ESC European Society of Cardiology

European Journal of Cardiovascular Nursing (2023) **00**, 1–8
https://doi.org/10.1093/eurjcn/zvad003

ORIGINAL RESEARCH

Amiodarone-induced phlebitis: incidence and adherence to a clinical practice guideline

Gunhild Brørs [1]*, Kari Hanne Gjeilo [1,2,3], Tonje Lund [1], Karin Skevik [1], Elizabeth Aa [4], Lise Husby Høvik [3,5], Torhild Skarsvaag [2], and Ole Christian Mjølstad [1,6]

[1]Clinic of Cardiology, St. Olavs Hospital, Trondheim University Hospital, Prinsesse Kristinas gate 3, 7030 Trondheim, Norway; [2]Department of Cardiothoracic Surgery, St. Olavs Hospital, Trondheim University Hospital, Prinsesse Kristinas gate 3, 7030 Trondheim, Norway; [3]Department of Public Health and Nursing, Norwegian University of Science and Technology, P.O. Box 8900, Torgarden, 7491 Trondheim, Norway; [4]Department of Clinical Pharmacology, St. Olavs Hospital, Trondheim University Hospital, Prinsesse Kristinas gate 3, 7030 Trondheim, Norway; [5]Department of Anaesthesia and Intensive Care, St. Olavs Hospital, Trondheim University Hospital, Prinsesse Kristinas gate 3, 7030 Trondheim, Norway; and [6]Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, P.O. Box 8900, Torgarden, 7491 Trondheim, Norway

Received 29 June 2022; revised 22 December 2022; accepted 31 December 2022; published 3 January 2023

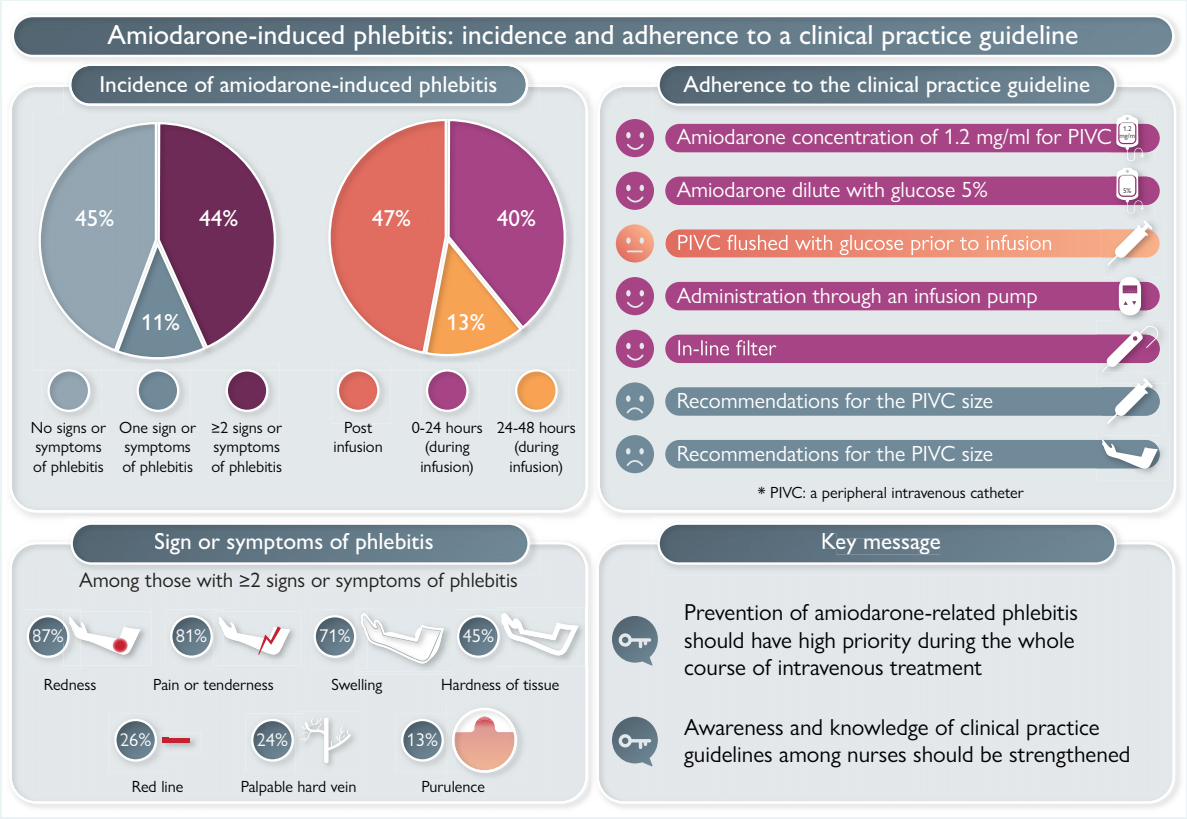
Aims Intravenous amiodarone is an irritant of peripheral blood vessels with phlebitis as an adverse effect. The aims were to determine the incidence of intravenous amiodarone-induced phlebitis, to describe adherence to a clinical practice guideline, and to determine how characteristics were distributed between those with and without phlebitis.

Methods and results A prospective observational study was conducted. Adult patients treated with amiodarone through a peripheral intravenous catheter (PIVC) or a central venous catheter were included. PIVC characteristics were measured using the PIVC mini questionnaire. Patients with ≥two signs of phlebitis were categorized as having phlebitis. Adherence to the clinical practice guideline was registered on a standard abstract sheet. Data were collected from the amiodarone start-up to 2 days after the amiodarone was discontinued. In total, 124 patients with amiodarone infusions were observed, of which 69% were administered via a PIVC. The phlebitis rate was 44%. Fifty-three per cent developed amiodarone-induced phlebitis during the infusion phase, while 47% presented phlebitis during the post-infusion phase. The three most observed signs or symptoms of phlebitis were redness (87%), pain (81%), and swelling (71%). The most commonly used PIVC site was the elbow, and 35% of the PIVCs were large (18 gauge), which was the last preferred site and size according to the clinical practice guideline.

Conclusion A large proportion of the patients developed amiodarone-induced phlebitis. The adherence to the clinical practice guideline was not optimal according to the PIVC recommendations. Prevention of amiodarone-induced phlebitis should have high priority to reduce patient harm.

* Corresponding author: Gunhild Brørs, Clinic of Cardiology, St. Olavs Hospital HF, PO Box 3250 Torgarden, NO-7006 Trondheim, Norway, Tel: +0047 412 59 563, Email: gunhild.brors@stolav.no

Graphical Abstract



Keywords Intravenous amiodarone • Cardiac arrhythmias • Phlebitis • Clinical practice guideline

Novelty

- Prevention of amiodarone-induced phlebitis should have high priority during the whole course of intravenous treatment, including the post-infusion phase.
- Assessing the adherence to clinical in-hospital guidelines is important to improve clinical practise and reduce patient harm.
- This study indicated that the phlebitis rate could be due to the choice of PIVC site and size, which underpin the importance of new measures within this area to overcome barriers to guidelines implementation within real world settings.
- This study expands the current knowledge to help inform the future development of a tailored clinical in-hospital guideline based on both theory and research evidence.

Introduction

Intravenous amiodarone remains an established treatment for supraventricular and ventricular arrhythmias.[1,2] However, intravenous amiodarone is an irritant of blood vessels with phlebitis as a well-known adverse effect of peripheral administration. The incidence of amiodarone-induced phlebitis has been reported to be up to 85%.[3,4] Administration via a central venous catheter (CVC) may be preferred.[5] However, this route is more complicated and not always feasible in an acute care setting, and a peripheral intravenous catheter (PIVC) is often the preferred choice. Currently available research on amiodarone-induced phlebitis is sparse, and the sample sizes are small.[3] Additionally, the knowledge of post-infusion phlebitis is limited, and phlebitis rates are probably hugely underreported.[6]

Phlebitis is defined as an inflammation of the tunica intima of the vein and is precipitated by mechanical, chemical or infective causes. Clinical signs or symptoms are pain, tenderness, oedema, and erythema.[7] Most cases of phlebitis from PIVCs are unrelated to infection.[8] However, phlebitis can, in some cases, lead to septic infection, which is a critical condition involving longer admissions, additional health care costs, discomfort, increased morbidity, and mortality.[9,10] Additionally, PIVC-related phlebitis with subsequent bloodstream infection followed by an infective endocarditis is a severe complication. Healthcare-associated infective endocarditis represents up to 30% of all cases of infective endocarditis, representing an important health problem.[11] Increased knowledge about factors that reduce amiodarone-induced phlebitis can enhance nursing practice and improve patient safety.

There are well-known chemical and mechanical risk factors for amiodarone-induced phlebitis.[3] Understanding the mechanisms behind amiodarone-induced phlebitis is crucial to prevent patient harm. Therefore, it is recommended to consider all primary and secondary factors that increase the risk of phlebitis.[12] The existing evidence on amiodarone-induced phlebitis highlights factors such as amiodarone concentration,[3] glucose as the only choice of diluent,[13] use of an infusion pump,[4] and an in-line filter to protect against crystallization.[3] Moreover, the risk of phlebitis is related to the PIVC insertion technique and maintenance, which can thus be reduced by adapting the appropriate PIVC size and site.[14,15] Based on evidence from previous studies,[3,4,15,16] a clinical practice guideline to prevent amiodarone-induced phlebitis was developed and implemented at a large university hospital in Norway. However, implementing such in-hospital guidelines in clinical practice is often challenging.[17] There are numerous barriers to guideline implementation within real-world settings, which have been categorized as; the guidelines themselves, patient, personnel, and organizational and external barriers.[18] For instance, knowledge, attitudes, and beliefs are known barriers to the implementation of evidence-based practice among nurses.[18,19] Therefore, identifying the fidelity, such as the degree to which the clinical practice guideline is implemented as intended and how this contributes to important health outcomes, is highly recommended.[20] However, only two previous studies in which nursing guidelines were implemented have assessed the incidence of amiodarone-induced phlebitis,[3] neither of which evaluated the nurses' adherence to the guidelines.

The aims of our study were; (i) to determine the incidence of intravenous amiodarone-induced phlebitis, (ii) to describe adherence to the clinical practice guideline implemented in a hospital practice setting, and iii. to determine how characteristics were distributed between those with and those without amiodarone-induced phlebitis.

Methods

Design and sample

A prospective descriptive observational study was conducted at St. Olavs, Trondheim University Hospital, Norway. Four different clinics participated in the study, including the majority of patients being treated for arrhythmias, and thereby most amiodarone infusions. Adult patients (age ≥18 years) being treated with intravenous amiodarone through a PIVC or CVC from March through May 2021 were included in the study. The study included patients with arrhythmias admitted to both medical and surgical clinics. The reporting of this study follows the recommendations of the Standards for Quality Improvement Reporting Excellence.[21] This quality improvement project was evaluated by the Data Protection Officer at St. Olavs, Trondheim University Hospital, Norway and it complied with the EU General Data Protection Regulation (Data Protection Impact Assessment—DPIA ID: 329). The data were collected anonymously and could not be linked to the patients' identities. The investigation conforms with the principles outlined in the Declaration of Helsinki.[22]

Data collection

All nurses at the clinics were instructed to identify eligible patients and to collect data in an abstraction sheet. Two dedicated research nurses performed a daily review of patients being treated with an amiodarone infusion and ensured that they were registered in an abstraction sheet. They also reviewed the abstraction sheet during the registration. In case of discrepancies in the abstraction sheet, they contacted the responsible nurse and corrected the registration. Data were collected 24/7, from the amiodarone start-up to 2 days after the intravenous amiodarone was discontinued.

Measures

A standard data abstraction sheet was developed by the interdisciplinary project group consisting of clinical nurses, nurse researchers, a cardiologist, and a clinical pharmacist. The outcome variables used in the abstraction sheet assessed the incidence of phlebitis and how well the clinical practice guideline was adhered to (*Figure 1*).

Demographic and clinical data collected included age, gender, unit of admission, and indication of amiodarone. Adherence to the clinical practice guideline was registered. PIVC characteristics were measured using the peripheral intravenous catheter mini questionnaire (PIVC-miniQ).[23] The PIVC-miniQ is a validated tool containing four main assessment areas (16 items) relating to clinical observations of the insertion site, dressing and documentation. The first area (nine items) reflects phlebitis-related signs and symptoms, the second area (five items) reflects PIVC dressing and IV connection related to PIVC failure, the third area reflects the process of documentation (one item), and the final area (one item) reflects indication for PIVC.[23] In this study, we used eight out of the nine items from the first assessment area reflecting signs or symptoms of phlebitis. The item 'Partial/complete dislodgement' was excluded because it does not measure phlebitis-related signs and symptoms (*Figure 1*). Each item was categorized as existing if a sign or symptom of phlebitis was observed (1 point) or non-existing (0 points) giving a possible score range from 0–8. The total score for the selected items from the PIVC-miniQ was further categorized as the presence of no signs or symptoms of phlebitis (0 points), one sign or symptom of phlebitis (one point), and two or more signs or symptoms of phlebitis (≥2 points). The latter category was defined as amiodarone-induced phlebitis. The PIVC-miniQ is shown to be a reliable and feasible tool to measure PIVC problem rates.[23,24]

Data analysis

Descriptive statistics, expressed as counts or percentages for categorical variables and as means and standard deviation (SD) for continuous variables, were used to describe the characteristics of all the patients treated with amiodarone, those with PIVC and CVC and for those who developed amiodarone-induced phlebitis. Pearson's χ^2 tests were used to determine the frequency distribution and describe how categorical variables are distributed between those with and without amiodarone-induced phlebitis. For continuous variables, we used the independent sample *t*-test to compare means between those with and without amiodarone-induced phlebitis. Data were analysed using IBM SPSS (Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp).

Results

Demographic and clinical data

In total, 124 patients treated with intravenous amiodarone were included. The mean age was 70.6 years (SD 13.5), and two-thirds of the patients were males. Atrial fibrillation was the main reason for treatment in most patients. Half of the patients were admitted to a hospital ward, while 37% were admitted to an intensive care unit. Of all the amiodarone infusions, 69% ($n = 86$) were administered via a PIVC. Moreover, a larger proportion of the patients treated with amiodarone via a PIVC received amiodarone for longer than 24 h, compared with those with a CVC (21% vs. 3%) (*Table 1*).

Incidence of phlebitis

Among the patients who received amiodarone via a PIVC, the rate of amiodarone-induced phlebitis (≥2 signs or symptoms of phlebitis) was 44% (*Figure 2*). Additionally, one in 10 had one sign or symptom of phlebitis, such as pain or tenderness, redness, and swelling. Thirty-five per cent of the patients who received amiodarone infusion ≤24 h developed phlebitis, while 75% of those treated with amiodarone infusion between 25 and 48 h, and 100% of those treated with infusion >48 h developed phlebitis (*Table 1*). Overall, 40% of the patients developed amiodarone-induced phlebitis during the first 24 h, and almost half of the patients treated with amiodarone infusion developed phlebitis during the post-infusion phase (*Figure 2*).

The mean age of those with amiodarone-induced phlebitis was 71 years (SD 16) and almost 60% were males (*Table 1*). However, there was no relationship between socio-demographics and the development

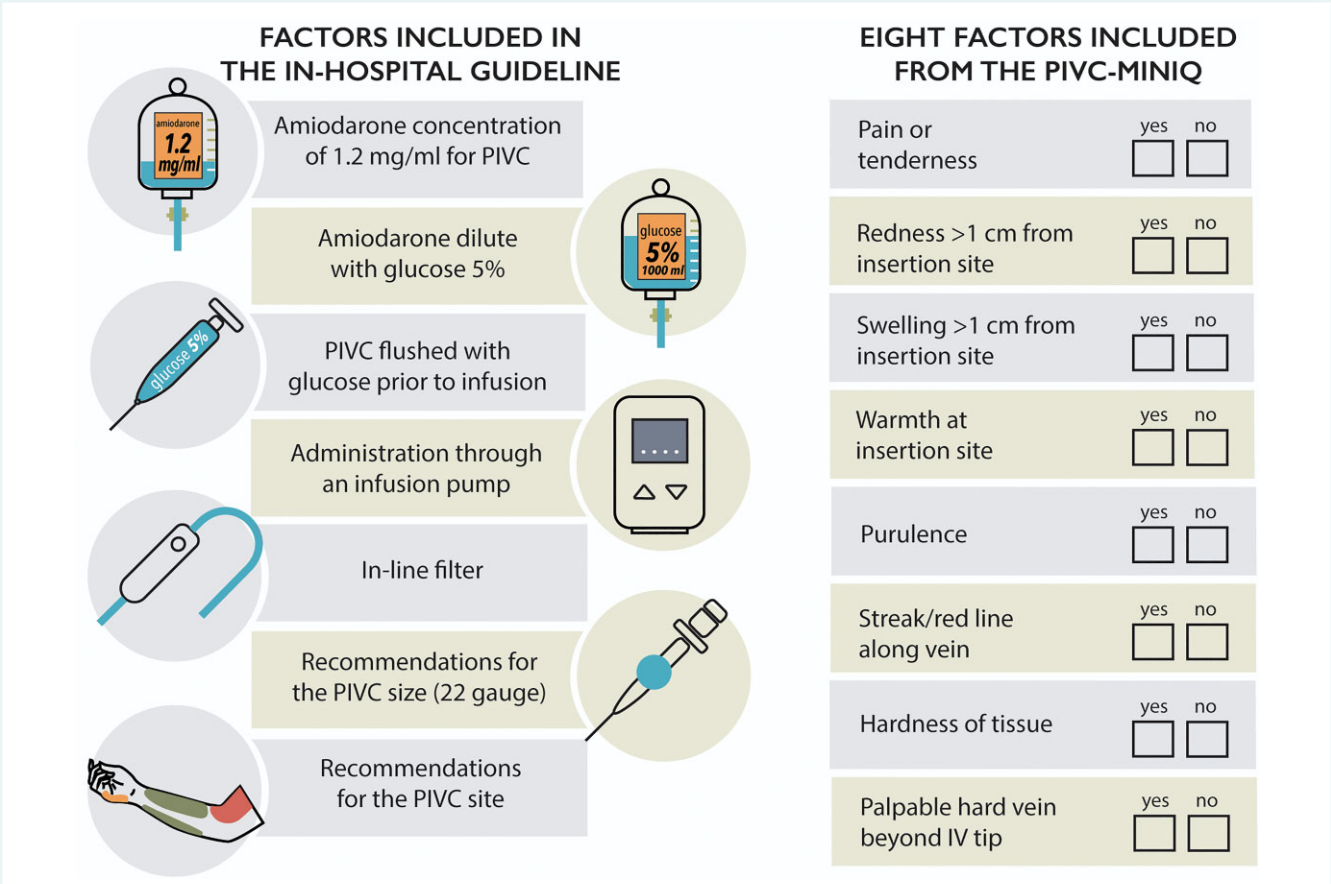


Figure 1 An overview over factors included in the clinical practice guideline at St. Olavs, Trondheim University Hospital and the Catheter mini questionnaire (PIVC-miniQ).[23] Abbreviations: PIVC, peripheral intravenous catheters; IV, intravenous.

of amiodarone-induced phlebitis (*Table 2*). Among those who developed phlebitis, two-thirds received amiodarone infusion for 24 h or less, and one-third for 25–48 h. Moreover, 42% of those with a medium PIVC (20 gauge) and 37% of those with a large PIVC (18 gauge) developed phlebitis (*Table 1*). PIVCs placed in the elbow or forearm accounted for four out of five of the phlebitis cases (*Table 1*). There was no statistical relationship between the size and site of the PIVC and phlebitis development (*Table 2*). However, *Table 3* showed that 26% of the 38 patients who developed amiodarone-induced phlebitis had a large PIVC (18 gauge) placed in the elbow.

Almost 90% of those who developed ≥2 signs or symptoms of amiodarone-induced phlebitis developed redness, and four out of five developed pain or tenderness. The third most observed sign or symptom was swelling at the PIVC insertion site (*Figure 3*).

Adherence to the clinical practice guideline

The amiodarone concentrations administered in a PIVC were 1.2 and 3.0 mg/mL in a CVC in over 80% of the infusions, which is in accordance with the clinical practice guideline. Two patients received a concentration of 3.0 mg/mL in their PIVC, of which both had ≥2 signs or symptoms of phlebitis. A dedicated in-line filter was used in four out of five infusions administered via a PIVC. The nurses reported to have flushed the PIVCs with glucose prior to starting the infusion in over 70% of the patients. This is not a satisfactory result, and almost one third of the patients were not protected against possible crystallization, which is considered a risk factor for amiodarone-induced phlebitis. An infusion pump was used for the amiodarone infusion in almost four out of five patients (*Table 1*).

The results indicated poor adherence to the clinical practice guideline recommendations for the PIVC size. Half of the PIVCs were of a medium size (20 gauge), and 35% were of a large size (18 gauge), of which both sizes were associated with a risk of phlebitis in the clinical practice guideline. Only 15% of the PIVCs were small (22 gauge), which was the recommended PIVC size in the clinical practice guideline. Poor adherence also appeared to occur for the recommendations relating to the PIVC site. Most PIVCs were placed in the elbow (35%), which is the last preferred site according to the clinical practice guideline. Thirty per cent of the PIVCs were inserted in the forearm, which should be the preferred site (*Table 1*). Overall, *Table 4* shows that 23% of the large PIVCs (18 gauge) were placed in the elbow, which, according to the clinical practice guideline, indicates a high risk factor for developing phlebitis. The result also shows that only 5% received a PIVC of a small size (22 gauge) placed at the forearm, which is in line with the clinical practice guideline.

Discussion

Despite implementation of an evidence-based clinical practice guideline, 44% of the patients developed amiodarone-induced phlebitis (≥2 signs or symptoms of phlebitis). The findings show that these patients

Table 1 Characteristics of all the patients treated with amiodarone, of those with PIVC and CVC and of those who developed amiodarone-induced phlebitis

	Total ($n = 124$)	PIVC ($n = 86$)	CVC ($n = 38$)	Phlebitis[a,b] ($n = 38$)
Age (year), mean (SD)	70.6 (13.5)	72.2 (13.8)	66.9 (12.0)	71.1 (16.1)
Age, range	22–97	22–97	27–79	22–95
Gender				
Male	75 (63)	46 (54)	29 (81)	21 (57)
Female	44 (37)	37 (43)	7 (19)	16 (43)
Administration methods				
PIVC	86 (69)	–	–	38 (100)
CVC	38 (31)	–	–	–
Hospital treatment unit				
Hospital ward	66 (55)	45 (54)	21 (57)	25 (68)
Intensive care unit	44 (37)	28 (34)	16 (43)	8 (22)
Acute medical unit	5 (4)	5 (6)	–	1 (3)
Operation unit	1 (1)	1 (1)	–	–
Other	4 (3)	4 (5)	–	3 (8)
Indication for amiodarone				
Atrial fibrillation	99 (82)	64 (75)	35 (97)	26 (68)
Ventricular arrhythmias	15 (12)	15 (18)	–	9 (24)
Other arrhythmias	7 (6)	6 (7)	1 (3)	3 (8)
Amiodarone concentration				
0.9 mg/mL	15 (12)	15 (17)	-	9 (24)
1.2 mg/mL	73 (60)	69 (80)	4 (11)	27 (71)
3.0 mg/mL	34 (28)	2 (2)	32 (89)	2 (5)
In-line filter	105 (83)	80 (93)	25 (66)	34 (90)
Flushed the PIVC with glucose	–	61 (72)	–	27 (71)
Infusion pump	98 (79)			29 (76.3)
Time of infusion				
≤24 h	105 (85)	68 (79)	37 (97)	24 (63)
25–48 h	17 (14)	16 (19)	1 (3)	12 (32)
>48 h	2 (1)	2 (2)	–	2 (5)
PIVC site				
Elbow	–	28 (35)	–	15 (39)
Forearm	–	24 (30)	–	14 (37)
Hand back	–	14 (18)	–	6 (16)
Dorsum of the hand	–	11 (14)	–	3 (8)
Foot/ankle	–	2 (3)	–	–
Upper arm	–	1 (1.3)	–	–
PIVC size				
18 gauge	–	29 (35)	–	14 (37)
20 gauge	–	41 (50)	–	16 (42)
22 gauge	–	12 (15)	–	8 (21)

Abbreviations: CVC, central venous catheter; PIVC, peripheral intravenous catheters. The figures are reported in *n* and (%).
[a] ≥ 2 signs or symptoms of phlebitis.
[b]The number (%) for PIVC site and size among those who developed amiodarone-related phlebitis is reported from the time the development of phlebitis took place

sustained harm such as pain, swelling, and redness. These results confirm the high incidence of amiodarone-induced phlebitis. However, using the validated PIVC-miniQ tool made it possible to identify which signs and symptoms the amiodarone infusion inflicted on the patients. Being aware of the harm to patients may impact on adherence to the clinical practice guideline and thus improve patient safety.[18] Moreover,

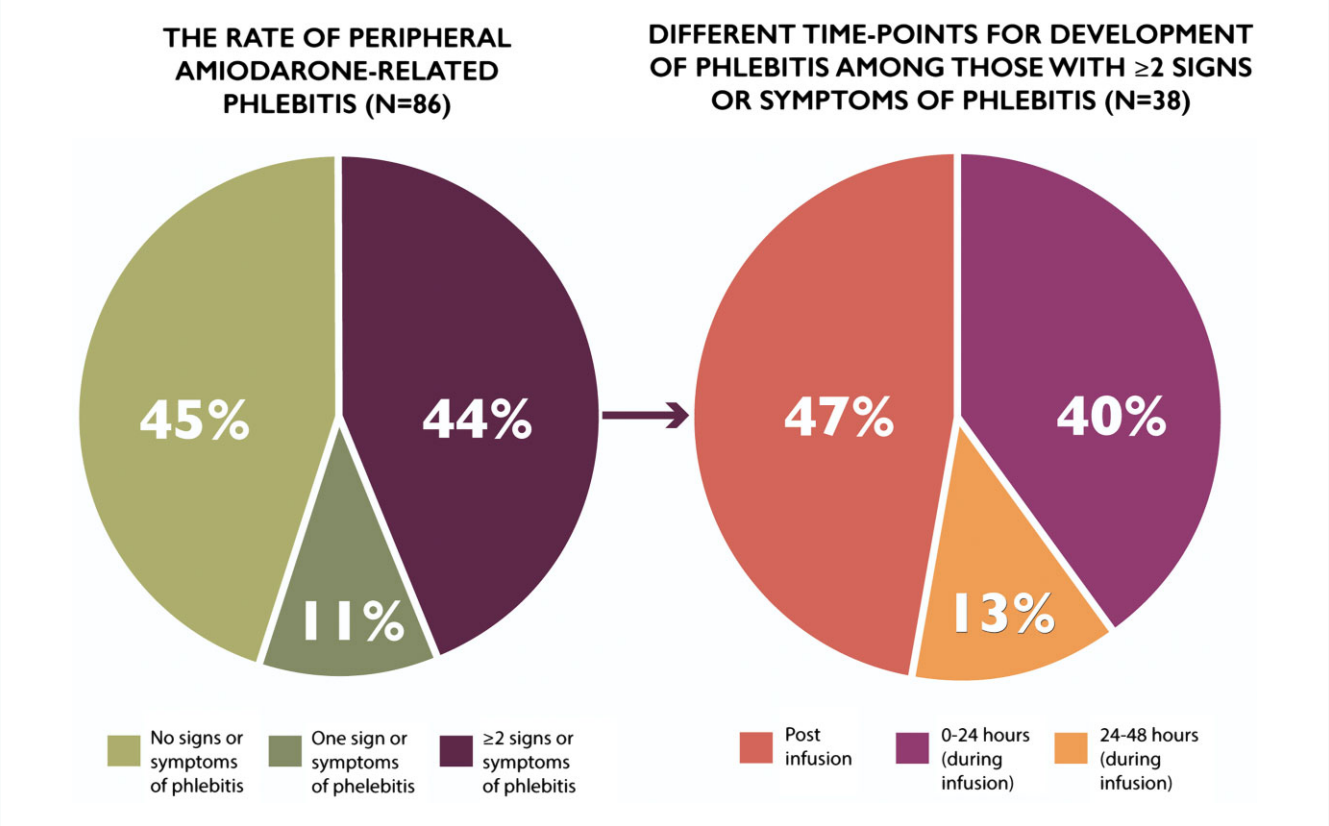


Figure 2 The rate of peripheral amiodarone-induced phlebitis and different time-points for development ≥2 signs or symptoms of phlebitis.

Table 2 Group statistics and correlations between phlebitis and other variables among patients with and without phlebitis

	Pearson χ^2	Mean difference (95% CI)	*P*-value
Age		1.9 (−4.47;8.28)	0.553
Gender[a]			1.000
Hospital treatment unit	8.624		0.071
Indication for amiodarone	1.919		0.383
Amiodarone concentration	4.762		0.092
PIVC site	7.588		0.108
PIVC size	4.905		0.086
In-line filter[a]			0.432
Glucose[a]			0.502

Abbreviations: CI, confidence interval; PIVC, peripheral intravenous catheters.
[a]Fisher's exact test.

Table 3 Different PIVC sites and sizes ($n = 38$) among those who developed amiodarone-induced phlebitis during the infusion phase or during the post-infusion phase

PIVC size PIVC site	18 gauge	20 gauge	22 gauge	Phlebitis
Elbow	10 (26)	5 (13)	–	15 (39)
Hand back	-	4 (11)	2 (5)	6 (16)
Dorsum of the hand	1 (3)	1 (3)	1 (3)	3 (8)
Forearm	3 (8)	6 (16)	5 (13)	14 (38)
Phlebitis	14 (21)	16 (42)	8 (21)	38 (100)

Data are presented as *n* (%). Abbreviation: PIVC, peripheral intravenous catheters.

to our knowledge, this is the first observational study to report a high proportion of patients developing amiodarone-induced phlebitis during the post-infusion phase. This result highlights that prevention of amiodarone-induced phlebitis should have high priority throughout the course of intravenous treatment, including the post-infusion phase. The findings also highlight a discrepancy between the clinical practice guideline and clinical practice, specifically relating to the size and site of PIVCs. This study indicates that the phlebitis rate could be due to the choice of PIVC site and size, which underpins the importance of new measures in this area to overcome barriers to guideline implementation within real-world settings. By expanding current knowledge and awareness of amiodarone-induced phlebitis, this study helps inform the future development of a tailored clinical in-hospital guideline to increase patient safety. However, to overcome the gaps in nurses' knowledge, familiarity and awareness of the clinical practice guideline, strategies and educational

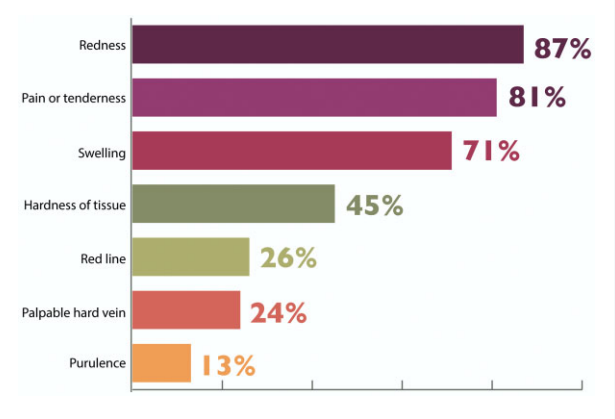


Figure 3 Symptoms of phlebitis among those with ≥2 signs or symptoms of phlebitis ($n = 38$).

Table 4 An overview over PIVC size and site ($n = 78$ valid cases)

PIVC size PIVC site	18 gauge	20 gauge	22 gauge	Total
Elbow	18 (23)	9 (12)	–	27 (35)
Hand back	1(1)	9 (12)	4 (5)	14 (23)
Dorsum of the hand	3 (1)	6 (8)	2 (3)	11 (14)
Forearm	6 (8)	13 (17)	4 (5)	23 (30)
Foot/ankle	–	1 (1)	1 (1)	2 (3)
Over arm	–	1 (1)	–	1 (1)
Total	28 (36)	39 (50)	11 (14)	

Data are presented as *n* (%). Abbreviation: PIVC, peripheral intravenous catheters.

activities should be further implemented to facilitate the best quality of care.[18]

There was a trend towards an increasing phlebitis incidence with a longer duration of the amiodarone infusion. A relationship between infusion duration and phlebitis rate has been demonstrated in one previous study.[16] However, a systematic review reported a higher phlebitis rate in patients with <24-h infusion than in patients with <48-hour infusion.[3] Moreover, in the current study, almost half of the patients developed phlebitis during the post-infusion phase. This is in accordance with a previous study, reporting that phlebitis occurs 24–96 h after an infusion.[7] However, this study reported on PIVCs in general and not specifically on amiodarone infusions. This indicates the importance of following up a PIVC site after the amiodarone infusion is terminated, and the PIVC removed.[6] Frequent inspections and early recognition of painful amiodarone-induced phlebitis can enable prompt interventions to minimize patient discomfort and harm.[25] Additionally, it is important to inform patients about to be discharged of the measures they can take if they feel pain along the vein used for amiodarone infusion.[6,7] In addition to the limited knowledge of post-infusion phlebitis, there is a knowledge gap relating to the consequences for patients who develop amiodarone-induced phlebitis in the short and long term. As previously mentioned, most cases of phlebitis from PIVCs are not related to infection.[8] However, it is also well known that phlebitis can lead to septic infection[9,10,16] and infective endocarditis,[11] underpinning the importance of prevention. Amiodarone administered as a bolus has shown lower phlebitis rates than studies in which amiodarone was administered as continuous infusion.[3,16] One previous study also recommended a change to oral amiodarone administration within 24 h, or that amiodarone infusions for more than 24 h may be considered for a CVC.[16] However, this also involves a risk of complications, such as CVC-related bloodstream infections with consequent morbidity, mortality and hospital costs.[26]

The results show a discrepancy between adherence to the clinical practice guideline and the PIVC site and size. This is important due to the trend towards increased rates of phlebitis when the PIVC was placed in the elbow and was of a large size. Although the results are not conclusive, the current study indicates that the phlebitis rate could be due to the choice of PIVC site and size. Larger PIVCs have been observed to be associated with a higher rate of phlebitis, and the smallest size (22 gauge) of PIVC possible for the treatment in question should be selected instead of bigger sizes.[4,15] Additionally, mechanical factors for the development of phlebitis include catheter insertion technique, maintenance, and location.

For peripheral infusion of tissue-damaging medication, it is recommended that the vein selected should be large and intact with good flow-return. According to an international recommendation, a peripheral infusion site should be selected in the following order of preference: forearm (basilica, cephalic and median antebrachial), dorsum of hand, wrist, and antecubital fossa.[14] However, a previous systematic review reported forearm insertion as entailing a risk of developing infusion phlebitis.[27] This reflects similar findings from a previous study reporting a discrepancy between guidelines and clinical practice for anatomical placement of PIVCs.[28] Such a discrepancy could lead to less trust in guidelines from the perspective of nurses, and become a barrier to implementation.[17,19] More research is needed here to determine how the phlebitis rate is associated with PIVC size and site.

Involvement in and assessment of recommendations for changes to practice based on individual nurses' own perception and trust in the evidence, is likely to optimize the implementation strategy.[20] Additionally, leaders and nurses should engage in developing local implementation strategies, such as educational meetings, workshops and educational materials in several formats to address barriers to implementation.[18]

While an in-line filter was used in almost all of the peripheral amiodarone infusions, only 70% flushed the PIVC with glucose prior to infusion. While several measures, such as in-line filters and flushing with glucose, were included in the clinical practice in-hospital guideline, it is not possible to identify the impact of this individual factor on the improved phlebitis rate. However, a systematic review reported that phlebitis rates were significantly higher in the absence of in-line filter use.[3] It is well known that amiodarone can precipitate at the time of administration, which can result in needle-shaped crystals irritating the vein. Additionally, the risk of crystallization increases if amiodarone is mixed with saline or other medications in the same PIVC, which could potentially induce phlebitis.[13] Therefore, an in-line filter[3] and flushing with glucose to protect against crystallization are recommended when administering amiodarone in PIVC.

The amiodarone concentration used was in accordance with the clinical practice guideline in almost all of the infusions. However, two out of 38 patients received a higher concentration (3.0 mg/mL) and both developed phlebitis. Although these numbers are small, they are in line with a previous study reporting a decreased phlebitis rate when the amiodarone concentration was >1.2 mg/mL.[13] There is a well-known relationship between low pH of an infusion and phlebitis development.[12] Amiodarone has an acidic pH level ranging from 3.46 to 4.35.[4,29] A higher phlebitis rate has been reported for amiodarone concentrations of ≥1.8 mg/mL compared with a concentration of 1.2 mg/mL.[3] This indicates that an amiodarone concentration of 1.2 mg/mL could prevent phlebitis, which should be underlined in the clinical practice guideline.

The main strength of this study was the prospective consecutive inclusion of patients administered intravenous amiodarone in a 'real world' setting. In addition, dedicated research nurses ensured that almost all patients in the period in question were included. Moreover, a reliable and validated tool for measuring phlebitis signs and symptoms was used. The study was performed within a single centre, which can be a limitation. However, it was performed within a hospital setting that was affected by the clinical practice guideline, concerned with the target users of intravenous amiodarone. The information on the abstraction sheet could have biased adherence to the clinical practice in-hospital guideline. This could be countered by being given a reminder of the guideline when filling out the instructions on the sheet, for example to use an in-line filter.

Due to the small sample size, we were unable to conduct an analysis to determine predictors (e.g. PIVC size and site) for development of phlebitis. This highlights the need for further research, preferably a larger trial, including several study sites.

Conclusion

The results highlight that prevention of amiodarone-induced phlebitis should have high priority. Due to the high phlebitis rate, treatment with amiodarone must be strongly indicated, and alternative treatment must be considered. Additionally, the results showed a discrepancy in adherence to the clinical practice in-hospital guideline, specifically relating to the PIVC size and site. This highlights the importance of providing trustworthy evidence and involving nurses in an effective implementation process to facilitate the best quality of care. This study expands the current knowledge to help inform the future development of a tailored clinical in-hospital guideline based on both theory and research evidence. Moreover, studies are needed to investigate consequences and harm in long-term follow-up of patients who develop amiodarone-induced phlebitis.

Acknowledgements

The authors acknowledge all the nurses who completed the data collection. The authors thank Lise Blomseth for the development of *Figures 1–3*, and of drafting the graphical abstract.

Funding

The project was funded through a grant from the Central Norway Regional Health Authority.

Conflict of interest: None declared.

Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals who participated.

References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrøm-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373–498.
2. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Van Veldhuisen DJ. 2015 European Society of Cardiology Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death summarized by co-chairs. *Eur Heart J* 2015;**36**:2757–2759.
3. Oragano CA, Patton D, Moore Z. Phlebitis in intravenous amiodarone administration: incidence and contributing factors. *Crit Care Nurse* 2019;**39**:e1–e12.
4. Spiering M. Peripheral amiodarone-related phlebitis: an institutional nursing guideline to reduce patient harm. *J Infus Nurs* 2014;**37**:453–460.
5. Electronic Medicines Compendium. Amiodarone 150 mg/3 mL Concentrate for Solution for Injection/Infusion. https://www.medicines.org.uk/emc/product/8739/smpc#CLINICAL_PRECAUTIONS (04.04.2022)
6. Webster J, McGrail M, Marsh N, Wallis MC, Ray-Barruel G, Rickard CM. Postinfusion phlebitis: incidence and risk factors. *Nurs Res Pract* 2015;**2015**:691934.
7. Macklin D. Phlebitis: A painful complication of peripheral IV catheterization that may be prevented. *Am J Nurs* 2003;**103**:55–60.
8. Mermel LA. Short-term peripheral venous catheter-related bloodstream infections: A systematic review. *Clin Infect Dis* 2017;**65**:1757–1762.
9. McCallum L, Higgins D. Care of peripheral venous cannula sites. *Nurs Times* 2012;**108**:14–15.
10. Saliba P, Hornero A, Cuervo G, Jimenez E, Berbel D, Martos P, Verge JM, Tebe C, Martı´nez-Sa´nchez JM, Shaw E, Gavalda L, Carratala J, Pujol M. Interventions to decrease short-term peripheral venous catheter-related bloodstream infections: impact on incidence and mortality. *J Hosp Infect* 2018;**100**:e178–e186.
11. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL; ESC Scientific Document Group. 2015 ESC guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European society of cardiology (ESC) Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015;**36**:3075–3128.
12. Stranz M, Kastango ES. A review of pH and osmolarity. *Int J Pharm Compd* 2002;**6**:216–220.
13. Mowry JL, Hartman LS. Intravascular thrombophlebitis related to the peripheral infusion of amiodarone and vancomycin. *West J Nurs Res* 2011;**33**:457–471.
14. Buter J, Steele KT, Chung KC, Elzinga K. Extravasation injury from chemotherapy and other non-antineoplastic vesicants. In. UpToDate; 2021.
15. Carroll H, Bennett S. Guideline: Peripheral intravenous catheter (PIVC). In: Health Do, (ed). www.health.qld.gov.au; 2015.
16. Norton L, Ottoboni LK, Varady A, Yang-Lu CY. Phlebitis in amiodarone administration: incidence, contributing factors, and clinical implications. *Am J Crit Care* 2013;**22**:498–505.
17. Beauchemin M, Cohn E, Shelton RC. Implementation of clinical practice guidelines in the health care setting: A concept analysis. *ANS Adv Nurs Sci* 2019;**42**:307–324.
18. Uchmanowicz I, Hoes A, Perk J, McKee G, Svavarsdóttir MH, Czerwińska-Jelonkiewicz K, Janssen A, Oleksiak A, Dendale P, Graham IM. Optimising implementation of European guidelines on cardiovascular disease prevention in clinical practice: what is needed? *Eur J Prev Cardiol* 2020;**28**:426–431.
19. Weng YH, Kuo KN, Yang CY, Lo HL, Chen C, Chiu YW. Implementation of evidence-based practice across medical, nursing, pharmacological and allied healthcare professionals: a questionnaire survey in nationwide hospital settings. *Implement Sci* 2013;**8**:112.
20. Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Implementation research: what it is and how to do it. *BMJ* 2013;**347**:f6753.
21. Davidoff F, Batalden P, Stevens D, Ogrinc G, Mooney S. Publication guidelines for quality improvement in health care: evolution of the SQUIRE project. *Qual Saf Health Care* 2008;**17**:i3–i9.
22. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;**310**:2191–2194.
23. Høvik LH, Gjeilo KH, Lydersen S, Rickard CM, Røtvold B, Damås JK, Solligård E, Gustad LT. Monitoring quality of care for peripheral intravenous catheters; feasibility and reliability of the peripheral intravenous catheters mini questionnaire (PIVC-miniQ). *BMC Health Serv Res* 2019;**19**:636.
24. Shrestha S, Vieler J, Haug NJ, Afset JE, Høvik LH, Lydersen S, Gustad LT. Quality of care for peripheral intravenous catheters (PIVCs) in Nepal: a cross-sectional study on feasibility and inter-rater agreement of the peripheral intravenous catheters-mini questionnaire (PIVC-miniQ) in a tertiary care hospital. *BMJ Open* 2021;**11**:e048370.
25. Higginson R, Parry A. Phlebitis: treatment, care and prevention. *Nurs Times* 2011;**107**:18–21.
26. Gahlot R, Nigam C, Kumar V, Yadav G, Anupurba S. Catheter-related bloodstream infections. *Int J Crit Illn Inj Sci* 2014;**4**:162–167.
27. Lv L, Zhang J. The incidence and risk of infusion phlebitis with peripheral intravenous catheters: A meta-analysis. *J Vasc Access* 2020;**21**:342–349.
28. Berger S, Winchester K, Principe RB, Culverwell E. Prevalence of peripheral intravenous catheters and policy adherence: A point prevalence in a tertiary care university hospital. *J Clin Nurs* 2021;**31**:2324–2330.
29. Goutos I, Cogswell LK, Giele H. Extravasation injuries: a review. *J Hand Surg Eur Vol* 2014;**39**:808–818.