

Angiotensin-converting enzyme inhibitor-induced bowel angioedema: clinical features, diagnostic challenges, and recovery predictors from survival analysis: a systematic review of current reported cases

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Abstract

Background Angiotensin-converting enzyme inhibitor-induced bowel angioedema (ACEi-IAE) is a rare and frequently under-recognized condition. Its nonspecific gastrointestinal symptoms could lead to missed diagnoses, unnecessary procedures and inappropriate treatments. Given the scarcity of studies, we conducted a systematic review to summarize the clinical characteristics of ACEi-IAE, the diagnostic approach and factors predicting delayed recovery.

Methods Electronic databases, including MEDLINE, OVID and EMBASE, were used to identify eligible studies from inception to November 2024. Eligible cases were required to have a clear diagnosis of ACEi-IAE. Kaplan-Meier and multivariate Cox regression analyses were used to identify factors associated with delayed recovery time.

Results Our systematic review included 81 eligible studies, comprising 117 ACEi-IAE cases with a mean age of 50 years, of which 83% were female. Patients were mainly African Americans (50%) taking lisinopril (71%). All patients (100%) presented with abdominal pain and other non-specific features. The median recovery time was 48 h after discontinuing ACEi. Patients who had been taking lisinopril for a longer than average period (25.9 months) had a statistically significantly lower hazard ratio for recovery (adjusted hazard ratio [aHR] 0.39, 95% confidence interval [CI] 0.19-0.81; $P=0.012$), as did patients who had radiographic evidence of jejunal edema (aHR 0.29, 95%CI 0.11-0.74; $P=0.010$). Diagnostic criteria were proposed and summarized based on the findings.

Conclusions Clinicians should be aware of ACEi-induced bowel angioedema, particularly in ACEi users with non-specific abdominal pain. Implementation of our proposed diagnostic criteria is recommended to prevent unnecessary investigation and inappropriate treatment.

Keywords Angiotensin-converting enzyme inhibitors, bowel angioedema, epidemiology

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Conflict of Interest: None

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Introduction

Angiotensin-converting enzyme inhibitors (ACEi) are commonly prescribed medications for cardiovascular diseases, used by at least 40 million people globally [1], and comprise at least one third of the anti-hypertensive drugs in the USA [2]. While generally well-tolerated, ACEi can cause angioedema, a serious side effect characterized by swelling of the deep layers of skin and mucosal tissue due to increased vascular permeability. The incidence of ACEi-induced angioedema is estimated to be between 0.1% and 0.7%, although the true incidence may be higher as a result of underdiagnosis [3]. The most well-known presentation is

angioedema of the face and oropharynx, contributing to 20–40% of angioedema presentations in the emergency room.

However, ACEi can also induce angioedema of the intestines, a less common and often overlooked complication. ACEi-induced intestinal angioedema poses a diagnostic challenge, as it presents with non-specific symptoms, such as abdominal pain, nausea, vomiting and diarrhea, often mimicking other gastrointestinal conditions [4]. This often results in delayed diagnosis, misdiagnosis, unnecessary invasive procedures and inappropriate treatments [5].

The scarcity of information regarding the factors associated with ACEi bowel-induced angioedema (ACEi-IAE) and the duration of recovery creates a complication for the diagnosis and treatment of this patient group. Therefore, we conducted a systematic case review to investigate all reported cases of ACEi-IAE and factors that may impact the duration of recovery, in order to better understand the clinical presentation, diagnostic challenges and management of the condition.

Materials and methods

Search strategy and eligibility

Two investigators (TS and NT) independently conducted searches in PubMed, OVID and EMBASE databases, without language restrictions, from inception through November 2024, using the search strategy specified in Supplementary Table 1. The investigators (TS and NT) independently assessed the eligibility of the retrieved records. Any conflicts were resolved through further discussions involving a third investigator (PD). The protocol was designed based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) checklist (Supplementary Table 2) [6]. The protocol was preregistered (PROSPERO: 618287). Eligible studies had to be published as case reports or case series in which ACEi-induced bowel angioedema was diagnosed. All reported patients must have been currently receiving an ACE inhibitor, whose removal led to resolution of the symptoms. No restrictions on age, country of origin, or language (provided that an English translation was available) was applied. Conference abstracts and peer-reviewed articles were incorporated into the study, provided that the case diagnosis was indicated.

Data extraction

To ensure consistency and rigor, we implemented a standardized data collection protocol across all included studies. This protocol facilitated the systematic extraction of key variables pertinent to our research objectives. Extracted data encompassed

demographic information, including the first author's surname, the country where the study was conducted, and the year of publication. Patient characteristics were meticulously recorded, capturing details such as age, sex, and self-reported race. Regarding the ACEi administration, we documented the specific type of ACEi prescribed, the administered dosage, and the duration of ACEi usage. Clinical manifestations of angioedema were captured, including the nature and severity of symptoms, radiographic findings—at least 1 of the following types of information was reported: segmental thickening, mesenteric edema (with areas of involvement if provided), target signs, infiltrate of a small bowel region, mucosal thickening or luminal narrowing—and the anatomical location of the angioedema. Finally, data regarding the resolution of angioedema, specifically the recovery time (defined as duration of hospital stay from the day of diagnosis until discharge), was collected to assess the clinical course of the adverse event. This detailed extraction process allowed for a comprehensive analysis of ACEi-induced angioedema.

Statistical analysis

Continuous variables were presented as mean \pm standard deviation, while categorical variables were presented as percentages. Recovery time was evaluated as a primary survival outcome using Kaplan-Meier analysis for the initial evaluation. Cox regression univariate and multivariate analyses were used to assess predictors of the duration of recovery time, reported in terms of a hazard ratio (HR) with 95% confidence ($P < 0.05$). A stepwise Cox regression method was used to identify variables that independently had a significant association with the recovery time. All data analyses were conducted using StataMP 17.0 software (StataCorp, College Station, Texas).

Results

Our search strategy identified 549 records. After removing 89 duplicates, we reviewed those studies by title and abstract and rejected a further 375 studies that did not meet the eligibility criteria related to study design or participants. Subsequently, we thoroughly reviewed 85 articles and excluded 4 for reporting different medication types [7–10]. Ultimately, 81 studies met the eligibility criteria for our systematic review, totaling 117 cases [4,5,11–91]. Fig. 1 illustrates our search methodology and selection process, and Supplementary Table 3 details each of the selected case reports.

Table 1 shows the baseline characteristics of all documented case reports. The average participant age was 50 years old, and 83% were female. The majority of the case reports came from the USA (72%), followed by Belgium (8%). Of the patients whose race was reported, 50% were African Americans, while 40% were White. Lisinopril was the most common medication that contributed to ACEi-induced bowel angioedema (71%). The average duration of medication intake was 24 months, and ACEi-induced bowel angioedema could occur from 12 h to 10 years after exposure. Abdominal pain was present in every

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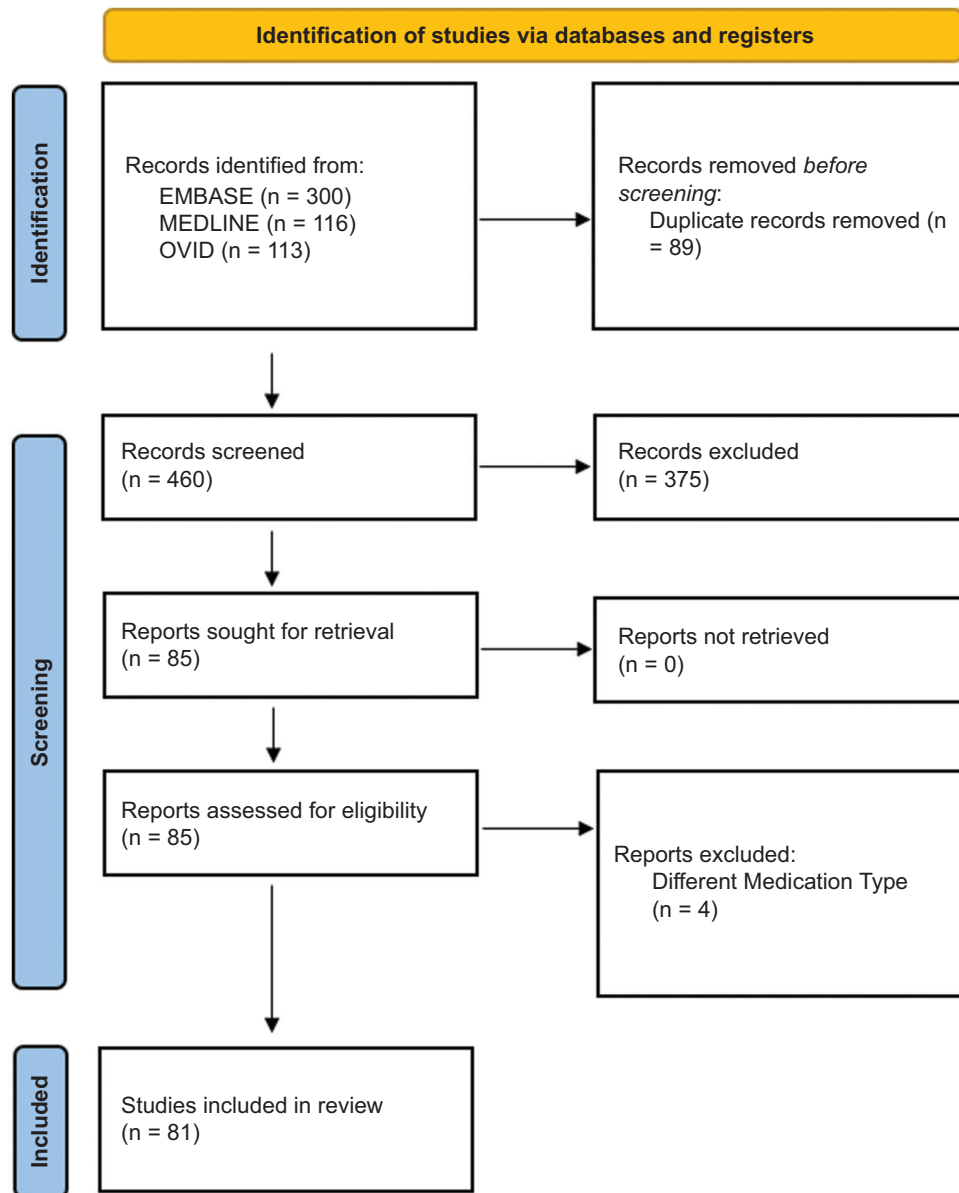


Figure 1 Study selection and PRISMA flow diagram

reported case, while 75% had nausea, 67% had vomiting and 45% had diarrhea. Small bowel radiographic edema constituted the largest category (34%) of bowel edemas seen on computed topography, followed by jejunum (24%) and ileum (17%).

Survival analysis

In all of the reported cases that recovered, the median recovery time was 48 h after discontinuing the medication. A Kaplan-Meier analysis of the recovery period is shown in Fig. 2. Patients with a longer-than-average duration (25.9 months) of lisinopril intake had a significantly lower crude hazard ratio (cHR 0.35, 95%CI 0.19-0.66; $P=0.001$) and adjusted hazard ratio (aHR 0.39, 95%CI 0.19-0.81; $P=0.012$) for recovery. In addition, patients who had radiographic

evidence of jejunal edema had a statistically significantly lower cHR (cHR 0.49, 95%CI 0.25-0.93; $P=0.03$) and aHR (aHR 0.29, 95%CI 0.11-0.74; $P=0.010$) for recovery. No other variables achieved statistical significance; thus, only the 2 aforementioned variables were used in the multiple Cox regression model. Univariate and multivariate Cox regression analyses are depicted in detail in Table 2. The survival curves generated by the final Cox regression model for a longer duration of lisinopril in Fig. 3.

Discussion

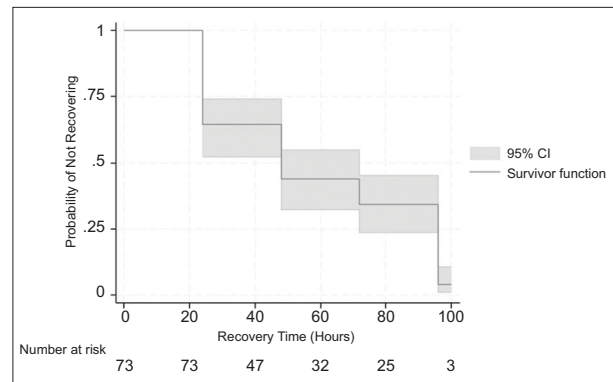
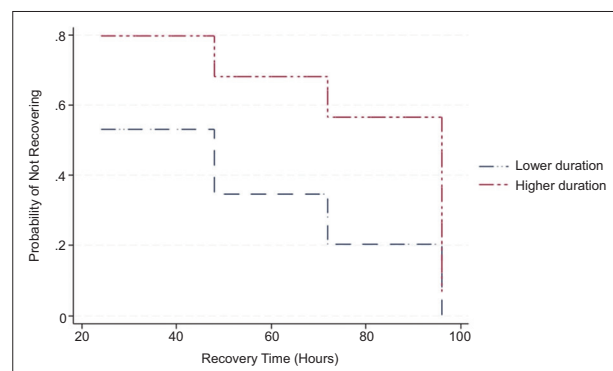
To date, this is the first systematic review of patients with ACEi-induced bowel angioedema. This meta-analysis comprised

Table 1 Results of data synthesis

Characteristics	Results	Number of cases with data, n (%)
Age, mean (years)	50.2±11.7	117 (100.0%)
Age, range (years)	23-85	117 (100.0%)
Country of origin		117 (100.0%)
USA	85 (72.9%)	
Belgium	10 (8.5%)	
Others	22 (18.7%)	
Sex		117 (100.0%)
Male	19 (16.1%)	
Female	98 (83.9%)	
Race		30 (25.4%)
African American	15 (50.0%)	
White	12 (40.0%)	
Others	3 (10.0%)	
Medication type		117 (100.0%)
Lisinopril	83 (71.2%)	
Enalapril	15 (12.7%)	
Perindopril	7 (5.9%)	
Others	12 (10.2%)	
Dosage, mean (mg)		
Lisinopril	23.3	21 (17.8%)
Enalapril	8.6	7 (5.9%)
Medication duration, mean (months)	24.5	107 (90.7%)
Lisinopril	25.9	76 (64.4%)
Enalapril	24.1	14 (11.9%)
Medication duration, range (months)	0.02-120	107 (90.7%)
Clinical symptoms		
Abdominal pain	117 (100.0%)	117 (100.0%)
Nausea	88 (75.4%)	117 (100.0%)
Vomiting	79 (67.8%)	117 (100.0%)
Diarrhea	54 (45.8%)	117 (100.0%)
Radiographic edema location		95 (80.5%)
Small bowel	32 (34.7%)	
Jejunum	23 (24.2%)	
Ileum	17 (17.9%)	
Others	21 (23.2%)	
Recovered	116 (100.0%)	116 (98.3%)
Recovery time, mean (h)	67.72	73 (61.9%)
Recovery time, range (h)	24-720	

81 studies and 117 patients. We report multiple novel findings from this study. Firstly, patients are predominantly middle-aged females, possibly indicating a disproportionate effect in this subpopulation. Secondly, lisinopril is the medication that most frequently causes ACEi-induced bowel angioedema, highlighting a possible concern about one of the most common medications prescribed worldwide. Finally, patients who took lisinopril for longer periods, and those who had evidence of jejunal edema, were at greater risk of a delayed recovery.

The first reported general angioedema was reported in 1876 [92], but ACEi medications were not discovered until

**Figure 2** Kaplan-Meier analysis of the recovery period
CI, confidence interval**Figure 3** Cox regression model: duration of lisinopril intake

100 years later, in 1975, and were first introduced to the general public in 1981 [93]. By then, reports of angioedema associated with ACEi had been published in 1977 and 1980 [94], and angioedema has been associated with ACEi ever since. However, the first ACEi-induced bowel angioedema surfaced in 1994, signifying a newly discovered unwanted effect that may possibly lead to a missed diagnosis in patients who regularly take ACEi. Interestingly, most patients in our analysis were middle-aged females, whereas earlier publications reported that ACEi-angioedema was more likely to be found in males [95]. This may stem from the differences in organ systems presentation, in which males are likely to present with skin and subcutaneous tissue findings, but women are likely to present with gastrointestinal symptoms [96].

We found that all patients presented with abdominal pain, while lisinopril was the major medication associated with ACEi-angioedema. More than 80% of new ACEi users received lisinopril [97], making it the most common medication reported to cause issues. Other gastrointestinal symptoms included nausea, vomiting and diarrhea. The radiographic evidence of small bowel edema seen in many cases was probably due to fluid sequestration in the abdomen, as seen in patients who later developed shock [64] and evidenced by double-balloon endoscopy [85]. Previous studies reported that 57% of patients had unnecessary surgery or biopsies [46], which could have been prevented if a detailed medication history had been obtained. Furthermore, given the short period of time for information collection, patients

Table 2 Univariate and multivariate Cox regression analysis of predictors for time to recovery

Variables	Univariate HR (95%CI)	P-value	Multivariate HR (95%CI)	P-value
Age	0.98 (0.96-1.01)	0.336		
Country of origin				
USA	Reference	0.278		
Belgium	2.20 (0.52-9.22)	0.133		
Others	1.61 (0.86-3.00)			
Sex				
Female	Reference			
Male	0.94 (0.50-1.77)	0.872		
Race				
African American	Reference			
White	1.45 (0.54-3.94)	0.455		
Others	0.94 (0.19-4.52)	0.949		
Medication type				
Lisinopril	Reference			
Enalapril	1.46 (0.64-3.32)	0.358		
Perindopril	1.16 (0.41-3.25)	0.774		
Others	2.21 (0.92-5.32)	0.076		
Dosage comparison ^a				
Lisinopril	0			
Enalapril	0.43 (0.09-2.04)	0.294		
Duration comparison ^b				
Lisinopril	0.35 (0.19-0.66)	0.001	0.39 (0.19-0.81)	0.012*
Enalapril	0.86 (0.15-4.72)	0.865		
Clinical symptoms				
Abdominal pain	Reference			
Nausea	1			
Vomiting	1			
Diarrhea	1			
Radiographic edema location				
Small bowel	Reference			
Jejunum	0.49 (0.25-0.93)	0.030	0.29 (0.11-0.74)	0.010*
Ileum	0.47 (0.21-1.03)	0.061		
Others	0.95 (0.46-1.91)	0.879		

* Only significant variables were included in the multivariate Cox regression model

^aComparison of effects between dosage levels above and below the mean

^bComparison of effects between treatment durations above and below the mean

HR, hazard ratio; CI confidence interval

are likely to be discharged from both emergency rooms and outpatients' departments [21,65], but they may later return and require admission. Some of these patients may suffer for up to 4 years before obtaining the correct diagnosis [60]. Table 3 shows the proposed diagnostic criteria [16] and factors that should be considered to indicate ACEi-induced bowel angioedema. A detailed history of medication usage in this subpopulation group may help in determining the diagnosis.

Even though all patients recovered, many patients reported severe pain as the condition progressed, requiring multiple pain medications [61,62,65]. We found that the recovery time was impacted by 2 factors: a higher dosage and a jejunal location of the edema. The gastrointestinal tract is innervated by multiple nerve systems, but given the limited information about differences between small intestine sections, further investigation will be necessary. One possible theory is that recovery capabilities

Table 3 Proposed diagnostic criteria and factors for ACEi-induced bowel angioedema

Proposed diagnostic criteria
• Use of ACEi (irrespective of dose and duration)
• Non-specific abdominal pain with presence of bowel edema
• Resolution of symptoms and radiographic changes after discontinuation of the drug
• Absence of other diagnosis
Other factors for consideration
• Repeated healthcare visits, with no other evidence for other disease
• Demographics: female, middle-age, African American
• Medication: long-term usage of ACEi
• Radiographic: ascites, jejunal edema

ACEi, angiotensin-converting enzyme inhibitors

in each of the gastrointestinal tract segment differs, as seen in the disproportionate impact of aging, whereas the distal

gastrointestinal tract is more affected [98]. A longer recovery time is debilitating for the patients, as prolonged symptoms have a negative impact on their quality of life and may lead to further unnecessary investigations. Although there is no dose-dependent relationship with traditional angioedema [99], it is possible that bradykinin may exert its effect on the gut differently from other organ systems [100]. A longer recovery time could also increase morbidity and mortality, as the prolonged length of stay could increase the number of hospital-acquired infections and conditions for these patients.

Our study had several limitations. First, the relatively small sample size may limit the ability of statistical methods to fully capture patient variability. Second, our survival analysis was an estimate based on the available data, that can lead to possible underreported of various socioeconomic status. Finally, we cannot definitively conclude that the factors identified are the most significant, as certain variables—such as treatment modalities, complications, underlying conditions and laboratory results—were excluded from the analysis because of the limited sample size and data availability. Further robust large-scale studies are necessary to validate our findings and assess their impact on patient outcomes.

Clinicians should suspect ACEi bowel angioedema in ACEi users presenting with non-specific abdominal pain. Prolonged lisinopril use and jejunal edema may be associated with delayed recovery after drug discontinuation. The proposed diagnostic criteria may help prevent missed and delayed diagnoses, thus avoiding unnecessary investigations and inappropriate treatments. Further research into the factors affecting the development and recovery period is crucial for understanding the underlying mechanisms and developing preventive strategies for this rare but debilitating condition.

Summary Box

What is already known:

- Angiotensin-converting enzyme inhibitors (ACEi) can cause angioedema, from generalized to intestinal angioedema
- The clinical features and factors impacting ACEi-induced intestinal angioedema recovery time are currently unknown
- ACEi-induced intestinal angioedema poses a diagnostic challenge and may lead to inappropriate treatments

What the new findings are:

- Patients who took lisinopril for a longer than average time had longer recovery times, as did those with jejunal edema
- Patients are overwhelmingly middle-aged, female and African American
- All patients with ACEi-induced bowel angioedema fully recovered, but they had various debilitating episodes before a final diagnosis was obtained

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Supplementary material

Supplementary Table 1 Search terms used in the study

PUBMED
((intestinal angioedema) OR (visceral angioedema)) OR (bowel angioedema) AND (((((((ACE Inhibitor) OR (lisinopril)) OR (captopril)) OR (enalapril)) OR (benazepril)) OR (ACE-inhibitor side effects)) OR (Ramipril)) OR (Fosinopril)) OR (Temocapril))
EMBASE
#1: 'dipeptidyl carboxypeptidase inhibitor'/exp OR 'dipeptidyl carboxypeptidase inhibitor'
#2: 'intestinal angioedema'
#3: visceral AND angioedema
#4: 'ace inhibitor' AND side AND effects
#5: intestinal AND angioedema
#6: #2 OR #3 OR #5
#7: #1 OR #5
#8: #6 AND #7
OVID
((intestinal angioedema) or (visceral angioedema) or (bowel angioedema)) AND ((ACE Inhibitor) or (lisinopril) or (captopril) or (enalapril) or (benazepril) or (ACE-inhibitor side effects) or (ramipril) or (fosinopril) or (temocapril)).mp, [mp=tx, bt, ti, ab, ct, sh, hw, tn, ot, dm, mf, fx, dv, kf, dq]

Supplementary Table 2 PRISMA checklist [6]

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	N/A
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective (s) or question (s) the review addresses.	4-5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5

(Contd...)

Supplementary Table 2 (*Continued*)

Section and Topic	Item #	Checklist item	Location where item is reported
METHODS			
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	N/A
Effect measures	12	Specify for each outcome the effect measure (s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice (s). If meta-analysis was performed, describe the model (s), method (s) to identify the presence and extent of statistical heterogeneity, and software package (s) used.	5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	6
Study characteristics	17	Cite each included study and present its characteristics.	6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	6

(Contd...)

Supplementary Table 2 (*Continued*)

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	7
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	7-9
	23b	Discuss any limitations of the evidence included in the review.	7-9
	23c	Discuss any limitations of the review processes used.	7-9
	23d	Discuss implications of the results for practice, policy, and future research.	7-9
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	2
Competing interests	26	Declare any competing interests of review authors.	2
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	2

Supplementary Table 3 List of case reports/series included in the study

Case	Paper	Year	Country	Age	Sex
1	Mullins	1996	Australia	59	Female
2	Abdelmalek	1997	USA	41	Female
3	Farraye	1988	USA	41	Female
4	Matsumura	1993	Japan	48	Female
5	Jacobs	1994	USA	51	Female
6	Gregory	1996	USA	58	Female
7	Dupasquier	1994	Switzerland	43	Female
8	Guy	1994	France	29	Female
9	Smoger	1998	USA	61	Male
10	Jardine	1999	New Zealand	46	Female
11	Byrne	2000	USA	67	Female
12	Byrne	2000	USA	41	Female
13	Chase	2000	USA	72	female
14	Oudit	2001	Canada	37	Female
15	Schmidt	2002	USA	56	Female
16	Kotlyar	2010	USA	38	Female
17	Chuah	2012	Australia	56	Female
18	Mujer	2018	USA	42	Male
19	Dobbels	2009	Belgium	42	Female
20	Dobbels	2009	Belgium	51	Female
21	Dobbels	2009	Belgium	67	Female
22	Dobbels	2009	Belgium	53	Male
23	Dobbels	2009	Belgium	69	Female
24	Dobbels	2009	Belgium	49	Female
25	Dobbels	2009	Belgium	39	Female
26	Siu	2013	USA	58	Female
27	Bloom	2015	USA	51	Male
28	Frankel	2009	USA	46	Female
29	Aggarwal	2011	USA	45	Female
30	Yarze	2017	USA	49	Female
31	Mir	2020	USA	23	Female
32	Wojciechowska	2018	Poland	44	Female
33	Arakawa	2005	Japan	44	Female
34	Marmery	2006	USA	48	Female
35	Dorsey	2007	USA	45	Female
36	Syed	2017	USA	58	Female
37	Smet	2013	Belgium	69	Male
38	Arshad	2023	USA	85	Female
39	Jha	2023	USA	47	Female
40	Cuypers	2011	Belgium	38	Female

(Contd...)

Supplementary Table 3 (Continued)

Case	Paper	Year	Country	Age	Sex
41	Goyal	2014	USA	44	Female
42	Srinivasan	2017	USA	36	Female
43	Razzano	2016	USA	65	Male
44	Wilin	2017	USA	62	Female
45	Frutuoso	2016	Portugal	42	Female
46	Oliveira	2016	Portugal	46	Female
47	Gillion	2019	Belgium	41	Female
48	Nguyen	2018	USA	58	Female
49	Gabriel	2016	USA	68	Female
50	Huynh	2022	Australia	44	Female
51	Adusumilli	2019	USA	34	Female
52	Atieh	2023	USA	65	Male
53	Benson	2013	USA	26	Female
54	Benson	2013	USA	42	Female
55	Benson	2013	USA	49	Female
56	Benson	2013	USA	25	Female
57	Bharwad	2023	USA	49	Male
58	Burroughs	2021	USA	75	Female
59	Campbell	2010	USA	45	Female
60	Coelho	2014	Portugal	36	Female
61	Gill	2020	USA	49	Female
62	Inayat	2016	USA	53	Female
63	Zeng	2024	China	23	Female
64	Johnson	2022	USA	63	Female
65	Khan	2007	USA	42	Female
66	Khan	2023	USA	38	Female
67	Korniyenko	2011	USA	57	Female
68	Krause	2019	USA	57	Female
69	Melendez	2020	N/A	53	Male
70	Mutnuri	2014	USA	60	Female
71	Myslinski	2017	USA	62	Male
72	Myslinski	2017	USA	33	Female
73	Niyibizi	2023	USA	61	Female
74	Orr	2004	USA	72	Female
75	Palmquist	2017	USA	42	Female
76	Parreira	2020	Portugal	32	Female
77	Pirzada	2023	USA	58	Female
78	Ricnic Antulov	2018	Denmark	45	Female
79	Rosenburg	2002	USA	38	Female
80	Sehmbey	2019	USA	24	Female
81	Shahani	2013	USA	50	Female

(Contd...)

Supplementary Table 3 (*Continued*)

Case	Paper	Year	Country	Age	Sex
82	Sharma	2021	USA	47	Female
83	Squillante	2020	USA	40	Female
84	Sravanthi	2020	USA	44	Male
85	Tojo	2006	Japan	77	Male
86	Tsuboi	2015	Japan	42	Male
87	Uy	2019	USA	48	Female
88	Vallabh	2017	USA	41	Female
89	Voore	2015	USA	43	Female
90	de Graaff	2012	Netherlands	49	Female
91	de Gruyter	2013	USA	45	Female
92	de Gruyter	2013	USA	45	Female
93	Habib	2022	USA	54	Male
94	Suwebatu	2008	USA	65	Male
95	Shahzad	2006	USA	45	Female
96	Spahn	2008	Germany	40	Female
97	Weingärtner	2008	Germany	67	Female
98-117	Scheirey	2011	USA	Case Series with mean age 56 years	