# Effectiveness and predictors of response to somatostatin analogues in patients with gastrointestinal angiodysplasias: a systematic review and individual patient data meta-analysis

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## Summary

**Background** Gastrointestinal angiodysplasias are vascular malformations that often cause red blood cell transfusion-dependent anaemia. Several studies suggest that somatostatin analogues might decrease rebleeding rates, but the true effect size is unknown. We therefore aimed to investigate the efficacy of somatostatin analogues on red blood cell transfusion requirements of patients with gastrointestinal angiodysplasias and to identify subgroups that might benefit the most from somatostatin analogue therapy.

**Methods** We did a systematic review and individual patient data meta-analysis. We searched MEDLINE, Embase, and Cochrane on Jan 15, 2016, with an updated search on April 25, 2021. All published randomised controlled trials and cohort studies that reported on somatostatin analogue therapy in patients with gastrointestinal angiodysplasias were eligible for screening. We excluded studies without original patient data, single case reports, small case series (ie, <10 participants), studies in which patients had a specific aetiology of gastrointestinal angiodysplasias, and studies in which somatostatin analogue therapy was initiated simultaneously with other treatment modalities. Authors of eligible studies were invited to share individual patient data. Aggregated data was used if individual patient data were not provided. The primary outcome was the mean reduction in the number of red blood cell transfusions during somatostatin analogue therapy, compared with baseline, expressed as the incidence rate ratio (IRR) and absolute mean decrease. We defined patients as either good responders (≥50% reduction in the number of red blood cell transfusions) or poor responders (<50% reduction). A mixed-effects negative binomial regression was used to account for clustering of patients and skewness in data. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42020213985.

**Findings** We identified 11 eligible studies (one randomised controlled trial and ten cohort studies) of moderate-to-high quality and obtained individual patient data from the authors of nine (82%) studies. The remaining two (18%) studies provided sufficient information in the published manuscript to extract individual patient data. In total, we analysed data from 212 patients. Somatostatin analogues reduced the number of red blood cell transfusions with an IRR of 0·18 (95% CI 0·14–0·24; p<0·0001) during a median treatment duration of 12 months (IQR 6·0–12·0) and follow-up period of 12 months (12·0–12·0), correlating with a mean absolute decrease in the number of red blood cell transfusions from 12·8 (95% CI 10·4–15·8) during baseline to 2·3 (1·9–2·9) during follow-up—ie, a reduction of 10·5 red blood cell transfusions (p<0·0001). 177 (83%) of 212 patients had a good response to somatostatin analogue therapy (defined as at least a 50% reduction in the number of red blood cell transfusions). Heterogeneity across studies was moderate ($I^2$=53%; p=0·02). Location of gastrointestinal angiodysplasias in the stomach compared with angiodysplasias in the small bowel and colon (IRR interaction 1·92 [95% CI 1·13–3·26]; p=0·02) was associated with worse treatment response. Octreotide was associated with a better treatment response than lanreotide therapy (IRR interaction 2·13 [95% CI 1·12–4·04]; p=0·02). The certainty of evidence was high for the randomised controlled trial and low for the ten cohort studies. Adverse events occurred in 38 (18%) of 212 patients receiving somatostatin analogue therapy, with ten (5%) discontinuing this therapy because of adverse events. The most common adverse events were loose stools (seven [3%] of 212), cholelithiasis (five [2%]), flatulence (four [2%]), and administration site reactions (erythema, five [2%]).

**Interpretation** Somatostatin analogue therapy is safe and effective in most patients with red blood cell transfusion-dependent bleeding due to gastrointestinal angiodysplasias. Somatostatin analogue therapy is more effective in patients with angiodysplasias located in the small bowel and colon, and octreotide therapy seems to be more effective than lanreotide therapy.

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## Research in context

### Evidence before this study

Gastrointestinal angiodysplasias are vascular malformations that easily bleed, resulting in symptomatic disease ranging from mild chronic anaemia to severe transfusion dependency that necessitates treatment in hospital. First-line treatment consists of endoscopic argon plasma coagulation, but rebleeding rates can reach up to 58% in 2 years. Repeated rebleeding events in patients who have exhausted endoscopic therapy result in refractory anaemia. Somatostatin analogues have emerged as an alternative treatment modality in severe gastrointestinal angiodysplasia-related bleeding because they possess anti-angiogenic effects. We searched MEDLINE, Embase, and Cochrane databases for studies on somatostatin analogue use in patients with symptomatic gastrointestinal angiodysplasias using the search terms "gastrointestinal angiodysplasia" and "somatostatin analogues" and their synonyms. Multiple cohort studies and one randomised controlled trial have been published that showed promising results, but heterogeneity among studies precludes direct comparison concerning clinically relevant primary outcomes. Two previous meta-analyses, published in 2009 and 2014, included no more than 75 patients from four studies in total. Furthermore, no study has used individual patient data to investigate differences in treatment effects.

### Added value of this study

We did a systematic review and individual patient data meta-analysis to estimate the true effect size of somatostatin analogue therapy on clinically relevant outcomes and to investigate whether patient characteristics, gastrointestinal angiodysplasia characteristics, and treatment characteristics affect clinical response. Individual patient data could be retrieved from all 11 cohorts found through our search, resulting in the inclusion of 212 patients. We showed that somatostatin analogue therapy results in a significant decrease in red blood cell transfusions during a median of 12 months of treatment in the vast majority of patients, which was associated with an increase in haemoglobin concentrations. Few patients on somatostatin analogue therapy had adverse events, with most adverse events being tolerable and self-limiting. We also showed that treatment response was affected by the location of gastrointestinal angiodysplasias, as patients with angiodysplasias in the stomach had worse treatment response than in other gastrointestinal locations, and by somatostatin analogue type, as octreotide was associated with better treatment response than lanreotide.

### Implications of all the available evidence

Our study shows that somatostatin analogue therapy is safe and effective in most patients with red blood cell transfusion-dependent bleeding due to gastrointestinal angiodysplasias. Treatment is more effective in patients with angiodysplasias located in the small bowel and colon, and octreotide seems to be more effective than lanreotide. Both findings might be linked to somatostatin receptor expression in the gastrointestinal tract. An increased somatostatin analogue dose did not result in a larger reduction of red blood cell transfusions and adverse events were solely reported in patients on a higher dose. Therefore, we recommend octreotide 10 mg long-acting release (injected intramuscularly) every 28 days in patients with red blood cell transfusion-dependent bleeding secondary to gastrointestinal angiodysplasias that cannot be adequately controlled with endoscopic therapy.

## Introduction

Gastrointestinal angiodysplasias are vascular malformations that consist of thin-walled, dilated arterial or venous capillaries located in the gastrointestinal mucosa. Patients usually have multiple gastrointestinal angiodysplasias, and they are most frequently located in the proximal colon and small bowel. Gastrointestinal angiodysplasias bleed easily, accounting for about 10% of all gastrointestinal bleeding cases and 60% of small bowel bleeding cases.[1]

Gastrointestinal angiodysplasias are more common in older patients (ie, >60 years), patients with valvular heart disease, and those with chronic renal failure.[1] Patients with this condition frequently have symptomatic disease, ranging from mild chronic iron deficiency anaemia to severe and acute red blood cell transfusion dependency. First-line treatment often consists of endoscopic argon plasma coagulation, with a clinical response of 90%.[2] However, rebleeding rates can reach up to 58% within 2 years.[3] Rebleeding episodes can result in refractory anaemia despite endoscopic therapy. Patients with refractory anaemia require frequent red blood cell transfusions, which is associated with a reduced quality of life, increased cardiovascular events, and substantial morbidity and mortality.[4]

Somatostatin analogues might offer an alternative therapeutic approach for severe bleeding associated with gastrointestinal angiodysplasias.[1] Somatostatin analogues reduce splanchnic blood flow, enhance platelet aggregation, and have anti-angiogenic effects.[1,5,6] Cohort studies have shown a beneficial effect of somatostatin analogues in decreasing rebleeding rates and red blood cell transfusion requirements of patients with gastrointestinal angiodysplasias.[7,8] Heterogeneity among these small studies, however, precludes direct comparison with clinically relevant outcomes and makes it difficult to translate perceived treatment effects to the individual patient.[8] Therefore, we aimed to assess the effect of somatostatin analogue therapy and to evaluate which factors predict better treatment response by analysing various subgroups. We hypothesised that somatostatin analogue therapy reduces the red blood cell transfusion requirements of patients with gastrointestinal angiodysplasias.

## Methods

### Search strategy and selection criteria

We did a systematic review and individual patient data meta-analysis. We searched the literature for randomised controlled trials and cohort studies using the following electronic databases: MEDLINE, Embase, and Cochrane on Jan 15, 2016, with an updated search on April 15, 2021. A clinical librarian assisted in creating the search syntax. The search terms "gastrointestinal angiodysplasias" and "somatostatin analogues" with synonyms were combined, and MeSH terms were used. The full search strategy for each database is provided in the appendix (p 2). We did not use any date or language restrictions.

We screened all articles based on the title and abstract to ensure they reported the reduction in the number of red blood cell transfusions during somatostatin analogue therapy in patients with endoscopically diagnosed gastrointestinal angiodysplasias. Duplicates were identified and removed. The remaining studies were assessed by examining the full-text papers for adherence to our inclusion and exclusion criteria (appendix p 3). Studies that included patients with left ventricular assist devices were excluded because of the specific aetiology of bleeding, as well as studies that included patients with hereditary haemorrhagic telangiectasias because the gastrointestinal bleeding is often accompanied by epistaxis.[9,10] Studies that involved simultaneous initiation or discontinuation of additional treatment modalities that potentially affect gastrointestinal angiodysplasia bleeding episodes (eg, anti-thrombotics and argon plasma coagulation) were also excluded, as well as studies that only included patients younger than 18 years.[11] Finally, case reports and cohort studies with fewer than ten patients were excluded because of the risk of selective reporting. Forward-citation and backward-citation searches were done on all eligible articles, including scanning and tracking citations and references in footnotes and bibliographies. Two researchers (LCMJG and KVG) independently did all the title and abstract screening. In cases for which no consensus could be reached, a third researcher was involved for a final consensus (EJMvG).

To collect individual participant data, authors of all eligible studies were contacted. Several strategies were adopted to establish communication with the authors. First and last authors were contacted initially. In case of no response, coauthors were contacted as well. Finally, to ensure that all authors' correct contact information was used, we reached out to the country's national gastrointestinal society where the research was done if we could not establish communication with the author directly.

### Data analysis

A standardised database was sent to the authors who agreed to collaborate. The following prespecified variables were collected: patient characteristics (age, sex, comorbidities, and use of anti-thrombotics), gastrointestinal angiodysplasia characteristics (previous argon plasma coagulation treatment and location), treatment characteristics (dose, frequency, and treatment duration), number of red blood cell transfusions (before and during treatment), haemoglobin concentrations (before and during treatment), and the incidence of adverse events. All collected databases were checked for completeness and internal consistency. The collaborators were directly contacted for missing data, and omissions were corrected. If individual patient data were not provided, the full-text article and supplementary files were screened for aggregated data. At the individual data level, patients with the following characteristics were excluded: no red blood cell transfusions in the year before initiating somatostatin analogue therapy, no complete endoscopic evaluation before initiating somatostatin analogue therapy (consisting of gastroduodenoscopy, colonoscopy, and enteroscopy or capsule endoscopy), gastrointestinal bleeding due to an unknown aetiology or causes other than gastrointestinal angiodysplasias (eg, gastric antral vascular ectasias and portal hypertensive gastropathy), left ventricular assist devices, haemorrhagic telangiectasias, and not receiving a single dose of somatostatin analogue therapy. All contributed databases were integrated into one final database by two authors (LCMJG and KVG).[12]

See Online for appendix

The primary outcome was the mean reduction in the number of red blood cell transfusions received by patients during somatostatin analogue therapy, compared with the period before initiating treatment (baseline). In the pooled analyses, we accounted for clustering of patients within studies and differences in study duration (baseline, treatment, and follow-up period) using a mixed-effects model with a random intercept, as advocated by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Patient Data (PRISMA-IPD) guidelines.[13] Negative binomial regression was used to determine the mean reduction in red blood cell transfusions expressed as the incidence rate ratio (IRR) and the absolute decrease in red blood cell transfusions expressed in geometric means, because the number of transfusions represents a count variable. The IRR represents the number of red blood cell transfusions patients received during somatostatin analogue therapy compared with the number of red blood cell transfusions they received at baseline. Negative binomial regression was selected to account for overdispersion. Patients were also divided into two groups on the basis of their percentage decrease in red blood cell transfusions during somatostatin analogue therapy. A good response to therapy was defined as at least a 50% reduction in the number of red blood cell transfusions. Patients who had less than 50% reduction in the number of red blood cell transfusions were classified as poor responders. This cutoff point was based on two previous studies.[14,15]

Secondary outcomes were the absolute increase in haemoglobin concentrations, the percentage of patients who had adverse events, and the percentage of patients who discontinued therapy because of adverse events.

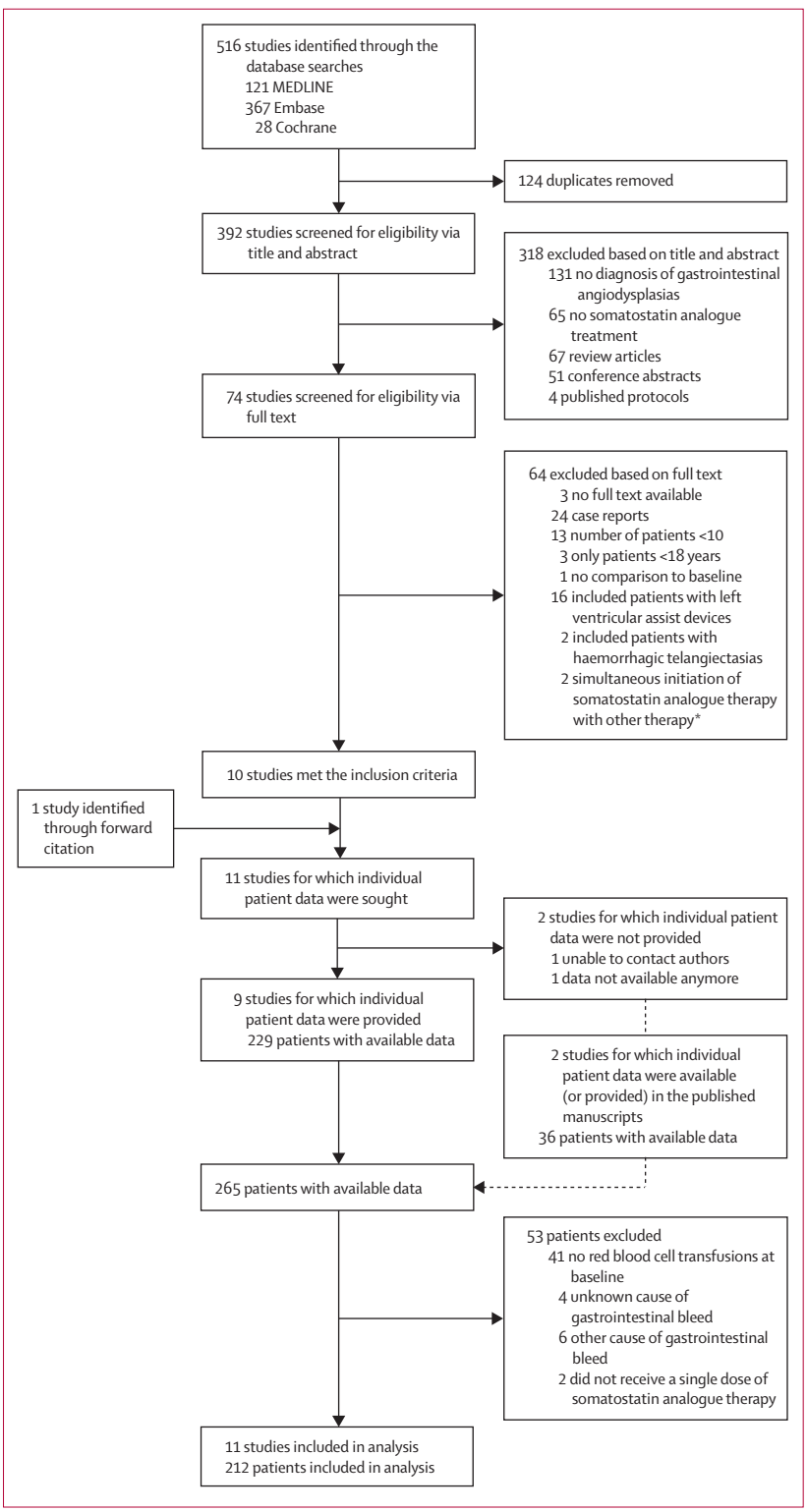



***Figure 1:*** **Study selection and obtainment of individual patient data**
*Simultaneous initiation of somatostatin analogue therapy with endoscopy (n=1) or anti-thrombotics (n=1).

Patient subgroups were based on patient characteristics, gastrointestinal angiodysplasia characteristics, and treatment characteristics. All characteristics were prespecified. Linear regression was used to determine the mean increase in haemoglobin concentrations. Results are presented as mean differences with 95% CIs. Negative binomial regression with an interaction term (predictor×time) was used to identify characteristics associated with a response to somatostatin analogue therapy. Multiple imputation methods were done if there were fewer than 50% of missing cases. Furthermore, Spearman's rank-order correlation was done to check for multicollinearity. Variables were selected for the multivariate model by use of backward selection. Results are presented as the IRR interaction with 95% CIs. The IRR interaction describes the ratio of the IRR of the patients who expressed or were treated with the indicated variable and the IRR of the patients who did not express or were not treated with the indicated variable.

The quality of included studies was assessed using the Newcastle-Ottawa Scale for cohort studies.[16] The validated Newcastle-Ottawa Scale consists of eight items, for which a maximum score of 9 can be awarded to each study. Scores of 0–3 were considered as low quality, 4–6 were considered as moderate quality, and 7–9 were considered as high quality. The critical appraisal was done independently by two researchers (LCMJG and KVG). Disagreements were resolved after discussion with a third researcher (EJMvG). Publication bias was assessed by constructing a funnel plot and by doing the Egger's test, using a random-effects model.[17] Between-study heterogeneity was assessed by constructing a forest plot and by determining the $I^2$ statistic, using a random-effects model. Heterogeneity of 30% was considered moderate, 60% was considered substantial, and 90% was considered considerable.[18] Subgroup analyses were done based on study design and on the Newcastle-Ottawa Scale quality assessment. Certainty of evidence per outcome was evaluated with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[19]

A two-tailed p value of 0·05 or less was considered significant in all statistical analyses. A detailed description of the statistical analysis is provided in the appendix (p 4). We did all the statistical analyses of the primary and secondary outcome measures with SPSS (version 25.0). The funnel plot was constructed in STATA (version 16.0), and the forest plot was constructed in Review Manager (version 5.3.5).

This study was done in accordance to the PRISMA-IPD guidelines[13] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42020213985.

## Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

Our systematic search yielded 516 articles, resulting in 392 unique publications after the removal of duplications. 318 articles were excluded based on screening of the title and abstract. Of the 74 remaining studies, 64 were excluded based on evaluation of the full text. Our final dataset consisted of ten articles.[14,15,20–27] We identified one additional article with forward citation that had not been indexed in the searched databases.[28] In total, 11 studies met our inclusion criteria: one randomised controlled trial, seven prospective cohort studies, and three retrospective cohort studies (figure 1).

Individual patient data were successfully retrieved from the authors of nine (82%) of 11 studies (n=226),[14,20–23,25–28] with one cohort also including unpublished data (n=3). The authors confirmed that the additional data were collected following the methodology of their original manuscript. No inconsistencies were found concerning data integrity.[23] Individual patient data could not be retrieved from the authors of two articles (n=36). We were unable to establish contact with the author of the first article (n=19).[15] The authors of the second article confirmed that the original data were destroyed (n=17).[24] However, both papers provided most individual data in the published manuscript, and these data were retrieved and included.[15,24] This methodology resulted in a merged dataset consisting of 265 patients with individual patient data. We excluded 53 patients from the merged dataset because data for red blood cell transfusions at baseline were absent (n=41), there was an unknown cause of gastrointestinal bleeding (n=4), patients had a diagnosis of another vascular malformation (n=6), or they did not receive a single dose of somatostatin analogue therapy (n=2). In total, 212 patients from 11 studies were included in our analysis.

All 11 studies investigated the effect of somatostatin analogue therapy in patients with endoscopically proven gastrointestinal angiodysplasias and gastrointestinal bleeding with red blood cell transfusion dependency. Patients either had refractory anaemia (defined as recurrent bleeding after at least one cycle of endoscopic treatment), were not eligible for repeated endoscopic procedures because of comorbidities, or had gastrointestinal angiodysplasias with difficult endoscopic access. The sample size per study varied from ten to 98 participants. The dose of somatostatin analogue therapy varied between studies. Octreotide 10 mg powder and solvent for suspension for injection vials long-acting release (which is roughly equivalent to lanreotide 60 mg per 0·3 mL solution for injection prefilled syringes long-acting release), octreotide 20 mg long-acting release (roughly equivalent to octreotide 100 µg per 1 mL solution for injection ampoules and lanreotide 90 mg long-acting release), and octreotide 30 mg long-acting release (roughly equivalent to lanreotide 120 mg long-acting release and pasireotide 60 mg powder and solvent for suspension and injection vials long-acting release) were administered.[29] One (9%) of 11 studies used short-acting somatostatin analogues during the entire treatment duration, which were administered subcutaneously three times a day.[24] The other ten (91%) studies used somatostatin analogue long-acting release formulations, which were administered intramuscularly every month or every 4 weeks. In eight (73%) studies, the dose was unchanged during the entire treatment period. In three (27%) studies, the somatostatin analogue dose was titrated on the basis of clinical response.[14,15,23] The median treatment duration between studies varied from 6 months to 33 months with a follow-up period ranging from 1 month to 120 months. Seven (64%) of 11 studies used the percentage of responders, defined as a reduction in the number of red blood cell transfusions between 30% and 100% during somatostatin analogue therapy compared with baseline, as their primary endpoint.[14,15,20,22,23,25,26] The primary endpoint in the other four (36%) studies was the mean decrease in the number of red blood cell transfusions during somatostatin analogue therapy compared with baseline.[21,24,27,28] Study characteristics are summarised in the appendix (pp 5–6).

The Newcastle-Ottawa Scale was used to assess study quality, regardless of data sharing.[13] The 11 studies were rated as moderate-to-high quality, with scores ranging from 5 to 7 out of a possible 9 (appendix p 7). Almost all studies included consecutive patients and had a follow-up period of 1 year or longer. All studies compared primary endpoint results with the baseline. One study also used a control group and did an independent, blind assessment of outcomes.[20] Visual inspection of the funnel plot and the Egger's test (p=0·071) showed no indication of publication bias (appendix p 8).[30] Figure 2 shows the reduction in the number of red blood cell transfusions per study. Effect estimates across the 11 studies followed the same direction

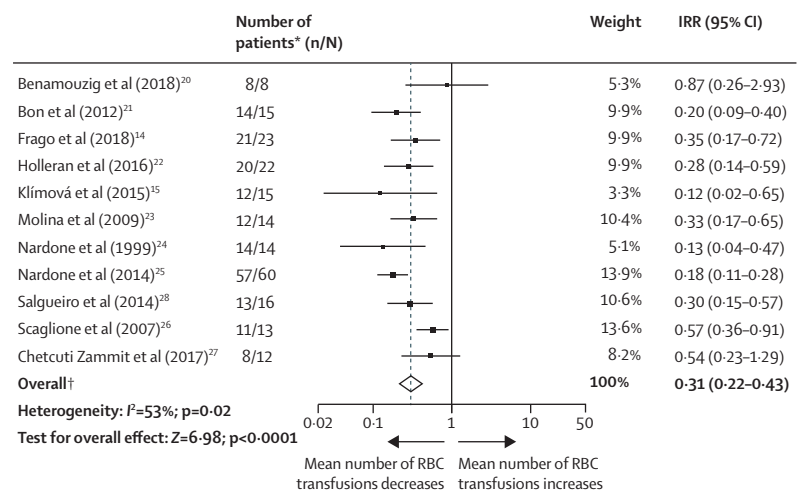



*Figure 2:* **Change in mean number of red blood cell transfusions in the included studies**
The forest plot shows the mean reduction in the number of red blood cell transfusions during baseline and during somatostatin analogue therapy. IRR=incidence rate ratio. *Number of patients with a decrease in blood transfusions. †Unadjusted for study and study duration.

| | Overall (n=212) | Female (n=85) | Male (n=112) | p value |
|---|---|---|---|---|
| **Patient characteristics** | | | | |
| Age (years) | 71 (12) | 68 (13) | 73 (11) | 0·42 |
| Comorbidities | .. | .. | .. | .. |
| Diabetes mellitus | 26/137 (19%) | 8/59 (14%) | 18/78 (23%) | 0·16 |
| Valvular heart disease | 45/137 (33%) | 23/59 (39%) | 22/78 (28%) | 0·18 |
| Ischaemic heart disease | 30/137 (22%) | 10/59 (17%) | 20/78 (26%) | 0·22 |
| Cirrhosis | 17/137 (12%) | 8/59 (14%) | 9/78 (12%) | 0·72 |
| Chronic kidney disease | 40/137 (29%) | 13/59 (22%) | 27/78 (35%) | 0·11 |
| Coagulation disorders* | 5/137 (4%) | 1/59 (2%) | 4/78 (5%) | 0·39 |
| Anti-thrombotics | .. | .. | .. | 0·46 |
| None | 53/138 (38%) | 18/50 (36%) | 35/73 (48%) | .. |
| Antiplatelets | 35/138 (25%) | 12/50 (24%) | 18/73 (25%) | .. |
| Anticoagulants | 36/138 (26%) | 16/50 (32%) | 17/73 (23%) | .. |
| Dual therapy | 13/138 (9%) | 4/50 (8%) | 3/73 (4%) | .. |
| **Gastrointestinal angiodysplasia characteristics** | | | | |
| Haemoglobin concentration (g/dL) | 7·1 (1·7) | 6·9 (1·7) | 7·3 (1·7) | 0·14 |
| Red blood cell transfusions | 9·0 (5·0–18·0) | 9·0 (4·0–20·0) | 9·0 (6·0–18·0) | 0·41 |
| Previous argon plasma coagulation | 128/210 (61%) | 49/84 (58%) | 70/111 (63%) | 0·50 |
| Location | .. | .. | .. | .. |
| Multiple locations | 83/195 (43%) | 37/85 (44%) | 46/110 (42%) | 0·81 |
| Stomach | 79/197 (44%) | 33/85 (39%) | 46/112 (41%) | 0·75 |
| Isolated | 15/195 (8%) | 6/85 (7%) | 9/110 (8%) | .. |
| Small bowel | 150/195 (77%) | 67/85 (79%) | 83/110 (75%) | 0·58 |
| Isolated | 86/195 (44%) | 36/85 (42%) | 50/110 (45%) | .. |
| Colon | 72/196 (37%) | 28/85 (33%) | 44/112 (39%) | 0·39 |
| Isolated | 11/195 (6%) | 6/85 (7%) | 5/110 (5%) | .. |
| **Therapy characteristics** | | | | |
| Type of somatostatin analogue | .. | .. | .. | 0·16 |
| Octreotide | 166/212 (78%) | 69/85 (81%) | 82/112 (73%) | .. |
| Lanreotide | 38/212 (18%) | 15/85 (18%) | 23/112 (21%) | .. |
| Pasireotide | 8/212 (4%) | 1/85 (1%) | 7/112 (6%) | .. |
| Dose of somatostatin analogue† | .. | .. | .. | 0·11 |
| 10 mg | 65/212 (31%) | 25/85 (29%) | 25/112 (22%) | .. |
| 20–30 mg | 147/212 (69%) | 60/85 (71%) | 87/112 (78%) | .. |
| Mode of action | .. | .. | .. | 0·10 |
| Short acting | 14/212 (7%) | 9/85 (11%) | 5/112 (4%) | .. |
| Long acting | 198/212 (93%) | 76/85 (89%) | 107/112 (96%) | .. |

Data are mean (SD), n (%), or median (IQR), unless otherwise specified. Total values do not always add up to 212 because of missing data from aggregated studies.[15,24] The initial dose was used in this table.[14,15,23] Fisher's exact test was used when the assumption tests of the Pearson $\chi^2$ test were violated. *Thrombocytopenia, von Willebrand disease, Glanzmann thrombasthenia, and factor V Leiden. †Doses are expressed as mg of octreotide long-acting release. Equivalent doses of lanreotide and pasireotide long-acting release were used.

***Table 1:*** **Baseline characteristics**

and the 95% CIs overlapped. The heterogeneity across studies was moderate ($I^2$=53%; p=0·02), which enabled us to pool data.[19] Subgroup analyses based on study design and on the Newcastle-Ottawa Scale quality assessment showed no significant difference in therapy effectiveness between the included studies (appendix p 9). The certainty of evidence of all outcomes was considered low for the ten cohort studies and high for the randomised controlled trial according to the GRADE approach. Evidence of the cohort studies was upgraded by 1 point because of the large effect (defined as a mean/IRR higher than 2·0 or lower than 0·5) and dose-response gradient (appendix p 10).[19]

We analysed individual patient data of 212 patients with red blood cell transfusion dependency due to gastrointestinal angiodysplasias who were treated with a somatostatin analogue (table 1). Patients had a mean age of 71 years (SD 12) and 112 (57%) of 197 patients without missing data were male; the number of patients does not always add up to 212 because of missing data. The mean haemoglobin concentration was 7·1 g/dL (SD 1·7) at baseline, with a median number of red blood cell transfusions in the year preceding somatostatin analogue therapy of 9·0 (IQR 5·0–18·0). Many patients had comorbidities (table 1). 84 (57%) of 138 patients used anti-thrombotics: 35 (25%) of 138 used antiplatelets, 36 (26%) used anticoagulants, and 13 (6%) used dual therapy consisting of combined antiplatelet and anticoagulant therapy. 83 (43%) of 195 patients had gastrointestinal angiodysplasias at multiple sites, with the small bowel being the most frequent location (150 [77%] of 195) and nearly equal distribution in patients with colon (72 [37%] of 196) and stomach (79 [40%] of 197) gastrointestinal angiodysplasias. Gastrointestinal angiodysplasias isolated to one gastrointestinal location were common in the small bowel (86 [44%] of 195), but uncommon in the stomach (15 [8%] of 195) and colon (11 [6%] of 195). 128 (61%) of 210 patients had at least one endoscopic treatment with argon plasma coagulation before initiating somatostatin analogue therapy. Octreotide was the most frequently prescribed somatostatin analogue (166 [78%] of 212), followed by lanreotide (38 [18%]) and pasireotide (eight [4%]); pasireotide was only used in one study.[20] 198 (93%) of 212 patients were prescribed long-acting somatostatin analogues at a dose equivalent to octreotide 20–30 mg (147 [69%] of 212).

Somatostatin analogue therapy resulted in a significant reduction in mean number of red blood cell transfusions, with a pooled IRR, adjusted for study and study duration, of 0·18 (95% CI 0·14–0·24; p<0·0001), a median treatment duration of 12 months (IQR 6·0–12·0), and follow-up period of 12 months (12·0–12·0). The absolute mean number of red blood cell transfusions decreased from 12·8 (95% CI 10·4–15·8) during baseline to 2·3 (1·9–2·9) during follow-up, a reduction of 10·5 red blood cell transfusions (p<0·0001).

177 (83%) of 212 patients had a good response to somatostatin analogues therapy , defined as at least a 50% reduction in the number of red blood cell transfusions. 109 (62%) of 177 patients were good responders who did not require any red blood cell transfusions while on somatostatin analogue therapy.

Haemoglobin concentrations increased significantly during somatostatin analogue therapy from a mean baseline concentration of 7·3 g/dL (95% CI 6·7–7·9) to

a mean concentration of 10·6 g/dL (10·0–11·2; p<0·0001).

Adverse events occurred in 38 (18%) of 212 patients receiving somatostatin analogue therapy. Most adverse events were gastrointestinal side-effects and included the following: loose stools (seven [3%] of 212 patients), cholelithiasis (five [2%]), flatulence (four [2%]), abdominal pain (three [1%]), nausea (two [1%]), and gallbladder sludge (one patient [<1%]). Administration site reactions were also relatively common and included erythema (five [2%] of 212 patients) and pain (three [1%]). Impaired glucose tolerance was also observed in four (2%) of 212 patients. Other adverse events were only reported once and included allergic reaction, thrombocytopenia, heart failure and acute kidney failure, and splenic infarction. Somatostatin analogue therapy was discontinued in ten (5%) of 212 patients because of adverse events. Reasons for discontinuation were cholelithiasis (two [1%] of 212 patients), abdominal pain (one [<1%]), flatulence (one [<1%]), pain at the injection site (one [<1%]), impaired glucose tolerance (one [<1%]), and all the other adverse events that were reported once (four [2%]). All adverse events were reported in patients who used a higher somatostatin analogue dose (20 mg or 30 mg octreotide, 90 mg or 120 mg lanreotide, and 60 mg pasireotide).

Three (27%) of 11 studies did not meet the criteria for multiple imputation, because 50% or more of the relevant variables were missing (n=89).[15,24,25] Therefore, 89 patients were partially excluded from the clinical treatment response prediction analyses. Baseline characteristics of the patients of the included and partially excluded studies were compared and showed no clinically relevant differences (appendix p 11). Doses of somatostatin analogue therapy were divided into a low (10 mg) and a high (20–30 mg) dose, as the Spearman's Rank-Order correlation showed a significant correlation between a somatostatin analogue dose of 30 mg and the somatostatin analogue pasireotide (p<0·0001). The somatostatin analogue dose of nine patients from three studies had been increased during the treatment period because of a poor response.[14,15,23] No information about the timing was available. Therefore, patients were analysed according to their initial dose.

Table 2 shows the results of the prediction analyses. The multivariate analysis included 197 (93%) of 212 patients. In figure 3, the mean number of red blood cell transfusions patients received in both groups at baseline and during the treatment period are shown. Octreotide was associated with better treatment response compared with lanreotide (IRR interaction 2·13 [95% CI 1·12–4·04]; p=0·02), whereas the location of gastrointestinal angiodysplasias in the stomach compared with angiodysplasias in the small bowel and colon (IRR interaction 1·92 [95% CI 1·13–3·26]; p=0·02) was associated with worse treatment response. Association of gastrointestinal angiodysplasias isolated to one gastrointestinal location was assessed in a separate prediction analysis of which the results are shown in the appendix (p 12).

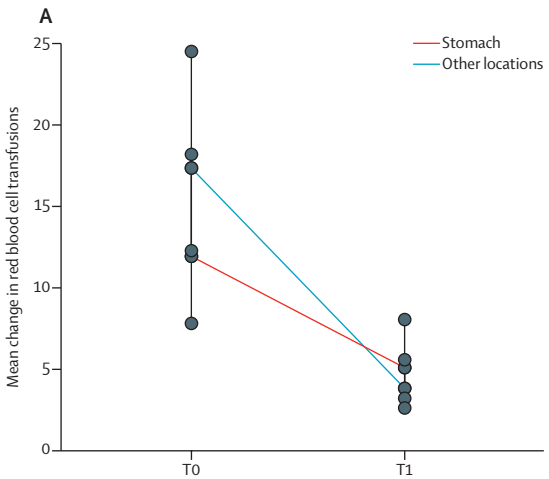
| | Univariate analysis (n=212) | | Multivariate analysis (n=197) | |
|---|---|---|---|---|
| | IRR (95% CI) | p value | IRR (95% CI) | p value |
| **Patient characteristics** | | | | |
| Age | 0·85 (0·44–1·61) | 0·61 | .. | .. |
| Sex | | | | |
| Male | Ref | .. | .. | .. |
| Female | 0·89 (0·52–1·53) | 0·68 | .. | .. |
| Comorbidities* | | | | |
| Diabetes mellitus | 1·16 (0·53–2·55) | 0·71 | .. | .. |
| Valvular heart disease | 1·24 (0·64–2·40) | 0·52 | .. | .. |
| Ischaemic heart disease | 0·95 (0·45–1·99) | 0·88 | .. | .. |
| Cirrhosis | 1·02 (0·39–2·66) | 0·96 | .. | .. |
| Chronic kidney disease | 1·28 (0·65–2·51) | 0·47 | .. | .. |
| Coagulation disorders‡ | 2·39 (0·48–11·98) | 0·29 | .. | .. |
| Anti-thrombotics | .. | 0·30 | .. | .. |
| None | Ref | .. | .. | .. |
| Antiplatelets | 0·95 (0·43–2·10) | 0·91 | .. | .. |
| Anticoagulants | 1·87 (0·86–4·05) | 0·11 | .. | .. |
| Dual therapy | 1·80 (0·52–6·20) | 0·35 | .. | .. |
| **Gastrointestinal angiodysplasia characteristics** | | | | |
| Previous argon plasma coagulation | 1·31 (0·76–2·24) | 0·33 | .. | .. |
| Location | .. | .. | .. | .. |
| Multiple locations | 1·37 (0·80–2·36) | 0·25 | .. | .. |
| Stomach | 2·06 (1·20–3·53) | 0·01 | 1·92 (1·13–3·26) | 0·02 |
| Small bowel | 0·89 (0·46–1·70) | 0·72 | .. | .. |
| Colon | 1·10 (0·64–1·90) | 0·74 | .. | .. |
| **Therapy characteristics** | | | | |
| Type of somatostatin analogue | .. | 0·03 | .. | 0·03 |
| Octreotide | Ref | .. | .. | .. |
| Lanreotide | 2·20 (1·15–4·18) | 0·02 | 2·13 (1·12–4·04) | 0·02 |
| Pasireotide | 2·67 (0·74–9·62) | 0·13 | 2·91 (0·82–10·36) | 0·10 |
| Dose of somatostatin analogue† | .. | .. | .. | .. |
| 10 mg | Ref | .. | .. | .. |
| 20–30 mg | 0·68 (0·37–1·26) | 0·22 | .. | .. |
| Mode of action | | | | |
| Short acting | Ref | .. | .. | .. |
| Long acting | 1·23 (0·39–3·89) | 0·72 | .. | .. |

Number of patients included in the univariate analysis ranged from 137 to 212 (table 1). Dichotomous values were used to assess influence of location. Influence of isolated gastrointestinal angiodysplasia locations was assessed in a separate analysis (appendix p 12). IRR=incidence rate ratio. Ref=reference. *Thrombocytopenia, von Willebrand disease, Glanzmann thrombasthenia, and factor V Leiden. †Doses are expressed as mg of octreotide long-acting release. Equivalent doses of lanreotide and pasireotide long-acting release were used.

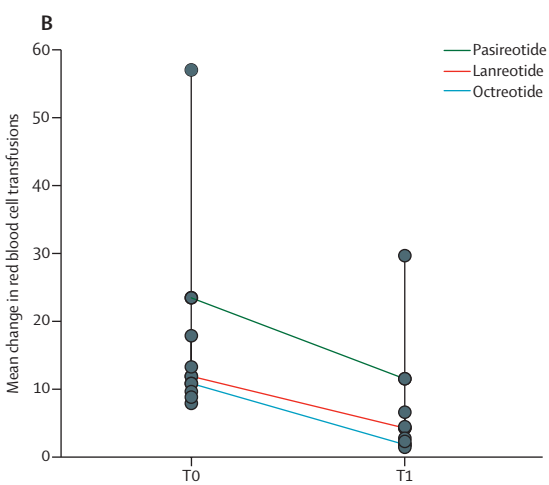
*Table 2:* **Characteristics associated with clinical treatment response**

## Discussion

This systematic review and meta-analysis, using individual patient data from 11 studies, shows that somatostatin analogue therapy in patients with active bleeding due to gastrointestinal angiodysplasias




| | $T_0$ | $T_1$ | IRR |
|---|---|---|---|
| Stomach | 12·0 (95% CI 7·9–18·2) | 5·1 (95% CI 3·3–8·1) | 0·43 |
| Other locations | 17·4 (95% CI 12·3–24·5) | 3·9 (95% CI 2·7–5·6) | 0·22 |




| | $T_0$ | $T_1$ | IRR |
|---|---|---|---|
| Octreotide | 10·8 (95% CI 8·8–13·2) | 1·8 (95% CI 1·4–2·3) | 0·17 |
| Lanreotide | 11·9 (95% CI 7·9–17·8) | 4·3 (95% CI 2·8–6·6) | 0·36 |
| Pasireotide | 23·4 (95% CI 9·6–56·8) | 11·5 (95% CI 4·5–29·6) | 0·49 |

***Figure 3:*** **Characteristics independently associated with clinical treatment response**
Error bars are 95% CIs. (A) Association of location of angiodysplasias in the stomach compared with angiodysplasias in the small bowel and colon. (B) Association of somatostatin analogue type. IRR=incidence rate ratio. $T_0$=baseline. $T_1$=treatment period.

reduces the need for red blood cell transfusions with an IRR of 0·18 during a median of 12 months of treatment. This finding was associated with an increase in haemoglobin concentrations (7·3 g/dL to 10·6 g/dL). Adverse events were reported in 38 (18%) of 212 patients and were mostly mild and self-limiting. We found that 177 (83%) of 212 patients had at least a 50% reduction in the number of red blood cell transfusions, of whom 109 (62%) did not require any red blood cell transfusions while on somatostatin analogue therapy.

Endoscopy with argon plasma coagulation is the first-line treatment for patients with few and accessible gastrointestinal angiodysplasias.[31] Although argon plasma coagulation treatment can provide immediate cessation of bleeding, the high volume of patients with rebleeding at 12 months follow-up makes this treatment less effective than somatostatin analogue therapy (mean reduction in the number of red blood cell transfusions of 55% *vs* 82%).[32,33] However, combination therapy should be considered in selected patients to optimise the difference in treatment approach of both modalities.[1,33]

Thalidomide, which also inhibits angiogenesis, is regarded as an alternative option in patients with gastrointestinal angiodysplasias that are refractory to argon plasma coagulation treatment. 1 year of treatment can result in an 82% reduction in the number of red blood cell transfusions; and in 71% of patients, it is associated with a decrease of at least 50% in the number of bleeding episodes.[34] Both outcomes are comparable to our results (82% reduction in the number of red blood cell transfusions and 83% of patients with a 50% or more decrease in the number of bleeding episodes). However, major drawbacks of thalidomide treatment exist, such as adverse events, which are reported in about 70% of patients.[34] Adverse events include drowsiness, tremor, and irreversible peripheral neuropathy. Neuropathy is seen in up to 80% of patients after at least 6 months of treatment and precludes long-term use of thalidomide.[35] We found that few patients on somatostatin analogue therapy have adverse events and that most adverse events were tolerable and self-limiting, necessitating discontinuation in ten (5%) of 212 patients.

Patients with transfusion-dependent gastrointestinal angiodysplasias required a mean of 12·8 red blood cell transfusions in the year before initiating somatostatin analogue therapy, which is associated with substantial use of health-care resources.[15] Transfusion requirements decreased to 2·3 red blood cell transfusions in the year after starting treatment, and so somatostatin analogue therapy is presumed to be cost-effective. Cost-effectiveness was also established in one of the included studies, which reported a reduction of approximately 60% in annual treatment costs of patients who used somatostatin analogue therapy.[15]

The response to somatostatin analogue therapy was not influenced by known risk factors associated with the development and clinical severity of gastrointestinal angiodysplasias, including age, comorbidities, and use of anti-thrombotics.[12] Moreover, previous endoscopic treatment with argon plasma coagulation did not affect the results of somatostatin analogue therapy. By contrast, the location of gastrointestinal angiodysplasias in the stomach

was associated with a significantly worse treatment response than other gastrointestinal angiodysplasia locations. A similar trend was seen when treatment response of gastrointestinal angiodysplasias isolated to one gastrointestinal location was assessed, but this difference was not significant, possibly due to the low number of patients who had isolated stomach angiodysplasias and colon angiodysplasias. A possible explanation for the observed difference in treatment response is the distribution of somatostatin receptors through the gastrointestinal tract. Octreotide and lanreotide preferentially bind to somatostatin receptor type 2 (SSTR2), which is low in abundance in the stomach.[36]

Furthermore, octreotide was more effective than lanreotide in this study. This finding could be explained by the 30% higher binding affinity of octreotide to SSTR2, which is primarily expressed in the small bowel and colon.[37] Moreover, the pharmacokinetic profiles of both somatostatin analogue types also vary. Long-acting octreotide maintains serum concentrations better than prolonged-release lanreotide. Lanreotide also causes a higher interindividual variability in serum concentrations.[38] Octreotide was also associated with better treatment response than pasireotide, which has the lowest binding affinity to SSTR2.[37] However, this difference was not significant, possibly due to the low number of patients who used pasireotide (n=8). An increased somatostatin analogue dose did not result in a larger reduction of red blood cell transfusions. This finding suggests that a low dose of octreotide (10 mg long-acting release) suffices for the effect. This result is of interest, because adverse events were solely reported in patients on a higher dose.

The main strength of our study is that we included the individual patient data provided by the authors of almost all identified studies. Additionally, we were able to extract data from the identified studies of which original data were not provided by the authors.[15,24] We used a mixed-effects model in our pooled analyses to account for clustering of patients within studies and for differences in study duration. However, our study has several limitations. First, only one of the studies had a control group and three studies had a retrospective design, increasing the risk of bias and therefore reducing the certainty of evidence.[14,20,25,28] Nevertheless, the treatment effects of studies with different designs and of different quality were all found to be comparable (appendix p 10). Second, data from three studies could only partially be used in our clinical treatment response prediction analyses.[15,24,25] We were unable to retrieve original data from two studies. However, most individual patient data were provided in the published manuscripts.[15,24] Therefore, only 15 (7%) of 212 patients were excluded from the independent prediction analysis. Furthermore, no clinically relevant differences were found between the baseline characteristics of patients from the partially excluded and fully included studies (appendix p 11). Third, we had no information about the number of gastrointestinal angiodysplasias patients had, which is an important indicator of bleeding severity. The transfusion requirements of patients with gastrointestinal angiodysplasias in multiple locations and of patients with isolated small bowel angiodysplasias were higher than the requirements of patients with isolated stomach angiodysplasias and colon angiodysplasias (appendix p 12). This finding is in line with the previous literature, which indicates most patients with small bowel angiodysplasias have multiple lesions.[1] Since location of gastrointestinal angiodysplasias in the small bowel was associated with the best response to somatostatin analogue therapy, having a high number of gastrointestinal angiodysplasias does not seem to influence treatment response negatively. Finally, although we noted a better treatment response of octreotide compared with lanreotide, and there was no difference in treatment response between somatostatin analogue doses, this study was not primarily designed to compare somatostatin analogue therapies. Results could therefore have been influenced by confounders we did not appropriately correct for and should therefore be interpreted with caution.

In light of the aforementioned points, we recommend octreotide 10 mg long-acting release (injected intramuscularly) every 28 days in patients with red blood cell transfusion-dependent bleeding secondary to gastrointestinal angiodysplasias that cannot be adequately controlled with endoscopic therapy. After 6 months, treatment effects should be evaluated by assessing changes in the number of red blood cell transfusions and haemoglobin concentrations. If the patient has a good response, somatostatin analogue therapy can be safely continued for multiple years.[14,26] Somatostatin analogue therapy could also be discontinued if patients are no longer transfusion-dependent, because treatment reduces the number and size of gastrointestinal angiodysplasias (or angiodysplasia lesions).[24,28] However, treatment should be resumed if the patient rebleeds.[25]

In conclusion, somatostatin analogue therapy is safe and effective in most patients with red blood cell transfusion-dependent bleeding due to gastrointestinal angiodysplasias. Treatment is more effective in patients with angiodysplasias located in the small bowel and colon, and octreotide therapy seems to be more effective than lanreotide therapy.

**Contributors**

LCMJG, KVG, WK, and EJMvG planned and designed the study. LCMJG and KVG did the literature search and assessed the quality of all eligible studies. LCMJG and KVG collected the data. LCMJG did the statistical analyses. LCMJG and KVG drafted the manuscript. KVG, AR, GH, SF, PSS, TA, GS, SCZ, RP-M, RB, GN, DM, MB, SM, RS, WK, JPHD, and EJMvG interpreted the data and critically reviewed the manuscript. EJMvG supervised the study. All authors approved the final draft of the manuscript. All authors had full access

to all the data in the study and accepted responsibility to submit for publication.

#### Declaration of interests

GH has received research funding from Health Research Board Ireland. JPHD has received research funding from Gilead to support hepatitis C elimination in the Netherlands. EJMvG has received research funding from Mylan, Boston Scientific, and Olympus; and served as a consultant for MTW-Endoskopie. All other authors declare no competing interests.

#### Data sharing

Summary data will be available with publication (with no end date) upon reasonable request to Lia Goltstein (lia.goltstein@radboudumc.nl), subject to an appropriate data sharing agreement. The study protocol and statistical analysis plan will be available in the appendix with publication of this Article. Individual patient data and a data dictionary defining each field in the set will be available, upon reasonable request to Lia Goltstein and in consultation with the coauthors that contributed to the datasets, subject to an appropriate data sharing agreement.

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