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ORIGINAL RESEARCH

Incidence and Risk Factors of QT Prolongation and Torsades de Pointes following Intravenous Amiodarone Administration for Atrial Fibrillation: A Cohort Study

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Abstract: **Introduction:** Amiodarone has been reported to be associated with QTc interval prolongation and Torsades de pointes (TdP). This study aimed to assess the incidence and identify the risk factors of QTc prolongation and TdP associated with intravenous amiodarone therapy in patients diagnosed with atrial fibrillation (AF). **Methods:** A retrospective cohort study was conducted using electronic health records of Buddhachinaraj Hospital, a tertiary care center in Thailand, between January 2016 and September 2019. The study population comprised patients with AF who received intravenous amiodarone therapy. Incidence and associated risk factors for QTc interval prolongation and TdP were assessed using multivariable logistic regression analysis. **Results:** A total of 2,944 patients were included in the analysis. Among these, 49 cases of intravenous amiodarone-associated QTc interval prolongation or TdP were identified (33 (1.12%) and 16 (0.54%) cases, respectively), corresponding to an overall incidence of 1.66% (95% confidence interval (CI): 1.23 - 2.19). Multivariable analysis revealed that diabetes mellitus (adjusted odds ratio (aOR): 1.85; 95% CI: 1.02 - 3.38; p-value = 0.045), history of stroke (aOR: 3.09; 95% CI: 1.26 - 7.57; p-value = 0.014), use of antipsychotic medications (aOR: 3.07; 95% CI: 1.64 - 5.74; p-value < 0.001), and use of anticholinergic medications (aOR: 3.89; 95% CI: 1.54 - 9.85; p-value = 0.004) were significantly associated with an increased risk of QTc interval prolongation and TdP following amiodarone therapy for AF patients. **Conclusion:** Although the incidence of QTc interval prolongation and TdP related to intravenous amiodarone therapy in patients with AF was relatively low, the risk was significantly elevated in individuals with diabetes mellitus, a history of stroke, or concurrent use of antipsychotic or anticholinergic agents. These findings underscore the importance of vigilant risk assessment and monitoring in clinical practice to mitigate the potential for intravenous amiodarone-induced arrhythmic complications.

Keywords: Administration ; Intravenous; Amiodarone ; Torsades de pointes; Atrial fibrillation

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1. Introduction

Amiodarone is a class III antiarrhythmic medication commonly used to treat various arrhythmias, including both ventricular and supraventricular types (1). Despite its proven efficacy, its clinical use is limited by the relatively high incidence of serious and potentially life-threatening adverse effects (2-4). Due to these significant cardiac and extracardiac adverse effects, amiodarone is generally not considered a first-line treatment for arrhythmias (5, 6).

Amiodarone exerts its antiarrhythmic effects by inhibiting multiple ion channels involved in cardiac action potential propagation, with a predominant effect on potassium channels. The blockade of these channels delays repolarization, thereby prolonging the duration of the action potential and

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increasing the refractoriness of myocardial tissue, which culminates in QTc interval prolongation on the electrocardiogram (7). Torsades de pointes (TdP) is a rare but potentially fatal arrhythmia associated with amiodarone use, although its incidence is considerably lower than with other antiarrhythmic drugs. The risk of TdP is heightened in patients with additional predisposing factors, such as underlying heart disease, advanced age, electrolyte imbalances, bradycardia, renal or hepatic dysfunction, use of concomitant medications, and intravenous administration of the drug (8-12).

While QTc interval prolongation and TdP are infrequent, their potential severity warrants careful monitoring. A thorough understanding of their incidence and associated risk factors is critical to mitigating adverse outcomes. Despite extensive reports of drug-induced QTc interval prolongation, data on intravenous amiodarone are scarce in large Asian cohorts. This study addresses this gap by investigating the incidence and risk factors of QTc interval prolongation and TdP among patients with atrial fibrillation (AF) receiving intravenous amiodarone.

2. Methods

2.1. Study design and setting

This was a retrospective cohort study and used the electronic health records from a tertiary medical center in Thailand between January 2016 and September 2019. The study population comprised patients with AF who received intravenous amiodarone therapy. Incidence and associated risk factors for QTc interval prolongation and TdP were assessed using multivariable logistic regression analysis.

The study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (13) and complied with the Declaration of Helsinki and was approved by the Human Investigation Committee of Buddhachinaraj Hospital (1,020 beds), Phitsanulok, Thailand (ethics approval number: IRB No. 136/62).

2.2. Study population and data collection

This study included patients diagnosed with AF between January 1, 2016, and September 30, 2019. Inclusion criteria comprised age ≥ 18 years and administration of intravenous amiodarone during hospitalization. Patients with a pre-existing implanted cardiac pacemaker or implantable cardioverter-defibrillator were excluded. The diagnosis of AF was identified using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code I48. Data on demographics (age, sex), comorbidities, concomitant medications, laboratory test results, and electrocardiographic findings were extracted from the electronic health records.

Given the lack of electrocardiographic monitoring for all patients receiving intravenous amiodarone, clinical outcomes were initially identified through ICD-10 diagnostic codes-including syncope (R55), ventricular arrhythmias (I472 and I49), and sudden cardiac death (I46). These outcomes were subsequently validated via detailed review of individual medical health records. All electrocardiograms and clinical outcomes were independently assessed by either a cardiologist or the attending physician to confirm the diagnoses.

2.3. Outcome measurement

QTc interval prolongation or TdP associated with intravenous amiodarone therapy was considered as main outcome. QTc interval prolongation associated with intravenous amiodarone therapy was defined as a heart rate-corrected QT (QTc) exceeding 450 milliseconds (ms) in men or 470 ms in women, or the presence of electrocardiographic evidence of TdP. QTc values were calculated using Bazett's formula ($QTc = QT/\sqrt{RR}$) (14).

2.4. Statistical analysis

Descriptive statistics were used to summarize baseline characteristics. Categorical variables are presented as absolute frequencies and percentages, whereas continuous variables are expressed as means with standard deviations or medians with interquartile ranges, based on data distribution. Group comparisons for categorical variables were conducted using Chi-square tests or Fisher's exact tests, and for continuous variables using Student's t-tests or Wilcoxon rank-sum tests, as appropriate.

The incidence of QTc interval prolongation and TdP was calculated by dividing the number of affected patients by the total number of patients treated with intravenous amiodarone and reported as a percentage. To identify factors associated with these outcomes, patients were stratified into two cohorts based on the presence or absence of QTc interval prolongation and TdP. Variables with a p-value < 0.2 in univariable analysis were entered into a multivariable logistic regression model to determine independent predictors (15). To assess the adequacy of the model, the Hosmer–Lemeshow goodness-of-fit test was performed, and model calibration was considered acceptable at $p > 0.05$ (16). In addition, potential multicollinearity among covariates was evaluated using the variance inflation factor (VIF), with VIF < 5 indicating no evidence of problematic collinearity (17). All statistical tests were two-tailed, with significance set at p-value < 0.05. Analyses were conducted using STATA software, version 16 (StataCorp).

3. Results

3.1. Baseline characteristics of studied patients

A total of 3,176 adult patients with AF who received amiodarone therapy were initially identified. Of these, 2,944 patients met the inclusion criteria and were included in the final analysis. Following associated outcome screening based on ICD-10 and subsequent electrocardiogram (ECG) confir-

mation, 2,895 patients were classified into the non-QTc prolongation/TdP group, whereas 49 patients were diagnosed with QTc interval prolongation or TdP (Figure 1).

The mean age of the cohort was 66.95±14.05 years, and 45.28% were female. The majority of patients were enrolled under the Universal Coverage Scheme (77.79%). Comorbidities were prevalent within the cohort. Approximately one-quarter of patients had a documented history of heart failure (25.10%), hypertension (22.96%), or diabetes mellitus (22.69%). Hypokalemia was reported in 30.26% of patients, while 23.88% were diagnosed with septicemia. Regarding concomitant medications, diuretics were the most frequently prescribed agents (62.06%), followed by antipsychotics (35.60%) and opioids (31.28%). A comprehensive summary of baseline characteristics is provided in Table 1.

Compared with patients who did not experience QTc interval prolongation or TdP, those with QTc interval prolongation or TdP demonstrated a significantly higher prevalence of coronary artery disease (26.53% vs. 11.99%; p-value = 0.006), stroke (12.24% vs. 4.80%; p-value = 0.031), and diabetes mellitus (38.78% vs. 22.42%; p-value = 0.010). Moreover, the use of antipsychotic (61.22% vs. 35.16%; p-value < 0.001) and anticholinergic medications, including atropine, (12.24% vs. 3.04%; p-value = 0.004) was significantly more common in the QTc interval prolongation or TdP group (Table 1).

3.2. Incidence and associated factors of QTc prolongation and TdP

Among the 2,944 patients included in the analysis, 49 cases of intravenous amiodarone-associated QTc interval prolongation (N = 33) or TdP (N = 16) were identified, corresponding to an overall incidence of 1.66% (95% confidence interval (CI): 1.23–2.19%).

Among the 49 patients who developed QTc interval prolongation or TdP following intravenous amiodarone therapy as confirmed by electrocardiographic evidence, however, baseline QTc interval data were available for 42 patients. The mean baseline QTc interval was 446.5 ± 31.0 ms, which increased to 513.4 ± 40.6 ms at the time of event. About a half of the patients (N = 26, 53.1%) demonstrated QTc interval prolongation within the range of 450 - 500 ms, whereas the remainder exhibited QTc interval values exceeding 500 ms. The median time to onset of QTc interval prolongation was 5 days (interquartile range (IQR): 2 - 8), ranging from the day of initiation to 12 days after. The median cumulative dose of intravenous amiodarone at the time of event onset was 2,100 milligrams (mg) (IQR: 1,100 - 3,600), with more than half of the patients (n = 27, 55.1%) receiving cumulative doses greater than 2,000 mg.

Multivariable logistic regression analysis identified the following independent predictors of intravenous amiodarone-associated QTc interval prolongation or TdP: diabetes mellitus (adjusted odds ratio (aOR): 1.85; 95% CI: 1.02 - 3.38), history of stroke (aOR: 3.09; 95% CI: 1.26 - 7.57), antipsychotic use (aOR: 3.07; 95% CI: 1.64 - 5.74), and anticholinergic use (aOR: 3.89; 95% CI: 1.54 - 9.85) (Table 2).

4. Discussion

This study aimed to evaluate the incidence and identify potential risk factors for QTc interval prolongation and TdP associated with intravenous amiodarone therapy in patients diagnosed with AF. The findings suggest that although the overall incidence of QTc interval prolongation and TdP is relatively low, the presence of certain comorbidities-specifically diabetes mellitus and stroke, as well as concomitant use of antipsychotic or anticholinergic (atropine) medications, is associated with a significantly elevated risk of these arrhythmic outcomes.

Previous epidemiological investigations have consistently identified amiodarone as a common cause of drug-induced QTc interval prolongation, particularly when administered via the intravenous route (18-20). A comprehensive review of the literature reported a 2.0% incidence of proarrhythmic events related to amiodarone, with TdP accounting for 0.7% across 17 uncontrolled studies (21). In concordance with these data, the present study observed a 1.66% incidence of QTc interval prolongation and TdP. Similarly, a retrospective analysis by Shenthar and colleagues conducted in India reported an incidence of approximately 1.5% for TdP associated with intravenous amiodarone (8).

The comparatively low incidence of QTc interval prolongation and TdP observed with amiodarone is not yet fully understood but is likely attributable to a combination of multiple factors. While amiodarone primarily prolongs the effective refractory period by inhibiting potassium channels, it also exerts inhibitory effects on sodium and calcium channels. Its calcium-channel blocking properties may attenuate the proarrhythmic potential of delayed repolarization (22, 23). Additionally, amiodarone induces less pronounced repolarization in Purkinje fibers compared to ventricular myocardium, thereby limiting QTc interval dispersion, an important electrophysiological factor implicated in the genesis of TdP (24). Nevertheless, these protective effects may be overridden in the presence of additional predisposing clinical conditions or pharmacological agents (8).

In our analysis, patients with a history of diabetes mellitus or stroke, and those receiving antipsychotic medications or atropine, an anticholinergic agent, were significantly more likely to experience QTc interval prolongation or TdP. These findings are consistent with previous studies that have addressed the pathophysiological mechanisms underlying these associations. For instance, stroke patients were found to have significantly greater absolute QTc interval dispersion compared to non-stroke patients, likely due to elevated plasma catecholamine levels associated with acute stroke, which contribute to increased QTc interval dispersion. However, indication bias was addressed by noting that patients with prior stroke may receive more frequent and closer ECG monitoring, thereby increasing the detection of long QTc interval dispersion events (25-27). A study by Li and

colleagues demonstrated that elevated postprandial glucose levels in patients with diabetes mellitus were independently associated with QTc interval prolongation. This relationship may be mediated by altered intracellular calcium concentrations and impaired sympathovagal balance. Additionally, the underlying pathophysiological mechanism of diabetes mellitus has also been implicated in QTc interval prolongation (28). The concomitant use of amiodarone with other medications, particularly antipsychotics and anticholinergics such as atropine, has been shown to significantly increase the risk of QTc interval prolongation or TdP. Bush and colleagues reported that patients exposed to both amiodarone and haloperidol experienced QTc interval prolongation more frequently than those receiving amiodarone alone (29). Similarly, a study by Girardin and colleagues found that antipsychotic drugs including haloperidol, clotiapine, phenothiazines, and sertindole were significantly more prevalent among patients with drug-induced long QT syndrome (30). Furthermore, Annila and colleagues observed that patients receiving atropine exhibited significant QTc interval prolongation. This effect was attributed to atropine's inhibition of the parasympathetic nervous system, which increases sympathetic tone and thereby contributes to susceptibility to QTc interval prolongation (31). In contrast, our findings differ somewhat from previous research, which identifies risk factors such as female sex (19, 32), hypokalemia (19, 33), left ventricular dysfunction (22), and the concurrent use of QTc interval-prolonging medications such as diuretics or beta-blockers (33) as contributors to increased susceptibility to drug-induced QTc interval prolongation or TdP. We hypothesize that the lack of a statistically significant association between classic predictors such as female sex and electrolyte imbalance (hypokalemia, hypomagnesemia) and QTc interval prolongation may be attributed to a combination of limited statistical power and the unique characteristics of our study population, where the effects of these predictors were potentially mitigated or overshadowed by other, stronger risk factors such as specific comorbidities and co-medications (e.g., antipsychotics and anticholinergics) or other treatments for the electrolyte imbalance.

Accordingly, electrocardiographic monitoring may be advisable for patients receiving intravenous amiodarone, particularly those with established risk factors (5, 6). Early detection of QTc interval prolongation may facilitate timely intervention and reduce the risk of adverse arrhythmic events. Clinicians should perform individualized risk assessments and, where feasible, modify or discontinue contributing medications to mitigate the risk of TdP.

5. Limitations

This study has several limitations that need to be acknowledged. First, as an observational study, it is susceptible to residual confounding, despite rigorous adjustment for known covariates in the multivariable analyses. Nonetheless, the real-world data utilized enhance the generalizability of the findings. Second, the true incidence of QTc interval prolongation/TdP may be underestimated due to undetected cases, particularly among patients who have not underwent routine ECG monitoring before or following intravenous amiodarone initiation, especially the patients who were not diagnosed with associated outcomes. Third, QTc values were obtained from ECG reports routinely interpreted by cardiologists or physicians in our hospital, where Bazett's formula is applied as standard practice. As a result, we were unable to perform a sensitivity analysis using other appropriate formulas such as Fridericia or Hodges, which should be considered when interpreting the findings (9), although reanalysis confirmed that the logistic regression model demonstrated an acceptable fit, the limited number of events raises the possibility of over-fitting, which may affect the stability of the risk estimates. Fourth, baseline QTc data were not available for all patients, which restricts the ability to fully assess pre-treatment risk and represents a potential source of bias that should be considered when interpreting the findings. In addition, the exact infusion rate could not be determined, as prescriptions of amiodarone loading dose were typically written as "IV stat," with the actual administration rate decided by nursing staff and not systematically recorded. Therefore, we were unable to evaluate infusion rate as a risk factor, and this limitation should be acknowledged when interpreting our results. Finally, pharmacogenomics should be considered, CYP450 polymorphism may have affected the pharmacokinetics and pharmacodynamics of amiodarone and its concomitant medications. In addition, several studies have reported that the mutations of the genes that encode the protein channels account for long QT syndrome (LQTS) and susceptibility to drug-induced toxicity (3).

6. Conclusions

While the overall incidence of QTc interval prolongation and TdP associated with intravenous amiodarone therapy in patients with AF was low, individuals with comorbidities such as diabetes mellitus or stroke, and those concurrently receiving antipsychotic or anticholinergic medications, were found to be at increased risk. These findings underscore the importance of comprehensive risk assessment and vigilant monitoring when initiating intravenous amiodarone therapy.

7. Declarations

7.1. Acknowledgments

We would like to express our heartfelt gratitude to information systems technician team of Buddhachinaraj hospital for data retrievals.

7.2. Author contributions

Yuttana Wongsalap and Niwat Saksit: conceived and designed the study. Yuttana Wongsalap, Niwat Saksit, Waruni Miliam, Suparpish Deesham, Arissara Thepsaen, Aphatsara Churasae, and Duangkamon Poolpun: collected the data.

Yuttana Wongsalap and Niwat Saksit: performed the statistical analysis and interpretation of data.
Tomon Thongsri and Duangkamon Poolpun supervised to modify the whole process and helped in study coordination.
Yuttana Wongsalap and Niwat Saksit: drafted the manuscript, critical revision of the manuscript and were responsible for the final editing of the manuscript.
All authors participated in the review and provided final approval of the manuscript to be published.

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7.4. Conflict of interest

The authors declare no conflict of interest.

7.5. Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Buddhachinaraj Hospital, Phitsanulok, Thailand (ethics approval number: IRB No. 136/62).

7.6. Patient consent for publication

Not required.

7.7. Availability of data and materials

The datasets generated or analyzed during the current study are available from the corresponding author upon reasonable request.

7.8. Using artificial intelligence chatbots

During the preparation of this work, the authors used ChatGPT for English language proofreading and correct grammatical errors. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

References

1. Hamilton D, Sr., Nandkeolyar S, Lan H, Desai P, Evans J, Hauschild C, et al. Amiodarone: A Comprehensive Guide for Clinicians. Am J Cardiovasc Drugs. 2020;20(6):549-58.
2. Colunga Biancatelli RM, Congedo V, Calvosa L, Ciacciarelli M, Polidoro A, Iuliano L. Adverse reactions of Amiodarone. J Geriatr Cardiol. 2019;16(7):552-66.
3. Nachimuthu S, Assar MD, Schussler JM. Drug-induced QT interval prolongation: mechanisms and clinical management. Ther Adv Drug Saf. 2012;3(5):241-53.
4. Barnes BJ, Hollands JM. Drug-induced arrhythmias. Crit Care Med. 2010;38(6 Suppl):S188-97.
5. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2024;83(1):109-279.
6. Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns H, et al. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2024;45(36):3314-414.
7. Gelman I, Sharma N, McKeeman O, Lee P, Campagna N, Tomei N, et al. The ion channel basis of pharmacological effects of amiodarone on myocardial electrophysiological properties, a comprehensive review. Biomed Pharmacother. 2024;174:116513.
8. Shenthar J, Rachaiah JM, Pillai V, Chakali SS, Balasubramanian V, Chollenhalli Nanjappa M. Incidence of drug-induced torsades de pointes with intravenous amiodarone. Indian Heart J. 2017;69(6):707-13.
9. Keller GA, Alvarez PA, Ponte ML, Belloso WH, Bagnes C, Sparanochia C, et al. Drug-Induced QTc Interval Prolongation: A Multicenter Study to Detect Drugs and Clinical Factors Involved in Every Day Practice. Curr Drug Saf. 2016;11(1):86-98.
10. Yang J, You M, Wang J, Sun R, Han L, Liu X, et al. Adverse events in different administration routes of amiodarone: a pharmacovigilance study based on the FDA adverse event reporting system. Front Pharmacol. 2025;16:1517616.
11. Tisdale JE, Chung MK, Campbell KB, Hammadah M, Joglar JA, Leclerc J, et al. Drug-Induced Arrhythmias: A Scientific Statement From the American Heart Association. Circulation. 2020;142(15):e214-e33.
12. Davies RA, Ladouceur VB, Green MS, Joza J, Juurlink DN, Krahn AD, et al. The 2023 Canadian Cardiovascular Society Clinical Practice Update on Management of the Patient With a Prolonged QT Interval. Can J Cardiol. 2023;39(10):1285-301.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Bmj. 2007;335(7624):806-8.
14. Bazett HC. An analysis of the time-relations of electrocardiograms. Heart. 1920;7:353-70.
15. Wang H, Peng J, Wang B, Lu X, Zheng JZ, Wang K, et al. Inconsistency Between Univariate and Multiple Logistic Regressions. Shanghai Arch Psychiatry. 2017;29(2):124-8.
16. Nattino G, Pennell ML, Lemeshow S. Assessing the goodness of fit of logistic regression models in large samples: A modification of the Hosmer-Lemeshow test. Biomet-

rics. 2020;76(2):549-60.
17. Vatcheva KP, Lee M, McCormick JB, Rahbar MH. Multicollinearity in Regression Analyses Conducted in Epidemiologic Studies. Epidemiology (Sunnyvale). 2016;6(2):227.
18. Sarganas G, Garbe E, Klimpel A, Hering RC, Bronder E, Haverkamp W. Epidemiology of symptomatic drug-induced long QT syndrome and Torsade de Pointes in Germany. Europace. 2014;16(1):101-8.
19. Geng DF, Jin DM, Wang JF, Luo YJ, Wu W. Clinical study of amiodarone-associated torsade de pointes in Chinese people. Pacing Clin Electrophysiol. 2006;29(7):712-8.
20. Tong KL, Lau YS, Teo WS. A case series of drug-induced long QT syndrome and Torsade de Pointes. Singapore Med J. 2001;42(12):566-70.
21. Hohnloser SH, Klingenheben T, Singh BN. Amiodarone-associated proarrhythmic effects. A review with special reference to torsade de pointes tachycardia. Ann Intern Med. 1994;121(7):529-35.
22. Lim HE, Pak HN, Ahn JC, Song WH, Kim YH. Torsade de pointes induced by short-term oral amiodarone therapy. Europace. 2006;8(12):1051-3.
23. van Erven L, Schalij MJ. Amiodarone: an effective antiarrhythmic drug with unusual side effects. Heart. 2010;96(19):1593-600.
24. Hii JT, Wyse DG, Gillis AM, Duff HJ, Solylo MA, Mitchell LB. Precordial QT interval dispersion as a marker of torsade de pointes. Disparate effects of class Ia antiarrhythmic drugs and amiodarone. Circulation. 1992;86(5):1376-82.
25. Lederman YS, Balucani C, Lazar J, Steinberg L, Gugger J, Levine SR. Relationship between QT interval dispersion in acute stroke and stroke prognosis: a systematic review. J Stroke Cerebrovasc Dis. 2014;23(10):2467-78.
26. Amin OSM, Al-Bajalan SJ, Mubarak A. QTc Interval Prolongation and Hemorrhagic Stroke: Any Difference Between Acute Spontaneous Intracerebral Hemorrhage and Acute Non-traumatic Subarachnoid Hemorrhage? Med Arch. 2017;71(3):193-7.
27. Tsivgoulis G, Palaiodimou L, Triantafyllou S, Köhrmann M, Dilaveris P, Tsioufis K, et al. Prolonged cardiac monitoring for stroke prevention: A systematic review and meta-analysis of randomized-controlled clinical trials. Eur Stroke J. 2023;8(1):106-16.
28. Li X, Ren H, Xu ZR, Liu YJ, Yang XP, Liu JQ. Prevalence and risk factors of prolonged QTc interval among Chinese patients with type 2 diabetes. Exp Diabetes Res. 2012;2012:234084.
29. Bush SE, Hatton RC, Winterstein AG, Thomson MR, Woo GW. Effects of concomitant amiodarone and haloperidol on Q-Tc interval prolongation. Am J Health Syst Pharm. 2008;65(23):2232-6.
30. Girardin FR, Gex-Fabry M, Berney P, Shah D, Gaspoz JM, Dayer P. Drug-induced long QT in adult psychiatric inpatients: the 5-year cross-sectional ECG Screening Outcome in Psychiatry study. Am J Psychiatry. 2013;170(12):1468-76.
31. Annila P, Yli-Hankala A, Lindgren L. Effect of atropine on the QT interval and T-wave amplitude in healthy volunteers. Br J Anaesth. 1993;71(5):736-7.
32. Wolbrette DL. Risk of proarrhythmia with class III antiarrhythmic agents: sex-based differences and other issues. Am J Cardiol. 2003;91(6a):39d-44d.
33. Schrickel JW, Schwab JO, Yang A, Bielik H, Bitzen A, Lüderitz B, et al. Pro-arrhythmic effects of amiodarone and concomitant rate-control medication. Europace. 2006;8(6):403-7.

Table 1: Comparing the baseline characteristics of studied cases between cases with and without QTc interval prolongation or Torsades de Pointes (TdP)

Characteristics	Total (N = 2,944)	QTc interval prolongation or TdP		P
		Yes (N = 49)	No (N = 2,895)	
Age (year)				
Mean ± SD	66.95 ± 14.05	67.94 ± 13.18	66.94 ± 14.07	0.621
< 65	1,138 (38.65)	16 (32.65)	1,122 (38.76)	0.460
≥ 65	1,806 (61.35)	33 (67.35)	1,773 (61.24)	
Sex				
Female	1,333 (45.28)	28 (57.14)	1,305 (45.08)	0.111
Male	1,611 (54.72)	21 (42.86)	1,590 (54.92)	
Insurance				
UC	2,290 (77.79)	37 (75.51)	2,253 (77.82)	0.608
SSS	114 (3.87)	3 (6.12)	111 (3.83)	
CSMBS	540 (18.34)	9 (18.37)	531 (18.34)	
Comorbidities				
Hypertension	676 (22.96)	12 (24.49)	664 (22.94)	0.735
Heart failure	739 (25.10)	17 (34.69)	722 (24.94)	0.134
Coronary artery disease	360 (12.23)	13 (26.53)	347 (11.99)	0.006
Diabetes	668 (22.69)	19 (38.78)	649 (22.42)	0.010
Hyperlipidemia	482 (16.37)	10 (20.41)	472 (16.30)	0.436
Thyroid disease	125 (4.25)	2 (4.08)	123 (4.25)	0.100
Liver disease	145 (4.93)	3 (6.12)	142 (4.91)	0.733
Chronic kidney disease	227 (7.71)	4 (8.16)	223 (7.70)	0.788
COPD/Asthma	157 (5.33)	1 (2.04)	156 (5.39)	0.518
Septicemia	703 (23.88)	7 (14.29)	696 (24.04)	0.129
Stroke	145 (4.93)	6 (12.24)	139 (4.80)	0.031
Hypokalemia	891 (30.26)	12 (24.49)	879 (30.36)	0.435
Hypomagnesemia	396 (13.45)	5 (10.20)	391 (13.51)	0.673
Hyponatremia	152 (5.16)	1 (2.04)	151 (5.22)	0.516
Concomitant medications				
Diuretics	1,827 (62.06)	31 (63.27)	1,796 (62.04)	1.000
Digoxin	179 (6.08)	3 (6.12)	176 (6.08)	1.000
Calcium channel blockers	308 (10.46)	3 (6.12)	305 (10.54)	0.477
Beta-blockers	132 (4.48)	2 (4.08)	130 (4.49)	1.000
Statins	403 (13.69)	10 (20.41)	393 (13.58)	0.204
Fluoroquinolones	180 (6.11)	2 (4.08)	178 (6.15)	0.767
Macrolides	440 (14.95)	8 (16.33)	432 (14.92)	0.691
Antipsychotics	1,048 (35.60)	30 (61.22)	1,018 (35.16)	< 0.001
Antidepressants	186 (6.32)	2 (4.08)	184 (6.36)	0.767
Opiates	921 (31.28)	11 (22.45)	910 (31.43)	0.214
Antiepileptics	152 (5.16)	2 (4.08)	150 (5.18)	1.000
Anticholinergic (Atropine)	94 (3.19)	6 (12.24)	88 (3.04)	0.004
H1-Antihistamines	292 (9.92)	2 (4.08)	290 (10.02)	0.228
Antimotility and Antiemetics	770 (26.15)	13 (26.53)	757 (26.15)	1.000
Intravenous amiodarone dose (mg/day)				
Median (IQR)	300 (150 - 900)	300 (150 - 900)	300 (150 - 900)	0.542
≤ 300	1,708 (58.02)	25 (51.02)	1,683 (58.13)	0.381
> 300	1,236 (41.98)	24 (48.98)	1,212 (41.87)	

Data are presented as number (%) or mean ± standard deviation (SD). COPD: chronic obstructive pulmonary disease; CSMBS: civil servant medical benefit scheme; IQR: interquartile range; mg: milligram; QTc: corrected QT; SD: standard deviation; SSS: social security scheme; TdP: Torsades de pointes; UC: universal coverage scheme.

Table 2: Independent risk factors of QT prolongation and Torsade de pointes following atrial fibrillation treatment with intravenous amiodarone based on multivariable logistic regression analysis

Factors	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P-value	aOR (95% CI)	P-value
Age ≥ 65 years	1.31 (0.72 - 2.38)	0.386	1.19 (0.64 - 2.22)	0.585
Female sex	1.62 (0.92 - 2.87)	0.096	1.56 (0.86 - 2.82)	0.139
Heart failure	1.60 (0.88 - 2.90)	0.122	1.08 (0.56 - 2.08)	0.826
Coronary artery disease	2.65 (1.39 - 5.05)	0.003	1.36 (0.64 - 2.91)	0.422
Diabetes mellitus	2.19 (1.23 - 3.92)	0.008	1.85 (1.02 - 3.38)	0.045
Stroke	2.77 (1.16 - 6.61)	0.022	3.09 (1.26 - 7.57)	0.014
Septicemia	0.53 (0.24 - 1.18)	0.118	0.66 (0.28 - 1.53)	0.331
Antipsychotics	2.91 (1.63 - 5.20)	< 0.001	3.07 (1.64 - 5.74)	< 0.001
Anticholinergic (atropine)	4.45 (1.85 - 10.73)	0.001	3.89 (1.54 - 9.85)	0.004
H1-antihistamines	0.38 (0.09 - 1.58)	0.184	0.38 (0.09 - 1.61)	0.190
Opioids	0.63 (0.32 - 1.24)	0.182	0.57 (0.28 - 1.17)	0.126
Statins	1.63 (0.81 - 3.30)	0.172	1.31 (0.63 - 2.72)	0.476
Amiodarone dose > 300 mg/day	1.33 (0.76 - 2.35)	0.319	1.31 (0.73 - 2.35)	0.357

aOR: adjusted odds ratio; CI: confidence interval; mg: milligram; OR: odds ratio.

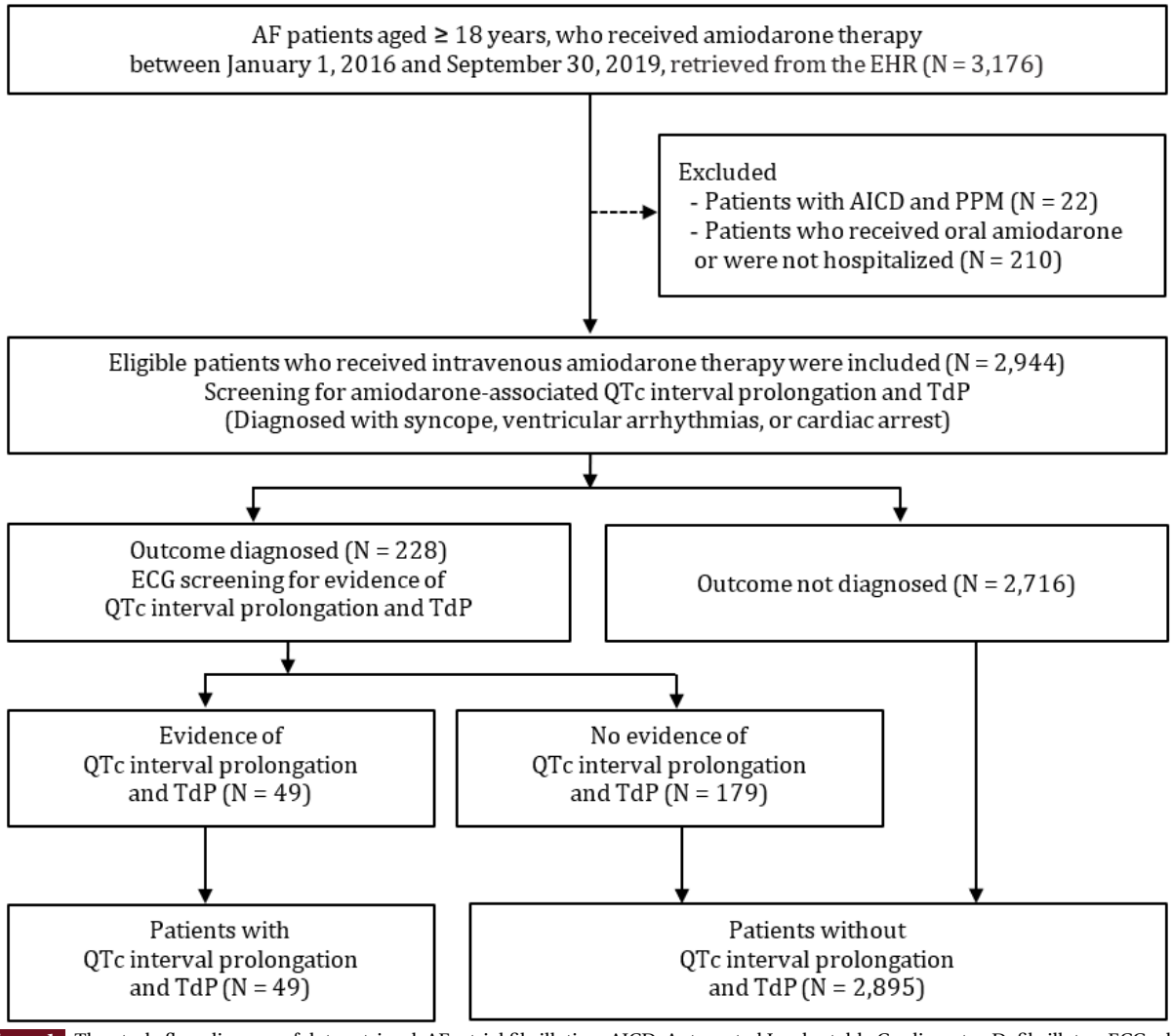

Figure 1: The study flow diagram of data retrieval. AF: atrial fibrillation; AICD: Automated Implantable Cardioverter-Defibrillator; ECG: electrocardiogram; EHR: electronic health record; QTc: corrected QT; PPM: permanent pacemaker; TdP: Torsades de pointes.