Annals of Medicine and Surgery 80 (2022) 104167

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Cohort Study

CLInical Profile and Side Effects of chronic use of oral Amiodarone in cardiology outpatients department (CLIPSE-A Study)- A prospective observational study

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ARTICLE INFO

Keywords:
Amiodarone
Atrial fibrillation
Atrial flutter
Ventricular tachycardia
Paroxysmal atrial fibrillation
Side-effects

ABSTRACT

Background: Amiodarone belongs to Class-III anti-arrhythmic drugs. It is one of the most effective anti-arrhythmic drugs used to treat or prevent several types of arrhythmias including atrial fibrillation, atrial flutter, ventricular tachycardia, and wide complex tachycardia, but unfortunately carries a high toxicity profile. Also, side effects of amiodarone involving various organs can be life-threatening.

Materials & methods: This was an observational study carried out for six months i.e from April to September. The study included patients who are on amiodarone for greater than or equal to six months. The required data was collected in-person from the case sheets, treatment charts, and by interviewing the patients. The data for 67 patients was documented in suitable data collection form for analysis.

Results: From our study data, it was noted that amiodarone was used for 3 different indications-atrial fibrillation, atrial flutter, and ventricular tachycardia. Among 67 patients enrolled, 38 had no side-effects. Side-effects data in the rest grouped basing on the organ system affected: 9 patients had renal effects, 6 patients had ophthalmic effects, 4 patients had endocrine effects, and 5 patients had hepatic effects.

Conclusion: From our study, it is concluded that amiodarone is a safe and effective anti-arrhythmic drug at lower doses i.e. 200-1100 mg/week. When treated in lower doses of 1400–2800 mg/week, many side effects have been incident. Although these effects are mild and develop only after prolonged usage of the drug, it should be used judiciously.

1. Introduction

Amiodarone was developed in the early 1960s as a treatment option for angina pectoris since it produces coronary vasodilation and decreases cardiac oxygen demand. However, its pronounced antiarrhythmic effects redirected its use and amiodarone has become a widely used class III anti-arrhythmic drug, which is used to treat and prevent several types of irregular heartbeats including ventricular tachycardia (VT), ventricular fibrillation (VF), and wide complex tachycardia as well as atrial fibrillation (AF) and paroxysmal supraventricular tachycardia (PSVT) [1] When compared to other antiarrhythmic drugs, it is more effective in treating both supraventricular and ventricular arrhythmias [2]. It can also be used to treat other supraventricular tachyarrhythmias, involving atrial flutter, refractory AV (atrioventricular) nodal, and AV tachycardia (commonly referred to as SVT). Eventually, Amiodarone is indicated for the treatment of ventricular arrhythmias, specifically monomorphic VT, non-torsade's polymorphic VT (secondary to myocardial ischemia with no association on QTc), as well as for pulseless

Abbreviations: VF, Ventricular Fibrillation; VT, Ventricular tachycardia; AF, Atrial fibrillation; PSVT, Paraoxysmal supraventricular tachycardia; AV, Atrioventricular; CPR, Cardiopulmonary resuscitation; INR, International normalized ratio; BMI, Body mass index; SGOT, Serum glutamic-oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; FDA, Food and drug administration; AIH, Amiodarone induced hypothyroidism; AIT, Amiodarone induced thyrotoxicosis; DEA, Des ethyl amiodarone.

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https://doi.org/10.1016/j.amsu.2022.104167
Received 25 May 2022; Received in revised form 8 July 2022; Accepted 8 July 2022
Available online 16 July 2022

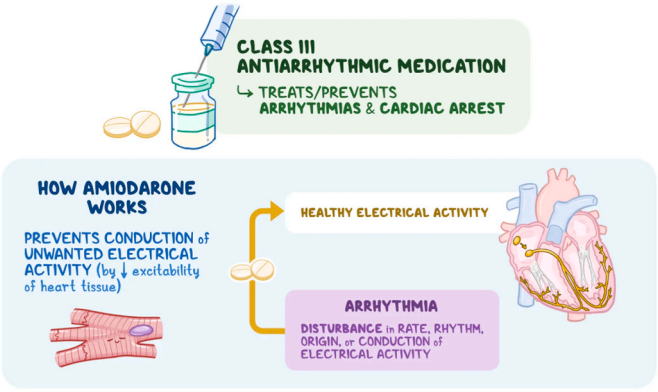


Figure-1. Mechanism of action of amiodarone (Adapted from Osmosis.org [6]).

ventricular fibrillation (VF) and pulseless VT) that fail to settle after CPR, defibrillation [3].

Although Amiodarone is an effective drug, it carries high toxicity profile. Its use is been complicated by safety issues, which are emphasized by several clinical reports associated with pulmonary, thyroid, ocular, and/or liver toxicity to drug therapy. It is also known to interact with a large variety of therapeutic agents (drug-drug interactions), resulting from inhibition of cytochrome P450–mediated metabolism, which raises systemic exposure of the targeted drug [4] Amiodarone is a challenging drug to use in clinical practice despite its efficacious outcomes, owing to its prolonged half-life, multiple adverse effects, and drug interactions. These adverse effects are particularly problematic for geriatrics who are more susceptible to drug toxicities and in patients who have higher rates of polypharmacy. Being used in a larger population of varying ages, its safety information in geriatrics is not clearly known [5] (Fig. 1).

1.1. Pharmacokinetics (Table 1)

1.2. Indications

Amiodarone is approved by Food & drug administration for recurrent ventricular fibrillation (VF) and recurrent hemodynamically unstable ventricular tachycardia (VT) and accentuated that this drug should only be used when clinically documented or when other drugs are not tolerated by patients. Its off-label indications include treatment of supraventricular tachyarrhythmias (atrial fibrillation, atrial flutter, refractory AV nodal and AV re-entrant tachycardia) and for prevention of ventricular tachyarrhythmias (VTs) in high-risk patients [7–9].

1.3. Side-effects

Amiodarone has an unusual spectrum of side effects with a prevalence of 15% in the first year, increasing up to 50% during long-term use. In most of the cases of atrial fibrillation, amiodarone is discontinued or altered in first year of treatment basing on risk/benefit ratio. Based on the data, each individual showed some side-effect (Fig. 2).

1.4. Drug interactions

Amiodarone has a high interaction potential with co-administered drugs. Because of its long half-life, these effects are expected to persist for weeks to months after discontinuation of Amiodarone [10] (Table 2).

2. Materials & methods

The study was descriptive cohort study conducted on patients attending cardiology outpatient department and on therapy with oral Amiodarone uninterrupted for greater than or equal to six months, which made-up inclusion criteria. Exclusion criteria included patients not willing to participate, patients who are using amiodarone on and off, and patients who are not using amiodarone for more than six months. The study has been reported in line with the STROCSS criteria [26].

Ethical approval

The present study was carried out at Asian Institute of Gastroenterology (AIG) Hospitals, Hyderabad. This study was approved by Institutional Ethics Committee- Asian Institute of Gastroenterology (IEC-AIG), Somajiguda, Hyderabad, India with **Regd No: ECR/346/Inst/AP/2013/RR-19.** The patients who meet the inclusion criteria will be recruited in the study with their consent after explaining the details of the study.

Table 1
Pharmacokinetics of amiodarone.

Absorption	Amiodarone is slowly and variably absorbed with a bioavailability of 50%. C_{max}:3–7 h after a single dose. Amiodarone is a lipophilic drug, whose absorption is enhanced with the intake of high-fat food.
Distribution	Highly protein-bound (approximately 96%); V_d:60L/kg Metabolite: DesEthyl Amiodarone (DEA) 10–30% of drug crosses the placenta and varying amount is excreted in breast milk.
Metabolism	Metabolized by CYP3A4 enzyme in the liver. Strong hepatic and renal metabolism inhibitor. It inhibits different cytochrome P450 pathways, including CYP2C9, CYP2D6, CYP3A4.
Excretion	Eliminated majorly through biliary excretion in the Gastrointestinal tract and minimally in urine
Half-life	Variable for long-term oral therapy. Half-life is between 60 and 142 days. For its active metabolite, DEA, it is 3 days.

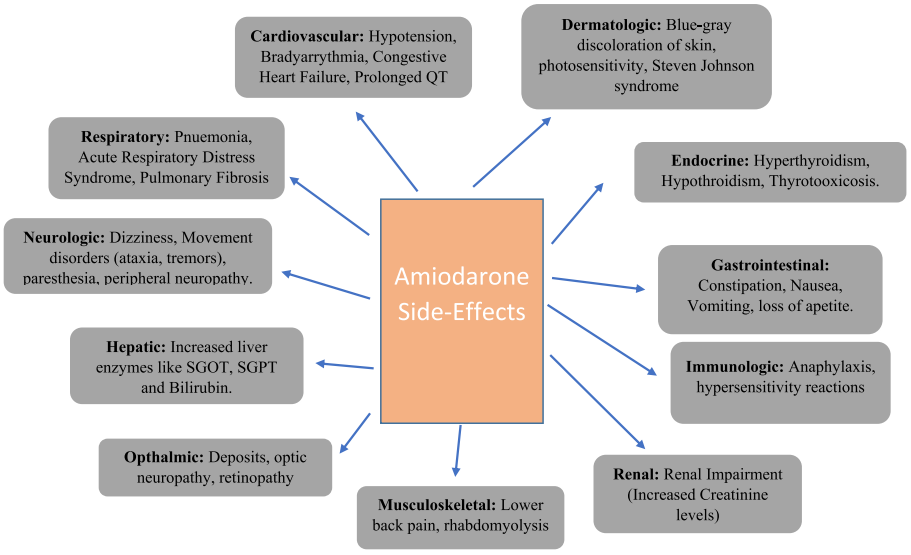


Fig. 2. Side-Effects of amiodarone.

Table 2
Drug interacting with amiodarone.

Drug Class	Example	Effect:
Anticoagulants [10]	Warfarin	Concurrent use may result in increased INR and risk of bleeding.
Anti-hypertensives [11]	Irbesartan, losartan	Concurrent use may result in increased plasma levels of anti-hypertensives.
HMG COA Reductase Inhibitors [12–14]	Atorvastatin, Simvastatin, Rosuvastatin	Concurrent use may cause increased exposure, risk of myopathy and with rosuvastatin, it causes elevation in serum transaminase levels.
Anti-diabetic agents [15]	Glimeperide, Glipizide, Glyburide, Tolbutamide, Nateglinide	Concurrent use may result in increased plasma concentration of adjuvant drug.
Anti-convulsants [16,17]	Phenytoin, Fosphenytoin, Clonazepam	Concurrent use may result in adjuvant drug toxicity.
Anti-thyroid Agents [18]	Methimazole	Concurrent use may result decreased T3/T4.
Anti-emetics [19]	Domperidone	Concurrent use may result in increased domperidone exposure and risk of QT prolongation.
Anti-histaminic [20]	Loratidine	Concurrent use may result in QT Prolongation.
Anti-HIV drugs [21]	Ritonavir, Indinavir, Neflinavir, Lopinavir, Saquinavir, Tipranvair	Concurrent use may cause amiodarone toxicity and increased amiodarone plasma concentrations.
Cardiac Glycoside [22]	Digoxin	Concurrent use may cause digoxin toxicity.
Corticosteroids [23]	Budesonide	Concurrent use of budesonide and Amiodarone may result in increased risk of developing Cushing's syndrome.
Anti-Viral Agents [24]	Sofosbuvir	Concurrent use may result in increased risk of bradycardia.
Anti-fungal Agents [25]	Fluconazole, ketoconazole, Posaconazole	Concurrent use may cause increased cardiotoxicity and QT prolongation.

2.1. Methodology (Fig. 3)

2.2. Data collection and analysis

The required data collected was entered in a Data Collection Form (DCF) and then analyzed. All the relevant and necessary data from patients' case sheets; treatment charts; laboratory reports; interviewing patients or patients care takers for side effects; any other relevant sources.

The data was entered into the MS Excel Sheet (Version 2016) and exported to SPSS Software (IBM) Version 22 was employed for further analysis.

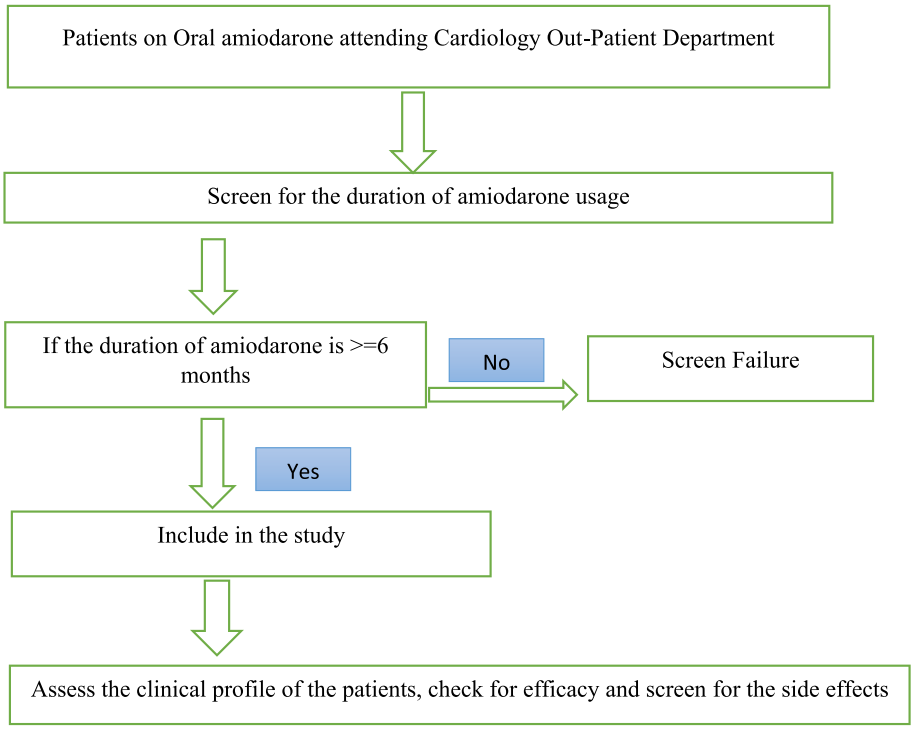


Fig. 3. Study methodology.

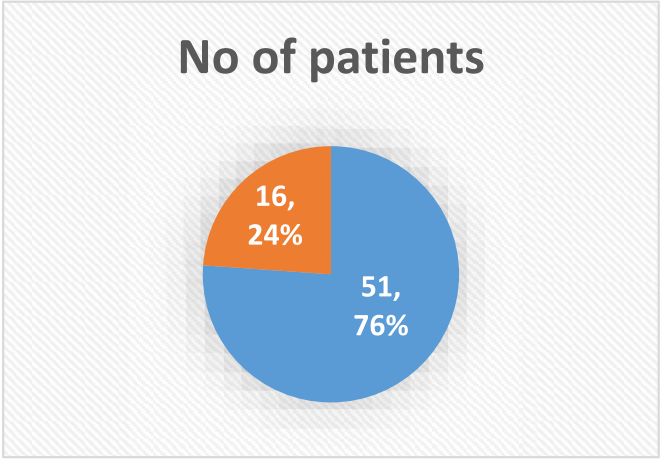


Fig. 4. Gender prevalence.

3. Results

The data was collected from 67 patients, among which there were **51 (76%)** males and **16 (24%)** females (Fig. 4).

The mean age of the study population was found to be 58.63 ± 13.3 with average BMI of 27.5 ± 3.8 kg/m2.

Analyzing the medical history of patients, it was found that there were 28 (41.8%) patients with Diabetes Mellitus. Similarly, there were 37 (55.2%) patients with Hypertension, 4 (5.9%) with Chronic kidney disease, 11 (16.5%) with Coronary artery diseases (Fig. 5).

The social history of these patients revealed that 1 (1.6%) was a smoker, 1 (1.6%) was an alcoholic, 1 (1.6%) was tobacco chewer.

Amiodarone was used for three indications in our study, 14 (20.9%) of patients had Atrial Flutter, 30 (44.8%) had Atrial Fibrillation, 23 (34.3%) had Ventricular Tachycardia (Fig. 6).

The weekly dose was calculated as 200–2800 mg/week. The mean range was 1428.3 ± 810.2, among which, there were 1 (1.49%) patient using 200 mg/week, 1 (1.49%) using 250 mg/week, 3 (4.5%) using 400 mg/week, 14 (20.9%) using 700 mg/week, 1 (1.49%) using 1100 mg/week, 27 (40.3%) using 1400 mg/week, 5 (7.5%) using 2100 mg/week, 15 (22.4%) using 2800 mg/week (Fig. 7).

The biochemistry reports of the patients' data was analyzed which showed that the mean range of serum values of creatinine was 1.2 ± 0.6 mg/dL, sodium was 138.6 ± 4.7 mEq/L, potassium was 4.5 ± 0.5 mEq/L, urea was 36.9 ± 16.4 mg/dL, magnesium was 2.0 ± 0.4 mg/dL, SGOT was 28.4 ± 14 IU/l, SGPT was 26 ± 10.9 U/L, ALP was 74.1 ± 58 U/L, bilirubin was 0.5 ± 0.3 mg/dl, albumin was 3.6 ± 1 gm/dl, T3 was 1.1 ± 0.5 ng/ml, T4 was 6.1 ± 2.7 μg/dl, TSH was 4.4 ± 2.9 IU/ml.

An eye examination was advised for 22 patients to check for ocular side effects, which showed that 5 (23%) of patients had vortex keratopathy, 1 (4%) had optic neuropathy, and 16 (73%) had no Amiodarone-induced effects (Fig. 8).

The side-effects were assessed based on the dose/week in 8 different doses ranging from 200 to 2800 mg/week. This data was grouped based

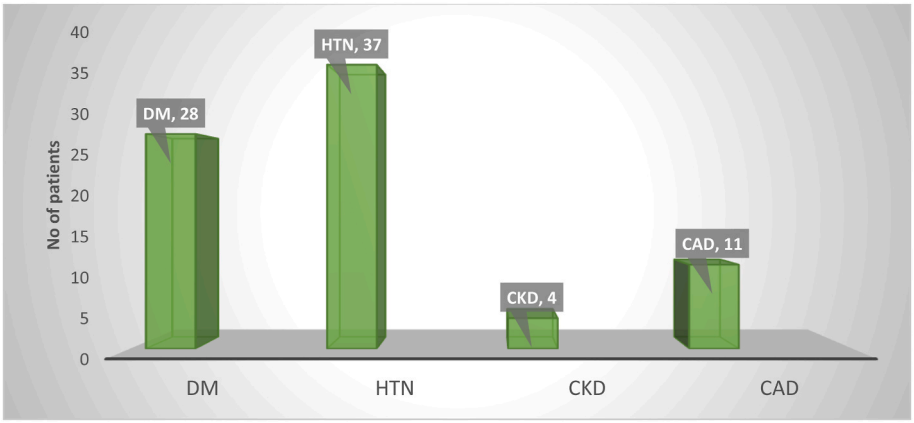


Fig. 5. Medical history of diseases.

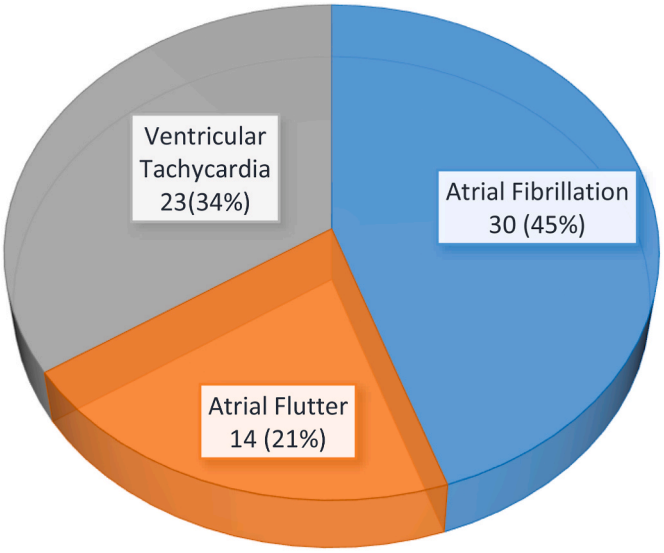


Fig. 6. Indications of amiodarone.

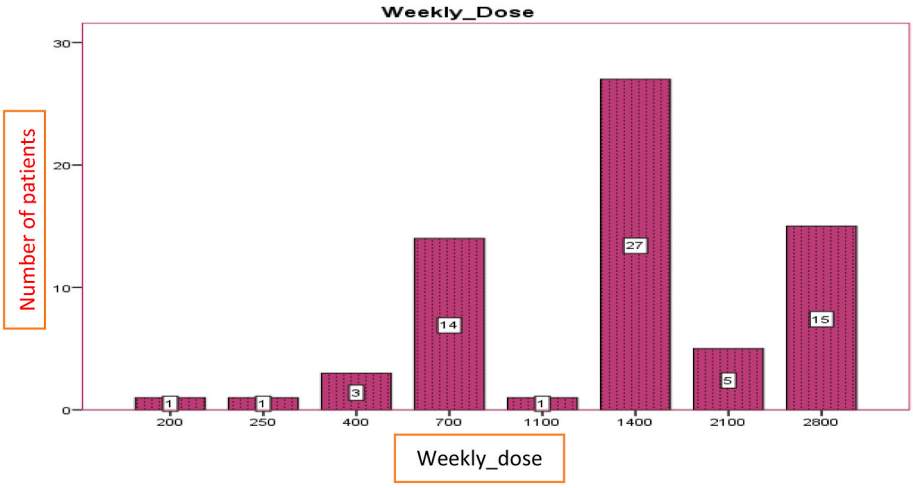


Fig. 7. Weekly dose for patients.

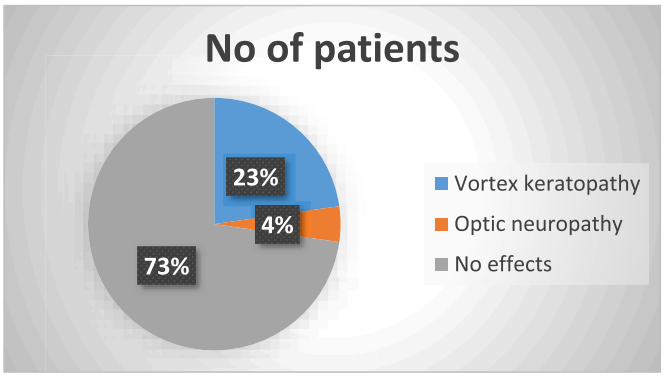


Fig. 8. Eye Examination data.

on the organ system which showed that 11 patients had endocrine effects [hyperthyroidism, hypothyroidism]; 6 had hepatic effect [increased SGOT and SGPT levels] 5 had ophthalmic effects [vortex keratopathy] 2 had renal effects [increased creatinine levels], and 43 patients had no side-effects (Fig. 9).

3.1. Dose Vs side effects (Fig. 10)

Our study demonstrates a lower incidence of side effects from low-dose Amiodarone. There were no significant side effects that has reported at the dose range of 200–1100 mg/week.

4. Discussions

One of the most often prescribed anti-arrhythmic medications is amiodarone. While the FDA has approved amiodarone for the treatment of life-threatening ventricular arrhythmias, it is frequently used off-label to treat supraventricular tachy-arrhythmias such atrial fibrillation and to prevent ventricular tachyarrhythmia in high-risk patients [27]. In our study, we observed that amiodarone was used in 45% of the patients with atrial fibrillation, 34% of the patients with Ventricular Tachycardia and 20% of the patients with atrial flutter.

The primary objective of our study is to determine the side effects of amiodarone when it is taken for long-term, such as more than 6 months. We noticed a few side effects, which are detailed here.

Adverse effects from amiodarone therapy might range from 15% within the first year of treatment to 50% after a year. Amiodarone is typically terminated in the first year of treatment for those with atrial fibrillation due to the risk/benefit ratio. During our study, we observed that most patients did not use amiodarone for longer than 6 months. Amiodarone medication is only recommended for patients who are not

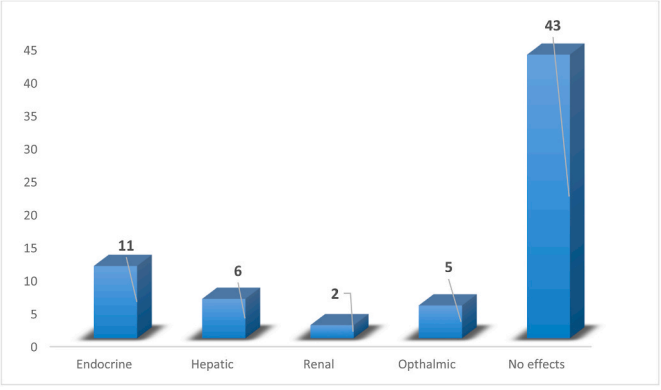
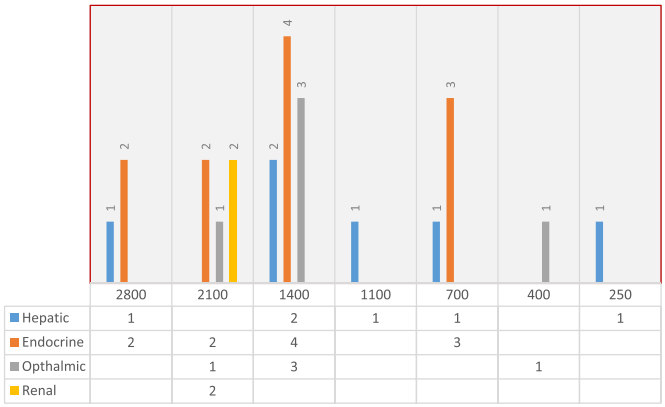


Fig. 9. Side effects.



	2800	2100	1400	1100	700	400	250
Hepatic	1		2	1	1		1
Endocrine	2	2	4		3		
Opthalmic		1	3			1	
Renal		2					

Fig. 10. Dose and Side-effect correlation.

stable or who have frequent arrhythmia events despite trying other drugs such as Sotalol and etc.

Amiodarone is not indicated for persons with second or third-degree heart block who do not have pacemakers. Amiodarone should be avoided in those who have a baseline QTc prolongation [28,29]. Although retrospective investigations have shown that iodine or iodinated contrast agent allergies are not an absolute contraindication to amiodarone, the incidence of hypersensitivity reactions to amiodarone in people who have been diagnosed with iodine allergies should be closely monitored [30,31].

W M Feinberg et al. conducted a study in 1995 that indicated that the prevalence of AF is associated to the patient's age, with a prevalence of 2.3% in persons over 40 years and 5.9% in people over 65 years. The study also found that 40% of patients over 75 years old were females [32]. Our study observed that the average age of the population was 58.6 ± 13.3 years, with 76% of men and 24% of females.

Thyroid problems have been documented in up to 14–18% of patients taking long-term amiodarone therapy, according to a meta-analysis published in 2009 by Mini Gopalan, whereas the frequency is 3.7% in individuals using low dosages of Amiodarone. The side effects include aberrant thyroid function test findings for apparent thyroid dysfunction, which could be Amiodarone-induced thyrotoxicosis (AIT) or Amiodarone-induced hypothyroidism (AIH) [33–36]. In our study, we found that patients developed thyroid problems at doses as low as 700 mg/week, which is likewise a modest dose.

In 1990, JH Lewis et al. conducted a study on Amiodarone-induced hepatotoxicity with a total of 104 individuals, with asymptomatic elevations of blood aminotransferase levels identified in roughly 1/4th of the patients [36,37]. We found no significant dose-dependent adverse effects in our study, as hepatotoxicity was observed in patients receiving 700 mg/week as well as 2800 mg/week, indicating that hepatotoxicity is an individual response rather than a dose response.

In 2004, P. Pollak and F. Alsohaibani conducted a 30-month cohort study with 65 participants. At 6 months, serum creatinine increased slowly, reaching a high of 11% above baseline ($p < 0.001$). After the first year of therapy, no further changes were observed. They came to the conclusion that Amiodarone has a distinct influence on serum creatinine levels. During the first year of medication, the maximum change in renal function parameters occurs around the time that DEA serum concentrations settle. The mechanism of action is unknown, however it could involve altered creatinine tubular secretion or a balance of afferent and efferent renal blood flow [38]. Our study demonstrated the lowest effect on serum creatinine which was observed in only 2 patients.

A decrease in the dose and discontinuation of Amiodarone were the most common interventions.

5. Conclusions

Our study observes that the dosage and duration of Amiodarone are the most important factors influencing the risk of developing side effects. Amiodarone is safe and effective drug at lower doses. It can be well tolerated at lower doses. Most of the side effects are mild and do not limit the use of the drug. However, many of the side effects develop only after prolonged periods of therapy. Hence, a careful follow up and monitoring of parameters like serum creatinine, thyroid hormones, liver enzymes on regular basis is essential.

5.1. Limitations

The study was carried out on a small population.

5.2. Future directions

The study should be carried out in a large population to get more accurate results; a drug with fewer side-effects should be discovered.

Conflicts of interest

None.

Consent

Written informed consent was taken from the participants in their own language. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Dr Calambur Narasimhan, Dr Daljeet K: decided on the study topic and the objectives for the study; finalized the manuscript. Nabeela Fatima, Fatima Khatoon, Juveria Badar, Syeda Fatima: collected the data and filled the data collection forms, analyzed the data, prepared the initial manuscript. Dr Wali Mohammed reviewed the results and edited the manuscript. Dr Kiranmai Mandava edited, revised and made the final manuscript.

Ethical approval

This study was approved by Institutional Ethics Committee- Asian Institute of Gastroenterology (IEC-AIG), Somajiguda, India. (**Ref: ECR/346/Inst/AP/2013/RR-19**).

Funding sources

No funding was received to carry out the study.

Registration of research studies

Name of the registry: CLINICAL PROFILE AND SIDE EFFECTS OF CHRONIC USE OF ORAL AMIODARONE IN CARDIOLOGY OUT-PATIENTS DEPARTMENT (CLIPSE-A Study)
Unique Identifying number or registration ID: **Regd No: ECR/346/Inst/AP/2013/RR-19.**
Hyperlink to your specific registration (must be publicly accessible and will be checked):

Provenance and peer review

Not commissioned, externally peer reviewed.

Guarantor

Nabeela Fatima, Dr. C Narasimhan, Dr Daljeet K, Dr Walli Mohammed.

Acknowledgement

Deepest gratitude to Dr. C Sridevi, who welcomed us with a lot of enthusiasm and trust to carry out our research project. The continual inspiration and supervision of the entire Cardiology and Electrophysiology department of AIG Hospital, assisted us in completing this study.

We'd like to thank Dr. Ajit Singh, Dr. T. Keerthi, and Dr. Kezia Sam for their timely inputs to our research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.104167.

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