Human & Veterinary Medicine
International Journal of the Bioflux Society HVM

OPEN ACCESS
Research Article

# Short term amiodarone treatment on inflammatory and cardiac biomarkers in patients with ischemic heart disease and paroxysmal atrial fibrillation

**[1,2]Alin Ionut Grosu, [1,2]Dan Radulescu, [1]Laura Cristina Grosu, [1,3]Dana Pop**

**[11] "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; [2]Cardiology Department, Clinical Municipal Hospital, Cluj-Napoca, Romania; [3] Cardiology-Rehabilitation Department, Clinical Rehabilitation Hospital, Cluj-Napoca, Romania.**

**Abstract.** Background: Paroxysmal atrial fibrillation in ischemic increases morbi-mortality, and amiodarone is the most effective antiarrhythmic drug for rhythm control. Our aim was to evaluate the influence of amiodarone on some inflammatory and cardiac biomarkers in these patients. Patients and Methods: We conducted a prospective case-control study on 100 ischemic patients. 50 patients were treated with amiodarone for paroxysmal atrial fibrillation, and 50 patients with documented paroxistic atrial fibrillation and no amiodarone therapy. The subjects were evaluated at the beginning and had a 3 months follow-up. Results: Amiodarone significantly decreased the N-terminal prohormone of brain natriuretic peptide levels, with no impact on troponin T levels after 3 months. High-sensitivity C reactive protein and interleukin-6 levels were not influenced. Conclusion: Our study emphasizes the beneficial effect of short-term amiodarone treatment on heart failure biomarkers in ischemic paroxysmal atrial fibrillation. No impact of amiodarone on inflammatory markers studied was identified.

**Key Words:** amiodarone, ischemic atrial fibrillation, inflammation, cardiac biomarkers.



**Corresponding Author**: L.C. Grosu; e-mail: laura.c.grosu@gmail.com

## Introduction

Being one of the most common causes of mortality, coronary artery disease (CAD) is accounted for more than 7.4 million deaths every year (Benjamin et al 2017). The coexistence of CAD and atrial fibrillation (AF) worsens the prognosis and requires serious treatment customization. Although the presence of AF increases mortality in patients with myocardial infarction (MI), the results are questionable in those with heart failure (HF). AF increases mortality only in patients with ischemic HF ( Pedersen et al 2006).

There has been no remarkable progress in antiarrhythmic drug therapy in recent years and amiodarone (AM) still remains the main antiarrhythmic drug in patients with CAD and AF. With up to 3 million annual prescriptions in the United States, AM is the drug of choice for maintaining the sinus rhythm (Goette et al 2012). The drug's efficacy is partially overshadowed by its adverse reactions that occur up to 50% of cases, especially on the thyroid, heart, liver and lungs. AM is the only medication approved for conversion and for long-term rhythm-control therapy in AF patients with HF with reduced ejection fraction, or severe aortic stenosis, (Kirchhof et al 2016). The onset of AF is favored by increased potassium channels conductance, and AM blocks these channels enhancing its antiarrhythmic effect (Dehghani-Samani et al 2019). AM also down-regulates beta-adrenergic receptors, exerts an important "verapamil-like" effect, inhibits the effects of thyroid hormones in the heart and modulates the autonomic nervous system (Nokin et al 1983; Wagner et al 1990; Shabalin et al 2002). Besides the electrophysiological effects, recent data suggests that AM has anti-inflammatory properties that contributes to its antiarrhythmic effects.

Interleukin 6 (IL-6) is a unique pleiotropic cytokine with both pro-inflammatory and anti-inflammatory properties that vary depending on the targeted cells. AF subjects exerts increased IL-6 plasmatic levels compared with normal population and are associated with an increased thrombotic risk in these patients (Deng et al 2013). IL-6 enhances the production of acute-phase proteins after myocardial ischemia, protects against cardiomyocyte apoptosis and triggers additional cellular inflammatory responses (Huang et al 2017).

High-sensitivity C reactive protein (hs-CRP) is the most studied and used biomarker of systemic inflammation in current practice. Elevated hs-CRP levels are associated with CAD (Casas et al 2008) and with an increased risk of AF, but per se does not increase the AF risk (Marott et al 2013). Moreover, persistent AF is correlated with higher hs-CRP levels and with left atrium (LA) enlargement, thus it is still unclear whether hs-CRP and the inflammatory state determines LA remodelling or the remodelling process from AF increases hs-CRP levels (Watanabe et al 2005).

Being one of the most used cardiac biomarkers, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) has proved its usefulness in diagnosis, treatment guidance, risk and prognosis assessment in patients with HF or CAD. The synthesis of NT-proBNP is stimulated mainly by the increase in ventricular pressure which causes myocyte stretching, but it can also be the result of neurohormonal activation, stimulation of cardiac fibroblasts and hypoxia, changes occurring in CAD. Brain natriuretic peptide (BNP), the final product of NT-proBNP increases diuresis and vasodilation and decreases the renin-angiotensin-aldosterone system (RAAS) (Hall 2005).

Besides the acute coronary syndrome, high-sensitivity troponin T (hsTnT) may provide strong prognostic information in patients with stable CAD, HF and even in healthy population. In AF, cardiac troponin levels are increased in a significant proportion of patients and independently predicts a worse outcome and greater cardio-embolic risk (Costabel et al 2017).

Study design

This is a prospective case-control study in which we aimed to assess the impact of short-term AM therapy (3 months) on inflammatory markers (IL-6, hs-CRP) and cardiac biomarkers (NT-proBNP, hsTnT) in patients with CAD and paroxysmal atrial fibrillation (PAF).

# Materials and methods

CAD has been defined as prior myocardial infarction, prior coronary revascularization, coronary heart disease confirmed by coronary angiography, perfusion defects induced by stress myocardial scintigraphy or positive dobutamine stress echocardiography. PAF has been defined as an episode of AF which lasts at least 30 seconds and terminates spontaneously or following pharmacological or electrical conversion in less than seven days, recorded either by resting ECG or during 24h ECG Holter monitoring. All patients were clinically evaluated in the Cardiology Department of the Cluj Municipal Clinical Hospital, Cluj-Napoca, Romania between January 2017 and May 2018. The present clinical study was approved by the local Ethics Committee and was performed in accordance with the principles of the Declaration of Helsinki (1964) and its later amendments. All patients included in this study have signed the informed consent form and were assigned to one of the two study groups.

**Amiodarone Group (A)**

A number of 61 consecutive patients with stable CAD and PAF were included in this study group. Inclusion criteria: minimum age of 18 years, signed informed consent form, documented CAD, PAF recorded either during resting ECG or by 24-hour ECG Holter monitoring, no contraindication for AM therapy, free of AF in the last 7 days, no signs or symptoms of HF in the last 14 days. Exclusion criteria: severe cognitive impairment, severe kidney failure defined as creatinine clearance <30 ml/min/m2, documented autoimmune diseases, acute or chronic infections, concomitant oral or inhalation corticotherapy, contraindication for oral AM therapy, hormone substitution therapy, hematological diseases.

All patients received AM as a strategy of rhythm control, as recommended by the guidelines of the European Society of Cardiology (Kirchhof et al 2016). Treatment for CAD was conducted by the recommendations of the European Society of Cardiology for stable coronary heart disease (Montalescot et al 2013). All patients started oral AM therapy; standard regimen was 600 mg/day for week 1, 400 mg/day for week 2, then 200 mg daily; protocol that could be subject to changes based on heart rate and the QT interval. Patient follow-up was decided at 3 months, the time set as necessary for optimal loading with AM, considered for a minimum of 10 g. All patients underwent clinical, electrocardiographic, echocardiographic and biological evaluation at baseline and at 90 days (±5 days).

**Control Group (C)**

A number of 53 consecutive patients with stable CAD and PAF without AM treatment were included in this study group. Treatment for CAD was conducted in accordance with the recommendations of the European Society of Cardiology for stable coronary heart disease (Montalescot et al 2013). Inclusion criteria: minimum age of 18 years, signed informed consent form, documented CAD, PAF recorded either during resting ECG or by 24-hour ECG Holter monitoring, no signs or symptoms of HF in the last 14 days. Exclusion criteria: unstable CAD, severe cognitive impairment, severe kidney failure defined as creatinine clearance <30 ml/min/m2, documented autoimmune diseases, acute or chronic infections, concomitant oral or inhalation corticotherapy, hormone substitution therapy, hematological diseases. All patients in group C presented at the outpatient clinic as part of follow-up program.

All patients underwent clinical, electrocardiographic, echocardiographic and biological evaluation at baseline and at 90 days (±7 days).

**Evaluated biomarkers**

No special patient preparation was required for the dosing of NT-proBNP; it was analyzed from the venous blood extracted in a vacutainer with/without separator gel. The serum (minimum 0.5 ml) was then separated by centrifugation, the dosage was established by immunochemistry and electrochemiluminescence was used as a detection method.

For hs-TnT dosage no special patient preparation was required and we used the same technical method as described for NT-proBNP determination.

IL-6 and hs-CRP levels were analysed on an empty stomach, from at least 0.5 ml venous blood, extracted in a vacutainer without separator gel. Serum was separated by centrifugation and the dosage was established using latex-enhanced immunoturbidimetry for hs-CRP and chemiluminescence quantitative immunohistochemical determination for IL-6. Due to the variation in hs-CRP levels over 24 hours in patients with stable CAD and diurnal variation of circulating IL-6 in humans (17),(18), all blood samples were taken between 7 and 9 in the morning, in order to avoid physiological fluctuations.

**Statistical Analysis**

The data obtained were statistically analyzed using Microsoft Excel 2013 Data Analysis (Microsoft Corp.), and SPSS statistical software. Continuous data were descried as median and 25-75 percentiles (non-normal distribution). Comparison between measurements were carried out using the two-way ANOVA for repeated measurements. A p values was considered statistically significant.

## Results

A total of 114 patients were enrolled in the study, 11 patients were lost in group A and 3 patients in group C. There was a 16.4% rate of AM discontinuation at 3 months, the causes being shown in Figure 1. Baseline demographic characteristics of patients in both groups (A and C) are described in Table 1.

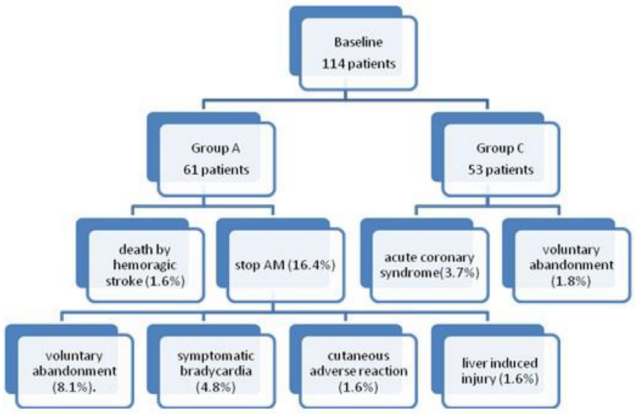


Fig. 1. Patients chart

Tabel 1. Patient demographic characteristics

| | Group A | Group C |
|---|---|---|
| **Age (years)** | 68.9± 6.2 | 67.5± 7.7 |
| **Gender (M=male)** | M 35 | M 33 |

**At baseline**

Regarding blood pressure values, no significant differences were observed at the first evaluation. Left atrium area was higher in group A (22 vs 20 $cm^2$).

Hs-TnT had slightly higher levels in both groups, the same results have been noticed for NT-proBNP levels and we did not find any statistical significance.

Concerning the inflammatory status, hs-CRP and IL-6 levels were evaluated in this study. At baseline, IL-6 levels did not differ between the two groups (Group A = 3.4 pg/ml, Group C = 3.3 pg/ml). The mean levels of hs-CRP were within the normal range in both groups, without any important differences (Group A = 0.4 ng/ml, Group C = 0.4 ng/ml).

**At 3 months**

All patients were re-evaluated after 3 months. They underwent clinical, electrocardiographic, biohumoral and echocardiographic evaluation.

At follow-up, diastolic blood pressure increased in AM patients, while it decreased in the control group, with statistically significant difference (Group A: 84 mmHg vs 84.5 mmHg; Group C: 83 mmHg vs 81 mmHg; p=0.001). AM significant decreased the heart rate with no alteration of systolic blood pressure.

At the end of the study left atrium area was lower in patients in group A and slightly increased in patients in group C (Group A: 22 vs 21 cm2; Group C: 20 vs 20.5 cm2; p=0.005), with a statistical significant change trend.

There was a significant decrease in NT-proBNP levels after the initiation of AM therapy in patients with PAF (355 pg/ml vs. 279.5 pg/ml, p=0.013). This was not observed in the control group, where there was no difference in NT-proBNP levels after 3 months (345 pg/ml vs. 337.5 pg/ml). Also, ACE inhibitors, BB, age and gender did not influence NT-proBNP. This is a universal trend and it is not based on important NT-proBNP changes of a small number of patients. There were no changes in Hs-TnT levels after 3 months of AM treatment (Group A = 38 µg/l vs. 36.5 µg/l, p=0.804), similar results were found in the control group (Group C = 37.5 µg/l vs. 39.5 µg/l, p=0.58).

When investigating the inflammatory status at 3 months, none of the patients in the AM group or the control group showed significant changes in IL-6 levels (Group A= 3.4 vs. 3.4 pg/ml; Group C= 3.3 pg/ml vs. 3.2 pg/ml, p= 0.446). At the end of the study, hs-CRP levels remained within the normal range in both groups of CAD patients (Group A= 0.400 mg/l vs. 0.385 mg/l; Group C= 0.400 mg/dl vs. 0385 mg/dl, p = 0.074). This is a universal trend and it is not based on important hs-CRP drops of a small number of patients.

Also, echocardiographic and electrocardiographic parameters, lipid panel, renal function, Thyroid-Stimulating Hormone, glycated haemoglobin, serum haemoglobin were evaluated. No significant changes were identified in any of these parameters. Their values are presented in the tables 2 and 3.

At study initiation, most patients were under specific treatment for CAD with ACE-inhibitors (Angiotensin-converting enzyme), statins and beta-blockers (BB). While a similar number of patients were under treatment with statins and ACE-inhibitors in both groups, BB were less used in group A. CAD specific medication are described in Table 4.

There is a high prevalence of type II diabetes mellitus (T2DM) among all patients with CAD, 34% of patients in Group A and 30% in Group C suffer from this disease. The mean value of glycated haemoglobin (HbA1c) was high in both groups, without any significant difference. Most diabetic patients in this study were under oral antidiabetic therapy, and the most commonly used molecule was metformin, the other oral agents used were in a smaller proportion (2 to 8% in both groups), In Group A 10% of patients were insulin-dependent vs. 6% in Group C. Mean daily doses of antihyperglycemic agents were similar, with the exception of insulin requirements that were higher in patients with AM (Table 5). To avoid bias and interference with inflammatory markers no changes in antidiabetic therapy were made during the study.

In terms of hypolipidemic treatment, the most commonly used statins were rosuvastatin and atorvastatin without any significant differences between groups (Table 6). No changes in dosage were made either at initiation or during the study in order to yield more relevant results.

## Discussion

AM is a drug with a high dropout rate due to multiple side effects. Compared to other studies showing high abandonment rate as 30-40%, in our study the discontinuation rate was evaluated as intermediate.

In AF, NT-proBNP is predominantly produced in the atria despite the presence of fewer myocardial cells (Knudsen et al 2016) and there are several studies showing that NT-proBNP levels are higher in AF patients than in those with normal sinus rhythm even in the absence of HF. In AF, the loss of atrial pump impairs LV diastolic filling with a reduced stroke volume and cardiac output, and an increased mean diastolic atrial pressure. NT-proBNP is produced and co-stored in atrial granules along

Tabel 2. Patients clinical and imaging parameters

| | Group | T0 | T1 | P |
|---|---|---|---|---|
| **SBP (mmHg)** | C | 134 (124; 145) | 134 (124.7; 142) | 0.332 |
| | A | 134 (124; 143.5) | 133.5 (125.7; 144.5) | |
| **DBP (mmHg)** | C | 83 (71; 97) | 81 (71; 88.5) | 0.001 |
| | A | 84 (74.2; 95) | 84.5 (77; 96) | |
| **LVEF (%)** | C | 57 (54; 58) | 55.5 (54; 58) | 0.883 |
| | A | 55 (51.7; 58) | 54.5 (52; 58) | |
| **LA area (cm2)** | C | 20 (18; 22) | 20.5 (18.7; 22) | 0.005 |
| | A | 22 (19.7; 25) | 21 (20; 24) | |
| **HR (b/min)** | C | 68 (64; 74.2) | 66.5 (62; 75.5) | <0.001 |
| | A | 71.500 (66.7; 76) | 62 (56.5; 62) | |
| **QTc (ms)** | C | 430 (420; 440) | 430 (420; 440) | <0.001 |
| | A | 430 (420; 440) | 445 (430; 451.2) | |
| **PR (ms)** | C | 175 (160; 180) | 175 (160; 180) | 0.238 |
| | A | 175 (160; 180) | 180 (170; 182.5) | |
| **QRS (ms)** | C | 100 (95; 110) | 100 (90; 110) | 0.025 |
| | A | 100 (90; 110) | 100 (98.7; 116.2) | |

Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure; LVEF: left ventricular ejection fraction; LA area: left atrium area; HR: heart rate

Table 3. Laboratory tests

| | Group | T0 | T1 | P |
|---|---|---|---|---|
| **LDL-C (mg/dl)** | C | 105 (74.5; 123.5) | 100.5 (70.7; 118) | 0.063 |
| | A | 110 (88.7; 129) | 105.5 (83.7; 122.5) | |
| **HDL-C (mg/dl)** | C | 35 (29.7; 41.2) | 38 (33; 46) | 0.65 |
| | A | 36.5 (32; 41) | 38 (34; 42) | |
| **HbA1c (mmol/l)** | C | 6.5 (5.9; 7.3) | 6.4 (5.9; 7.2) | 0.687 |
| | A | 6.5 (5.9; 7.3) | 6.6 (6.1; 7.2) | |
| **Hs-CRP (mg/l)** | C | 0.4 (0.3; 0.4) | 0.3 (0.3; 0.4) | 0.074 |
| | A | 0.4 (0.3; 0.5) | 0.3 (0.2; 0.5) | |
| **Hb (mg/dl)** | C | 12.5 (11.7; 13.5) | 12.4 (11.7; 13.6) | 0.941 |
| | A | 12.7 (11.6; 13.5) | 12.8 (12.1; 13.2) | |
| **Creatinina (mg/dl)** | C | 1.09 (0.9; 1.2) | 1.09 (0.9; 1.3) | 0.395 |
| | A | 1.1 (1; 1.2) | 1 (0.9; 1.3) | |
| **NT-proBNP (pg/ml)** | C | 345 (245; 593.7) | 337.5 (240.7; 564.5) | 0.013 |
| | A | 355 (251.5; 665.7) | 279.5 (234; 422) | |
| **Hs-TnT (ng/ml)** | C | 37.5 (30.7; 46.2) | 39.5 (34; 48) | 0.007 |
| | A | 38 (29.7; 45.5) | 36.5 (27; 45.2) | |
| **TSH (µU/ml)** | C | 2.8 (1.8; 3.4) | 2.8 (2.2; 3.5) | 0.375 |
| | A | 2.8 (2.1; 3.4) | 3.1 (2.3; 4.1) | |
| **IL-6 (pg/ml)** | C | 3.3 (2.6; 4.5) | 3.2 (2.3; 4.2) | 0.446 |
| | A | 3.4 (2.6; 4.5) | 3.4 (2.7; 4.5) | |

Abbreviations: LDL-C: low density liporotein cholesterol; HDL-C: high density lipoprotein cholesterol; HbA1c: glycosylated hemoglobin; hs-CRP: high sensitivity C reactive protein; Hb: hemoglobin; NT-proBNP: N-terminal natriuretic brain peptide; Hs-TnT: high sensitivity Troponin T; TSH: thyroid stimulating hormone; IL-1B: IL-6: interleukin 6

Table 4. CAD specific medication

| Number of patients | | T0 | T1 |
|---|---|---|---|
| **Statins** | C | 50 | 48 |
| | A | 48 | 47 |
| **ACE Inhibitors** | C | 45 | 45 |
| | A | 43 | 43 |
| **Beta-Blockers** | C | 48 | 44 |
| | A | 41 | 39 |

Abbreviations: T0: baseline; T1: 3 months; ACE: angiotensin converting enzyme

Table 5. Anti-diabetic treatment and dosage

| Hypoglycemic agents | Group A (17 patients) | | Group C (15 patients) | |
|---|---|---|---|---|
| | Number of patients | Mean daily dose | Number of patients | Mean daily dose |
| **Metformin** | 8 | 1250 mg | 6 | 1100 mg |
| **Gliclazide** | 3 | 60 mg | 4 | 60 mg |
| **Glimepiride** | 3 | 3 mg | 1 | 2 mg |
| **Sitagliptin** | 4 | 65 mg | 2 | 80 mg |
| **Exenatide** | 1 | 5 µg | 0 | |
| **Insulin (short/intermediate/ long acting-glargine)** | 5 | 52/24 IU | 3 | 45/16 IU |

Table 6. Statin therapy and dosage

| Statin | Group A (48 patients) | | Group C (50 patients) | |
|---|---|---|---|---|
| | n: | Mean daily dose (mg) | n: | Mean daily dose (mg) |
| **Atorvastatin** | 18 | 40 | 20 | 30 |
| **Rosuvastatin** | 24 | 10 | 25 | 10 |
| **Simvastatin** | 4 | 40 | 5 | 40 |
| **Pravastatin** | 2 | 20 | 0 | 0 |

with the atrial natriuretic peptide and due to variations in cycle length and ventricular filling times in AF, there may be chaotic microregional variations within the atrial cardiomyocyte strain. This can trigger the release of NT-proBNP in the absence of increased mean intra-cardiac or transmural pressure. Inflammatory, fibrotic and hypertrophic changes may also promote the increase in the expression and release of natriuretic peptides, including NT-proBNP (Richards et al 2013).

NT-proBNP may be a marker of recurrent AF and it is associated with the risk of stroke in these patients (Darkner et al 2017; Hijazi et al 2012). There was a significant decrease in NT-proBNP levels after 3 months of AM treatment for PAF. Each episode of PAF can trigger HF, one of the most frequent complications of CAD. Heart rate control in patients with CAD and HF is a key component to successful therapy, AM reduced basal HR in patients with PAF, and this may be a hypothesis in reducing NT-proBNP levels. Compared to the control group, patients with CAD and PAF who received AM for 3 months showed a significant left atrial area reduction. A smaller LA suggests reverse remodeling with reduced fibrotic and inflammatory changes and an improvement in atrial function, consequently leading to a decrease in the synthesis of natriuretic peptides; in our opinion this can contribute to the significant drop in NT-proBNP levels. In PAF, rapid and irregular atrial rates may increase troponin levels after excessive myocardial fiber stretching, altering the structure of certain integrins and allowing the release of troponin from the cytosolic pool into the bloodstream. After 3-month therapy with AM, CAD patients with PAF did not show a significant decrease in hs-TnT levels. AF episodes probably did not last long enough for an important increase in hs-TnT levels.

Higher IL-6 levels were associated with greater AF risk in the general population and in patients who underwent coronary artery bypass grafting, as well as with AF recurrence after electric conversion or ablation (Wu et al 2013). There are different findings regarding the effect of AM on IL-6. Even if it can stimulate IL-6 production in cultured cells (Nakajima et al 2001) reported that therapeutic concentrations of AM inhibited TNF-α and IL-6 production in human peripheral blood mononuclear cells, there was no change in IL-6 levels after 3 months of AM in clinical practice. Although it does not exert an anti-inflammatory effect

by lowering the levels of this cytokine, the neutral effect brings added safety to the administration of this drug in ischemic patients. This is the first study evaluating the impact of AM on IL-6, and further studies are needed to evaluate long-term serum IL-6 level dynamics in patients with CAD ± HF treated with AM.

Even if the exact cause can not be identified, previous studies have demonstrated the ability of AM to reduce the activation and mobilization of neutrophils, being able to limit the activation of human T cells by inhibiting - in a dose dependent manner - the production of cytokines, including IL-4, IL-2, TNF alpha and Interferon-gamma (Cheng et al 2015), suggesting a favorable effect of AM on hs-CRP levels in ischemic patients. At the end of our study, hs-CRP was not influenced by AM treatment. There is no data on the long-term impact on this marker in CAD patients treated with AM and thus further research is needed.

One of findings in this paper is the increase of diastolic blood pressure in AM patients. Diastolic blood pressure values do not exceed the normal upper limit and do not influence blood pressure management.

The anti-inflammatory effect of statin therapy is well documented. Atorvastatin, one of the most used statins in our study, can increase IL-6 levels and decrease hs-CRP levels (Yao et al 2017), this is precisely why the daily doses have not been modified during the study, in order to avoid changes in the dynamics of hs-CRP and IL-6 that could be attributed to statins.

Regarding the antidiabetic treatment, many of the frequently used molecules have an influence on both HF and inflammatory markers; in our study, metformin was the most used oral drug in both groups. Metformin can inhibit IL-6 signalling (Mishra et al 2019) and in special conditions it is able to reduce CRP levels (Wang et al 2017). Even if there were no significant differences in the number of patients treated with this medication in both groups, AM - due to its ability to inhibit CYP2A -may lead to an increase in metformin concentrations (May & Schindler 2016), and as a consequence it may influence the levels of the studied inflammatory markers. There is no clear evidence of the impact of gliclazide and glimepiride on the biomarkers evaluated in this study, and the small number of users leads to an insignificant impact on their dynamics. Regarding dipeptidyl peptidase-4 inhibitors, due to the low number of users and the absence of important pharmacological interactions with AM, we believe that sitagliptin does not play an important role in reducing the level BNP induced by AM. Therapy with insulin glargine increases concentrations of NT- proBNP by 20%, but does not alter hs-TnT levels. The exact mechanism is unknown, but could reflect changes in sodium or fluid retention, or alterations in glucose metabolism. In AM treated group, 10% of CAD patients required insulin, alone or in addition to oral drugs for glycaemic control. The required doses of insulin glargine were significantly higher in group A and theoretically, this would lead to an increase in the level of NT-proBNP in PAF patients, not observed in AM treated patients. No important AM-insulin glargine interactions have been documented in the literature.

**Limitations of the study**

Despite the fact that patients with recent infections were excluded from the study, infectious interferences were not evaluated during the follow-up period, and this could play an important role in the dynamics of both inflammatory and cardiac biomarkers. Due to the relatively small number of patients included in the study and the significant rate of AM discontinuation, we consider it appropriate to confirm these results in larger-scale studies.

# Conclusions

Administration of AM for PAF episodes in stable CAD patients resulted in a significant decrease in the serum level of NT-proBNP, but it did not determine any changes in and hs-CRP, IL-6 and hs-TnT levels. A lower NT-proBNP levels provides added safety in the use of AM in ischemic patients, implicitly improving prognosis and symptomatology. This is the first study to evaluate the anti-inflammatory effect of short-term AM therapy in this category of patients.

# Acknowledgements

This study was partially funded by the "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, through the PhD Research Project-2016 (No. 7690/53/ 15.04.2016). Financial support has been used to purchase test kits and laboratory materials.

AIG, RD, DP created the study design, performed the patient's explorations both at the beginning and at the follow-up. LCG performed the laboratory determinations and statistical analysis. All authors contributed to discussions and conclusions, and all authors reviewed and gave their consent for publication.

# References

Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association. Circulation. 2017 Mar;135(10).

Casas JP, Shah T, Hingorani AD, Danesh J, Pepys MB. C-reactive protein and coronary heart disease: a critical review. J Intern Med. 2008 Oct;264(4):295–314.

Cheng S-M, Lin W-H, Lin C-S, Ho L-J, Tsai T-N, Wu C-H, et al. Modulation of both activator protein-1 and nuclear factor-kappa B signal transduction of human T cells by amiodarone. Exp Biol Med. 2015 Jan;240(1):99–108.

Costabel JP, Burgos LM, Trivi M. The Significance Of Troponin Elevation In Atrial Fibrillation. J Atr Fibrillation. 2017;9(6):1530.

Darkner S, Goetze JP, Chen X, Henningsen K, Pehrson S, Svendsen JH. Natriuretic Propeptides as Markers of Atrial Fibrillation Burden and Recurrence (from the AMIO-CAT Trial). Am J Cardiol. 2017 Oct;120(8):1309–15.

Dehghani-Samani A, Madreseh-Ghahfarokhi S, Dehghani-Samani A. Mutations of Voltage-Gated Ionic Channels and Risk of Severe Cardiac Arrhythmias. Acta Cardiol Sin. 2019 Mar;35(2):99.

Deng X-T, Jiang M-H, Zhu J-H, Ge L-J, Guo J, Gao S-P, et al. The Association of Interleukin 6−634C/G Polymorphism With Left Atrial Thrombus and Severe Spontaneous Echocontrast in Patients With Atrial Fibrillation. Clin Appl Thromb. 2013 Nov;19(6):673–8.

Goette A, Schön N, Kirchhof P, Breithardt G, Fetsch T, Häusler KG, et al. Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation (ANTIPAF) Trial. Circ Arrhythmia Electrophysiol. 2012 Feb;5(1):43–51.

Hall C. NT-ProBNP: the mechanism behind the marker. J Card Fail. 2005 Jun;11(5 Suppl):S81-3.

Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, et al. Cardiac Biomarkers Are Associated With an Increased Risk of Stroke and Death in Patients With Atrial Fibrillation. Circulation. 2012 Apr;125(13):1605–16.

Huang W-C, Chou R-H, Chang C-C, Hsu C-Y, Ku Y-C, Huang H-F, et al. Systemic Inflammatory Response Syndrome is an Independent Predictor of One-Year Mortality in Patients with Acute Myocardial Infarction. Acta Cardiol Sin. 2017 Sep;33(5):477–85.

Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016 Oct;37(38):2893–962.

Knudsen CW, Omland T, Clopton P, Westheim A, Wu AHB, Duc P, et al. Impact of Atrial Fibrillation on the Diagnostic Performance of B-Type Natriuretic Peptide Concentration in Dyspneic Patients. J Am Coll Cardiol. 2005 Sep;46(5):838–44.

Koc M, Karaarslan O, Abali G, Batur MK. Variation in high-sensitivity C-reactive protein levels over 24 hours in patients with stable coronary artery disease. Texas Hear Inst J.

Marott SCW, Nordestgaard BG, Zacho J, Friberg J, Jensen GB, Tybjærg-Hansen A, et al. Does Elevated C-Reactive Protein Increase Atrial Fibrillation Risk? J Am Coll Cardiol. 2010 Aug;56(10):789–95.

May M, Schindler C. Clinically and pharmacologically relevant interactions of antidiabetic drugs. Ther Adv Endocrinol Metab. 2016 Apr;7(2):69–83.

Mishra AK, Dingli D. Metformin inhibits IL-6 signaling by decreasing IL-6R expression on multiple myeloma cells. Leukemia. 2019;33(10)

Nakajima K, Yamazaki K, Yamada E, Kanaji Y, Kosaka S, Sato K, et al. Amiodarone Stimulates Interleukin-6 Production in Cultured Human Thyrocytes, Exerting Cytotoxic Effects on Thyroid Follicles in Suspension Culture. Thyroid. 2001 Feb;11(2):101–9.

Nilsonne G, Lekander M, Åkerstedt T, Axelsson J, Ingre M. Diurnal Variation of Circulating Interleukin-6 in Humans: A Meta-Analysis. Bartell PA, editor. PLoS One. 2016;11(11):e0165799.

Nokin P, Clinet M, Schoenfeld P. Cardiac β-adrenoceptor modulation by amiodarone. Biochem Pharmacol. 1983 Sep;32(17):2473–7.

Pedersen OD, Sondergaard P, Nielsen T, Nielsen SJ, Nielsen ES, Falstie-Jensen N, et al. Atrial fibrillation, ischaemic heart disease, and the risk of death in patients with heart failure. Eur Heart J. 2006 Nov;27(23):2866–70.

Richards M, Di Somma S, Mueller C, Nowak R, Peacock WF, Ponikowski P, et al. Atrial Fibrillation Impairs the Diagnostic Performance of Cardiac Natriuretic Peptides in Dyspneic Patients. JACC Hear Fail. 2013 Jun;1(3):192–9.

Shabalin A V, Shaposhnikova IS, Guseva IA. Effect of amiodarone on autonomic status and its efficacy in the treatment of different variants of paroxysmal atrial fibrillation. Kardiologiia. 2002;42(8):25–9.

Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J. 2013 Oct;34(38):2949–3003.

Wagner JA, Weisman HF, Levine JH, Snowman AM, Snyder SH. Differential effects of amiodarone and desethylamiodarone on calcium antagonist receptors. J Cardiovasc Pharmacol. 1990 Mar;15(3):501–7.

Wang J, Zhu L, Hu K, Tang Y, Zeng X, Liu J, et al. Effects of metformin treatment on serum levels of C-reactive protein and interleukin-6 in women with polycystic ovary syndrome. Medicine (Baltimore). 2017 Sep;96(39):e8183.

Watanabe T, Takeishi Y, Hirono O, Itoh M, Matsui M, Nakamura K, et al. C-Reactive protein elevation predicts the occurrence of atrial structural remodeling in patients with paroxysmal atrial fibrillation. Heart Vessels. 2005 Mar;20(2):45–9.

Wu N, Xu B, Xiang Y, Wu L, Zhang Y, Ma X, et al. Association of inflammatory factors with occurrence and recurrence of atrial fibrillation: A meta-analysis. Int J Cardiol. 2013 Oct;169(1):62–72.

Yao H, Lv J. Statin Attenuated Myocardial Inflammation Induced by PM2.5 in Rats. Acta Cardiol Sin. 2017 Nov;33(6):637–45.

# Authors

•Alin Ionut Grosu, Department of Internal Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy, 11 Tabacarilor Street, 400139, Cluj-Napoca, Romania; Department of Cardiology, Clinical Municipal Hospital Cluj-Napoca, 11 Tabacarilor Street, Cluj-Napoca, 400139, Romania; email: alinionutgrosu@gmail.com

•Dan Radulescu, Department of Internal Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy, 11 Tabacarilor Street, 400139, Cluj-Napoca, Romania; Department of Cardiology, Clinical Municipal Hospital Cluj-Napoca, 11 Tabacarilor Street, Cluj-Napoca, 400139, Romania; email: Dan.Radulescu@umfcluj.ro

•Laura Grosu, Department of Neurosciences, "Iuliu Hatieganu" University of Medicine and Pharmacy, 43 Victor Babes Street, 400012, Cluj-Napoca, Romania; email: laura.c.grosu@gmail.com

•Dana Pop, Department of Cardiology-Recovery, "Iuliu Hatieganu" University of Medicine and Pharmacy, 46-50 Viilor Street, 400347, Cluj-Napoca, Romania; Cardiology-Rehabilitation Department, Clinical Rehabilitation Hospital, Cluj-Napoca, Romania; email:dana.pop@umfcluj.ro

| | |
|---|---|
| **Citation** | Grosu AI, Radulescu D, Grosu LC, Pop D. Short term amiodarone treatment on inflammatory and cardiac biomarkers in patients with ischemic heart disease and paroxysmal atrial fibrillation. HVM Bioflux 2020;12(1):40-46. |
| **Editor** | Antonia Macarie |
| **Received** | 11 February 2020 |
| **Accepted** | 15 March 2020 |
| **Published Online** | 23 March 2020 |
| **Funding** | This study was partially funded by the "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, through the PhD Research Project-2016 (No. 7690/53/15.04.2016). |
| **Conflicts/ Competing Interests** | None reported |