PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Incidence and outcomes of acute mesenteric ischaemia: a systematic review and meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Tamme, Kadri; Reintam Blaser, Annika; Laisaar, Kaja-Triin; Mândul, Merli; Kals, Jaak; Forbes, Alastair; Kiss, Olga; Acosta, Stefan; Bjørck, Martin; Starkopf, Joel</td>
</tr>
</tbody>
</table>

VERSION 1 – REVIEW

| REVIEWER             | Geelkerken, Robert H. Medisch Spectrum Twente, Vascular Surgery |
| REVIEW RETURNED      | 04-Apr-2022 |

GENERAL COMMENTS

Dr Tamme and colleagues performed a review of the incidence and outcomes of acute mesenteric ischaemia. The review is thoroughly and appropriately performed and has the potency to reflect the development of incidence and outcomes of AMI in the last 60 years. The manuscript is well written and the senior authors are respected scientists in this domain.

General comment
1) ***Unfortunately but understandable a meta-analyses on criteria predicting outcomes was not performed due to a lack of consistently reported data. The result is more close to a valuable narrative review and I suggest to adapt the title and the manuscript accordingly

Introduction

2) ***As the authors mentioned there are several reviews published in the past highlighting the incidence and the outcome of AMI. It would be valuable if a few words were spend how the current review differs from the previous literature and what knowledge gap is being filled

Material and methods

3) ***Page 6 line 45; please explain in detail the criteria of diagnosis of AMI based on clinical data

4) ***Page 6 line 45; please explain in detail the criteria of diagnosis of AMI based on imaging

5) Page 8 line 20-22; “clarify the languages understood by at least one member of the study team

6) Page 8 line 46-48; Please substantiate that studies receiving four or more stars represent low risk of selection bias

7) *Page 7 line 45-53. I missed a clear definition of AMI in all its manifestations. ‘All forms’ means also including left sided ischemic colitis which is notoriously difficult to diagnose irrefutably. See also your remarks in the discussion paragraph page 17 line 22-34.

8) ***Page 8 line 54; If only one member of the study team masters the language, how is it possible to review the abstract by at least two reviewers

9) **Page 11 line 8; Did you observed a difference in outcome
between retrospective and prospective studies concerning incidence and mortality?

Results
10) ***Page 13-14 table 1; It makes your review that spans nearly 80 years of inclusion even more valuable if you, for example, report the most important parameters (incidence and mortality) per 10-year period instead of two more or less random chosen periods before and after 2000.
11) *Page 13-14 line 51-17; Is it possible to analyze the mortality rate in the different decades/periods of this study for the distinguished causes of AMI?
12) ***Is there a trend of improved outcome in patients treated percutaneous endovascular or with ROMS compared to classical operative revascularization techniques? If not you have to weighted this in the discussion paragraph because there is expert consensus that endo first is the way to go.

Discussion
13) ***Page 14 line 45-50; Is there a correlation between the thoroughness with which the incidence in the individual studies was determined and the reported incidences in those studies?
14) Page 16 line 10-15; and 41-45; I think it is worth trying to analyze whether there is a relation between AMI incidence and overall autopsy rate in the different countries/publications?
15) *Page 15 line 41; A review scrapes together the data from many individual studies. Does the risk of an information bias become smaller in a narrative review compared to the individual reports?

Figures
16) **Figure 2 and 3; It’s remarkable that none of the individual studies had hardly any overlap in the observed incidences. Please elaborate on this observation in the discussion paragraph. Does this reflect a comparison of apples and oranges?

Supplements
17) ** Search strategy; Please explain why (left and/or right) sided ischemic colitis was not part of the search strategy. If you include these search terms does this change the number of studies popped up?
18) **Quality assessment; Did you observed a difference in incidence and/or outcome in high and low quality reports?

In summary; The present manuscript is a state of the art narrative review with the potential to analyze in detail the development of incidence and outcome of AMI. It was a pleasure to read the manuscript which is without doubt valuable to publish. I formulate some questions and suggestions to further improve this review. I also advise a thoroughly review by a statistical expert.

REVIEWER
Zimmitti, Giuseppe
Fondazione Poliambulanza istituto ospedaliero d’eccellenza

GENERAL COMMENTS
In this systematic review and metanalysis, the authors investigated available studies concerning acute mesenteric ischaemia (AMI) and assessed AMI incidence (among general population and hospitalized patients) and AMI mortality in general and according to AMI cause, to period of diagnosis, and to eventual arterial revascularization.

This manuscript is well written, the aims of the study are adequately presented, the methodology and results well reported. The discussion is interesting and well relates study results with existing
I have only two comments: few grammatical mistakes can be found in the manuscript (for example, line 36, page 17: focuseed should be replaced by focused).

When analyzing study limitation, I suggest to associate to each limitation a study merit which someway could mitigate the limitation self.

the authors included in their analysis acute ischaemia of both jejunum and colon: it would be interesting to perform a subanalysis taking into account these two different pathological entities, which usually differ in terms of management and outcomes.

---

**REVIEWER**  
Sumbal, Ramish  
Dow University of Health Sciences

---

**GENERAL COMMENTS**

Thankyou for offering to review this important manuscript. It was always important to quantify the incidence of AMI and its various forms. Since I was asked to statistically review the manuscript, my review would be limited to it.

Overall forest plots seems to be okay. The effect size used and subgroup analysis was also justified. The only thing I seem lacking from the manuscript was a proper description of the statistical analysis.

There should be a description of what effect size was used to evaluate which data.

Details of pre-planned subgroup analysis should also be given. In addition, there should be a clear detail of how each analysis was performed.

The reason for using the random effects model should be clearly stated.

The name of the software used for analysis should also be written.

Overall a correctly performed review with some lacking statistical details as mentioned above.

---

**VERSION 1 – AUTHOR RESPONSE**

**Reviewer: 1**  
Prof. Robert H. Geelkerken, Medisch Spectrum Twente, University of Twente

Comments to the Author:

Dr Tamme and colleagues performed a review of the incidence and outcomes of acute mesenteric ischaemia. The review is thoroughly and appropriate performed and has the potency to reflect the development of incidence and outcomes of AMI in the last 60 years. The manuscript is well written and the senior authors are respected scientists in this domain

General comment

1. *Unfortunately but understandable a meta-analyses on criteria predicting outcomes was not performed due to a lack of consistently reported data. The result is more close to a valuable narrative review and I suggest to adapt the title and the manuscript accordingly*
Respectfully, we disagree with the reviewer.

We conducted a systematic review according to a predefined protocol. The protocol followed the items presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Although there are several classifications of reviews used in the scientific community, narrative very often refers to just going through some information (articles) without clearly outlined system.

We would also keep it "a systematic review and meta-analysis", as our aim was to pool data (conduct several meta-analyses). In certain cases, and for certain outcomes it was not reasonable due to limited and/or very heterogeneous information.

Technically we could have pooled data every time when it was available from more than one study, but most likely it would not make sense "clinically", as two studies (compared to one study) would not improve the level of evidence in most cases. We could have also pooled data from very heterogeneous studies, but this is not recommended.

In our opinion, informing that population-based incidence and mortality data are limited, is valuable for conducting research on AMI in the future, e.g. planning new studies.

Introduction

2. As the authors mentioned there are several reviews published in the past highlighting the incidence and the outcome of AMI. It would be valuable if a few words were spend how the current review differs from the previous literature and what knowledge gap is being filled

The main aim of the study was to clarify the incidence of AMI amongst adults in the general population and amongst hospitalized patients. While there are many studies on outcome of AMI, we did not find any systematic review on incidence of AMI. This has been stated in the Introduction section of the manuscript (page 5, line 20-21). We have highlighted further the absence of incidence data in the revised manuscript.

While there were two systematic reviews of outcomes of AMI, no systematic analysis included data from the last decade. As diagnostic and treatment methods have improved, it made sense to look at the change over time in outcomes. Unfortunately, however, a separate analysis of the last decade was not possible as most studies have included patients over 10 years and longer.

Material and methods

3. Page 6 line 45; please explain in detail the criteria of diagnosis of AMI based on clinical data

A core set of clinical symptoms uniform in all publications could not be defined as this is a review of published articles, most of them retrospective studies. To ensure inclusion of studies of "true" acute mesenteric ischaemia, we included only studies where the diagnosis of AMI was confirmed with radiological methods (CT-scan or angiography) and/or surgery and/or autopsy in addition to clinical symptoms.

4. Page 6 line 45; please explain in detail the criteria of diagnosis of AMI based on imaging

Uniform imaging criteria could not be identified as this is a systematic review of studies published over a period of more than 60 years. Methods of imaging have changed over the time period. To ensure inclusion of studies of "true" acute mesenteric ischaemia, we included only studies where the diagnosis of AMI was confirmed with radiological methods (CT-scan or angiography) and/or surgery and/or autopsy in addition to clinical symptoms.
In the Methods section we added the following explanation:

"We included studies where the diagnosis of AMI was based on clinical data, imaging (computed tomography (CT) or angiography), and laparotomy and/or autopsy report as reported in the original study."

5. **Page 8 line 20-22; “clarify the languages understood by at least one member of the study team**

The information has been added to the text of the manuscript.

6. **Page 8 line 46-48; Please substantiate that studies receiving four or more stars represent low risk of selection bias**

The sentence in the manuscript the reviewer refers to is the following: "Studies were considered at low risk of bias when receiving four or more stars.". This applies to the total study quality score, ranging from 5 to 7 in our review. Selection bias was just one of the criteria while assessing each of the original studies included in the review. Please see the details in Supplementary Table 1 in Supplement 2.

7. **Page 7 line 45-53. I missed a clear definition of AMI in all its manifestations. ‘All forms’ means also including left sided ischemic colitis which is notoriously difficult to diagnose irrefutable. See also your remarks in the discussion paragraph page 17 line 22-34.**

Originally, the term AMI was applied to a wide spectrum of bowel injury within the distribution of the superior mesenteric vessels (Kaleya RN, Boley SJ. Acute mesenteric ischaemia. Crit Care Clin 1995; 11: 479 – 512 PubMed ), and the superior mesenteric artery territory ends at mid-transverse colon. Most cases of isolated left-sided colonic ischaemia are mild and resolve spontaneously (Brandt LJ, Feuerstadt P, Longstreth GF, Boley S. ACG Clinical Guideline: Epidemiology, Risk factors, patterns of presentation, diagnosis and management of colon ischemia (CI). Am J Gastroenterol 2015; 110: 18 – 74 PubMed ). These cases have never been included in AMI reviews and the misnomer ischemic colitis (misleading the clinicians that this condition is a primary chronic inflammatory condition) is a diagnosis made by endoscopy-driven gastroenterologists, performing elective/subacute colonoscopy visualizing secondary inflammation of milder disease. Colonoscopy should never be performed in patients with peritonitis or CT-verified irreversible ischemic damage due to colonic ischaemia. In the more contemporary literature there is no uniform consensus about the forms of mesenteric ischaemia that should be included in the definition of AMI. We follow the ESVS guidelines (Björck M et al. Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2017;53:460-510). We are aware that due to different definitions some studies may have included only patients with small bowel ischaemia. However, we defined and analyzed AMI forms as of arterial, venous and non-occlusive origin. All these forms can also result in colonic ischaemia. Thus, separate search of publications of ischaemic colitis would not have enabled analysis according to these separate forms of AMI. We have added this to limitations of the study (page 19).

8. **Page 8 line 54; If only one member of the study team masters the language, how is it possible to review the abstract by at least two reviewers**

All the publications had English language abstracts. Only full texts were in different languages.

9. **Page 11 line 8; Did you observed a difference in outcome between retrospective and prospective studies concerning incidence and mortality?**
Thank you for the comment, that would be interesting to know. Unfortunately, there are no prospective studies of the incidence of all forms of acute mesenteric ischaemia. This analysis is not possible.

Short-term mortality of all patients independent of treatment method was 51.7% in prospective (n=9) and 62.9% in retrospective (n=39) studies (p= 0.15).

Results

10. Page 13-14 table 1; It makes your review that spans nearly 80 years of inclusion even more valuable if you, for example, report the most important parameters (incidence and mortality) per 10-year period instead of two more or less random chosen periods before and after 2000.

Thank you for the comment. This would be a very interesting analysis. However, since most of the studies, especially those before 2000, include patients over decades, this analysis is not possible.

11. Page 13-14 line 51-17; Is it possible to analyze the mortality rate in the different decades/periods of this study for the distinguished causes of AMI?

In all figures, the studies are arranged according to the inclusion period of the patients. By visual assessment some trends in some subgroups could be observed. However, the data are too scattered, i.e. the time periods of inclusions are overlapping, for meaningful analysis in subgroups.

12. Is there a trend of improved outcome in patients treated percutaneous endovascular or with ROMS compared to classical operative revascularization techniques? If not you have to weighted this in the discussion paragraph because there is expert consensus that endo first is the way to go.

Comparing efficacy of different methods of revascularization is definitely important and the results would be interesting and valuable. However, in current study we focused on incidence and survival outcomes and did not gather data about the efficacy of different treatment methods in targeted fashion. The patients were divided into treatment groups (operated, revascularized) only in order not to compare mortality of actively treated patients to those who received only palliative treatment.

We are collecting detailed treatment data in an ongoing prospective multicentre observational study conducted within the same project.

Discussion

13. Page 14 line 45-50; Is there a correlation between the thoroughness with which the incidence in the individual studies was determined and the reported incidences in those studies?

Thank you for this comment. We did not identify such differences in methodology of included studies that would clearly explain the observed variability. We believe this is a combination of study methods, evolving of diagnostics over time, and autopsy rate.

We added in the Discussion section:

"There were considerable differences in the incidences of AMI found in different studies which might be explained by study methods, evolving of diagnostics over time and autopsy rate."

14. Page 16 line 10-15; and 41-45; I think it is worth trying to analyze whether there is a relation between AMI incidence and overall autopsy rate in the different countries/publications?
Thank you for this important comment. The proportion of AMI deaths identified only at autopsies may have significant impact. Unfortunately, the data are scarce for reasonable analysis of this. Except for Acosta et al., who is reporting the remarkable autopsy rate of 87% in Sweden, the others do not report this important influencing factor in their countries/populations. From indirect sources, we found that the autopsy rate in Finland (for study by Kärkkanen et al) was 23.9-31.1% from 2009 to 2013. In United Kingdom the rate was 27% in 1984 and 23.2% in 2001 (useable with reservations for Wilson et al, 1973-1984, and Huerta et al, 1994-2000; vide). In United States, autopsy rate of 8.5% is reported in 2007 (applicable to Crawford et al 2009-2013, https://www.cdc.gov/nchs/data/databriefs/db67.pdf). With these indirect and only partly applicable data we thought it is not worthy for analyze the relation between AMI incidence and overall autopsy rate.

Page 15 line 41; A review scrapes together the data from many individual studies. Does the risk of an information bias become smaller in a narrative review compared to the individual reports? Pooling data from studies including information bias is likely to increase bias, especially in a narrative review. Thus, to counteract biases associated with synthesizing information from several original studies, we (prospectively) developed a protocol for our systematic review, and followed it throughout the study.

Figures

15. Figure 2 and 3; It’s remarkable that none of the individual studies had hardly any overlap in the observed incidences. Please elaborate on this observation in the discussion paragraph. Does this reflect a comparison of apples and oranges?

Please see answer to comment 13 and the changes in the Discussion section.

Supplements

16. Search strategy; Please explain why (left and/or right) sided ischemic colitis was not part of the search strategy. If you include these search terms does this change the number of studies popped up?

We are aware that not adding the term ischaemic colitis to the search we might have missed some publications of AMI. Please see answer to comment 7. We have addressed this issue in limitation of the study section in the Discussion section.

Quality assessment; Did you observed a difference in incidence and/or outcome in high and low quality reports?

All studies included in meta-analyses received more than four points on the modified NOS, indicating low risk of bias (see Supplementary table 1 in Supplement 2). This is accounted for by the robustness of the outcomes we studied (AMI and mortality) and on the assumption that most patients with AMI were detected. Thus, we cannot differentiate the studies as suggested by the reviewer. Further differentiation (7 vs 5-6 points) was discussed by the research team, but was not considered reasonable, as per protocol the high/low quality threshold was set at 4.

In summary; The present manuscript is a state of the art narrative review with the potential to analyze in detail the development of incidence and outcome of AMI. It was a pleasure to read the manuscript which is without doubt valuable to publish. I formulate some questions and suggestions to further improve this review. I also advise a thoroughly review by a statistical expert.

Thank-you for those kind words!
Reviewer: 2
Dr. Giuseppe Zimmitti, Fondazione Poliambulanza istituto ospedaliero d'eccellenza

Comments to the Author:
In this systematic review and metaanalysis, the authors investigated available studies concerning acute mesenteric ischaemia (AMI) and assessed AMI incidence (among general population and hospitalized patients) and AMI mortality in general and according to AMI cause, to period of diagnosis, and to eventual arterial revascularization.

This manuscript is well written, the aims of the study are adequately presented, the methodology and results well reported. The discussion is interesting and well relates study results with existing literature.

I have only two comments:

1. Few grammatical mistakes can be found in the manuscript (for example, line 36, page 17: focused should be replaced by focused)

The mistakes have been corrected in the manuscript, thank you!

2. When analyzing study limitation, I suggest to associate to each limitation a study merit which someway could mitigate the limitation self.

Thank-you for this comment! We have added some merits after each limitation.

3. The authors included in their analysis acute ischaemia of both jejunum and colon: it would be interesting to perform a subanalysis taking into account these two different pathological entities, which usually differ in terms of management and outcomes.

Thank you for the comment. We divided the AMI forms as arterial, venous and non-occlusive, which may occur in jejunum as well as in colon. We did not compare these two anatomical ischaemic segments, since reporting in articles is almost exclusively based on the diagnosis of AMI and the AMI forms differentiated based on pathophysiological mechanism. The ileum is usually affected in addition to ischaemia of the jejunum and/or colon in all three studied AMI forms, which makes specific comparisons of ischemic segments very difficult.

Reviewer: 3
Dr. Ramish Sumbal, Dow University of Health Sciences

Comments to the Author:
Thank you for offering to review this important manuscript. It was always important to quantify the incidence of AMI and its various forms. Since I was asked to statistically review the manuscript, my review would be limited to it.

Overall forest plots seems to be okay. The effect size used and subgroup analysis was also justified. The only thing I seem lacking from the manuscript was a proper description of the statistical analysis.

1. There should be a description of what effect size was used to evaluate which data

Short description has been added to the manuscript. Also, a detailed description of the analysis has been added as Supplement 3.

2. Details of pre-planned subgroup analysis should also be given.

There were no preplanned subgroup analyses. The patients were divided into subgroups based on treatment methods in order not to compare the mortality of actively treated patients to those who received only palliative treatment. We did not compare the efficacy of different treatment methods.
3. In addition, there should be a clear detail of how each analysis was performed. Detailed description of each analysis has been added to supplementary material (Supplement 3).

4. The reason for using the random effects model should be clearly stated. The information has been added to the manuscript (page 9).

5. The name of the software used for analysis should also be written. The information has been added to the manuscript.

Overall a correctly performed review with some lacking statistical details as mentioned above.

**VERSION 2 – REVIEW**

| REVIEWER | Zimmitti, Giuseppe  
Fondazione Poliambulanza istituto ospedaliero d'eccellenza |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>REVIEW RETURNED</td>
<td>24-Aug-2022</td>
</tr>
<tr>
<td>GENERAL COMMENTS</td>
<td>The authors adequately responded to my comments and accordingly modified the manuscript.</td>
</tr>
</tbody>
</table>

| REVIEWER | Sumbal, Ramish  
Dow University of Health Sciences |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>REVIEW RETURNED</td>
<td>21-Aug-2022</td>
</tr>
<tr>
<td>GENERAL COMMENTS</td>
<td>Thank you for the opportunity to review the manuscript. My concerns have been addressed. I have no further objections or comments regarding the statistics of the manuscript.</td>
</tr>
</tbody>
</table>