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Efficacy and safety of dronedarone in patients with amiodarone-induced hyperthyroidism: a clinical study

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Abstract. – OBJECTIVE: The aim of the study was to examine the safety and efficacy of dronedarone in patients with a history of atrial fibrillation and amiodarone-induced hyperthyroidism.

PATIENTS AND METHODS: We conducted a prospective study to evaluate the use of amiodarone and dronedarone in 124 patients with a history of paroxysmal atrial fibrillation who had no additional structural heart disease. All patients received amiodarone 200 mg qd. Out of 124 patients, 56 (45%) switched to dronedarone 400 mg bid due to amiodarone-induced hyperthyroidism and the remaining 68 patients (55%), with normal thyroid function, continued to receive amiodarone. The follow-up period was 12 months, and the patients were regularly monitored.

RESULTS: The primary outcome after 6 months dronedarone and amiodarone group was 56 and 68, including 38 (68%) and 54 (79.4%) (Odds ratio [OR] = 1.17, 95% confidence interval [95% CI] = 0.68-2.02) patients with sinus rhythm (SR) and 18 (32.14%) and 14 (28.6%) (odds ratio [OR] = 0.64, confidence interval [95% CI] = 0.29-1.40) patients with atrial fibrillation (AF). The secondary outcome after 12 months showed significant difference in thyroid function in the dronedarone group. Out of 46 patients, 24 (56.18%) patients reduced hyperthyroidism compared to the amiodarone group; out of 68, 6 (8.9%) patients were observed to have hyperthyroidism. At 12 months, there were 24 (43%) and 22 (62%) (odds ratio [OR] = 0.75, confidence interval [95% CI] = 0.38-1.49) patients with SR, and 32 (57%) and 26 (38%) (odds ratio [OR] = 0.67, confidence interval [95% CI] = 0.36-1.25) patients with AF.

CONCLUSIONS: In our study, dronedarone appears to be a good therapeutic option in the treatment of atrial fibrillation in patients with amiodarone-induced hyperthyroidism. However, long-term studies are needed to estimate the efficacy and toxicity of both drugs.

Key Words:
Dronedarone, Atrial fibrillation, Amiodarone, Hyperthyroidism.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults[1]. According to the data from the Framingham study[2], the risk of developing AF at 40 years old is about 26% for men and 23% for women. The prevalence of the disease will further increase in the future and is estimated that the number of patients with AF will double or triple in the next 30 years[3]. The main causes of atrial fibrillation are hypertension and structural heart disease, often caused by heart failure, coronary heart disease and heart valve disease. Recent studies[4,5] have shown that obesity also increases the risk of AF. Obesity has adverse effects on cardiovascular hemodynamics, cardiac structure and function, and increases the prevalence of AF, partly related to electroanatomic remodeling in obese patients[6]. Several studies[7-9] have shown that weight loss and reduction of oxidized low-density lipoprotein (ox-LDL)

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reduces the incidence of AF and cardiovascular risk factors. Management interventions for AF may be based on 'rate control' or 'rhythm control' approaches, depending on the patient characteristics and clinical context. Currently, the safety of antiarrhythmic drugs shows serious ventricular proarrhythmic effects and extracardiac toxicity[10]. Amiodarone is one of the most used drugs in the treatment of atrial fibrillation, but it has important side effects such as thyroid, hepatic, pulmonary and ocular dysfunction. Dronedarone appears to be safe and reduce hospital stay in patients with AF and stable coronary heart disease[9]. The use of amiodarone and dronedarone are both frequently employed for rhythm control in atrial fibrillation[11,12]. Amiodarone is iodine rich benzofuran derivative resembles that of thyroid hormone seen in Figure 1; it acts in liver and pituitary gland as thyroid analog[12]. The amiodarone-induced hyperthyroidism is the most frequent side effect during amiodarone therapy[13]. The occurrence in women and men is 1.5:1 ratio and the risk of developing hyperthyroidism is 14 times greater in patients treated with amiodarone[14,15]. Very often it is necessary to stop the treatment with amiodarone and to start other medical therapy, based on the patient's clinical condition and heart disease[16]. Previous studies in patients with hyperthyroidism and atrial fibrillation have shown that early detection of hyperthyroidism can decrease the risk of dangerous metabolic and cardiovascular effects. Therefore, regular screening of thyroid blood tests is necessary during amiodarone therapy[17,18]. The clinical diagnosis of amiodarone induced-hyperthyroidism is important and has a major influence on the therapeutic management of the patients; before switching to a specific therapeutic option, it is necessary to assess the possibility of withdrawing the amiodarone and selecting the treatment depending on the amiodarone-induced hyperthyroidism[19]. Dronedarone is a benzofuran derivative without iodine. For the treatment of atrial fibrillation approved by the Food and Drug Administration (FDA), it shows reduced toxic effects compared to amiodarone (Figure 1). Dronedarone has very short half-life compared with amiodarone (30h versus 60 days) and is less lipophilic because of its additional methane-sulfonyl group[20]. It helps preventing the occurrence of microcirculatory abnormalities in the ventricles and is safer and well-tolerated drug with preserved left ventricle function during AF with a very little effect on QT-interval and pro-arrhythmic risk[21]. Dronedarone has been evaluated in a few controlled trials due to its unclear mechanism; the lack of practical experience in the clinical context and the safety profile of the drug are not established. Therefore, we conducted a study to monitor the safety and efficacy of dronedarone and amiodarone in patients admitted to the University Hospital of Tor Vergata and to assess potential difference regarding the outcome of the treatment.

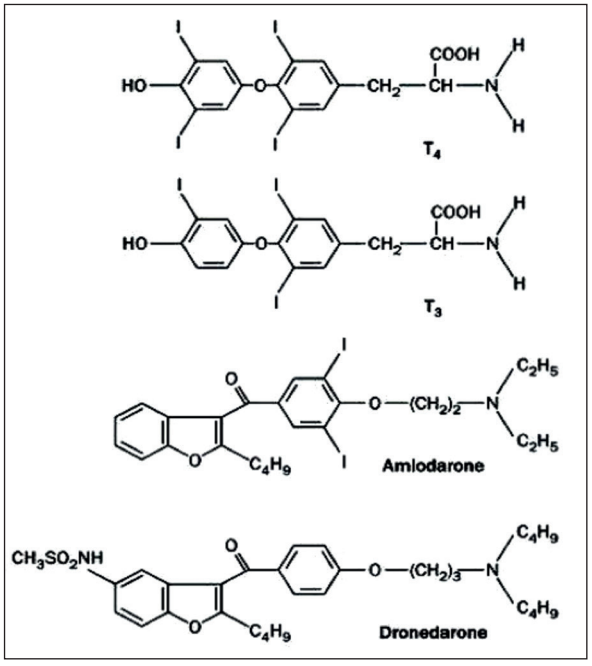

Figure 1. Structure of T_3, T_4, amiodarone, and dronedarone.

Patients and Methods

From January 2016 to January 2017 potentially eligible patients were prospectively identified in the Department of Cardiovascular Disease of the University Hospital of Tor Vergata in Rome, Italy. The study was approved by the local Ethics Committee, and each patient signed the informed consent. To be eligible, patients had to meet the following requirements: symptomatic paroxysmal atrial fibrillation verified by the Electrocardiogram (ECG), normal renal, hepatic, pneumological and ophthalmological examination. Patients were enrolled and treated with amiodarone 200 mg qd and dronedarone 400 mg bid. Initiation of therapy always started in the hospital setting. During the scheduled hospital stay, the patients were continuously monitored using ECG. Inclusion criteria: patients with a

history of paroxysmal atrial fibrillation in the absence of cardiopathy previously not benefited with flecainide and propafenone. Exclusion criteria: heart failure, kidney and liver failure.

Follow-Up

Patients were followed up for a minimum of 6 and 12 months. Every visit was scheduled in our out-patient department and assessed by ECG, laboratory blood analysis and clinical evaluations every three months. On each occasion, kidney serum markers, electrolytes, hepatic serum enzymes and thyroid blood tests were determined. Depending on the patient's clinical condition, additional diagnostic procedures were performed.

Statistical Analysis

Statistical analysis was performed by using SPSS statistics (SPSS 21.0; IBM Corporation, Armonk, NY, USA) and data are presented as mean ± standard deviation. The outcome was assessed by estimating the odds ratios (ORs) 95% Confidence Interval (CI) followed by post-hoc Bonferroni ANOVA analysis for comparison of significant differences between the groups. All reported *p*-values are less than 0.05 and were considered statistically significant.

Results

A total of 124 patients with a history of paroxysmal atrial fibrillation were enrolled, all of whom were receiving amiodarone 200 mg qd. Out of 124 patients, 56 (45%) patients triggered amiodarone-induced hyperthyroidism were switched to receive dronedarone 400 mg bid and the remaining 68 (55%) patients, with normal thyroid function, continued to receive amiodarone. These groups were well matched with respect to demographic details shown in Table I. Overall, the mean ages were 64 ± 18 in the dronedarone

Table I. Clinical characteristics of AF patients with baseline and follow-up characteristics.

	Dronedarone group 400 mg bid (n = 56)		Amiodarone group 200 mg qd (n = 68)
Age*	64 ± 18		67 ± 11
Male	36 (64%)		46 (68%)
Female	20 (36%)		22 (32%)
Hypertension	79%		74%
	Dronedarone group (n = 56)		
	Baseline*	**After 6 months***	**After 12 months***
Creatinine	01.05 ± 00.16	00.99 ± 00.16	00.98 ± 00.13
BUN	14.14 ± 02.27	14.21 ± 02.33	14.71 ± 02.14
Total bilirubin	00.78 ± 00.21	00.78 ± 00.18	00.88 ± 00.13
Conjugated bilirubin	00.54 ± 00.19	00.65 ± 00.22	00.88 ± 00.15
Unconjugated bilirubin	00.47 ± 00.15	00.68 ± 00.17	00.75 ± 00.23
AST	19.10 ± 03.25	19.14 ± 03.95	19.17 ± 03.90
ALT	21.29 ± 03.69	22.10 ± 04.22	22.75 ± 03.65
GGT	31.87 ± 05.80	33.21 ± 05.59	33.53 ± 05.67
	Amiodarone group (n=68)		
Creatinine	00.97 ± 00.16	01.00 ± 00.13	00.98 ± 00.15
BUN	14.32 ± 02.19	13.81 ± 01.85	16.41 ± 02.60
Total bilirubin	00.84 ± 00.22	00.89 ± 00.22	00.84 ± 00.22
Conjugated bilirubin	00.69 ± 00.23	00.96 ± 00.12	00.69 ± 00.23
Unconjugated bilirubin	00.72 ± 00.19	00.93 ± 00.17	00.72 ± 00.19
AST	19.91 ± 04.01	19.79 ± 04.76	19.29 ± 04.45
ALT	22.20 ± 03.88	22.37 ± 03.51	22.90 ± 03.96
GGT	33.58 ± 05.17	33.76 ± 03.86	33.14 ± 05.21

Footnote: AF, atrial fibrillation; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; LDL, low-density lipoproteins, *Mean (±SD).

Table II. Rate of sinus rhythm during 6 and 12 months follow-up period.

Treatment baseline	Dronedarone group (n=56) After 6 months follow-up Treatment (SR)	OR (95% CI)	Amiodarone group (n=68) After 12 months follow-up Treatment (SR)	OR (95% CI)	*p*-value
56	38 (68%)	11.17 (0.68-2.2.02)	24 (43%)	0.75 (0.38-1.49)	$p < 0.2262$
68	54 (79.41%)		22 (62%)		

Footnote: SR, sinus rhythm; OR, odds ratio; CI, confidence interval, Chi square test, $p < 0.05$.

Table III. Incidence of atrial fibrillation during 6 and 12 months follow-up period.

Treatment baseline	Dronedarone group (n=56) After 6 months follow-up Treatment (AF)	OR (95% CI)	Amiodarone group (n=68) After 12 months follow-up Treatment (AF)	OR (95% CI)	*p*-value
56	18 (32.14%)	0.64 (0.29-1.40)	32 (57%)	0.67 (0.36-1.25)	$p < 0.9126$
68	14 (20.60%)		26 (38.23%)		

Footnote: AF, atrial fibrillation; OD, odds ratio; CI, confidence interval, Chi square test, $p < 0.05$.

group and 67 ± 11 in the amiodarone group. The mean (± SD) duration of follow-up among all patients was every 6 and 12 months, the maximum duration of follow-up was one year. We scheduled follow-up visits that included review symptoms, assessment of clinical parameters and performance of ECG on days 21 and at 4, 6, and 12 months. The thyroid blood tests were repeated every 6 and 12 months.

After 6 Months of Follow-Up

Among 56 patients assigned to receive dronedarone, a primary outcome included 38 (68%) patients with a sinus rhythm (SR) and 18 (32.14%) patients with atrial fibrillation (AF). Compared to the amiodarone group, 68 patients had a primary outcome, including 54 (80%) and 14 (20.60%) patients with SR and AF (Tables II and III). During the study period, the effect of the dronedarone and amiodarone was consistent and there was no pathological evidence of QT-interval prolongation seen in both the groups (438±35 ms and 414 ± 11 ms) (Table IV). The occurrence of important treatment-emergent adverse events like creatinine level, hepatic, pulmonary symptoms and hospitalization was not observed in the two groups. In the dronedarone group, a post-hoc analysis revealed that there is no significant difference of hyperthyroidism compared to the amiodarone group (Figures 2 and 3).

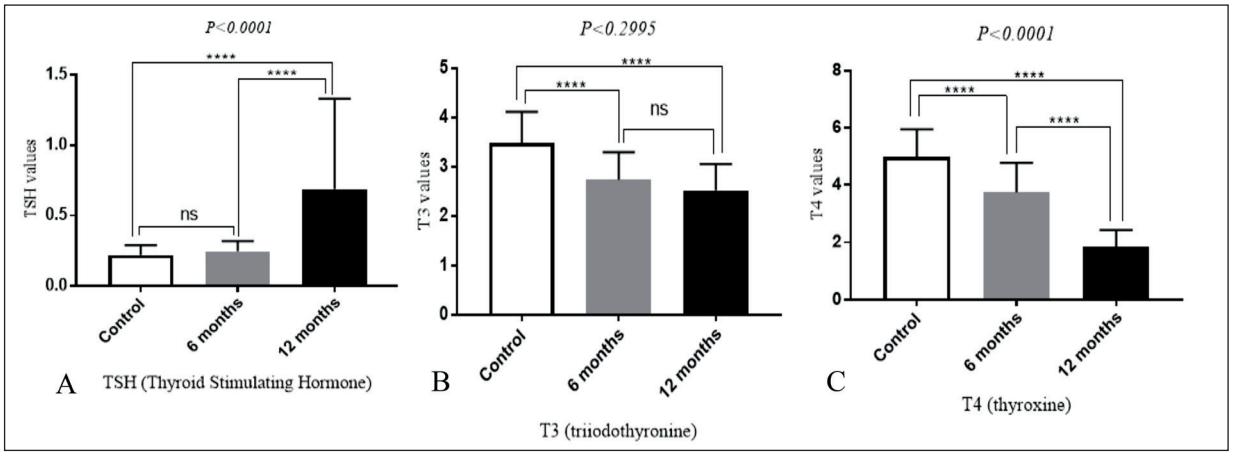

Figure 2. **(A)** TSH, **(B)** T3, and **(C)** T4 Thyroid values in dronedarone group (n=56), after the administration of dronedarone 400 mg bid, expressed as the mean±SD. *($p < 0.05$), ***($p < 0.01$), ****($p < 0.0001$).

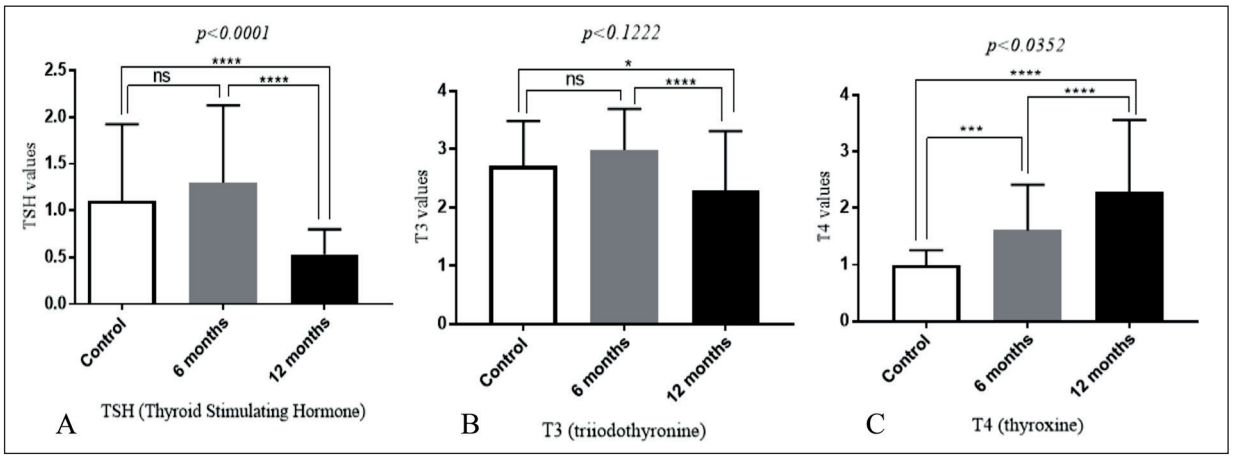

Figure 3. **(A)** TSH, **(B)** T3, and **(C)** T4 Thyroid values in amiodarone group (n=56), after the administration of amiodarone 200 mg qd, expressed as the mean±SD. *($p < 0.05$), ***($p < 0.01$), ****($p < 0.0001$).

After 12 Months of Follow-Up

In the dronedarone group, out of 56 patients, 24 (43%) and 32 (57%) patients had SR and AF. Compared to the amiodarone group, 22 (62%) and 26 (38.23%) patients had SR and AF (Tables II and III). No significant adverse events and pathological QT-prolongation were observed in the two groups (Tables I and IV). The effect of treatment showed a significant difference in thyroid function in the amiodarone group compared to the dronedarone group. 24 (56.18%) patients showed normal thyroid profile in the dronedarone group; 6 (8.9%) patients were observed to have hyperthyroidism in the amiodarone group (Table V). The post-hoc analysis revealed that there is a significant difference in thyroid values between the two groups (Figures 2 and 3).

Safety and Efficacy of Dronedarone and Amiodarone Group

Among these groups, after 12 month's follow-up, 24 patients with normal thyroid profile were observed in the dronedarone group. Compared to the amiodarone group, 6 patients were observed to have hyperthyroidism. Whereas, the incidence of atrial fibrillation after 6 and 12 months in the dronedarone group was observed in 18 and 32 patients, while in the amiodarone group in 14 and 26 patients (Tables II and III). During follow-up, deaths were not reported in any of the dronedarone and amiodarone group patients and showed that there were no statistically significant differences regarding the frequency of adverse events. During the study, no cases of kidney, liver, pulmonary or ocular toxicity were observed. The major findings of this work were that the atrial fibrillation with amiodarone-induced hyperthyroidism patients receiving dronedarone was considered to be a favorable drug choice in such patients, compared to the amiodarone group.

Discussion

Amiodarone is extensively used in AF and is associated with amiodarone-induced hyperthyroidism. Although it is commonly prescribed for the maintenance of sinus rhythm, its use has been plagued by dose-dependent end-organ toxicities, including thyroid dysfunction, hepatic failure, renal failure and pulmonary fibrosis. On the other hand, dronedarone showed to be effective and

Table IV. Follow-up of QT-prolongation in dronedarone and amiodarone group.

	Prolongation of QT (mean ± SD)		
	Baseline	**6 months**	**12 months**
Dronedarone group (n = 56)	416 ± 24	438 ± 34	436 ± 32
Amiodarone group (n = 68)	388 ± 12	414 ± 11	414 ± 10

safe in AF with less toxicity and short half-life compared to amiodarone[22]. A 200 mg amiodarone tablet contains 75 mg of iodine and releases approximately 10% (i.e., 7 mg) of free iodide in circulatory system, which is significantly higher than the daily need of 100-200 micrograms[23]. This elevates the plasma and urinary iodine levels to 40 folds. Amiodarone has a half-life as long as 100 days[24]. This is directly related to the exogenous release of excess iodide and its interference with thyroid hormone metabolism. We observed that, on long-term therapy 14% to 18% of patients develop amiodarone-induced hyperthyroidism[22], whereas in one-year follow-up 8.9% of patients. Danzi and Klien[25] showed that amiodarone has a significant impact in the reduction of thyroid dysfunction in the first months of interruption, but with a considerable increase in episodes of AF. In our study, after 6 months follow-up there was no significant difference in the two groups; instead, after 12 months follow-up 8.9% of hyperthyroidism was observed in the amiodarone group and 56.18% of patients in the dronedarone group showed normal thyroid function. On the other hand, no significant differences were observed in the recurrences of atrial fibrillation between the two groups. In ATHENA (A Trial with Dronedarone to prevent Hospitalization or Death in Patients with Atrial Fibrillation) study, dronedarone was shown to reduce morbidity and cardiovascular mortality in patients with AF who had additional cardiometabolic risk factors compared with amiodarone. In another study[26], dronedarone, as prescribed to AF patients in Sweden, has not exposed to the risk of mortality or liver disease. Therefore, amiodarone is the most widely prescribed antiarrhythmic drug in AF, partly because several studies has shown that its use is not associated with an increase in mortality even in patients with advanced structural heart disease[27]. However, its profile of extracardiac side effects may limit its use. Dronedarone, on the other hand, appears to be a useful drug in patients with paroxysmal atrial fibrillation, but cannot be used in patients with heart failure or permanent atrial fibrillation[28]. In our work, there were no cases of liver failure, renal failure or other dangerous side effects in the two groups at 1-year follow-up. In general, several studies[29,30,31] have shown that AF pharmacotherapy is limited by toxicities that constantly threaten patient safety and quality of life. Finally, given the limited power of the available studies and limitations in our work, it remains unclear whether treatment with dronedarone confers a survival benefit in long-term follow-up, compared to amiodarone. In our patients, the impact of dronedarone and amiodarone at 1-year follow-up was similar.

Conclusions

We showed that amiodarone is a standard drug in the treatment of AF. However, dronedarone may be a good therapeutic option to replace amiodarone in selected patients with amiodarone-induced hyperthyroidism for short-term discontinuation and have the same efficacy and safety. More long-term trials are needed to refine these estimates and to define the optimum balance of efficacy and toxicity for patients with AF.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Eckman MH, Costea A, Attari M, Munjal J, Wise RE, Knochelmann C, Flaherty ML, Baker P, Ireton R, Harnett BM, Leonard AC, Steen D, Rose A, Kues J. Atrial fibrillation decision support tool: population perspective. Am Heart J 2017; 194: 49-60.
2) Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 2004; 110: 1042-1046.
3) Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med 2002; 113: 359-364.
4) Asad Z, Abbas M, Javed I, Korantzopoulos P, Stavrakis S. Obesity is associated with incident atrial fibrillation independent of gender: a meta-analysis. J Cardiovasc Electrophysiol 2018; 29: 752-732.
5) De Lorenzo A, Bernardini S, Gualtieri P, Cabibbo A, Perrone MA, Giambini I, Di Renzo L. Mediterranean meal versus Western meal effects on postprandial ox-LDL, oxidative and inflammatory gene expression in healthy subjects: a randomized controlled trial for nutrigenomic approach in cardiometabolic risk. Acta Diabetol 2017; 54: 141-149.
6) Lavie CJ, Pandey A, Lau DH, Alpert MA, Sanders P. Obesity and atrial fibrillation prevalence, pathogenesis, and prognosis: effects of weight loss and exercise. J Am Coll Cardiol 2017; 70: 2022-2035.

7) Colica C, Merra G, Gasbarrini A, De Lorenzo A, Ciocoloni G, Gualtieri P, Perrone MA, Bernardini S, Bernardo V, Di Renzo L, Marchetti M. Efficacy and safety of very-low-calorie ketogenic diet: a double blind randomized crossover study. Eur Rev Med Pharmacol Sci 2017; 21: 2274-2289.

8) Di Renzo L, Merra G, Botta R, Gualtieri P, Manzo A, Perrone MA, Mazza M, Cascapera S, De Lorenzo A. Post-prandial effects of hazelnut-enriched high fat meal on LDL oxidative status, oxidative and inflammatory gene expression of healthy subjects: a randomized trial. Eur Rev Med Pharmacol Sci 2017; 21: 1610-1626.

9) Merra G, Gratteri S, De Lorenzo A, Barrucco S, Perrone MA, Avolio E, Bernardini S, Marchetti M, Di Renzo L. Effects of very-low-calorie diet on body composition, metabolic state, and genes expression: a randomized double-blind placebo-controlled trial. Eur Rev Med Pharmacol Sci 2017; 21: 329-345.

10) Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ; ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009; 360: 668-678.

11) Vamos M, Hohnloser SH. Amiodarone and dronedarone: an update. Trends Cardiovasc Med 2016; 26: 597-602.

12) Pisters R, Hohnloser SH, Connolly SJ, Torp-Pedersen C, Naditch-Brule L, Page RL, Crijns HJ. Effect of dronedarone on clinical endpoints in patients with atrial fibrillation and coronary heart disease: insights from the ATHENA trial. Europace 2014; 16: 174-181.

13) Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Europace 2010; 12: 1360-1420.

14) Le Heuzey JY, De Ferrari GM, Radzik D, Santini M, Zhu J, Davy JM. A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the DIONYSOS study. J Cardiovasc Electrophysiol 2010; 21: 597-605.

15) Cohen-Lehman J, Dahl P, Danzi S, Klein I. Effects of amiodarone therapy on thyroid function. Nat Rev Endocrinol 2010; 6: 34-41.

16) Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001; 344: 501-509.

17) Bogazzi F, Bartalena L, Dell'Unto E, Tomisti L, Rossi G, Pepe P, Tanda ML, Grasso L, Macchia E, Aghini-Lombardi F, Pinchera A, Martino E. Proportion of type 1 and type 2 amiodarone-induced thyrotoxicosis has changed over to 27-year period in Italy. Clin Endocrinol (Oxf) 2007; 67: 533-537.

18) Martino E, Bartalena L, Bogazzi F, Braverman LE. The effects of amiodarone on the thyroid. Endocr Rev 2001; 22: 240-254.

19) Bartalena L, Wiersinga WM, Tanda ML, Bogazzi F, Piantanida E, Lai A, Martino E. Diagnosis and management of amiodarone-induced thyrotoxicosis in Europe: results of an international survey among members of the European Thyroid Association. Clin Endocrinol (Oxf) 2004; 61: 494-502.

20) Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ; ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009; 360: 668-678.

21) Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, Radzik D, Aliot EM, Hohnloser SH; EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med 2007; 357: 987.

22) Pacheco Capote C, Mena Bares LM, Benítez Velazco A, Louhibi Rubio L, Contreras Puertas PI, Maza Muret FR, Latre Romero JM. Usefulness of thyroid scintigraphy in the therapeutic management of amiodarone-induced hyperthyroidism]. Rev Esp Med Nucl 2007; 26: 270-276.

23) Dale KM, White CM. Dronedarone: an amiodarone analog for the treatment of atrial fibrillation and atrial flutter. Ann Pharmacotherapy 2007; 41: 599-605.

24) Friberg L. Safety of dronedarone in routine clinical care. J Am Coll Cardiol 2014; 63: 2376-2384.

25) Danzi S, Klein I. Amiodarone-induced thyroid dysfunction. J Intensive Care Med 2015; 30: 179-185.

26) Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ; ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009; 360: 668-678.

27) Ursella S, Testa A, Mazzone M, Gentiloni Silveri N. Amiodarone-induced thyroid dysfunction in clinical practice. Eur Rev Med Pharmacol Sci 2006; 10: 269-278.

28) Martino E, Bartalena L, Bogazzi F, Braverman LE. The effects of amiodarone on the thyroid. Endocr Rev 2001; 22: 240-254.

29) Roti E, Bianconi L, De Chiara F, Minelli R, Tosi C, Gardini E, Salvi M, Braverman LE. Thyroid ultrasonography in patients with a previous episode of amiodarone induced thyrotoxicosis. J Endocrinol Invest 1994; 17: 259-262.

30) Migneco A, Ojetti V, Testa A, De Lorenzo A, Gentiloni Silveri N. Management of thyrotoxic crisis. Eur Rev Med Pharmacol Sci 2005; 9: 69-74.

31) Harjai KJ, Licata AA. Effects of amiodarone on thyroid function. Ann Intern Med 1997; 126: 63-73.