Phlebitis in **Intravenous Amiodarone Administration:** Incidence and Contributing Factors

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BACKGROUND Intravenous amiodarone is the gold-standard treatment for arrhythmias, but phlebitis is a common adverse effect.
OBJECTIVES To determine the incidence and contributing factors of amiodarone-induced phlebitis and examine phlebitis severity.
METHODS A systematic review was conducted of articles published before February 2016 in the Cumulative Index to Nursing and Allied Health Literature, Cochrane Library, MEDLINE, Embase, Web of Science, and gray databases (Bielefeld, Lenus, EUGrey, RIAN, and DART). All studies in which amiodarone-induced phlebitis was a primary or secondary outcome were included. Meta-analysis was not appropriate because of study heterogeneity. Studies of the same contributing factors were analyzed together.
RESULTS In the 20 included studies, phlebitis incidence ranged from 0% to 85%. Increasing the infusion concentration from 1.2 mg/mL to 1.8 mg/mL increased the phlebitis rate ($P < .001$). Total amiodarone doses greater than 1 g resulted in higher phlebitis rates than did doses less than 0.45 mg ($P < .001$). Most infusion durations and rates were not correlated with phlebitis incidence. However, phlebitis incidence was lower with bolus administration than with longer infusions ($P = .002$). The use of in-line filters and nursing guidelines significantly reduced phlebitis rates ($P < .001$) and phlebitis severity. The most common phlebitis severity grades, in descending order, were 0, 1, 2, 3, and 4.
CONCLUSIONS Understanding factors that increase the risk of amiodarone-induced phlebitis can guide better practice. In-line filters and nursing guidelines should always be implemented when administering intravenous amiodarone. Increased surveillance is required when higher dosages and concentrations are used. (*Critical Care Nurse*. 2019;39[1]:e1-e12)

Amiodarone is an antiarrhythmic drug that remains the first-line treatment for ventricular and supraventricular arrhythmias, which frequently occur in critical care settings.[1-6] Phlebitis is a common adverse effect of peripheral intravenous administration of amiodarone.[5-7] Amiodarone was first used in 1961,[8] but phlebitis was soon found to be a common adverse effect of peripheral intravenous administration.[1,9,10] Administration via a central venous catheter was therefore recommended.[11-14] However, this route is not always feasible in emergency situations,[4-6] and central venous catheters also carry the risk of life-threatening complications such as pneumothorax, arrhythmias, hematoma, and infection.[15-18]

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To understand the incidence of amiodarone-induced phlebitis, it is important to first understand the causes of phlebitis. *Phlebitis* means inflammation of the vein wall, which can cause pain, tenderness, edema, and erythema; skin is hot to the touch and may have a palpable cord.[19,20] The 3 types of phlebitis are chemical, physical, and infective.[21] Amiodarone-induced phlebitis is caused by chemical and physical phlebitis.[22,23] Chemical phlebitis is caused by amiodarone's acidic pH range (3.5-4.5). Drugs with a pH below 7, and especially those with a pH below 4.1, can damage the vein intima.[20] Additionally, amiodarone can precipitate at the time of administration, resulting in needle-shaped crystals adhering to the vein intima and irritating the delicate endothelium. This process is known as *crystallization*. Phlebitis symptoms may not be apparent for several hours.[10,23,24] Manufacturer guidelines[11] recommend using in-line filters to protect against crystallization. Evidence for their use is mixed. Boyce and Yee[25] found that filters made no improvement, whereas Slim et al[3] found the contrary.

Physical phlebitis is related to poor catheter insertion technique and maintenance. Because amiodarone is the first-line treatment for life-threatening arrhythmias,[4] it most often be administered without a peripheral venous catheter in place. Rushed cannulation could result in intimal damage and vein tearing.[21,26,27] Furthermore, inserting large peripheral venous catheters into small veins can cause trauma.[21,28] Spiering[29] found that a small peripheral venous catheter placed in a large vein resulted in the lowest phlebitis rate. The reason is that hemodilution of acidic infusions is the best way to reduce phlebitis rates.[23,26] The Infusion Nurses Society[20] also recommends using a large vein because of better blood flow. Although most incidents of phlebitis are caused by chemical and physical phlebitis,[30] a vein with untreated phlebitis can become infected and progress to infective phlebitis.[21,31,32]

Understanding factors that increase amiodarone-induced phlebitis can guide better nursing practice.

In several published studies,[9,33-35] phlebitis was the most common adverse effect of amiodarone administration, and the phlebitis rate was well above the acceptable Infusion Nurses Society benchmark rate of 5%.[20] Alarmingly, Spiering[29] reported a phlebitis rate of 85%, and the phlebitis rate in the descriptive study by Boyce and Yee[25] was 67%. The authors of several other studies also reported extremely high phlebitis rates, ranging from 36% to 58%.[33,36-38] In contrast, phlebitis rates in other studies were lower, ranging from 0% to 27%.[3,6,34,35,39-48] An initial review of the literature suggested that differences in amiodarone infusion rate, total dose, duration, and concentration can affect phlebitis rate. For instance, continuous infusions[6,25,29,34-40,42-44,47,48] yielded higher phlebitis rates than did bolus administration.[23,45,46] Norton et al[37] found that phlebitis rates increased with infusion duration and also with total amiodarone doses reaching 3 g. In vitro studies on rabbit ears by Ward and Yalkowsky[22-24,49,50] also confirmed that precipitation worsens with prolonged and increased contact of amiodarone with the vein wall. Hilleman and Hansen[51] and Mowry and Hartman[6] found when amiodarone concentration decreased, the phlebitis rate also decreased. Manufacturers[11] recommend using amiodarone concentrations below 2 mg/mL. However, Slim et al[3] found that even concentrations of 1.8 mg/mL caused phlebitis.

Variations in phlebitis severity, including some extreme cases, have been reported.[9,52-55] Simoni et al[55] published a report of a patient who developed acute necrosis of the soft tissue on the arm. Authors of other studies[25,29,34,38,42,45,46,54] have reported phlebitis grades based on the seminal Infusion Nurses Society scale,[20] a standardized scale of phlebitis grades ranging from 0 (no phlebitis) to 4 (severe phlebitis) (Table 1). Severe phlebitis has major implications; it prolongs hospitalization and can cause the patient discomfort and pain.[3,6,32,53] Boyce and Yee[25] found hospital stays to be increased by a day, and Slim et al[3] found hospital stays to be increased by 6 days. This finding has implications for the health service budget, litigation, and patient satisfaction.[21,31]

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Table 1 Phlebitis severity grades (based on Infusion Nurses Society scale[20a]) among patients in included studies

Source	Patients with INS phlebitis grade 0	Patients with INS phlebitis grade 1	Patients with INS phlebitis grade 2	Patients with INS phlebitis grade 3	Patients with INS phlebitis grade 4	Type of phlebitis scale
Spiering[29] (part A)[b]	5	5	18	2	4	INS scale
Spiering[29] (part B)[b]	21	4	4	5	0	INS scale
Boyce and Yee[25]	4	4	1	2	1	Modified INS scale; 0+ range was merged with grade 1 (highest phlebitis grade was used for each patient)
Bagheri-Nesami et al[38]	15	0	4	9	8	Jackson VIP scale; grade 5 was merged with grade 4
Kreiss et al[34]	15	5	0	0	0	No scale; severity graded by described symptoms
Hofmann et al[45]	78	0	0	0	0	No scale; severity graded by described symptoms
Hofmann et al[46]	49	1	0	0	0	No scale; severity graded by described symptoms
Vietti-Ramus et al[42]	35	9	0	0	0	No scale; severity graded by described symptoms
Total	**222**	**28**	**27**	**18**	**13**	**308 (total patients assessed for severity)**
Overall phlebitis severity,[c] %	**Grade 0 74**	**Grade 1 9**	**Grade 2 9**	**Grade 3 6**	**Grade 4 4**	

Abbreviations: INS, Infusion Nurses Society; VIP, Visual Infusion Phlebitis.

[a] Grade 0, no symptoms; grade 1, erythema at access site with or without pain; grade 2, pain at access site with erythema and/or edema; grade 3, pain at access site with erythema and/or edema, streak formation, palpable venous cord; grade 4, pain at access site with erythema and/or edema, streak formation, palpable venous cord greater than 1 in in length with purulent discharge.

[b] The Spiering study was conducted in 2 parts and separated in this table as parts A and B.

[c] Overall phlebitis severity percentage for each grade was calculated by dividing the total number of patients for each grade by the overall total number of patients that were assessed for phlebitis severity, then multiplied by 100.

Currently available research on amiodarone-induced phlebitis is sparse, and sample sizes are small. Two previous systematic reviews[7,35] examined the overall safety of amiodarone but did not focus solely on phlebitis or explore the relationships between phlebitis rates and factors contributing to phlebitis. In this systematic review we analyzed all studies in which amiodarone-induced phlebitis was the primary or secondary endpoint. We examined the incidence of amiodarone-induced phlebitis and factors contributing to different phlebitis rates among studies, focusing on the contributing factors of infusion concentration, total dose, infusion rate, and infusion duration. Where appropriate, we pooled data to increase the statistical power and overall sample size because doing so yields more meaningful results.[56] We also assessed the effects of in-line filters and nursing guidelines on phlebitis rates. We reviewed severity grades of phlebitis as a secondary outcome. The purpose of this systematic review was to help improve future practice guidelines and potentially reduce patient harm.

Patients in the target population for our systematic review had an underlying cardiac condition or had undergone cardiac surgical procedures and required intravenous amiodarone administration. These patients are more vulnerable than others to phlebitis because they tend to be elderly and have underlying conditions that make their veins more fragile.[26,57]

Methods

Search Strategy

We searched the following databases for relevant articles published before February 2016: Cumulative Index to Nursing and Allied Health Literature, Cochrane Library, MEDLINE, Embase, Web of Science, and gray databases (Bielefeld, Lenus, EUGrey, RIAN, and DART). We searched for the keywords *phlebitis, thrombophlebitis,* or *extravasation* as a group and then combined with the keywords *amiodarone* or *Cordarone*. We reviewed all gray literature for potential relevance to avoid reporting bias.[58,59] Gray literature is literature not readily available to the public. We contacted 2 experts[13,14] regarding their poster presentations on amiodarone-induced phlebitis. Unfortunately, both confirmed that their research was never published. However, 1 expert[14] provided via email relevant statistics pertaining to amiodarone-induced phlebitis that decreased with the implementation of nursing guidelines.

We screened the titles and abstracts of all articles retrieved by the search for relevance. We included English-language primary research reports of patients with cardiac conditions (surgical or medical) who had received peripherally administered intravenous amiodarone.

Increased surveillance is required with higher doses and concentrations of intravenous amiodarone.

We excluded studies of pediatric or nonhuman patients, secondary research reports (literature reviews and letters), and studies in which patients received amiodarone orally or via a central venous catheter.

Data Analysis

In the studies that met the inclusion criteria, we used review management software[60] to assess the strength of association or nonindependence between phlebitis rates and its contributing factors, where appropriate. Dichotomous data were summarized with the odds ratio (OR).[60-62] An overall meta-analysis was not appropriate because of the heterogeneity of the included studies.[63] Studies that incorporated the same contributing factors were grouped together for analysis. Not all of the studies were randomized controlled trials, so rather than analyzing data within studies (ie, comparing interventions against controls), we compared contributing factors between studies. For instance, we compared the results of studies that did not use nursing guidelines with the results of studies that used guidelines. Likewise, we compared results of studies in which in-line filters were used with results of studies in which no filters were used. We also analyzed infusion concentration, duration, rate, and total dose between studies.

Quality Appraisal of Included Studies

We appraised study quality using the Evidence-based Librarianship Critical Appraisal checklist.[64] This checklist employs questions with possible responses of "yes," "no," "unclear," or "not applicable" to assess the external and internal validity of each section of the study process and to provide an overall score for each study. If "yes" responses are 75% or more of total responses, or if the sum of "no" and "unclear" responses is 25% or less of total responses, then the study is considered valid.[64]

To avoid reporting bias and overrepresentation of positive or significant results,[65-69] we searched for unpublished data, but none were available. Additionally, we excluded 5 case studies[9,52-55] because they reported only extreme or unusual cases of phlebitis and were not representative of the broader population.[61] Attrition bias was less than 1% and therefore did not affect our overall results.[66] Language bias was unavoidable because we included only English-language studies (no translation services were available). We included 2 systematic reviews. We reviewed 1 of these systematic reviews and appraised its quality with the PRISMA 2009 checklist.[70] We extracted 3 studies from the other systematic review and reviewed them individually; the other studies within that systematic review did not focus on phlebitis.

Results

Our search identified 216 records. We found 2 additional studies in the reference lists of 2 literature reviews retrieved during the screening process. Seven studies linked from the Cochrane database proved to be not applicable. After removing duplicates, 192 entries remained; we screened these by reviewing their titles and abstracts. We excluded 174 articles: 10 were not in English, 97 were not applicable, 53 were not primary studies, and 14 were based on nonhuman studies or pediatric populations. We reviewed the full texts of the remaining 18 articles. We excluded 5 case studies, 1 systematic review, and 1 study that did not confirm phlebitis rate, retaining 11 studies in our systematic review. We found 9 more

Table 2 Overall phlebitis rates among patients in included studies

Source	No. of patients	Patients with phlebitis, No. (%)	Patients without phlebitis, No. (%)
Spiering[29] (part A)[a]	34	29 (85)	5 (25)
Boyce and Yee[25]	12	8 (67)	4 (33)
Bagheri-Nesami et al[38]	36	21 (58)	15 (42)
Martinho and Rodrigues[33]	40	22 (55)	18 (45)
Norton et al[37]	105	42 (40)	63 (60)
Spiering[29] (part B)[a]	34	13 (38)	21 (62)
Kochiadakis et al[36]	33	12 (36)	21 (64)
Schützenberger et al[39]	26	7 (27)	19 (73)
Kreiss et al[34]	20	5 (25)	15 (75)
Vietti-Ramus et al[42]	44	9 (20)	35 (80)
Vardas et al[44]	108	17 (16)	91 (84)
Cotter et al[43]	50	8 (16)	42 (84)
Slim et al[3]	36	5 (14)	31 (86)
Mowry and Hartman[6] (part C)[b]	69	16 (23)	53 (89)
Mowry and Hartman[6] (part A)[b]	97	10 (10)	87 (90)
Xanthos et al[47]	113	11 (10)	102 (90)
Hilleman and Spinler[35]	550	44 (8)	506 (92)
Halonen et al[48]	157	11 (7)	146 (93)
Mowry and Hartman[6] (part B)[b]	173	10 (6)	163 (94)
Kowey et al[40] (part B)[a]	105	3 (3)	102 (97)
Galve et al[41]	50	1 (2)	49 (98)
Hofmann et al (2006)[46]	50	1 (2)	49 (98)
Hofmann et al (2004)[45]	78	0	78 (100)
Kowey et al[40] (part A)[a]	94	0	94 (100)
TOTAL	**2114**	**305 (14)**	**1809 (86)**

[a] The Spiering and Kowey et al studies were conducted in 2 parts and are represented in the table as parts A and B.
[b] The Mowry and Hartman study was conducted in 3 parts and is represented in the table as parts A, B, and C.

articles by screening the reference lists of the included studies, yielding a total of 20 included articles.

Overview of Included Studies

This systematic review included 5 retrospective studies,[3,6,29,33,37] 1 randomized controlled trial,[38] and 1 descriptive study[25] in which amiodarone-induced phlebitis was the primary outcome. In the remaining studies (3 prospective studies,[34,42,45] 1 systematic review,[35] and 9 randomized controlled trials[36,39-41,43,44,46-48]), amiodarone-induced phlebitis was a secondary outcome.

Included studies were carried out in the United States,[3,6,25,29,37,40] Europe,[34,36,39,41-48] Brazil,[33] and Iran[38] in various critical care, telemetry unit, and emergency department settings. Patients included in the studies had cardiac conditions (surgical or medical) that required intravenous amiodarone administration. Sample sizes varied. The systematic review conducted by Hilleman and Spinler[35] encompassed 550 patients. The largest study, by Halonen et al,[48] included 316 patients. The study by Boyce and Yee[25] was the smallest, with 12 patients. The mean (SD) number of patients in the included studies was 88 (107).

Our systematic review encompassed 2114 patients with an overall phlebitis rate of 14%. Phlebitis rates in the included studies ranged from 0% to 85% (Table 2). We grouped together studies that focused on the same

Table 3 Phlebitis rates and amiodarone concentrations

Source	Sample size	Patients with phlebitis, No. (%)	Concentration of amiodarone infusion, mg/mL
Spiering[29] (part A)[a]	34	29 (85)	1.8
Boyce and Yee[25]	12	8 (67)	1.8
Bagheri-Nesami et al[38]	36	21 (58)	1.8
Martinho and Rodrigues[33]	40	22 (55)	up to 3.6
Norton et al[37]	105	42 (40)	1.8
Spiering[29] (part B)[a]	34	13 (38)	1.8
Slim et al[3]	36	5 (14)	1.8
Mowry and Hartman[6] (part C)[b]	69	16 (23)	1.8
Mowry and Hartman[6] (part A)[b]	97	10 (10)	1.8
Mowry and Hartman[6] (part B)[b]	173	10 (6)	1.2
Galve et al[41]	50	1 (2)	1.2

[a] The Spiering study was conducted in 2 parts and is represented in the table as parts A and B.
[b] The Mowry and Hartman study was conducted in 3 parts and is represented in the table as parts A, B, and C.

contributing factor to analyze how these factors affected phlebitis rates.

Infusion Concentration

Phlebitis rates were higher with amiodarone concentrations of 1.8 mg/mL or greater[3,25,29,33,37,38] than with an amiodarone concentration of 1.2 mg/mL[6,41] (OR, 0.09; 95% CI, 0.05-0.18; $P < .001$; Table 3). The 1.8 mg/mL or greater concentration was used in 7 studies; the 1.2 mg/mL concentration was used in 2 studies. The study by Mowry and Hartman[6] was conducted in 3 parts. The 1.8 mg/mL concentration was used in parts A and C; the 1.2 mg/mL concentration was used in part B. The phlebitis rate in part B was significantly lower than in parts A and C.

Total Dose

The total dose of intravenous amiodarone administered to patients in the studies ranged from 0.25 g to 4.8 g. For doses of 1 g and higher, increasing doses were not associated with increasing phlebitis rates (Table 4). For example, the phlebitis rate in patients receiving a dose of 4.8 g in 1 study[40] was lower than phlebitis rates of patients receiving doses of only 1.05 g in other studies.[25,29,38,39] However, doses of 0.45 g or less[40,45,46] were associated with lower phlebitis rates than were doses greater than 1 g (OR, 0.02; 95% CI, 0.00-0.16; $P = .002$).[25,29,34-39,42-44,47,48] Norton et al[37] also showed that initial phlebitis rates were considerably lower when patients received an initial dose of less than 1 g of intravenous amiodarone, but once the total dose reached 3 g, phlebitis rates increased significantly by 40% ($P < .001$). In a 2-part study by Kowey et al,[40] the total dose in part A was 4820 mg; the total dose in part B was only 246.35 mg. Part A participants had a phlebitis rate of 2.86%, whereas part B participants had a phlebitis rate of 0%.

Infusion Rate

Intravenous amiodarone infusion rates ranged from 0.1 mg/min to 2 mg/min (Table 5). Infusion rate and phlebitis rate were not correlated. For instance, participants in the study by Cotter et al[43] received an infusion rate of 2 mg/min and had a lower phlebitis rate (16%) than participants in some studies with infusion rates of less than 0.75 mg/min.[29,34,36,38,39]

Infusion Duration

Infusion duration ranged from 1-minute boluses to 48-hour continuous infusions. We found no overall relationship between infusion duration and phlebitis rate. For example, phlebitis rates in some studies with 24-hour infusions[29,34,36-39,42-44] were higher than in studies with 48-hour infusions.[40,48] An exception was the study by Norton et al,[37] in which phlebitis significantly increased as infusion duration increased ($P = .03$). Studies in which amiodarone was administered as a bolus[45,46] yielded significantly lower phlebitis rates (< 2%) than studies in

Table 4 Phlebitis rates and total doses of intravenous amiodarone

Source	No. of patients	Patients with phlebitis, No. (%)	Total dose of amiodarone, g	Comments
Spiering[29] (part A)[a]	34	29 (85)	1.05	
Spiering[29] (part B)[a]	34	13 (38)	1.05	
Boyce and Yee[25]	12	8 (67)	1.05	
Bagheri-Nesami et al[38]	36	21 (58)	1.05	
Norton et al[37]	105	42 (40)	3	
Kochiadakis et al[36]	33	12 (36)	1.7	Minimal dose[b]
Shützenberger et al[39]	26	7 (27)	1.05	
Kreiss et al[34]	20	5 (25)	1.2	
Vietti-Ramus et al[42]	44	9 (20)	1.4	Mean[b]
Vardas et al[44]	108	17 (16)	1.7	Minimal dose[b]
Cotter et al[43]	50	8 (16)	3	
Xanthos et al[47]	113	11 (10)	1.3	
Hilleman and Spinler[35]	550	44 (8)	1.2	Mean[b]
Halonen et al[48]	157	11 (7)	2	Maximum dose[b]
Kowey et al[40] (part B)[a]	105	3 (3)	4.8	
Galve et al[41]	50	1 (2)	1.5	Minimal dose[b]
Hofmann et al (2006)[46]	50	1 (2)	0.45	
Hofmann et al (2004)[45]	78	0 (0)	0.45	
Kowey et al[40] (part A)[a]	94	0	0.25	

[a] The Spiering and Kowey et al studies were conducted in 2 parts and represented in the table as parts A and B.
[b] For some studies, the author used mean or approximate total dose for this analysis.

which amiodarone was administered as continuous infusions[6,25,29,34-40,42-44,47,48] (OR, 0.05; 95% CI, 0.01-0.33; $P = .002$; Figure 1). Additionally, in the study by Norton et al,[37] phlebitis rates were lower when amiodarone was administered in boluses ($P < .05$).

Effectiveness of Nursing Guidelines

The absence of nursing guidelines increased phlebitis rates (OR, 0.13; 95% CI, 0.09-0.20; $P < .001$). Studies in which guidelines were implemented[6,29] had phlebitis rates ranging from 5.8% to 38%. Studies with no nursing guidelines[25,29,33,37] had phlebitis rates ranging from 40% to 85% (Table 6). The Spiering[29] study was divided into 2 parts. Nursing guidelines were not used in part A but were used in part B. The phlebitis rate was 85% in part A and fell to 38% in part B after guidelines were introduced.

Absence or Presence of In-line Filter

Studies in which in-line filters were used[6,25,29] had phlebitis rates ranging from 5.8% to 67%, whereas those in which no filters were used[3,29,37] had phlebitis rates ranging from 13.9% to 85%. Phlebitis rates were significantly higher in the absence of filter use (OR, 0.23; 95% CI, 0.15-0.34; $P < .001$; Figure 2).

Secondary Outcome

Our secondary outcome was phlebitis severity measured with the Infusion Nurses Society phlebitis scale.[20] Seven studies reported phlebitis severity, and some used different scales.[25,38] To facilitate analysis, we converted all of these to the Infusion Nurses Society scale.[20] Other studies[34,42,45-46] did not specify a phlebitis scale or grade but did report phlebitis symptoms, so we graded phlebitis on the basis of the descriptions (Table 1). The most common phlebitis grade overall was 0 (no phlebitis), followed by grades 1, 2, 3, and 4. Spiering[29] indicated that phlebitis severity decreased when nursing guidelines were implemented, and only 1 episode of grade 1 phlebitis was reported in the 2 studies of bolus administration.[45,46]

Table 5 Phlebitis rates and intravenous amiodarone infusion rates

Source	No. of patients	Patients with phlebitis, No. (%)	Infusion rate, mg/min
Spiering[29] (part A)[a]	34	29 (85)	0.62
Boyce and Yee[25]	12	8 (67)	0.62
Bagheri-Nesami et al[38]	36	21 (58)	0.62
Norton et al[37]	105	42 (40)	0.75
Spiering[29] (part B)[a]	34	13 (38)	0.62
Kochiadakis et al[36]	33	12 (36)	1
Shützenberger et al[39]	26	7 (27)	0.73
Kreiss et al[34]	20	5 (25)	0.63
Vietti-Ramus et al[42]	44	9 (20)	0.97
Vardas et al[44]	108	17 (16)	1.2
Cotter et al[43]	50	8 (16)	2
Slim et al[3]	36	5 (14)	0.62
Mowry and Hartman[6] (part C)[b]	69	16 (23)	0.5
Mowry and Hartman[6] (part A)[b]	97	10 (10)	0.5
Xanthos et al[47]	113	11 (10)	0.69
Hilleman and Spinler[35]	550	44 (8)	0.62
Halonen et al[48]	157	11 (7)	0.69
Mowry and Hartman[6] (part B)b	173	10 (6)	0.5
Kowey et al[40] (part B)[a]	105	3 (3)	0.75
Galve et al[41]	50	1 (2)	0.83
Kowey et al[40] (part A)[a]	94	0	0.1

[a] The Spiering and Kowey et al studies were conducted in 2 parts and represented in the table as parts A and B.
[b] The Mowry study was conducted in 3 parts and represented in the table as parts A, B, and C.

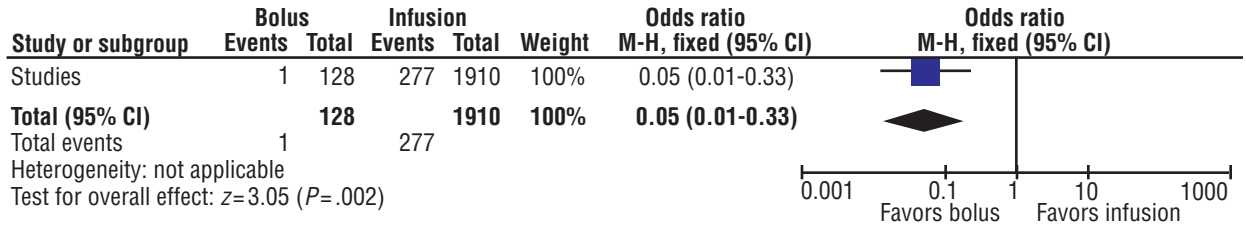

Figure 1 Continuous infusion versus bolus forest plot.

Abbreviation: M-H, Mantel-Haenszel test.

Quality Appraisal Outcomes

We appraised the quality of the systematic review[35] by using the PRISMA 2009 checklist.[70] Most steps were completed, but randomization details and the data collection process were not described and the data extraction tool was not validated. The remaining studies were valid and of high quality, with overall Evidence-based Librarianship Checklist scores ranging from 79% to 96%. Authors of 14 studies[3,33,34,36,39-48] failed to clarify whether their data collection tools were validated. Testing of data collection tools is essential because it confirms whether the appropriate data are collected in a valid and reliable manner.[71]

Table 6 Phlebitis rates and use of nursing guidelines

Source	No. of patients	Phlebitis present, No. (%)	Nursing guidelines used
Spiering[29] (part A)[a]	34	29 (85)	No
Boyce and Yee[25]	12	8 (67)	No
Martinho and Rodrigues[33]	40	22 (55)	No
Norton et al[37]	105	42 (40)	No
Spiering[29] (part B)[a]	34	13 (38)	Yes
Mowry and Hartman[6] (part C)[b]	69	16 (23)	Yes
Mowry and Hartman[6] (part A)[b]	97	10 (10)	Yes
Mowry and Hartman[6] (part B)[b]	173	10 (6)	Yes

[a] The Spiering study was conducted in 2 parts and represented in the table as parts A and B.
[b] The Mowry study was conducted in 3 parts and represented in the table as parts A, B, and C.

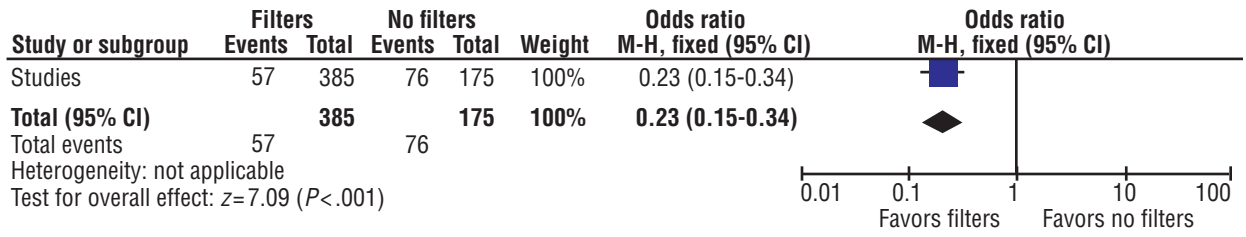

Figure 2 Filter versus no filter.

Abbreviation: M-H, Mantel-Haenszel test.

Martinho and Rodrigues[33] used a data collection tool based on a semistructured script, which is open to interpretation—inconsistencies that could introduce bias.[61] Three studies[25,37,38] had robust data collection tools; their phlebitis scales were validated, piloted, and approved by nursing experts. We assessed the studies for detection, selection, performance, reporting, and attrition bias.

Detection Bias. Our systematic review included 2 double-blinded studies[38,40] and 3 single-blinded studies,[36,41,47] which helped eliminate detection bias. However, the remaining studies were not blinded. Authors of 2 studies[6,25] mentioned that staff members were involved in data collection but did not confirm whether they were also involved in caring for the participants.

Selection Bias. Five retrospective,[3,6,29,33,37] 3 prospective,[34,42,45] and 1 descriptive[25] study used nonprobability sampling techniques, which introduce selection bias.

Performance Bias. Two double-blinded studies[38,40] and 3 single-blinded studies[36,41,47] helped eliminate performance bias. Hofmann et al[46] confirmed that randomization was performed by using sealed envelopes but did not state whether the study was single- or double-blinded. Likewise, authors of 3 randomized controlled trials[39,43,44] did not confirm whether their studies were blinded. The remaining studies were not blinded.[3,6,25,29,33,34,37,42,45,48]

Reporting Bias. All included studies reported data on the outcomes under investigation.[3,6,25,29,33-48]

Attrition Bias. Shützenberger et al[39] withdrew 1 patient because of an adverse event. Kowey et al[40] stated that 14% of participants died, and Halonen et al[48] stated that 1 person died during treatment. In addition, 10 studies[3,6,25,29,33,37,38,41,46,47] did not report attrition. Six studies confirmed that there was no attrition.[34,36,42-45]

Discussion

The wide range in phlebitis rates among studies was partly due to the different contributing factors. Identifying the contributing factors that affected phlebitis rates

was difficult because more than 1 of these factors were often present. For example, the phlebitis rate in the study by Kowey et al[40] was 0%. In that study both the amiodarone infusion rate (0.1 mg/min) and the total amiodarone dose (0.25 g) were low, so ascertaining which factor affected the phlebitis rate was challenging. However, among all of the included studies, total doses greater than 1 g were associated with increased phlebitis rates.[25,29,34-39,42-44,47,48]

Studies in which in-line filters were used[6,29] had lower phlebitis rates than did studies in which filters were not used. However, in these studies, nursing guidelines (which reduce phlebitis rates) were also used. It was therefore initially difficult to distinguish if nursing guidelines or filters improved phlebitis rates. In the study by Boyce and Yee,[25] filters but no nursing guidelines were used, and the authors stated that filters made no difference in reducing their phlebitis rates. Therefore, their high phlebitis rate (67%) could be due to the absence of nursing guidelines. The Boyce and Yee study[25] had a small sample size, inhibiting the ability to draw reliable conclusions. The Spiering[29] study clearly demonstrated the benefits of nursing guidelines. Even though filters were used in parts A and B of their study, the phlebitis rate dramatically decreased (from 85% to 38%) in part B, when nursing guidelines were introduced. On the other hand, Slim et al[3] noted that after their study was completed, they introduced filters and their phlebitis rates decreased. The study by Martinho and Rodrigues[33] confirmed that the absence of nursing guidelines was an important extrinsic factor in increasing phlebitis rates. In summary, both nursing guidelines and filters could individually and collectively reduce phlebitis rates.

Inline filters and nursing guidelines have been shown to reduce phlebitis rates.

Different study designs meant that a meta-analysis was impossible because studies were not homogeneous.[67] Despite this heterogeneity, a subanalysis of groups of studies focusing on the same contributing factors was possible. These results should be viewed with caution because the wide range in phlebitis rates could also be due to different practice standards among the studies. The study by Bagheri-Nesami et al[38] had a high phlebitis rate (58%) even though the infusion rate was only 0.62 mg/min. This high phlebitis rate may have been due to the infusion site. Patients in this study received amiodarone infusions via veins in the hand, which tend to be fragile and prone to phlebitis.[28] Norton et al[37] also stated that some peripheral catheters were placed in hand veins, which could be a reason for their 40% phlebitis rate.

Peripheral venous catheter site and catheter size were not always noted, and a reasonable assumption is that these factors were inconsistent throughout studies. Spiering[29] suggested that 22-gauge catheters yielded the lowest phlebitis rates, yet Boyce and Yee[25] found that catheter size and peripheral venous catheter site made no difference to phlebitis rates. Dedicated catheter use was also inconsistent within the studies, potentially affecting phlebitis rates. Dedicated catheters were used in the studies by Spiering[29] and Mowry and Hartman,[6] but the remaining studies were not consistent in this regard. Martinho and Rodrigues[33] highlighted that the absence of dedicated catheter use in their study increased phlebitis rates.

Different study designs yielded variation in phlebitis rates. The observation and descriptive studies introduced an element of observer bias. Spiering[29] and Mowry and Hartman[6] stated that it was hard to distinguish if reduced phlebitis rates were due solely to the improvements made or due to heightened awareness during their studies. The 5 retrospective studies[3,6,29,33,37] introduced the risk of recall bias.[61] Retrospective data can be incomplete or subjective because the data were not originally collected for research purposes.[61] Norton et al[37] and Boyce and Yee[25] highlighted retrospective data collection as a study limitation. In the 3 prospective studies,[34,42,45] data were collected as they became available, yielding more meaningful data specific to the research question.[61]

Different sampling techniques introduced an element of selection, performance, and detection bias, which is likely to have contributed to the variation in phlebitis rates.[61,71] The wide range in phlebitis rates may also have arisen because some studies' sample sizes were too small to draw conclusions in isolation.[25,34,39] However, despite all of these variations, the studies included in our systematic review had excellent internal validity. Pooling the studies for analysis increased the overall power of evidence.[56,62] Furthermore, the demographic profile of patients within the included studies was homogeneous. Most patients were older than 60 years old. Martinho and Rodrigues[33] suggested that patient age is an intrinsic cause of phlebitis; older patients have fragile veins.

Implications for Nurses

Nurses should be aware of the potential for phlebitis, including the specific phlebitis rates for their clinical areas, and be mindful of the associated contributing factors. Understanding the contributing factors that could potentially increase phlebitis risk can prompt nurses to be vigilant and take immediate action to avoid further progression.[21,25] Frequent routine assessment and documentation of phlebitis grades and nursing interventions are important.[21,25,31] Introducing nursing guidelines and in-line filters may reduce the phlebitis rate, potentially reducing costs and shortening hospital stays.[3,25]

Conclusions

Our review revealed a wide range in phlebitis rates (0%-85%) that was apparently dependent on certain contributing factors. An increase in amiodarone concentration was associated with an increase in phlebitis rate. Total intravenous amiodarone doses of 0.45 g or less were associated with lower phlebitis rates than were doses greater than 1 g. We did not identify a relationship between phlebitis rate and infusion rate or infusion duration. However, the 2 studies in which amiodarone was administered as an intravenous bolus[45,46] reported extremely low phlebitis rates and minimal severity compared with studies in which amiodarone was administered as a continuous infusion.[6,25,29,34-40,42-44,47,48] The most common phlebitis severity grade was 0 (no phlebitis), followed by grades 1, 2, 3, and 4. The results of this systematic review suggest that using nursing guidelines and in-line filters reduces phlebitis rates, with 1 study also showing a reduction in severity. The evidence is not robust, however, because it is based on 2 retrospective studies and 1 descriptive study.[6,25,29] Increased awareness, monitoring, and education during the course of these studies probably also contributed to reduced phlebitis rates.

The wide variations in phlebitis rates were due not only to contributing factors but also to heterogeneity among studies in elements such as peripheral venous catheter location, catheter size, and dedicated catheter use. The variations in methodological approach limit the overall certainty of the evidence, highlighting the need for further research, preferably a large, well-designed randomized controlled trial. Nonetheless, this systematic review shows that educating nurses about potential contributing factors for amiodarone-induced phlebitis and implementing nursing guidelines and in-line filters will help reduce phlebitis rates. Nursing guidelines should also emphasize that higher amiodarone infusion concentrations and total administered doses require increased surveillance. CCN

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None reported.

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