georg Y, Tartaglia E, et al. Chronic mesenteric ischemia: 20 year experience of open surgical treatment. Eur J Vasc Endovasc Surg 2015; 49(5):587–92.

22. Mateo RB, O'Hara PJ, Hertzer NR, et al. Elective surgical treatment of symptomatic chronic mesenteric occlusive disease: Early results and late outcomes. J Vasc Surg 1999;29(5):821–32.

23. Peck MA, Conrad MF, Kwolek CJ, et al. Intermediate-term outcomes of endovascular treatment for symptomatic chronic mesenteric ischemia. J Vasc Surg 2010;51(1):140–7.e2.

24. Sana A, van Noord D, Mensink PB, et al. Patients with chronic gastrointestinal ischemia have a higher cardiovascular disease risk and mortality. Atherosclerosis 2012;224(1):235–41.

SMALL BOWEL