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Review

# Amiodarone in ventricular arrhythmias: still a valuable resource?

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Ventricular arrhythmias still represent an important cause of morbidity and mortality, especially in patients with heart failure and reduced left ventricular ejection fraction. Amiodarone is a Class III Vaughan-Williams anti-arrhythmic drug widely used in ventricular arrhythmias for its efficacy and low pro-arrhythmogenic effect. On the other hand, a significant limitation in its use is represented by toxicity. In this review, the pharmacology of the drug is discussed to provide the mechanistic basis for its clinical use. Moreover, all the latest evidence on its role in different clinical settings is provided, including the prevention of sudden cardiac death, implanted cardioverter defibrillators, ischemic and non-ischemic cardiomyopathies. A special focus is placed on everyday clinical practice learning points, such as dosage, indications, and contraindications from the latest guidelines.

*Keywords*

Amiodarone; Heart failure; Ventricular tachycardia; Catheter ablation; Pharmacology

## 1. Introduction

Amiodarone is one of the most widely used anti-arrhythmic drugs (AAD) [1–3], and an option to treat ventricular arrhythmias (VAs) in the context of heart failure (HF). The aim of this review is to discuss the role of amiodarone, in the era of optimal medical therapy (OMT), ablation therapy, and implantable cardiac devices.

## 2. Pharmacology

### *2.1 Pharmacodynamics and pharmacokinetics*

Amiodarone ($C_{25}H_{29}I_2NO_3$) is a smalliodinated benzofuran derivative. Since the late 60s, amiodarone was used against angina pectoris, because of its vasodilatatory effects, likely mediated by the cyclooxygenase pathway, the activation of nitric oxide synthase, and the blockade of alpha-adrenergic receptors [4]. As a result of its high efficacy and its very low incidence of pro-arrhythmogenic effects, amiodarone is still widely used. Through the inhibition of potassium channels (class III AAD following Vaughan-Williams classification), it has a role in prolonging the phase 3 (i.e., myocyte repolarization) of the cardiac action potential; it also prolongs the myocyte refractory period, especially on sinus and atrioventricular nodes, with no impact on the bundle of His and the Purkinje fibers. Despite belonging to class III AAD, the acute administration of amiodarone shows slightly different effects including non-competitive beta-blocker effects (class II AAD) and sodium channel inhibition (class I AAD); it also causes shortening of the action potential in the Purkinje fibers and a slowing-down effect on the conduction through the AV node as a result of its effects on the calcium channels (class IV AAD) [5]. This behavior might also explain the relative safety of acute amiodarone i.v. administration in life-threatening VA. Given the complex pharmacodynamics of amiodarone and other drugs, a new classification of AAD based on their actions on arrhythmogenic mechanisms has been proposed, "The Sicilian Gambit" [6].

Amiodarone administration requires a loading dose and a maintenance regimen that has been established on the basis of clinical experience and pharmacokinetics experiments [7] (Table 1). Amiodarone's calculated half-life reaches one or two months, mainly due to the prolonged terminal elimination phase. Nevertheless, half-life variability is present after a single dose, depending on the rapid uptake into lipophilic tissues; furthermore, the complex kinetics of distribution and

**Table 1. Posology schemes for intravenous route and oral route.**

| | Loading dose | Maintenance dose |
|---|---|---|
| Intravenous route | 300 mg in 1 hr (50 mL/h) | 600 mg in 12 hr (20 mL/h) |
| Oral route | 600 mg twice a day for ten days | 200–400 mg once a day |

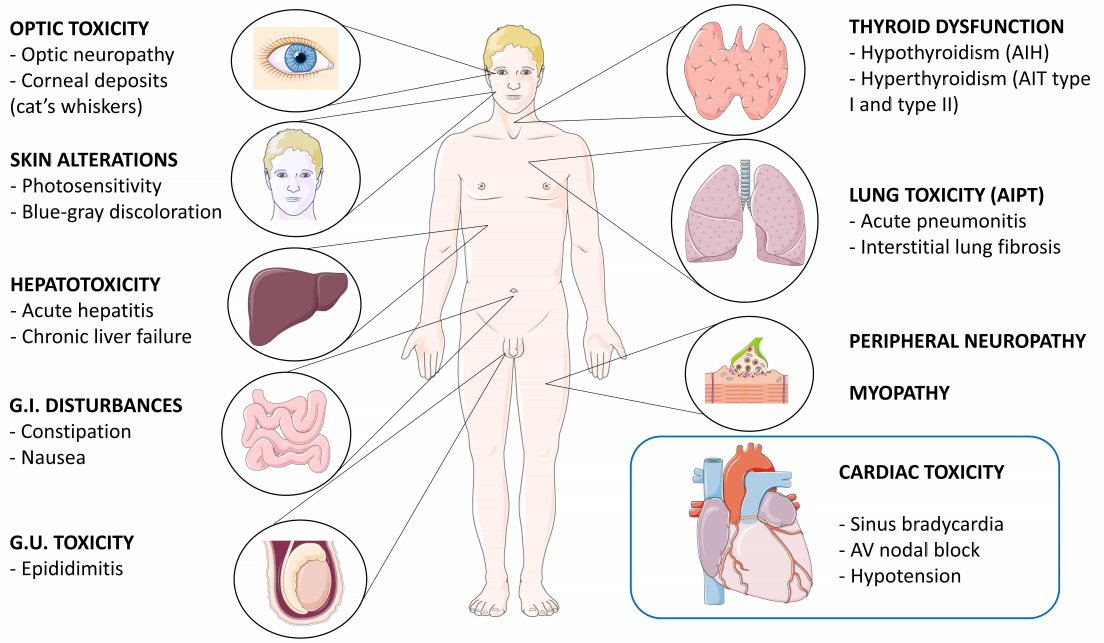


**Fig. 1. Amiodarone side effects.** Amiodarone side effects include: optic toxicity, skin alterations, hepatotoxicity, gastrointestinal problems, epididymitis, thyroid dysfunction, lung toxicity, peripheral neuropathy and myopathy, cardiac toxicity.

elimination and the presence of active metabolites (principally desethylamiodarone [DEA]), prolong its effect [8, 9]. From a practical point of view, 2–3 days of therapy discontinuation is usually sufficient to revert amiodarone effects, including the most acute side effects, such as bradycardia.

Amiodarone is almost exclusively metabolized by the liver, mainly by cytochrome CYP3A4 with a contribution of cytochrome 1A1 and 2C8, which are moderately inhibited by amiodarone itself. Drug metabolism is therefore sensitive to inhibitors of cytochromes (e.g., grapefruit juice, ketoconazole, clarithromycin, HIV protease inhibitors, and HCV medication sofosbuvir) and to pharmacometabolic inducers (e.g., rifampicin, phenobarbital, phenytoin, carbamazepine, nevirapine, efavirenz and pioglitazone).

### *2.2 Adverse effects*

Despite its efficacy, amiodarone use is associated with several side effects that should be considered in clinical practice. Furthermore, it should be noted that no specific therapies or antidotes for amiodarone toxicity have been established (Fig. 1).

Acute intravenous administration of amiodarone, if not performed in a proper way (especially when a loading dose is administered), can induce hypotension, bradycardia, and heart block. However, reducing the rate of infusion can help to avoid the necessity to interrupt the administration. Hypotension is not directly related to amiodarone, but it is an effect of the solvent polysorbate. Hence, amiodarone preparations without a solvent (e.g., "aqueous amiodarone") are devoid of such effects. All of the adverse effects of amiodarone discussed in the following sections are associated with its chronic oral use; therefore, intravenous administration of amiodarone does not cause such effects and is considered safe even in patients with thyroid disease.

#### *2.2.1 Thyroid*

A well-known and frequent side effect of amiodarone is dysthyroidism, and either hypo or hyper thyroid functionality can occur [8–10]. In particular, the presence of antithyroperoxidase antibodies increases the risk of hypothyroidism [11]. The leading mechanism seems to be related to the metabolic competition between amiodarone and levothyroxine. In particular, amiodarone can play a crucial role in the partial inhibition of peripheral type I deiodinase and in the central type II deiodinase (in the hypothalamic-pituitary tract). In the event of hypothyroidism, when amiodarone is the only available antiarrhythmic option, levothyroxine replacement therapy should be started. A larger dose of levothyroxine is often required to counteract amiodarone's inhibitory effects on deiodinase enzymes.

Two different types of hyperthyroidism induced by amiodarone have been described: the type I hyperthyroidism (T1H) occurs in normal thyroid glands and is mediated by

the abnormal synthesis and release of thyroid hormones. The type II hyperthyroidism (T2H) occurs when a destructive thyroiditis leads to a release of thyroid hormones from damaged follicular cells. If amiodarone is deemed necessary for life-threatening arrhythmias it can be continued while treating the hyperthyroidism. Thionamides are the best drug solution in the case of T1H, but not in the case of T2H, where glucocorticoids can be effective because of their anti-inflammatory effects.

#### *2.2.2 Lungs*

In 5–10% of cases, the lungs can be affected by amiodarone toxicity [12], which usually occurs after several weeks or months of chronic therapy. Both direct toxicity and an immunologic reaction are implicated in pulmonary side effects, such as interstitial aseptic pneumonitis. Acute lung toxicity is associated with high mortality in up to 50% of cases and, albeit rare, can also occur as an idiosyncratic reaction or more often associated to recent lung surgery or pulmonary angiography. In this event of lung toxicity, stopping amiodarone and administering corticosteroids is the standard treatment, although it might be insufficient due to the long half-life of amiodarone [13].

#### *2.2.3 Liver*

Abnormal hepatic function tests, are a rather common finding during chronic amiodarone treatment, with up to half of patients being diagnosed with cirrhosis, hepatitis, or jaundice. Therefore, a 6-month monitoring of liver function is advised.

However, it must be underlined that the presence of areas in the CT scan of the liver with higher than normal densities may be a result of the accumulated iodinated drug and may not indicate real liver damage [14].

High dose intravenous administration can also lead to liver toxicity, although occurrences of liver insufficiency are rare. The mechanism of acute toxicity from intravenous amiodarone administration is different from the one involved in prolonged oral administration, possibly involving also hypoperfusion of the tissue [15]. In rare cases, Reye's syndrome has been associated with amiodarone therapy in children [16]. The molecular mechanism is unknown, but it may be related to non-specific damage of the mitochondria, lysosomes, and membranes in general [17].

#### *2.2.4 Eyes*

Keratopathy due to the deposition of micro-deposits is often present, even if asymptomatic, in chronic amiodarone therapy [18]. This deposition has been proposed as a biomarker to monitor amiodarone therapy and toxicity by corneal densitometry. Other ophthalmic conditions (e.g., optic neuropathy or non-arteritic anterior ischemic optic neuropathy) occur rarely and are not dose-dependent [19].

#### *2.2.5 Skin*

Skin involvement may appear after several months (or years) of amiodarone use with a typical long-lasting grayish discoloration of the skin and a certain degree of photosensitivity. Therefore, patients are advised to avoid exposure to the sun and to use sunscreens [20].

#### *2.2.6 Other systems*

Non-specific side effects, usually reverted by dosage adjustment, have been reported especially during the loading dose period at the level of the nervous (e.g., ataxia, paresthesia, tremor and peripheral neuropathy) and gastrointestinal (e.g., constipation and nausea) systems. Very rare adverse events concerning the bone marrow (e.g., suppression or granuloma-induced pancytopenia) have also been reported as well as a modest increase in the risk of cancer (borderline significance in men receiving high doses) [19].

## 3. Amiodarone and electrocardiographic effects

There are numerous drugs that can cause electrocardiogram (ECG) changes, and the diagnosis of abnormal ECGs encountered in a specific toxicity can challenge experienced physicians [19, 21].

Alterations of the T wave (which can become bifid), QT prolongation and, less frequently, the appearance of U-wave, are often associated with amiodarone, even though these signs should not be considered as an expression of drug toxicity [22, 23].

Symptomatic sinus bradycardia, AV block of 2nd or 3rd grades (in less than 2% of patients), SA blocks or SA node dysfunction require drug suspension. Other uncommon side effects include Torsade de Pointes (TdP) [24] and asystole. TdP is not related only to the drug, but it occurs, in most cases, concomitant with other factors, like the use of drugs that prolong QT, Long QT Syndromes, Electrolyte Disorders (ex. hypokalemia), etc. Therefore, the administration of amiodarone alone is rarely associated to TdP [24–26]. In fact, with Amiodarone, the QT dispersion, a trigger to the onset of TdP, remains unchanged [27]. Rather, amiodarone can reduce the transmural dispersion of repolarization without causing dispersion in the duration of the action potential in the different ventricular areas, avoiding afterdepolarizations potentials [28]. The only remarkable exception is represented by the QTc longer than 500 ms, and in these cases, the drug should be discontinued because of the risk of TdP [27, 28]. The risk of TdP is also increased when the QTc interval becomes prolonged more than 60 ms compared with the pretreatment value [29–31].

## 4. Acute treatment of ventricular arrhythmias

The first study of amiodarone in the acute treatment of VAs was conducted in patients with hemodynamically unstable VAs refractory to lidocaine, procainamide, and bretilyum.

**Table 2. European guidelines for amiodarone use in heart failure.**

| Recommendation | Class of evidence | Level of evidence |
|---|---|---|
| Amiodarone should be considered in patients that are symptomatic due to PVCs or NSVTs, or if PVCs or NSVTs contribute to reduced LVEF | II a | B |
| Amiodarone should be considered to prevent VT in patients with or without an ICD | II a | C |
| Amiodarone or catheter ablation is recommended in patients with recurrent ICD shocks due to sustained VT | I | B |
| Amiodarone or catheter ablation should be considered after a first episode of sustained VT in patients with an ICD | II a | B |

Acute treatment with amiodarone has shown a 46% success rate in restoring cardiac rhythm in patients with ventricular tachycardia/ventricular fibrillation (VT/VF) [32]. Hypotension was observed as a dose-related effect, but when compared to bretylium, amiodarone showed fewer side effects with similar survival rates in patients with hemodynamically unstable VAs [33]. In a similar subset of patients with incessant or recurrent hemodynamically destabilizing VTs refractory to AAD, intravenous (i.v.) amiodarone administration reduced VT/VF event rates and increased the time to first recurrence with a dose related effect [34].

In the acute treatment of incessant VTs (more than 50% hemodynamically unstable) refractory to direct current cardioversion (DC shock), when compared to i.v. lidocaine, i.v. amiodarone was found to significantly increase the acute VT termination (78 % vs 27%) and to improve survival rates at 1 hr and 24 hr after the arrhythmic event [35].

Amiodarone was also compared to procainamide in hemodynamically stable wide-QRS complex tachycardia (PROCAMIO trial): procainamide resulted in less adverse cardiac events than amiodarone 40 minutes after administration with a higher rate of VT termination (67% vs 38%). These results were also consistent in structural heart disease [36].

## 5. Primary prevention of sudden cardiac death in heart failure

Low left ventricular ejection fraction (LVEF) is a major risk factor for sudden cardiac death (SCD) [37]. Moreover, VAs are more frequent in heart failure with reduced ejection fraction (HFrEF) and can further deteriorate LVEF. ESC Guidelines' recommendations are listed in Table 2 [38].

The efficacy of amiodarone in HFrEF has been controversial. In the GESICA trial, adding amiodarone in patients treated with ace inhibitors, diuretics, digoxin but not beta-blockers, reduced hard endpoints like overall mortality, SCD, and hospitalizations. These results were independent from the reduction of arrhythmic burden [39].

However, subsequent trials did not confirm these findings. In patients with congestive heart failure and asymptomatic VAs, who had not been extensively treated with beta blockers, amiodarone was found to have no effect on SCD and overall mortality despite significantly suppressing VAs and increasing LVEF. A trend toward a reduction in mortality rates among patients with non-ischemic cardiomyopathies was found, which may explain the results of GESICA trial, where the proportion of patients with ischemic heart disease was lower [40].

After the introduction of ICD in the primary prevention of SCD, different trials compared it to amiodarone. The SCD-HeFT was conducted in patients with a LVEF of less than 35% and optimal medical therapy (OMT) for HF. It compared ICD to amiodarone or placebo, and found a reduction in overall mortality with ICD compared to amiodarone and placebo and no difference between amiodarone and placebo.

## 6. Premature ventricular complex-induced cardiomyopathy

Patients with frequent premature ventricular complexes (PVCs) are at risk of developing ventricular dysfunction and dilatation, a condition named as "premature ventricular complex-induced cardiomyopathy" (PIC). Suppression of ventricular ectopy, with either ablation therapy or antiarrhythmic drugs, has been demonstrated to reverse the systolic dysfunction observed in PIC [38, 39, 41].

The STAT CHF trial randomized 674 patients with symptoms of congestive heart failure, LVEF $\leq$40%, or 10 or more PVCs/hour, to either amiodarone or placebo. At two-year follow-up, no difference in the primary endpoint of overall mortality was observed, but a striking reduction in the PVCs frequency in the amiodarone group (from 254 $\pm$ 370/hour to 44 $\pm$ 145/hour ($p < 0.001$) at three months) was recorded. This result was accompanied by a statistically significant increase of approximately 9% in the LVEF in the amiodarone group, while LVEF was unchanged in the control group. Of note, approximately 70% of patients presented with an ischemic etiology for heart failure, giving rise to the hypothesis that frequent PVCs mediate and contribute to systolic dysfunction. For this reason, PVCs suppression may become a target to enhance recovery of systolic function.

Because of its side effects, routine amiodarone use in idiopathic PIC it is not recommended. Especially in young patients, catheter ablation is the preferred option.

## 7. Left ventricular assist devices

Left ventricular assist devices (LVADs) are increasingly used in end-stage HFrEF. VAs in LVAD patients can occur with different mechanisms: (1) reentry circuits in scar areas or (2) suction events with a contact of the inflow cannula with ventricular walls [42].

One study analyzed amiodarone in LVAD patients and reported that patients with LVAD and contemporaneous ther-

apy with amiodarone were more likely to have CRT-D implanted and had a higher VAs burden. Amiodarone use prior to LVAD implantation and continued after implantation was independently associated to an increased mortality via multivariate regression [43].

In another retrospective analysis, the use of amiodarone and/or beta-blockers did not appear to reduce the burden of VAs in patients with LVAD, and the use of both AADs was associated with the highest number of readmissions [44].

## 8. Secondary prevention of sudden cardiac death and ICD

Different studies demonstrated that amiodarone should be considered in patients with documented spontaneous sustained VT or cardiac arrest unresponsive to other AADs; the recommendation is based on its effects in reducing the recurrence rate of sustained VT, VF, and cardiac arrest. The efficacy of amiodarone was consistent with different etiologies. The risk factors for SCD during amiodarone therapy were coronary artery disease (CAD), low LVEF and history of cardiac arrest [45].

MADIT trials opened a new era in the prevention of SCD, introducing the implanted cardiac defibrillator (ICD) [44–47] both in primary and in secondary prevention. Since then, different trials have compared amiodarone with ICD in different clinical settings.

The AVID trial was conducted in secondary prevention among patients with resuscitated VT or VF. It demonstrated that ICD improved survival when compared with amiodarone. In the subgroup analysis, there was no statistically significant difference between treatments in patients with an ejection fraction of more than 35% and in patients with non-ischemic heart disease [48].

These results, were later confirmed by the CASH trial. In patients with resuscitated VT or VF and a mean ejection fraction of 46%, ICD was superior to amiodarone or metoprolol for all-cause mortality but the benefit was not statistically significant [49].

The CIDS trial, conducted in the same clinical setting as the AVID and CASH trials, demonstrated a non-statistically significant reduction in all-cause and arrhythmic mortality with ICD therapy compared with amiodarone. These results can be explained by less consistent use of beta-blockers in the ICD group and more consistent use in the amiodarone group, which indicates a potential synergistic effect of amiodarone and beta blockers.

Amiodarone therapy is often used concomitantly with an ICD implantation to reduce VA burden and appropriate and inappropriate ICD shocks. The rationale behind the use of AADs with a defibrillator is that ICD is effective in most but not all VT/VF episodes; indeed, shock is ineffective in up to 9% of patients in the Umbrella registry [50]. Thus, reducing the VA burden can reduce the incidence of refractory VAs. Furthermore, appropriate and inappropriate ICD shocks are associated with an increase in mortality [51], and a reduction in rates of shocks may have a benefit on survival.

The randomized CASCADE study was conducted in secondary prevention of survivors of out of hospital cardiac arrests (OHCA) due to VF and thought to be at high risk of recurrence because of CAD or heart failure. Amiodarone, compared to class I AAD, reduced endpoints of cardiac death, cardiac arrest from ventricular fibrillation with resuscitation, and rates of ICD shock [52].

In a retrospective Japanese study, amiodarone did not reduce mortality and arrhythmic events compared to the placebo in patients with ICD, but a significant reduction in inappropriate shocks was observed with amiodarone [53].

The OPTIC trial was conducted in patients with reduced LVEF and documented or inducible VT/VF who underwent ICD implantation. It demonstrated that amiodarone plus beta-blockers reduced ICD shocks compared to beta-blockers alone or to sotalol [54].

The efficacy of amiodarone in reducing inappropriate shocks was confirmed in patients with ICD both in secondary and in primary prevention that were at high risk of inappropriate shocks because of AF or CHF (NYHA at least III). In this clinical setting, amiodarone was superior to beta blockers and showed a non-significant benefit compared to sotalol [55]. The reduction of inappropriate shocks can be explained by the antiarrhythmic effects of amiodarone, not only on VAs but also on supraventricular arrhythmias.

Finally, the ALPHEE trial was designed to investigate the efficacy of another AAD, celivarone, versus placebo in preventing ICD interventions or death in patients with LVEF less than 40% and at least one ICD intervention. Amiodarone was used as a calibrator. Celivarone was not superior to the placebo, but interestingly, amiodarone, compared to the placebo, reduced the VT/VF-triggered ICD intervention and the incidence of SCD [56].

Catheter ablation is an effective and safe alternative to reduce ICD shocks [57]. In patients with ischemic cardiomyopathy and an ICD, who had VT despite an AAD therapy, the VANISH trial compared catheter ablation with escalation in AAD therapy, including amiodarone; ablation was superior for the outcomes of death, ventricular tachycardia storm, and appropriate ICD shock [58].

## 9. Cardiac arrest and resuscitation

Amiodarone use in cardiac arrest during a resuscitation protocol has been assessed by the ARREST and ALIVE trials [59, 60]. In both trials amiodarone demonstrated increased rates of survival at admission to the hospital. Subsequent studies and meta-analysis showed that amiodarone and lidocaine equally improve survival at hospital admission but no improvement in the long-term outcome was observed [61, 62]; furthermore, its effect is reduced in hypothermic cardiac arrest [63]. This clinical outcome was confirmed also when other drugs were considered; in a meta-analysis, the benefits of esmolol and bretylium against placebo or of

**Table 3. European guidelines for amiodarone use in CAD.**

| Recommendation | Class of evidence | Level of evidence |
|---|---|---|
| Intravenous amiodarone is recommended for the treatment of VT, expecially if polymorphic, if not controlled by successive electrical DC shocks | I | C |
| Intravenous amiodarone is recommended for the treatment of VF after ACS if not controlled by successive electrical DC shocks | II a | |
| Amiodarone should be considered in emodinamically relevant NSVT | II a | |
| Profilactic treatment with AADs other than beta-blockers is not recommended | III | B |
| In stable coronary artery disease (CAD) amiodarone may be considered for relief of symptoms in symptomatic but not life-threatening VAs (PVCs or short and slow NSVT) in survivors of a myocardial infarction but it has no effect on mortality | II b | B |

nifekalant against lidocaine were demonstrated only for survival to admission [64]. Cardiac resuscitation protocol guidelines recommend: (1) To administer 300 mg IV amiodarone for adult patients in cardiac arrest who are in VF/pVT after three shocks have been administered; (2) To administer an additional dose of 150 mg IV amiodarone for adult patients in cardiac arrest who are in VF/pVT after five shocks have been administered; (3) 100 mg IV Lidocaine may be used as an alternative if amiodarone is not available or if a local decision has been made to use lidocaine instead of amiodarone. An additional bolus of 50 mg lidocaine can also be administered after five defibrillation attempts [65, 66].

Despite the higher rates of return of spontaneous circulation, in the recent ROC-ALPS trial, neither amiodarone nor lidocaine demonstrated better survival rates with good neurological outcomes or greater likelihood of hospital discharge [67].

In particular, the authors reported that among 1934 patients with bystander-witnessed arrest, the survival rate was higher with amiodarone (27.7%) or lidocaine administration (27.8%) than with placebo (22.7%), ($p$ = NS). Subanalysis showed a survival benefit only in bystander-witnessed out-of-hospital cardiac arrests, with either amiodarone or lidocaine yielding a 5% reduction in mortality [68], underling the importance of early recognition and treatment of cardiac arrest besides AAD [69].

## 10. Cardiomyopathies

### *10.1 Ischemic heart disease*

VAs represent the major cause of death in patients with acute coronary syndromes (ACS). Despite an early reperfusion strategy, the rate of in hospital sustained VT/VF is 4.7% in STEMI [70] and 2.6% in NSTEMI [71]. The ESC recommendations on the use of amiodarone in this setting are listed in Table 3 [72, 73].

The CAST trials [74] tested the hypothesis that reducing the burden of PVCs in patients after a myocardial infarction (MI) would reduce mortality. The results demonstrated that class IC AADs, such as encainide, flecainide, and moricizine were effective in suppressing VAs but increased overall mortality, cardiac deaths, and arrhythmic deaths.

Amiodarone was effective in suppressing VT where other class I AADs had failed [75]. In patients with recent MI, with contraindications to beta-blockers, amiodarone reduced VAs, overall mortality, cardiac mortality, and SCD [76–78]; these results were consistent both in primary prevention and in patients with asymptomatic multiform or repetitive PVCs [62, 63].

In patients with CAD and HFrEF, amiodarone has shown conflicting results. The first reports, before the use of beta-blockers, did not find amiodarone to be effective in preventing SCD in patients with LVEF of 40% or less [79].

On the other hand, in patients treated consistently with beta-blockers, amiodarone demonstrated a significant reduction of SCD, even in patients with reduced LVEF after a recent MI. However, amiodarone did not reduce all-cause mortality, in part because of its adverse side effects [80].

In the GEMICA trial, the prophylactic use of high doses of amiodarone in recent ACS increased mortality. This outcome was driven by an increase in non-cardiac deaths. In the same trial low doses of amiodarone failed to show any significant difference in mortality compared to the placebo. Low dose amiodarone was not harmful, and a non-significant trend towards a reduction in mortality was observed [81].

### *10.2 Non ischemic dilated cardiomyopathy*

Holter monitoring studies have demonstrated that PVCs (often multifocal) are present in up to 90% of patients with non-ischemic dilated cardiomyopathy (NIDCM), while non-sustained VT is seen in 40% to 60% of cases [82]. Amiodarone should be considered in patients with an ICD that experience recurrent appropriate shocks despite optimal device programming (Class IIa, ESC guidelines) [83], but it should not be used to treat asymptomatic episodes of non-sustained VT (NSVT) (Class III A, ESC guidelines). According to current AHA/ACC/HRS Guidelines [84], in patients with NIDCM who survive a cardiac arrest, have sustained VT, or have symptomatic VAs who are ineligible for an ICD (due to a limited life-expectancy and/or functional status or lack of access to an ICD), amiodarone may be considered for the prevention of SCD.

Current recommendations for amiodarone in patients with NIDCM are based on several randomized trials. The AMIOVIRT trial [85] was conducted in NIDCM patients

with reduced LVEF and asymptomatic NSVT. Patients were randomized to an ICD group or an amiodarone group. Total mortality was not found to be statistically different between groups; however, there was a trend towards amiodarone being more effective than ICD in arrhythmia free survival.

Furthermore, in the CHF-STAT trial, which was conducted in patients with HFrEF and asymptomatic VAs (at least 10 PVCs per hour), amiodarone was found to be ineffective in preventing SCD and overall mortality, despite significantly suppressing VAs and increasing LVEF. Interestingly, a trend towards a reduction in mortality rates among patients with NIDCM was found [40].

#### *10.3 Hypertrophic cardiomyopathy*

According to current AHA/ACC/HRS Guidelines [84], amiodarone may be considered when an ICD is not feasible or not preferred by the patient to prevent the incidence of NSVT, which is associated with a substantial increase in sudden death risk in young patients with hypertrophic cardiomyopathy (HCM) [86].

Conversely, in recent retrospective studies, amiodarone failed to prevent SCD, which occurred with a reported incidence of 20% in patients on amiodarone [87]; however, combined low-dose amiodarone plus a beta-blocker in HCM patients with malignant VAs significantly shortened QT dispersion and reduced the incidence of PVCs and VT [88].

#### *10.4 Arrhythmogenic cardiomyopathy*

About two-thirds of patients with arrhythmogenic cardiomyopathy (AC) will experience VAs, usually from the right ventricular scar. According to the ESC guidelines on the prevention of SCD [89], beta blockers, in particular sotalol titrated to the maximal tolerated dose, are recommended as the first-line therapy to improve symptoms in patients with frequent PVCs and VT (Class I C).

Amiodarone is considered a second line drug in patients who are intolerant or have contraindications to beta-blockers (Class IIa C). There is little evidence about combination therapy of amiodarone and beta-blockers although they may have a synergistic effect in the treatment of AC [90].

## 11. Conclusions

VAs still represent an important cause of morbidity and mortality, especially in patients with heart failure and reduced LVEF. Amiodarone is a powerful tool in the treatment of VAs, but its common and often severe side effects prompt judicious use based on guidelines and clinical practice.

## Author contributions

LP—substantial contributions to research design; drafting the paper; approval of the submitted and final versions. GDA—substantial contributions to research design; drafting the paper; approval of the submitted and final versions. SG—substantial contributions to research design; approval of the submitted and final versions. GF—drafting the paper; approval of the submitted and final versions. LB—drafting the paper; approval of the submitted and final versions. AF—substantial contributions to research design; approval of the submitted and final versions. LC—drafting the paper; approval of the submitted and final versions. LB—substantial contributions to research design; drafting the paper; approval of the submitted and final versions. PO—drafting the paper; approval of the submitted and final versions. FM—substantial contributions to research design; revising the paper critically; approval of the submitted and final versions. GDB—substantial contributions to research design; drafting the paper; approval of the submitted and final versions. LM—substantial contributions to research design; drafting the paper; approval of the submitted and final versions. GL—substantial contributions to research design; revising the paper critically; approval of the submitted and final versions. AM—substantial contributions to research design; revising the paper critically; approval of the submitted and final versions. PDB—substantial contributions to research design; drafting the paper; approval of the submitted and final versions. DZ—substantial contributions to research design; drafting the paper; approval of the submitted and final versions. PV—substantial contributions to research design; drafting the paper; approval of the submitted and final versions. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.


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